CHAPTER

44 Malignant Hypertension and Other Hypertensive Crises

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THE CLINICAL SPECTRUM OF SEVERE HYPERTENSION

The vast majority of hypertensive patients are asymptomatic for many years until complications due to atherosclerosis, cerebrovascular disease, or congestive heart failure develop. In a minority of patients this "benign" course is punctuated by a hypertensive crisis.

A 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. The haste with which the elevated blood pressure must be controlled varies with each crisis. However, the crucial role of hypertension in the disease process must be identified and a plan for management of the blood pressure successfully implemented if the outcome is to be optimal. The absolute level of blood pressure is not the most important factor in determining the existence of a hypertensive crisis. In children, pregnant women, and other previously normotensive individuals in whom moderate hypertension develops suddenly, a hypertensive crisis can occur at a diastolic blood pressure normally well tolerated by adults with chronic hypertension. Furthermore, in adults with only mild to moderate hypertension, a crisis can occur when there is concomitant acute end-organ dysfunction involving the heart or brain.

Approximately 1% to 2% of patients with hypertension will have a hypertensive emergency at some time in their life. A recent study explored changes in the frequency of hospitalizations and in-hospital mortality for hypertensive emergencies before and after the publication of the Seventh Joint National Committee (JNC7) on the prevention, detection, evaluation, and treatment of high blood pressure.[1] Using the Nationwide Inpatient Sample from 2000 to 2007, adult patients hospitalized with a diagnosis of hypertensive emergency were identified based on International Classification of Diseases, 9th revision, clinical modification codes. A total of 456,259 hospitalizations with the diagnosis of hypertensive emergency occurred from the start of calendar year 2000 to the end of calendar year 2007. Analysis revealed that the frequency of hospitalizations in the United States with a hypertensive emergency increased about 1.11% over this time period from 101/100,000 population in 2000 to 111/100,000 population in 2007. Despite this increase in hospitalizations, the all-cause in-hospital mortality rate for hypertensive emergencies decreased from 2.8% in the pre-JNC7 era to 2.6% in the post-JNC7 era (odds ratio [OR] 0.91, 95% confidence interval [CI] 0.86–0.96). The authors conclude that although the number of patients with hypertensive emergency increased from 2000 to 2007, the mortality rates decreased significantly after publication of the JNC7 guidelines. The spectrum of hypertensive crises and other categories of severe hypertension are outlined in Table 44.1.

Malignant hypertension is a clinical syndrome characterized by marked elevation of blood pressure with widespread acute arteriolar injury. The clinical sine qua non of malignant hypertension is the finding of hypertensive neuroretinopathy. Hypertensive encephalopathy is a medical emergency in which cerebral malfunction is attributed to the severe elevation of blood pressure. It is one of the most serious complications of malignant hypertension. However, hypertensive encephalopathy can also occur in the absence of malignant hypertension (neuroretinopathy). Hypertensive encephalopathy can develop in the setting of severe hypertension of any cause, especially when acute blood pressure elevation occurs in previously normotensive individuals with eclampsia, acute glomerulonephritis, pheochromocytoma, or drug withdrawal hypertension. Clinical features include severe headache, blurred vision or blindness, nausea, vomiting, and mental confusion. If aggressive treatment is not initiated, stupor, convulsions, and death can ensue within hours. There is a prompt and dramatic clinical response to antihypertensive therapy.

On occasion, hypertension that is not in the malignant phase (hypertensive neuroretinopathy is absent) may still qualify as a hypertensive crisis when acute end-organ dysfunction occurs in the presence of even moderate hypertension. The term benign hypertension with acute complications includes hypertension complicating acute

44.1 The Clinical Syndromes of Severe Hypertension

Hypertensive crises

- Malignant hypertension (hypertensive neuroretinopathy present)
- Hypertensive encephalopathy
- Benign hypertension with acute complications (acute organ system dysfunction but no hypertensive neuroretinopathy)
  - Acute hypertensive heart failure (acute diastolic dysfunction with pulmonary edema)
  - Atherosclerotic coronary vascular disease
    - Acute myocardial infarction
    - Unstable angina
  - Acute aortic dissection
  - Active bleeding including postoperative bleeding
  - Central nervous system catastrophe
    - Hypertensive encephalopathy
    - Intracerebral hemorrhage
    - Subarachnoid hemorrhage
    - Severe head trauma
  - Catecholamine excess states
    - Pheochromocytoma crisis
    - Monoamine oxidase inhibitor-tyramine interactions
    - Antihypertensive drug withdrawal syndromes
    - Phenylpropanolamine overdose
  - Preeclampsia and eclampsia
  - Poorly controlled hypertension in a patient requiring emergency surgery
  - Severe postoperative hypertension
  - Scleroderma renal crisis
  - Miscellaneous hypertensive crises
    - Severe hypertension complicating extensive burn injury
    - High-dose cyclosporine in children after bone marrow transplantation
    - Autonomic hyperreflexia in quadriplegic patients
    - Severe hypertension with acute rejection or transplant renal artery stenosis in renal allograft recipients
    - Hypoglycemia in patients receiving β-adrenergic receptor blockers

(continued)

44.1 The Clinical Syndromes of Severe Hypertension (continued)

Benign hypertension with chronic stable complications (chronic end-organ dysfunction but no hypertensive neuroretinopathy)
Chronic renal insufficiency due to primary renal parenchymal disease
Chronic congestive heart failure with diastolic dysfunction
Atherosclerotic coronary vascular disease
Stable angina
Previous myocardial infarction
Chronic cerebrovascular disease
Transient ischemic attacks
Prior cerebrovascular accident
Severe uncomplicated hypertension (severe hypertension without hypertensive neuroretinopathy or end-organ dysfunction)

pulmonary edema (acute diastolic dysfunction), acute myocardial infarction or unstable angina, acute aortic dissection, active bleeding, or central nervous system (CNS) catastrophe (hypertensive encephalopathy, intracerebral or subarachnoid hemorrhage, or severe head trauma). In each case, adequate control of the blood pressure is the cornerstone of successful therapy.

Catecholamine excess states—such as pheochromocytoma crisis, monoamine oxidase inhibitor–tyramine interactions, use of sympathomimetic drugs (cocaine, amphetamines, phencyclidine, or high-dose phenylpropanolamine), and abrupt withdrawal of antihypertensive medications (clonidine, methyldopa, or guanabenz)—can produce life-threatening hypertensive crises. The clinical presentation usually includes marked elevation of blood pressure with headache, diaphoresis, and tachycardia. With the severe acute elevation of blood pressure a number of complications can occur, including hypertensive encephalopathy, intracerebral hemorrhage, and pulmonary edema due to acute left ventricular diastolic dysfunction. Thus, catecholamine-related hypertensive crises require prompt recognition and control of blood pressure to avert disaster.

Preeclampsia is a hypertensive disorder unique to pregnancy that usually presents after the 20th week of gestation with proteinuria, edema, and hypertension. Eclamptic seizures may ensue and without treatment may result in death. Eclampsia is considered to be a subtype of hypertensive encephalopathy.[2]

Poorly controlled hypertension in a patient requiring emergency surgery is a hypertensive crisis because of the increased cardiovascular risk that accompanies inadequate preoperative blood pressure control. Surgical manipulation of the carotid arteries or open heart surgery (especially coronary artery bypass) is occasionally followed by severe hypertension in the immediate postoperative period. Severe postoperative hypertension represents a crisis requiring immediate blood pressure control because it can cause hypertensive encephalopathy or intracerebral hemorrhage, or jeopardize the integrity of vascular suture lines and thereby lead to postoperative hemorrhage.

In patients with progressive systemic sclerosis, scleroderma renal crisis can occur with sudden onset of hypertension that may enter the malignant phase. There is a rapid progression to end-stage renal disease (ESRD) within days to weeks unless the vicious cycle of hypertension, renal ischemia, and activation of the renin–angiotensin–aldosterone axis is interrupted.

Severe acute hypertension can also occur in patients with extensive burns or children receiving high-dose cyclosporine for allogeneic bone marrow transplantation. In quadriplegic patients, hypertensive crises may develop due to autonomic hyperreflexia resulting from stimulation of nerves below the level of the spinal cord injury. Hypertensive crises due to autonomic hyperreflexia can also develop in Guillain-Barré syndrome. Hypertensive crises may also complicate acute rejection or transplant renal artery stenosis

in patients with renal allografts. In each of these conditions, a sudden increase in blood pressure may cause acute pulmonary edema, hypertensive encephalopathy, cerebrovascular accident, and death.

On the other hand, severe hypertension or the presence of hypertensive complications does not always imply the existence of a hypertensive crisis requiring immediate control of the blood pressure. Patients with benign hypertension (no hypertensive neuroretinopathy) and chronic stable end-organ dysfunction do not require emergent reduction of blood pressure, although a long-term lack of adequate blood pressure control often results in further deterioration of end-organ function. The term benign hypertension with chronic stable complications includes hypertension occurring in the setting of primary renal parenchymal disease with chronic kidney disease, chronic congestive heart failure, atherosclerotic coronary vascular disease (stable angina pectoris or prior myocardial infarction), or chronic cerebral vascular disease (prior transient ischemic attacks or cerebrovascular accident).

It is important to emphasize that the finding of severe hypertension does not always imply that a hypertensive crisis is present. In patients with severe hypertension that is not accompanied by acute end-organ dysfunction or evidence of malignant hypertension (hypertensive neuroretinopathy) eventual complications due to stroke, myocardial infarction, or congestive heart failure occur over a time frame of months to years rather than hours to days. Although long-term control of blood pressure can prevent these complications, a hypertensive crisis cannot be diagnosed, as there is no evidence that acute reduction of blood pressure results in any improvement in short-term or long-term prognosis. Severe uncomplicated hypertension is defined by a diastolic blood pressure higher than 115 mm Hg without evidence of malignant hypertension (no hypertensive neuroretinopathy) or signs of acute end-organ dysfunction. Although this is not a true hypertensive crisis as defined earlier, it is the most common presentation of severe hypertension. Severe uncomplicated hypertension is usually found in patients with chronic essential hypertension who are undiagnosed, undertreated, or not adherent with medical therapy. It is most often discovered incidentally in an otherwise asymptomatic patient. There is no evidence of hypertensive encephalopathy or other acute end-organ dysfunction. The fundi do not show striate hemorrhages, cotton-wool spots, or papilledema. Because the potential complications of severe uncomplicated hypertension develop with a time frame of months to years, the once common practice of abrupt reduction of blood pressure with oral antihypertensive agents prior to discharge from the acute care setting is no longer accepted as the standard of care.[3–5] Instead, the goal of treatment should be the gradual reduction of blood pressure to normotensive levels over a few days in conjunction with frequent outpatient follow-up visits to modify the antihypertensive regimen and reinforce the importance of lifelong adherence with medical therapy. In the past this entity has been termed urgent hypertension. Use of the more descriptive term severe uncomplicated hypertension is preferable because there is no need for urgent reduction of blood pressure as would be required in patients with true hypertensive crises.

MALIGNANT HYPERTENSION

Etiologies of Malignant Hypertension

Hypertension of virtually any etiology can enter a malignant phase (Table 44.2). Thus, malignant hypertension is not a single disease entity but rather a syndrome in which hypertension can be either primary (essential) or secondary to

44.2 Etiologies of Malignant Hypertension

Primary (essential) malignant hypertension[a]
Secondary malignant hypertension
Chronic kidney disease
Chronic glomerulonephritis[a]
Chronic pyelonephritis[a]
Analgesic nephropathy[a]
Immunoglobulin A nephropathy[a]
Acute glomerulonephritis
Radiation nephritis
Ask-Upmark kidney
Renovascular hypertension[a]
Oral contraceptives
Renal cholesterol embolization
Scleroderma renal crisis
Antiphospholipid (anticardiolipin) antibody syndrome
Chronic lead poisoning
Endocrine hypertension
Pheochromocytoma
Aldosterone-producing adenoma
Cushing syndrome
Congenital adrenal hyperplasia

[a]Most common underlying etiologies.

one of any number of different etiologies.[10] Moreover, in the individual patient with malignant hypertension, on clinical grounds it is often difficult to distinguish whether the underlying hypertension is primary or secondary.

Malignant hypertension usually develops in patients with preexisting, poorly controlled, or undiagnosed hypertension. However, occasional patients have been described who experience an abrupt onset of so-called de novo malignant hypertension without a preceding phase of benign hypertension.[7] The presence of de novo malignant hypertension almost always indicates an underlying secondary cause of hypertension.[7]

Primary (Essential) Malignant Hypertension

In the era prior to the introduction of antihypertensive drugs, malignant hypertension evolved from underlying essential hypertension in more than 50% of patients.[8] However, more recent series found a lower incidence of primary malignant hypertension, most likely reflecting prevention of malignant hypertension through effective control of blood pressure among patients with essential hypertension.[9] In a series of patients collected between 1979 and 1985, primary malignant hypertension was found in only 20%.[10] This observation may not apply to black patients, because among blacks, essential hypertension continues to represent the most common underlying etiology of malignant hypertension.[11–13] Essential hypertension appears to be a rare cause of malignant hypertension in children. Secondary causes of hypertension such as chronic pyelonephritis, chronic glomerulonephritis, and renovascular hypertension are much more common in this younger age group.[14]

Secondary Malignant Hypertension

The most common secondary cause of malignant hypertension is primary renal parenchymal disease. Chronic glomerulonephritis was reported to underlie the development of malignant hypertension in up to 20% of patients.[10] Unless a history of an acute nephritic episode or long-standing hematuria or proteinuria is available, the underlying glomerulonephritis may be apparent only if a renal biopsy is performed. Underlying IgA nephropathy has been reported as a relatively common secondary cause of malignant hypertension.[14,15] Vesicoureteral reflux with chronic pyelonephritis may lead to malignant hypertension in children and young adults.[16] Superimposed malignant hypertension may also occur as a complication of analgesic nephropathy.[23] Malignant hypertension may develop as an early or late complication of radiation nephritis.[17] Renovascular hypertension due to either fibromuscular dysplasia or atherosclerotic renal artery stenosis is a well-recognized cause of malignant hypertension. In a series of 123 patients with malignant hypertension, renovascular hypertension was found in 43% of white patients and 7% of black patients.[18] Scleroderma renal crisis is the most acute and life-threatening manifestation of progressive systemic sclerosis. It is characterized by severe hypertension (sometimes malignant) with rapidly progressive renal failure. In one large series, scleroderma renal crisis occurred in 7% of white patients and 21% of black patients with progressive systemic sclerosis.[19] The renal histology in scleroderma renal crisis is often virtually indistinguishable from that of primary malignant nephrosclerosis.[20] However, in progressive systemic sclerosis, involvement of the renal vasculature, with proliferative endarteritis involving the interlobular arteries and fibrinoid necrosis of the afferent arterioles, may be a primary event that precedes either hypertension or renal insufficiency.[20] The renal ischemia that results from these lesions causes hypertension through activation of the renin–angiotensin system, leading to a vicious cycle of severe hypertension and renal ischemic injury. Scleroderma renal crisis was once a uniformly fatal complication of progressive systemic sclerosis. With the introduction of angiotensin-converting enzyme (ACE) inhibitors as treatment, outcomes have improved significantly, although 39% to 50% of patients with scleroderma renal crisis continue to have poor outcomes, including ESRD and death.

Epidemiology of Malignant Hypertension

Incidence

Although malignant hypertension is often a complication of preexisting hypertension, the risk of its development in hypertensive patients is difficult to estimate. In early series the incidence of malignant hypertension among hypertensive patients was 1% to 7%.[21] In the era of effective antihypertensive therapy for benign hypertension, the incidence of malignant hypertension appears to have declined to some extent. A review of death certificates in New York City between 1958 and 1974 revealed that the overall mortality due to malignant hypertension had declined by 78% from 2.25 deaths to 0.48 deaths/100,000 population/year.[22] Although some of the decreased mortality was probably due to successful treatment of patients with malignant hypertension with antihypertensive drugs and dialysis, the authors speculated that the overall incidence of malignant hypertension had declined to less than 1% due to successful treatment of benign hypertension. However, despite recent advances in the treatment of essential hypertension, malignant hypertension is clearly not a disease that has vanished. In the United States, during the period from 1983 to 1992, the number of hospital admissions with malignant hypertension or accelerated hypertension as the primary diagnosis (International Classification of Diseases, ICD-9 Code 401.0) doubled from approximately 16,000 to 32,000. Moreover, the number of admissions in which one of these conditions was listed as a diagnosis tripled from approximately 23,000 to 75,000.[23] Reported experience in a multiracial population in England indicates that malignant hypertension is still common with a small proportion of hypertensive patients presenting with malignant hypertension each year.[24] The incidence rate of malignant hypertension for the entire population was approximately one to two cases/100,000/year. Moreover, the

incidence rate did not change over the 24-year period from 1970 to 1993. Recent studies have examined the changing demography of patients with malignant hypertension over the last 40 years.[25,26] The incidence rate for malignant hypertension has remained relatively stable over time. In one study from the United Kingdom, 446 patients with malignant hypertension were included.[25] Mean age was 48 ± 12 years, 65.5% were male gender, 64.7% white European, 20.4% African-Caribbean, and 14.8% South Asian. No significant demographic differences at diagnosis were evident over the 40 years, with the exception of a significant increase in the proportion of malignant hypertension among ethnic minorities (South Asian and Afro-Caribbeans).

Age

Malignant hypertension tends to occurs more frequently in younger subjects. The mean age of patients with malignant hypertension ranges from 40 to 50 years, with 57% of patients between 30 and 50 years old.[21] No difference has been found in the age at onset in men compared to women or whites compared to blacks.[21,27] The age dependency of malignant hypertension could be related to the increased frequency of secondary, more severe forms of hypertension in the young. Alternatively, it is possible that hypertension in patients destined to enter the malignant phase may be more rapidly progressive from the onset, so that the disease would be expected to occur predominantly in younger patients. Malignant hypertension is a rare development in patients beyond the age of 65.[28] The declining incidence of malignant hypertension in patients with essential hypertension relative to age is in marked contrast to the overall incidence of benign hypertension, which reaches a peak in the eighth decade. Patients over age 60 with malignant hypertension usually have underlying renovascular hypertension or primary renal parenchymal disease.[21] In most series of patients with malignant hypertension, males predominate over females by as much as 2 to 1.[21,27]

Race

Blacks have an increased incidence of essential hypertension compared to whites. Moreover, several studies demonstrate that blacks with essential hypertension also have an increased risk of developing malignant hypertension. In a population in which 31% of all hypertensive patients were black, 46% of 200 patients with malignant hypertension were found to be black.[29] In a study of 135 pairs of black and white hypertensive patients matched for age and gender, 4.4% of the black patients had retinopathy consistent with malignant hypertension, whereas only 0.74% of the white patients had these funduscopic findings.[29] The increased frequency of malignant hypertension among blacks may be due to the fact that they presented later in the course of essential hypertension, that antihypertensive therapy in blacks was inadequate to prevent the development of malignant hypertension, or that essential hypertension may be more aggressive and likely to enter the malignant phase in blacks than whites.[30]

Preceding Duration of Benign Hypertension

Although there are occasional case reports in which the malignant phase appears to begin de novo, the majority of patients show evidence of a variable period of preceding benign hypertension before the onset of malignant hypertension. Among 77 patients with malignant hypertension, the documented duration of benign hypertension was 0 to 6 months in 4%, 6 months to 1 year in 10%, 1 to 2 years in 12%, 2 to 4 years in 23%, 4 to 6 years in 16%, 6 to 8 years in 17%, and 8 to 10 years in 4%. Only 14% had benign hypertension for more than 10 years prior to the onset of the malignant phase.[21]

Additional Risk factors for Hypertensive Crisis

A number of additional risk factors have been associated with hypertensive crisis. These include smoking[31,33] and obesity.[41] However, a major under recognized risk factor for hypertensive crisis is nonadherence to therapeutic regimens. In a recent study of 89 patients at a single center, 33 potential risk factors were assessed. Nonadherence to antihypertensive medications was the most important risk identified.[34]

Clinical Features of Malignant Hypertension

The clinical features of untreated malignant hypertension as outlined by Volhard and Fahr in 1914[35] are still valid today: (1) elevation of diastolic blood pressure, usually fixed and severe; (2) funduscopic changes of hypertensive neuroretinopathy with striate hemorrhages, cotton-wool spots, and papilledema; (3) renal insufficiency; (4) rapid progression to a fatal outcome, usually due to uremia if inadequately treated; and (5) renal histology demonstrating malignant nephrosclerosis with fibrinoid necrosis of afferent arterioles and proliferative endarteritis of interlobular arteries.

Unless hypertensive neuroretinopathy is present, malignant hypertension cannot be diagnosed regardless of the height of the arterial blood pressure.[36] However, the other clinical features need not be present initially to substantiate a diagnosis of malignant hypertension. There is no critical level of blood pressure that defines the presence of malignant hypertension. An acute increase in blood pressure in previously normotensive individuals can precipitate the malignant phase at a diastolic blood pressure as low as 100 to 110 mm Hg. Conversely, very high diastolic blood pressures may persist for many years in patients with essential hypertension without the development of malignant hypertension.[37]

With untreated malignant hypertension, severe renal impairment inevitably occurs, although there may be minimal renal involvement at the time of presentation. In this regard, in patients dying early in the course of malignant hypertension due to cerebrovascular accident or congestive heart failure, histologic features of malignant nephrosclerosis may be absent.

Some authors have distinguished accelerated hypertension (hemorrhages and cotton-wool spots) from malignant hypertension (hemorrhages, cotton-wool spots, and papilledema). However, since the finding of striate hemorrhages and cotton-wool spots has the same prognostic significance whether or not papilledema is present,[38,39] it has been recommended that accelerated hypertension and malignant hypertension be regarded as synonymous terms for a clinical syndrome in which there is widespread hypertension-induced acute arteriolar injury. In this regard, the World Health Organization has recommended that the term malignant hypertension be used to describe this disease process.[36]

Presenting Symptoms

The most common presenting complaints in patients with malignant hypertension are headache, blurred vision, and weight loss. Less common presenting symptoms include dyspnea, fatigue, malaise, gastrointestinal complaints (nausea, vomiting, epigastric pain), polyuria, nocturia, and gross hematuria. In many series, the onset of symptoms was noted to be remarkably sudden, such that it could often be dated precisely. In contrast, an "asymptomatic" presentation of malignant hypertension is not uncommon, especially in young black males who deny any prior symptoms when they present in the end-stage of the hypertensive process with florid failure of the brain, heart, and kidneys.

Weight loss is a very common symptom early in the course of malignant hypertension, and often occurs before the onset of anorexia or uremia.[21] In many patients, at least a portion of the weight loss can be attributed to volume depletion resulting from a spontaneous natriuresis with the onset of malignant hypertension.[17,21]

Level of Blood Pressure

There is apparently no absolute level of blood pressure above which malignant hypertension invariably occurs. In most series of patients with malignant hypertension, the average diastolic blood pressure is higher than 120 to 130 mm Hg.[21] However, two series found considerable overlap of blood pressure levels in patients with benign and malignant hypertension.[21,40]

Funduscopic Manifestations

Examination of the ocular fundus is of great importance in the assessment of patients with severe hypertension, especially with regard to prognosis.[41–44]

Although the original classification of hypertensive retinopathy by Keith[45] has proven useful, a number of authorities have recommended abandonment of the Keith and Wagener classification in favor of the hypertensive retinopathy classification initially proposed by Fishberg and Oppenheimer.[42] This classification draws a distinction between retinal arteriosclerosis with arteriosclerotic retinopathy, which is characteristic of benign hypertension, and hypertensive neuroretinopathy, which defines the presence of malignant hypertension (Table 44.3). In essence, two different types of retinal disease occur in patients with hypertension: one that reflects changes induced by arteriolar narrowing (retinal arteriosclerosis) and one that represents acute retinal vascular injury induced by severe hypertension (hypertensive neuroretinopathy).

Retinal arteriosclerosis with or without arteriosclerotic retinopathy is seen in patients with long-standing benign hypertension from either primary or secondary causes. Retinal arteriosclerosis (arteriolosclerosis) is characterized histologically by the accumulation of hyaline material in arterioles. Funduscopic changes reflecting retinal arteriosclerosis include irregularity of the lumen and focal narrowing, arteriovenous crossing changes, broadening of the light reflex, copper or silver wiring, perivasculitis (parallel white lines around blood column), and generalized arteriolar narrowing. Arteriosclerotic retinopathy, which results from this arteriosclerotic process, is manifested by the presence of hemorrhages and hard exudates. The hemorrhages are usually solitary, round, or oval and confined to the

44.3 Retinal Changes in Hypertension

Retinal arteriosclerosis and arteriosclerotic retinopathy
Arteriolar narrowing (diffuse)
Focal arteriolar narrowing
Arteriovenous crossing changes
Broadening of the light reflex
Copper or silver wiring
Perivasculitis
Solitary round hemorrhages
Hard exudates
Central or branch venous occlusion
Hypertensive neuroretinopathy
Generalized arteriolar narrowing
Striate (flame-shaped) hemorrhages[a]
Cotton-wool spots (soft exudates)[a]
Bilateral papilledema[a]
Macular star

[a]Features that distinguish hypertensive neuroretinopathy (characteristic of malignant hypertension) from retinal arteriosclerosis (characteristic of benign hypertension).

periphery of the fundus. They are caused by venous or arterial occlusion.[43] Hard exudates may appear as multiple small white dots that give a powdery appearance to the retina, or they may appear as large glistening spots that are sharply defined from the adjacent retina. Arteriosclerotic retinopathy can also cause localized areas of retinal edema and hemorrhage due to occlusion of small branch veins. However, the principal findings of hypertensive neuroretinopathy, namely, striate hemorrhages, cotton-wool spots, and papilledema, are absent (Table 44.3). The finding of retinal arteriosclerosis in hypertensive patients usually does not imply a poor prognosis.

The lack of clinical significance of retinal arteriosclerosis in hypertensive patients contrasts markedly with the importance and prognostic significance of the finding of hypertensive neuroretinopathy. The appearance of striate hemorrhages and cotton-wool spots with or without papilledema closely parallels the development of severe arteriolar damage (fibrinoid necrosis and proliferative endarteritis) in the circulation of other organs including the brain and kidneys. Hypertensive neuroretinopathy is the clinical sine qua non of malignant hypertension and therefore signifies a far more ominous prognosis than does the finding of retinal arteriosclerosis in benign hypertension.

The appearance of small striate (so-called flame-shaped) hemorrhages is often the first sign that malignant hypertension has developed (Fig. 44.1).

Cotton-wool spots are the most characteristic feature of malignant hypertension and are the result of ischemic infarction of nerve fiber bundles caused by arteriolar occlusion. They usually surround the optic disc and most commonly occur within three disc diameters of the optic disc (Figs. 44.2 to 44.4). Cotton-wool spots begin as grayish-white discoloration of the retina, but within 24 hours they become shiny white with fluffy margins. Red dots may be seen in the bed of the exudate (microaneurysms). Cotton-wool spots are not specific for hypertensive neuroretinopathy and can also be seen with diabetic retinopathy, retinal emboli, and central and branch retinal vein occlusion. However, differentiation of these disorders from malignant hypertension is usually not difficult.

Papilledema can occur in patients with hypertensive neuroretinopathy, but it is not invariably present. In malignant

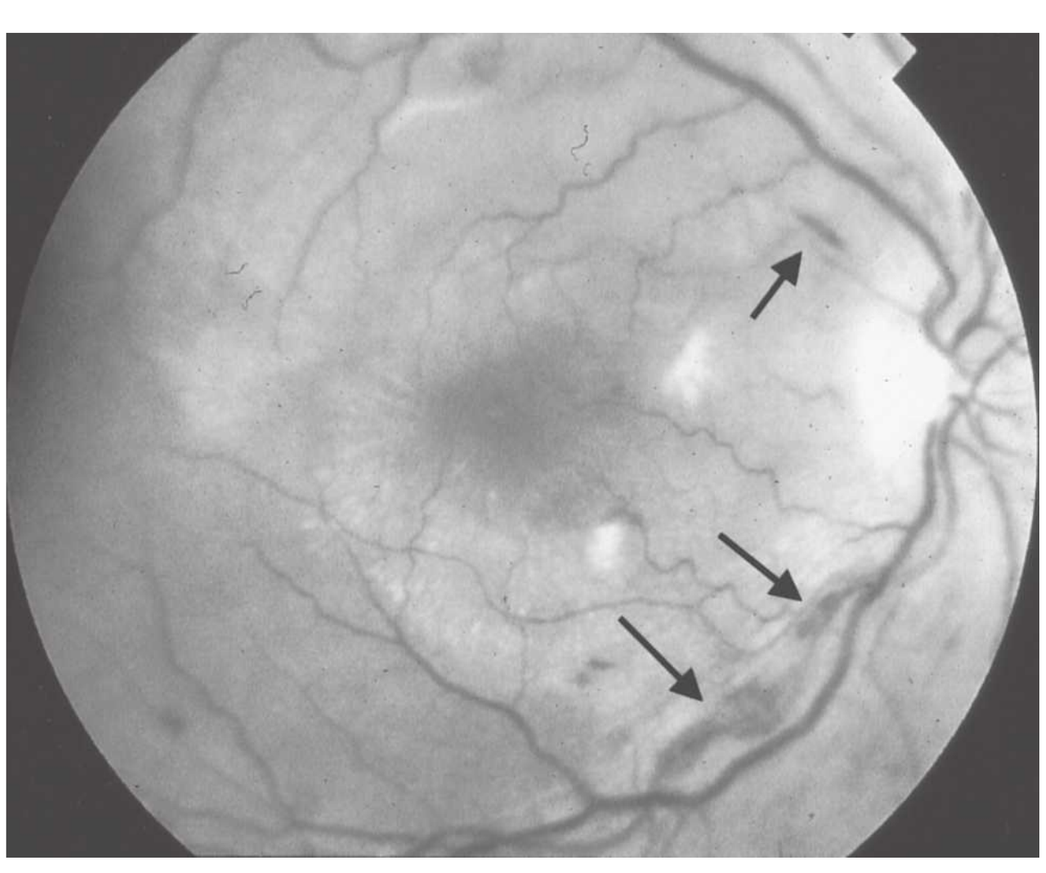


FIGURE 44.1 Striate hemorrhages (*arrows*) in the fundus of a 48-year-old white woman with secondary malignant hypertension due to underlying immunoglobulin A nephropathy.

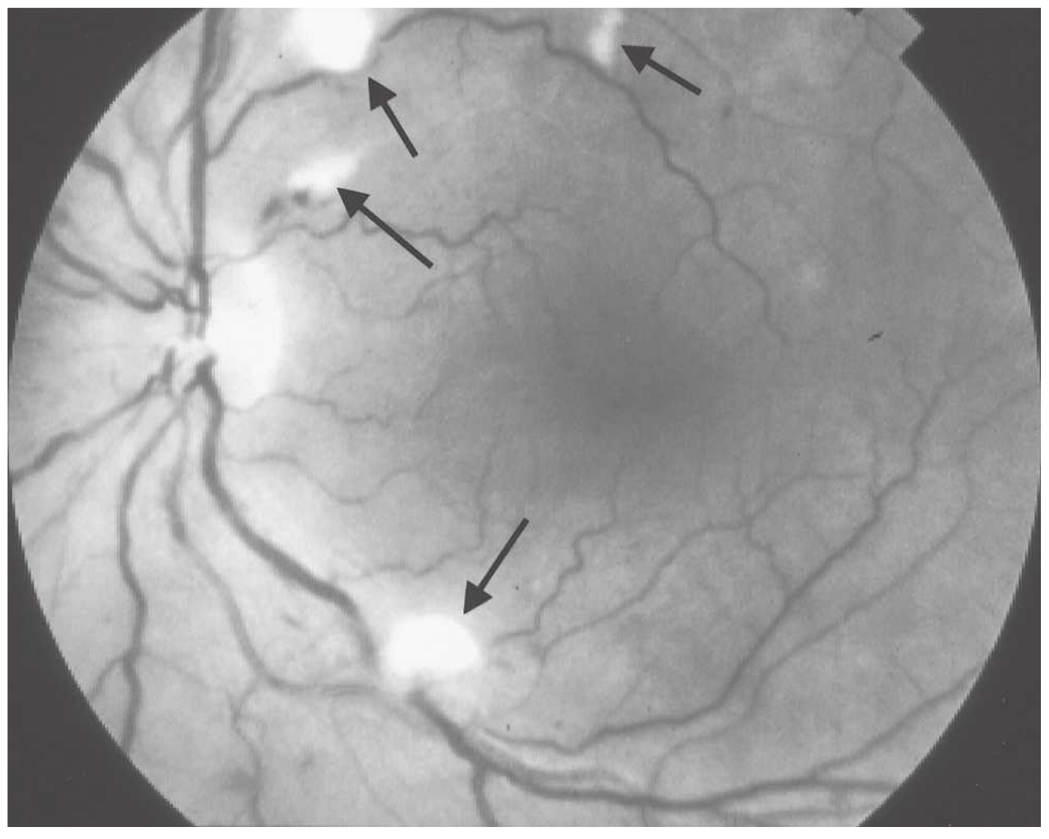


FIGURE 44.2 Cotton-wool spots (*arrows*) in the fundus of a 48-year-old white woman with secondary malignant hypertension due to underlying immunoglobulin A nephropathy. Striate hemorrhages are also seen adjacent to some of the cotton-wool spots.

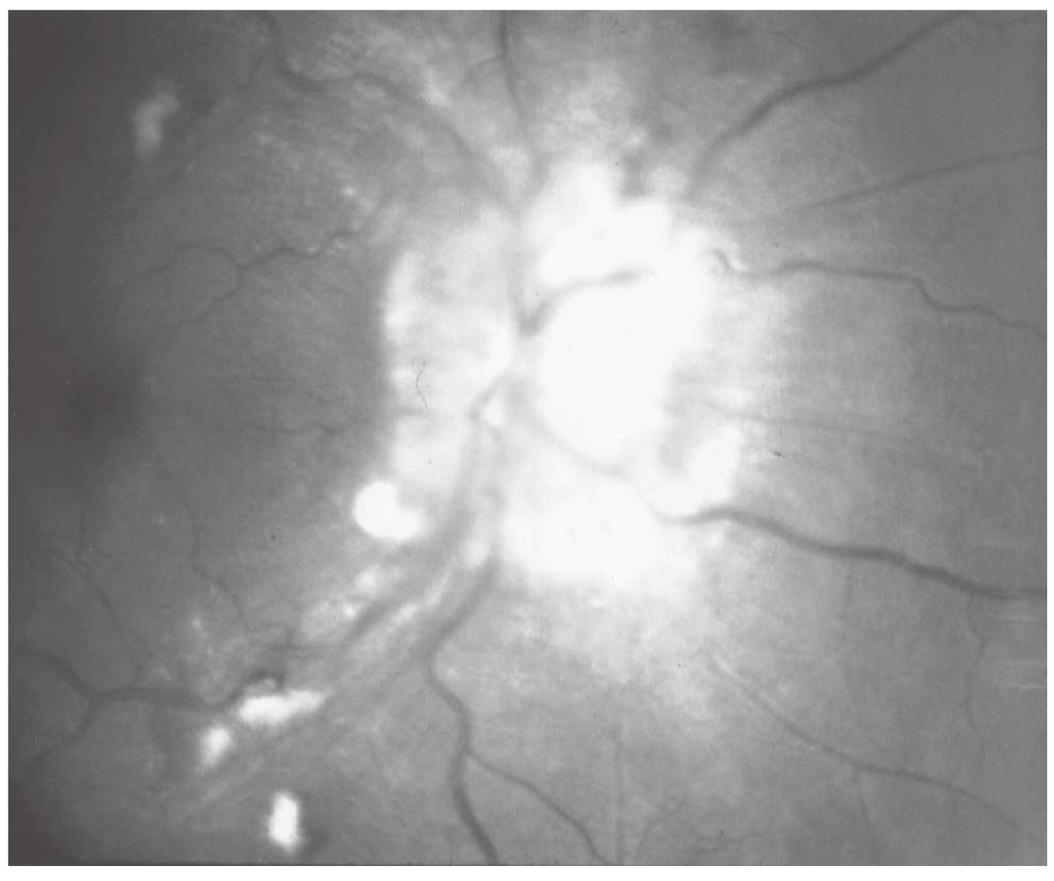


FIGURE 44.3 Papilledema in the fundus of an 18-year-old African American man with primary malignant hypertension. Cotton-wool spots are also apparent. This asymptomatic patient was incidentally noted to have severe hypertension during a routine dental examination.

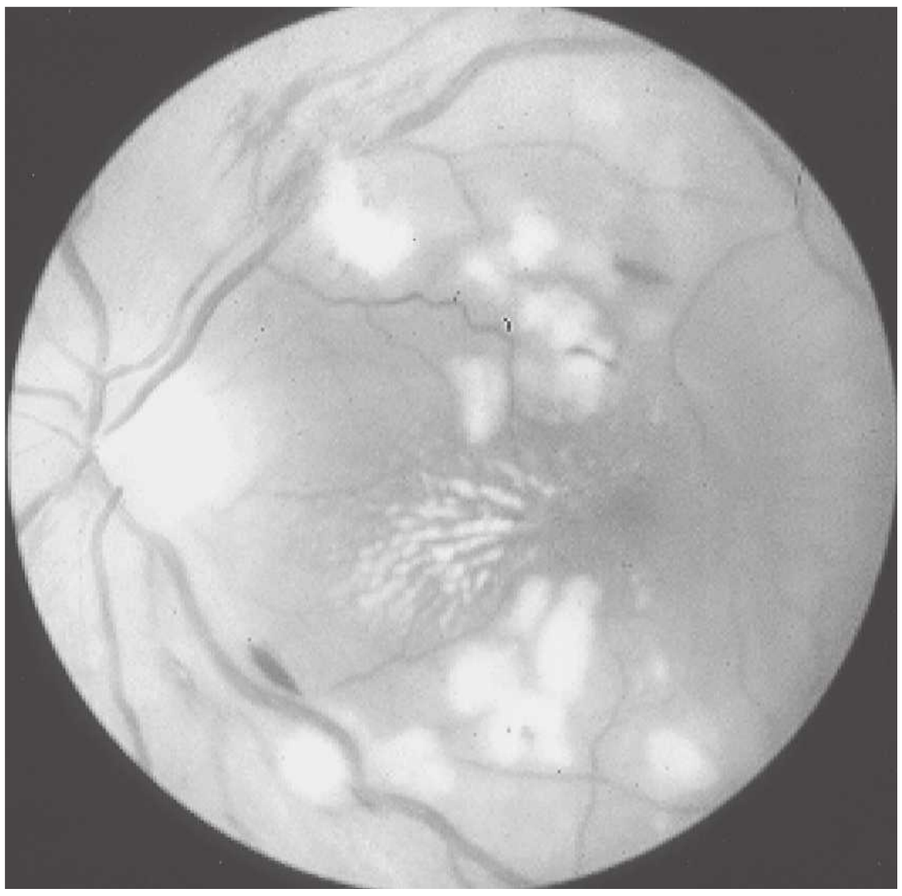


FIGURE 44.4 Full-blown hypertensive neuroretinopathy in the fundus of a 30-year-old man with malignant hypertension demonstrating linear (striate) hemorrhages, cotton-wool spots, papilledema, and a star figure at the macula. (Photograph courtesy of Daniel J. Mayer, MD.)

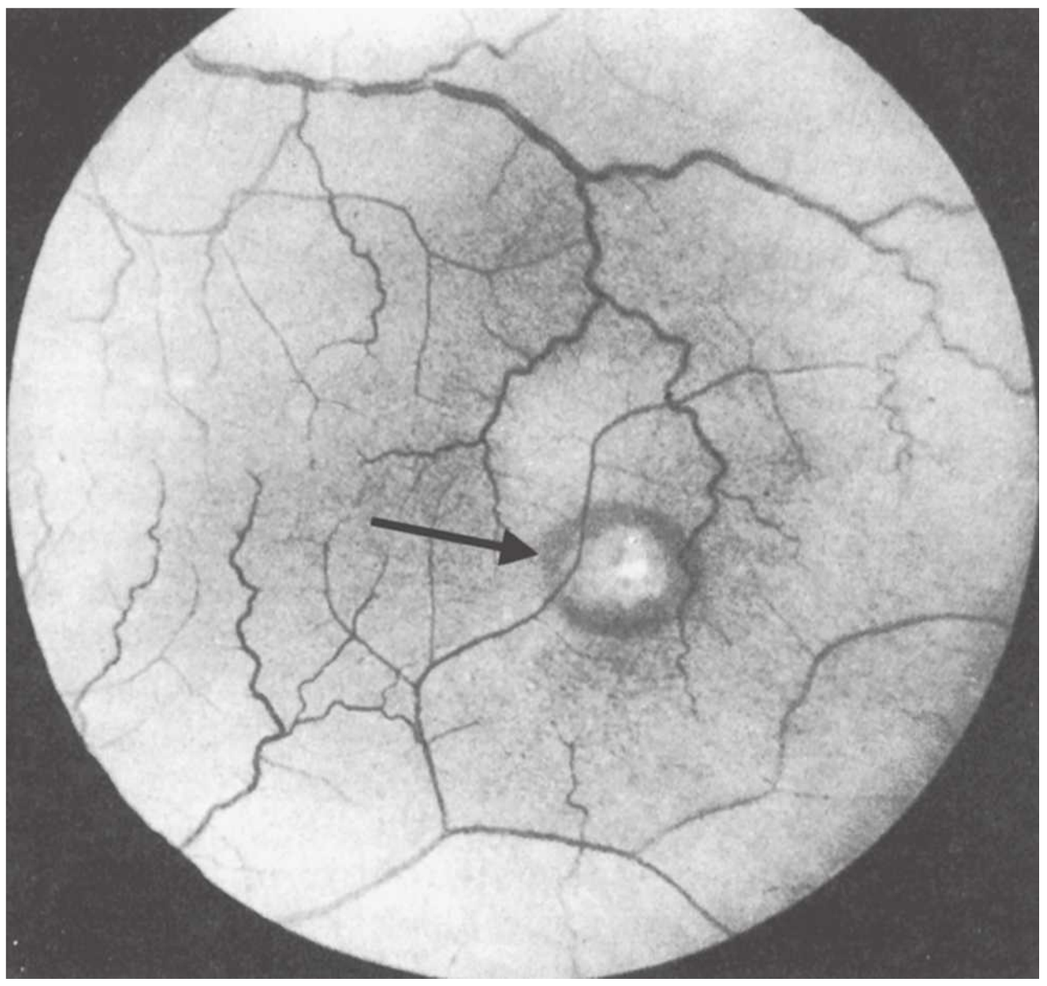


FIGURE 44.5 Hypertensive choroidopathy in malignant hypertension demonstrating focal serous detachment of the sensory retina with a whitish lesion at the level of the retinal pigment epithelium (acute Elschnig's spot). (From de Venecia G, Jampol LM. The eye in accelerated hypertension: II. Localized serous detachments of the retina in patients. *Arch Ophthalmol.* 1984;102:68, © 1984, American Medical Association, with permission.)

hypertension, papilledema is usually accompanied by striate hemorrhages and cotton-wool spots (Figs. 44.3 and 44.4). When papilledema occurs alone, the possibility of a primary intracranial process such as a tumor or cerebrovascular accident should be considered.

Hypertensive neuroretinopathy almost always precedes clinically apparent damage in other end organs but there are occasional reports of malignant nephrosclerosis appearing before the onset of hypertensive neuroretinopathy.[46] It should also be noted that the findings of striate hemorrhages, cotton-wool spots, and papilledema are not specific for malignant hypertension. Funduscopic findings that are indistinguishable from those of hypertensive neuroretinopathy can occur with severe anemia, subacute bacterial endocarditis, systemic lupus erythematosus, polyarteritis, temporal arteritis, and scleroderma. In these disorders the retinopathy may develop even in the absence of hypertension. Central retinal vein occlusion can also mimic hypertensive neuroretinopathy but is usually unilateral, whereas hypertensive neuroretinopathy is almost always bilateral.

Severe hypertension can also affect the choroidal as well as the retinal circulation. Hypertensive choroidopathy can occur with malignant hypertension and is manifested by lesions known as acute Elschnig spots, which are white areas of retinal pigment epithelial necrosis with overlying localized serous detachments of the retina (Fig. 44.5).[47] The serous retinal detachments may vary from one-third to six disc diameters. Fluorescein angiography reveals staining of the damaged pigment epithelium and leakage into the subretinal space.[47] Although most patients with this hypertensive choroidopathy also have typical changes of hypertensive neuroretinopathy with striate hemorrhages and cotton-wool spots, if the elevation of blood pressure is relatively sudden, the changes of hypertensive choroidopathy may predominate.[47]

It is important to note that papilledema should not be regarded as an essential requirement for the diagnosis of malignant hypertension. By life table analysis, the 10-year survival rate for hypertensive patients was 46% in patients with hemorrhages and exudates and 48% when papilledema was also present.[48] The lack of association between papilledema and the length of survival was confirmed using the Cox's proportional hazards model, which revealed associations between survival and age, smoking habit, initial serum creatinine concentration, and the level of blood pressure control achieved with therapy. No association was found with papilledema. When controlled for these covariates, no association was found between the presence of papilledema and survival (Fig. 44.6). There is no evidence to indicate that the apparent severity of hypertensive neuroretinopathy is predictive of a more severe hypertensive vasculopathy or more advanced end-organ destruction. Papilledema is not always present even when there is severe malignant nephrosclerosis presenting as oliguric acute renal failure. In four series with a total of 25 patients presenting with malignant hypertension and acute renal failure, only 14 patients had papilledema. The other 11 patients had hemorrhages and cotton-wool spots

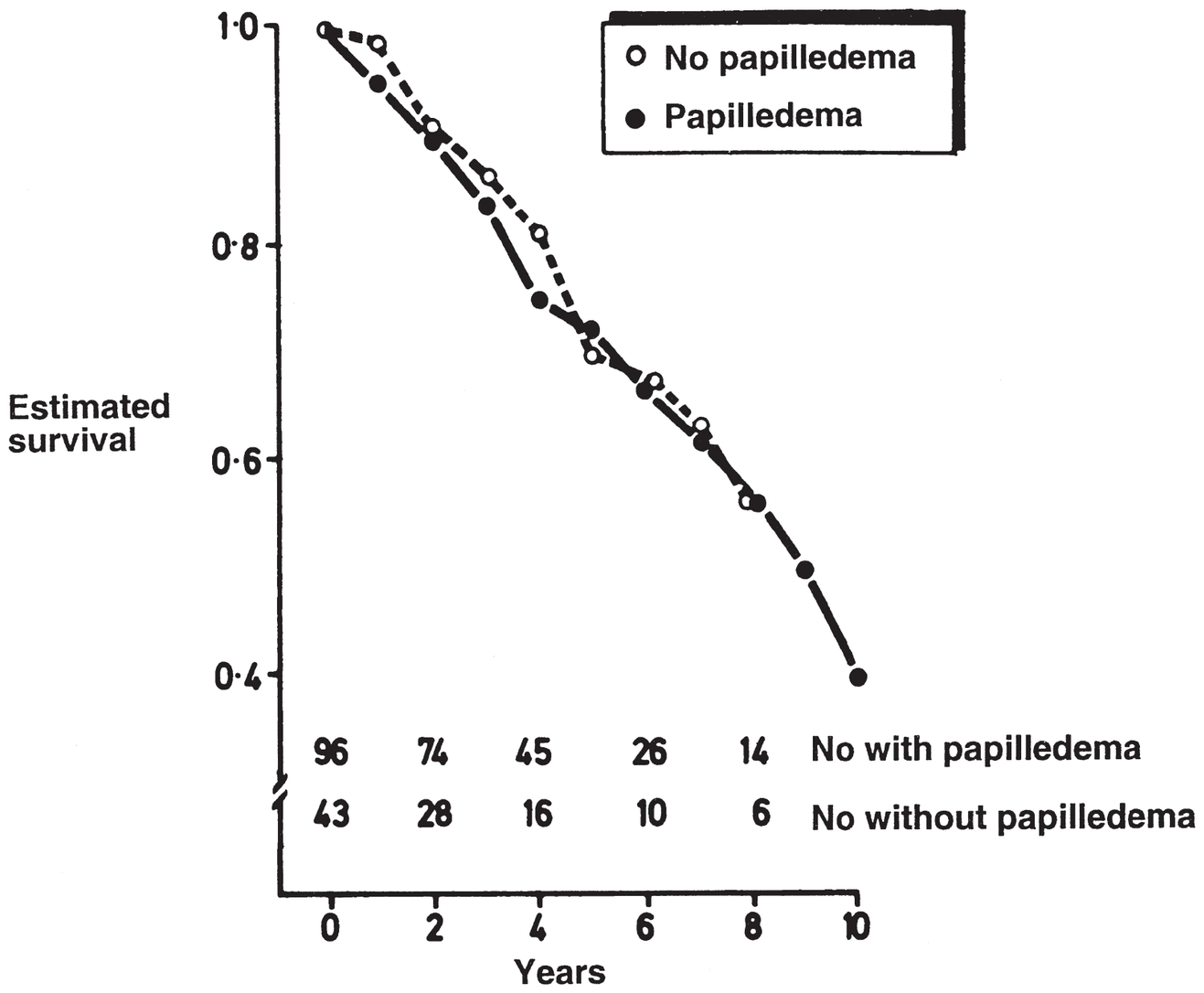


FIGURE 44.6 Relation between papilledema and survival in 139 hypertensive patients with bilateral retinal hemorrhages and exudates after controlling for age, gender, smoking habit, initial serum creatinine concentration, and initial and achieved blood pressure by multivariate analysis. Failure of papilledema to influence prognosis was confirmed by likelihood ratio test ($X = 0.89$, 1 df, $P = .34$). (From McGregor E, et al. Retinal changes in malignant hypertension. *Br Med J.* 1986;292:233, with permission.)

but no papilledema.[49–52] This lack of a difference in prognosis for patients with hypertensive neuroretinopathy whether or not it is accompanied by papilledema may be explained by the fact that cotton-wool spots and papilledema share a similar pathogenesis (see later discussion).[53,54]

Renal Manifestations

Malignant hypertension is a progressive systemic vasculopathy in which renal involvement is a secondary and relatively late development. Patients with malignant hypertension may present with a spectrum of renal involvement ranging from minimal albuminuria with normal renal function to ESRD indistinguishable from that seen in patients with primary renal parenchymal disease.[21,27]

The first sign of renal involvement in malignant hypertension is often the abrupt appearance of proteinuria. About 20% of patients also have painless gross hematuria, while 50% have microhematuria.[21] Quantitation of 24-hour protein excretion in patients with malignant hypertension has revealed less than 2 g in one third, between 2 and 4 g in one third, and more than 4 g in one third of patients.[26] The level of protein excretion is of little value in the differentiation of primary (essential) malignant hypertension from malignant hypertension due to secondary causes.[21,27]

Renal size is variable and depends on the duration of prior benign hypertension. In patients with primary (essential) malignant hypertension, the size of the kidneys may be normal to only slightly reduced. In fact, there may be little reduction in renal size even when patients develop terminal renal failure.[21]

The clinical spectrum of renal involvement in malignant hypertension is variable. Four clinical renal syndromes have been described. Progressive subacute deterioration of renal function leading to ESRD occurs in some patients. In patients presenting with malignant hypertension and initially normal renal function, in the absence of adequate treatment, it is common to observe deterioration of renal function with progression to ESRD over a period of weeks to months. The second clinical renal syndrome observed in malignant hypertension is transient deterioration of renal function following the initial control of blood pressure. This well-described entity occurs in patients presenting with mild to moderate renal impairment. In the third clinical renal syndrome, patients with malignant hypertension present with established renal failure. The close similarity between the terminal stage of primary malignant nephrosclerosis and chronic kidney disease with superimposed malignant hypertension has long been recognized. In this regard, it may not be possible to ascertain whether a patient presenting with severe hypertension, hypertensive neuroretinopathy, and renal failure has primary or secondary malignant hypertension. In the fourth clinical renal syndrome, patients with malignant hypertension present with oliguric acute renal failure. Cases of malignant hypertension have been described that were characterized by diastolic blood pressure higher than 130 mm Hg; advanced hypertensive neuroretinopathy; marked weight loss; and with an active urine sediment with proteinuria, hematuria, and red blood cell casts.[51,52] Renal size was normal. There was often evidence of microangiopathic hemolytic anemia. Although the initial blood urea nitrogen (BUN) concentration was less than 60 mg per dL, in each case oliguric renal failure occurred and necessitated the initiation of dialysis within a few days of hospitalization. Despite dialytic therapy, the blood pressure was extremely difficult to control and each patient died. Renal histology revealed malignant nephrosclerosis with fibrinoid necrosis

and proliferative endarteritis. The glomeruli were normal except for ischemic changes. Multifocal tubular necrosis was present and presumed to be secondary to ischemia. In most of these patients, the diagnosis of malignant hypertension was delayed because the patients were initially considered to have rapidly progressive glomerulonephritis or systemic vasculitis, which was treated with high-dose steroids. The diagnosis of malignant hypertension was not suspected until autopsy revealed malignant nephrosclerosis.

Neurologic Manifestations

Clarke and Murphy[55] detail the neurologic findings among 190 patients with malignant hypertension. CNS involvement was present at some time during the course in 42% of patients. Of the 65 patients for whom a cause of death could be ascertained, 33 had a fatal neurologic event. Of the total deaths, 20% were due to a neurologic cause. Intracerebral hemorrhage occurred in 23 patients. Episodes of focal brain ischemia, presumed due to cerebral thrombosis, occurred in 35 patients. Generalized seizures occurred in 11 patients and focal seizures in 8. Bell's palsy occurred in seven patients. Primary subarachnoid hemorrhage occurred in four patients. In this series, hypertensive encephalopathy was found in only 1% of patients; however, other series reported a higher incidence.[56] The clinical presentation, pathophysiology, and treatment of hypertensive encephalopathy are discussed in detail later in this chapter within Hypertensive Encephalopathy.

Gastrointestinal Manifestations

The most common gastrointestinal (GI) manifestations of malignant hypertension are nonspecific symptoms including nausea, vomiting, and epigastric pain. However, acute pancreatitis has been reported as a rare complication. In a series of 42 patients with malignant hypertension, severe acute pancreatitis that could not be attributed to gallstones or alcohol abuse developed in seven patients.[57]

Patients with malignant hypertension can present with an acute abdomen.[58] Abdominal exploration revealed necrotic bowel with involvement of the distal ileum and ascending colon. Moreover, malignant hypertension may increase the risk of subsequent development of mesenteric ischemia in patients on chronic hemodialysis.[59] GI hemorrhage can occur in patients with malignant hypertension due to hypertension-induced necrotizing mesenteric arteriolitis.[60]

Hematologic Manifestations

A variety of hematologic findings have been observed in patients with malignant hypertension. The hemoglobin concentration at the time of presentation may correlate with the etiology of the malignant phase. A hemoglobin concentration higher than 12.5 g per dL is more often associated with primary malignant hypertension, whereas a lower value is more often associated with chronic glomerulonephritis or pyelonephritis.[21]

There are numerous reports of microangiopathic hemolytic anemia in association with malignant hypertension. In one series of 24 patients with malignant hypertension, 16 were found to have evidence of microangiopathic hemolysis.[61] Other significant abnormalities reported with malignant hypertension include thrombocytopenia, increased fibrin degradation products, increased factor VIII levels, increased fibrinogen, and increased urokinase sensitivity consistent with decreased fibrinolysis.[62]

Cardiac Manifestations

Congestive heart failure can be a presenting feature of malignant hypertension. Moreover, heart failure, alone or in combination with uremia, was a common cause of death prior to the advent of effective antihypertensive drugs. Heart failure in patients with malignant hypertension is predominantly left-sided with pulmonary congestion resulting in orthopnea, paroxysmal nocturnal dyspnea, cardiac asthma, and recurrent episodes of acute pulmonary edema. Peripheral venous congestion with dependent edema or hepatic congestion may be minimal or absent even when death results from congestive heart failure.

Angina and acute myocardial infarction, although common with long-standing benign hypertension, are uncommon with malignant hypertension.[21] Aortic dissection is also rare in patients with malignant hypertension.[22]

Abnormalities of the Renin-Angiotensin-Aldosterone Axis

Evidence of activation of the renin–angiotensin–aldosterone axis is present in many, but not all, patients with malignant hypertension.[63] Among 53 patients with malignant hypertension not secondary to renal artery stenosis, 55% had increased plasma renin activity (PRA).[64] Among 25 patients with malignant hypertension secondary to renal artery stenosis, PRA was consistently elevated.[64]

Aldosterone secretion rate has been studied in patients with malignant hypertension.[65] There was a marked increase in secretion rate in seven of eight patients with malignant hypertension (papilledema present), and in five of eight patients with accelerated hypertension (retinal hemorrhages without papilledema). The aldosterone secretion rate in these patients was often higher than that seen in patients with aldosterone-producing adenoma.

Electrolyte Abnormalities

Hypokalemic metabolic alkalosis was found in up to 50% of patients with malignant hypertension, presumably reflecting a state of hyperreninemia and secondary hyperaldosteronism.[65] After effective therapy, aldosterone hypersecretion can persist long after volume depletion is corrected and renin levels have returned to normal. Thus, the findings of hypokalemia, increased urinary potassium losses, and aldosterone hypersecretion with suppressed PRA may mimic the findings of primary hyperaldosteronism.[63]

Hyponatremia is not uncommon in patients with malignant hypertension, particularly when sodium restriction is instituted. Patients with malignant hypertension due to renal artery stenosis occasionally present with the striking hyponatremic hypertensive syndrome.[66,67] The characteristic features of this syndrome include severe hypertension, hypertensive neuroretinopathy, polyuria, polydipsia, weight loss, and salt craving. Biochemical changes include hyponatremia, hypokalemia, and low total exchangeable sodium and potassium, with markedly elevated PRA, angiotensin II, aldosterone, and arginine vasopressin (AVP) levels. This syndrome may result from a vicious cycle of volume depletion with further activation of the renin–angiotensin–aldosterone axis as a result of a pressure-induced natriuresis from the contralateral kidney.

Pathologic Findings

Renal Pathology

With malignant nephrosclerosis, small pinpoint petechial hemorrhages may be present on the cortical surface, giving the kidney a peculiar flea-bitten appearance. The renal size varies depending on the duration of preexisting benign hypertension or the presence of underlying primary renal parenchymal disease. When terminal renal failure occurs in patients with primary malignant hypertension, the kidneys may be normal in size.[37] However, when secondary malignant hypertension is superimposed on primary renal disease, the kidneys may be small.

Fibrinoid necrosis of the afferent arterioles has traditionally been regarded as the hallmark of malignant nephrosclerosis (Fig. 44.7).[21] The characteristic finding is the deposition in the arteriolar wall of a granular material that appears bright pink with hematoxylin and eosin stain. On trichrome staining, this granular material is deep red. This fibrinoid material is usually found in the media, but it may also be present in the intima. Histochemical and immunofluorescent techniques have identified this material as fibrin. Within the media, muscle fibers cannot be identified and cell nuclei are lost or fragmented. Whole or fragmented erythrocytes may be extravasated into the arteriolar wall. The hemorrhages that occur may account for the petechiae observed on the cortical surface. The arteriolar lumen may be reduced in size as a result of wall thickening and intraluminal fibrin thrombi. Infrequently, polymorphonuclear leukocytes and monocytes may infiltrate the arterioles, giving the appearance of necrotizing arteriolitis.

The interlobular arteries reveal characteristic lesions variously referred to as proliferative endarteritis, productive endarteritis, endarteritis *fi*brosa, or the onionskin lesion. The typical finding is intimal thickening that causes moderate to severe luminal narrowing. In severely affected vessels, the luminal diameter may be reduced to the size of a single red blood cell. Occasionally, there is complete obliteration of the lumen by a fibrin thrombus.

Traditionally, three patterns of intimal thickening in malignant nephrosclerosis have been described.[68] The onionskin pattern consists of pale layers of elongated, concentrically arranged, myointimal cells. Delicate connective tissue fibrils give rise to a lamellated appearance (Fig. 44.8). The media often appears as an attenuated layer stretched around the expanded intima. Mucinous intimal thickening consists of a scarcely cellular lesion containing a lucent, faintly basophilic-staining

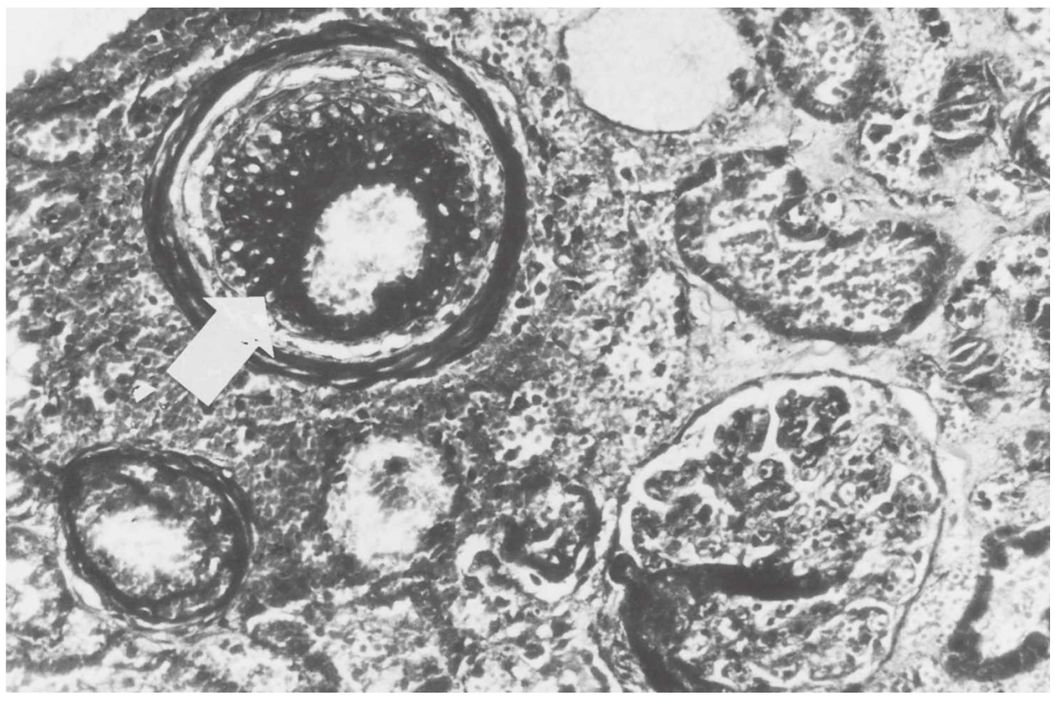


FIGURE 44.7 Fibrinoid necrosis in a large arteriole (*arrow*). Intimal onionskin formation is also present. (Trichrome stain.) (Photograph courtesy of Steve Guggenheim, MD.)

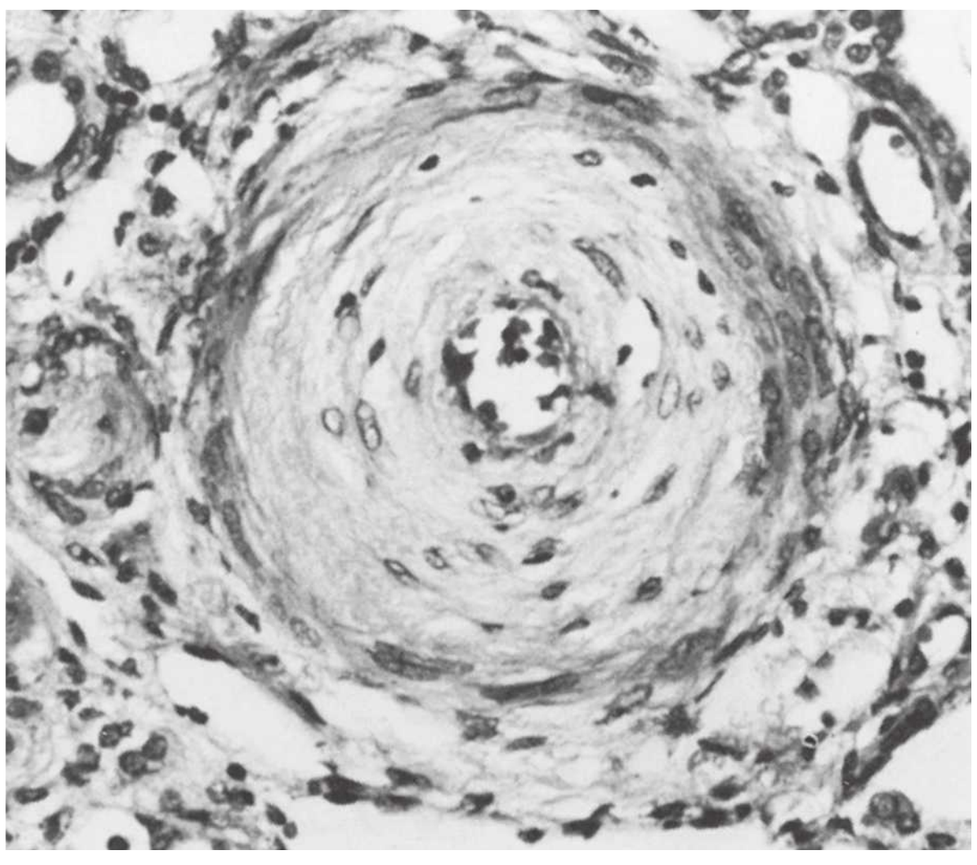


FIGURE 44.8 Onionskin lesion consisting of pale layers of elongated, concentrically arranged myointimal cells and delicate connective tissue fibrils that produce a lamellated appearance. The media is attenuated and stretched around the thickened intima. (Hematoxylin and eosin stain ×350.) (From Sinclair RA, Antonovych TT, Mostofi FK. Renal proliferative arteriopathies and associated glomerular changes: a light and electron microscopic study. *Hum Pathol*. 1976;7:565, with permission.)

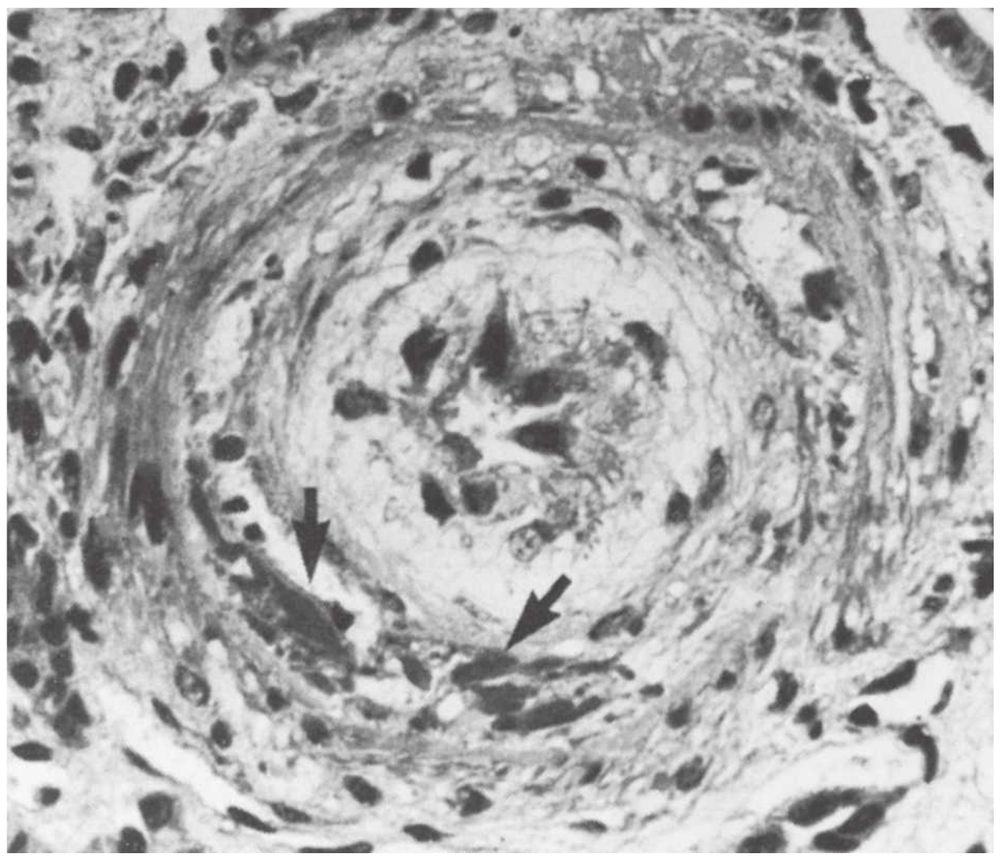


FIGURE 44.9 Mucinous intimal thickening. The lesion is sparsely cellular and consists mainly of a lucent, faintly basophilic-staining amorphous material. There are small foci of fibrinoid necrosis (*arrows*) deep within the intima. (Hematoxylin and eosin stain ×350.) (From Sinclair RA, Antonovych TT, Mostofi FK. Renal proliferative arteriopathies and associated glomerular changes: a light and electron microscopic study. *Hum Pathol.* 1976;7:565, with permission.)

amorphous material (Fig. 44.9). In *f*ibrous intimal thickening, there are hyaline deposits, reduplicated bands of elastica, and coarse layers of pale connective tissue with the staining properties of collagen (Fig. 44.10). In rare cases, fibrinoid necrosis may also be apparent in the interlobular arteries.[68]

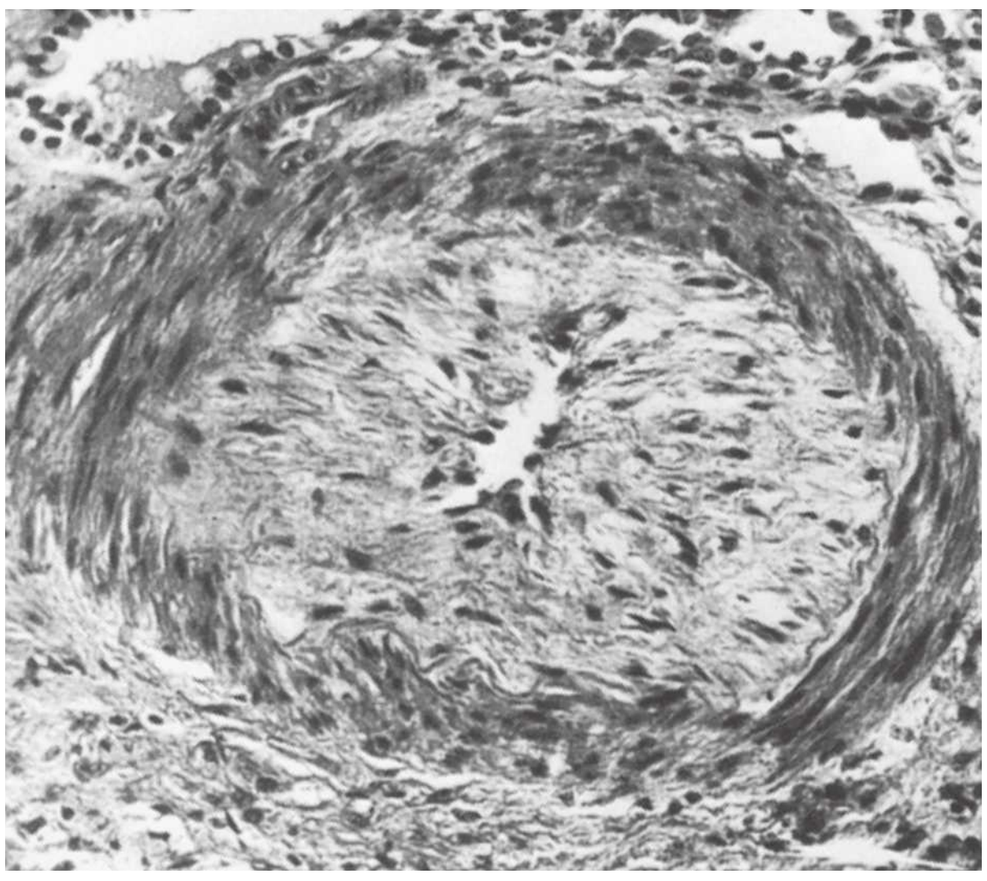


FIGURE 44.10 Fibrous intimal thickening. The lesion consists of a thick layer of connective tissue, which stains for collagen and elastin. (Hematoxylin and eosin stain ×300.) (From Sinclair RA, Antonovych TT, Mostofi FK. Renal proliferative arteriopathies and associated glomerular changes: a light and electron microscopic study. *Hum Pathol.* 1976;7:565, with permission.)

The renal histology in blacks with malignant hypertension may be somewhat different.[69,70] Although fibrinoid necrosis of the afferent arterioles is not found, there is instead a marked degree of arteriolar hyalinization. In addition, there is a prominent and characteristic finding in the larger arterioles and interlobular arteries known as musculomucoid intimal hyperplasia (Fig. 44.11).[69–71] The arterial walls are thickened due to the presence of hyperplastic smooth muscle cells. A small amount of myxoid material, which stains light blue with hematoxylin and eosin, is observed between the cells. With periodic acid-Schiff staining this material resembles basement membrane. Staining for acid mucopolysaccharide suggests the presence of chondroitin sulfate and possibly hyaluronic acid.

By electron microscopy, in each of the above-mentioned types of intimal thickening, the most abundant cellular element is a modified smooth muscle cell called a myointimal cell. In these cells there are smooth musclelike ultrastructural features including cytoplasmic myofilaments and abundant rough endoplasmic reticulum.[68,72] In the pure onionskin variant, the intercellular space is occupied by multiple strands of nonperiodic fibrils with the ultrastructural features of basement membrane.[68] In the mucinous variant, broad electron-lucent zones with scattered finely granular material are found in the intercellular space.[72] With the fibrous variant, numerous bundles of collagen, recognizable by characteristic banding, are dispersed between the myointimal cells.[72]

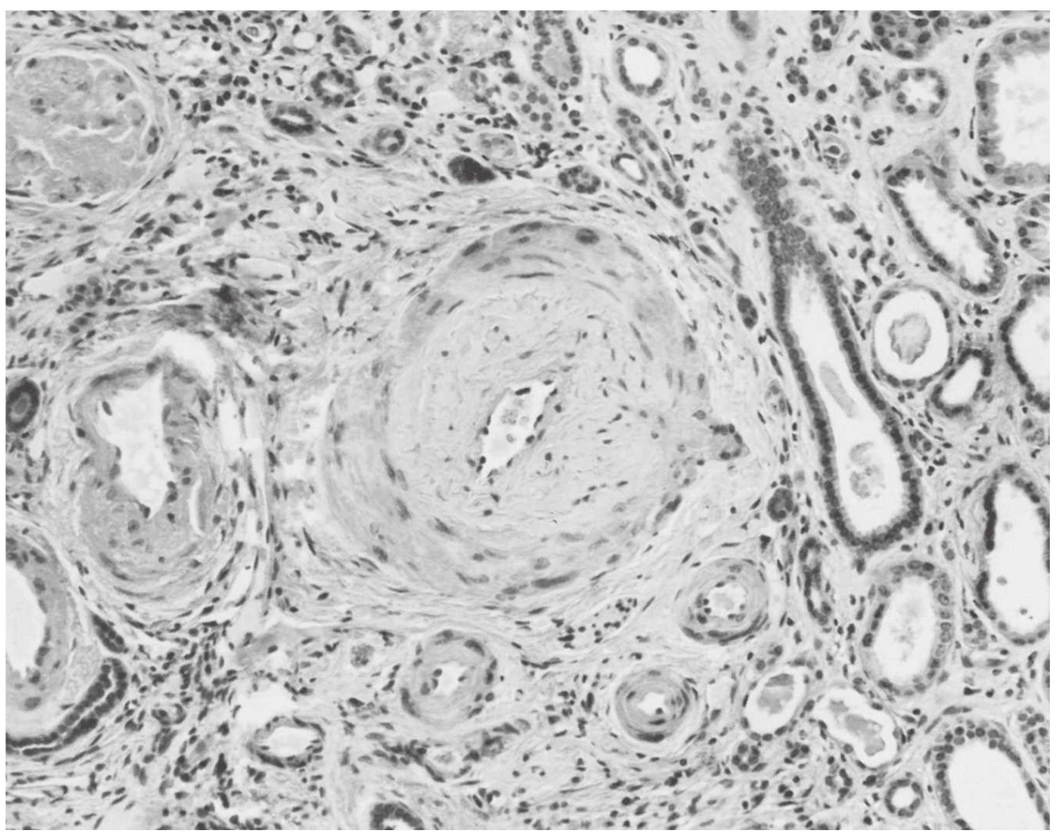


FIGURE 44.11 Musculomucoid intimal hyperplasia of an interlobular artery. The arterial walls are thickened by hyperplastic smooth muscle cells. A small amount of myxoid material is seen between the smooth muscle cells. (Hematoxylin and eosin stain ×170.) (From Pitcock JA, Johnson JG, Hatch FE, et al. Malignant hypertension in blacks: malignant intrarenal arterial disease as observed by light and electron microscopy. *Hum Pathol.* 1976;7:333, with permission.)

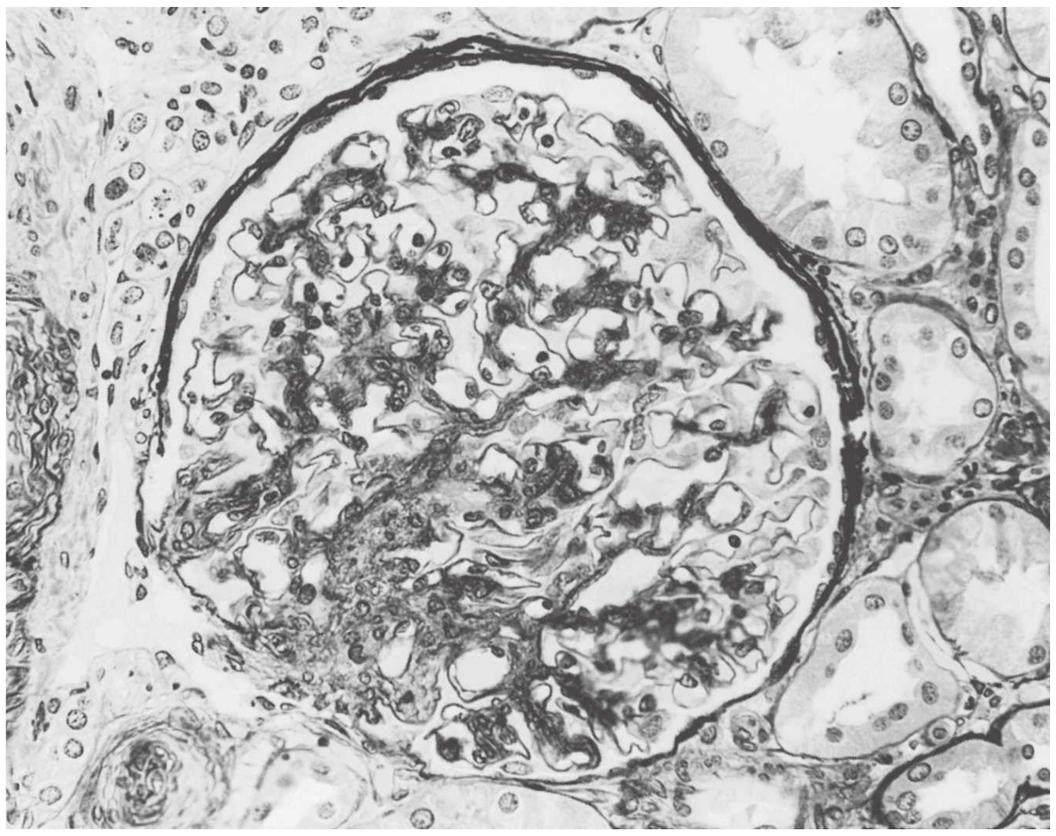


FIGURE 44.12 The earliest ischemic glomerular change in malignant hypertension consists of some basement membrane wrinkling, particularly in areas adjacent to the mesangium, with a slight increase in mesangial matrix. (Periodic acid–silver methenamine stain ×250.) (From Pitcock JA, Johnson JG, Hatch FE, et al. Malignant hypertension in blacks: malignant intrarenal arterial disease as observed by light and electron microscopy. *Hum Pathol.* 1976; 7:333, with permission.)

In patients who have received antihypertensive therapy, as well as blacks with treated or untreated malignant hypertension, the most characteristic glomerular lesion in malignant nephrosclerosis is accelerated glomerular obsolescence secondary to the intense ischemia produced by the obliterative arterial lesions.[70,73] The earliest glomerular changes consist of thickening and wrinkling of the basement membrane (Fig. 44.12).[75,78] Later, there is shrinkage of the tuft such that it does not fill Bowman's space. There is laminar reduplication of Bowman's capsule around the shrunken glomerulus.[68] The end stage is the obsolescent glomerulus, which is an avascular, wrinkled glomerular tuft surrounded by a collagenous scar that fills Bowman's space (Fig. 44.13). Focal segmental glomerulosclerosis may occur in primary malignant hypertension either as the result of glomerular hyperfiltration or fibrinoid necrosis, and may contribute to renal dysfunction. In an autopsy series of 38 black South Africans with primary malignant hypertension, mucoid intimal hyperplasia was present in all sections whereas fibrinoid necrosis was seen in 76%. Glomerulosclerosis was present in 38 cases, and was axially distributed in 18%, segmental in 58%, and global in 24% of sections. Cases with segmental sclerosis tended to have the highest proteinuria, whereas those with global glomerulosclerosis had the highest serum creatinine levels.[74]

By electron microscopy, the lamina densa of the glomerular capillary basement membrane is thickened and wrinkled (Fig. 44.14).[73] Eventually, the entire basement membrane becomes thickened. These glomerular

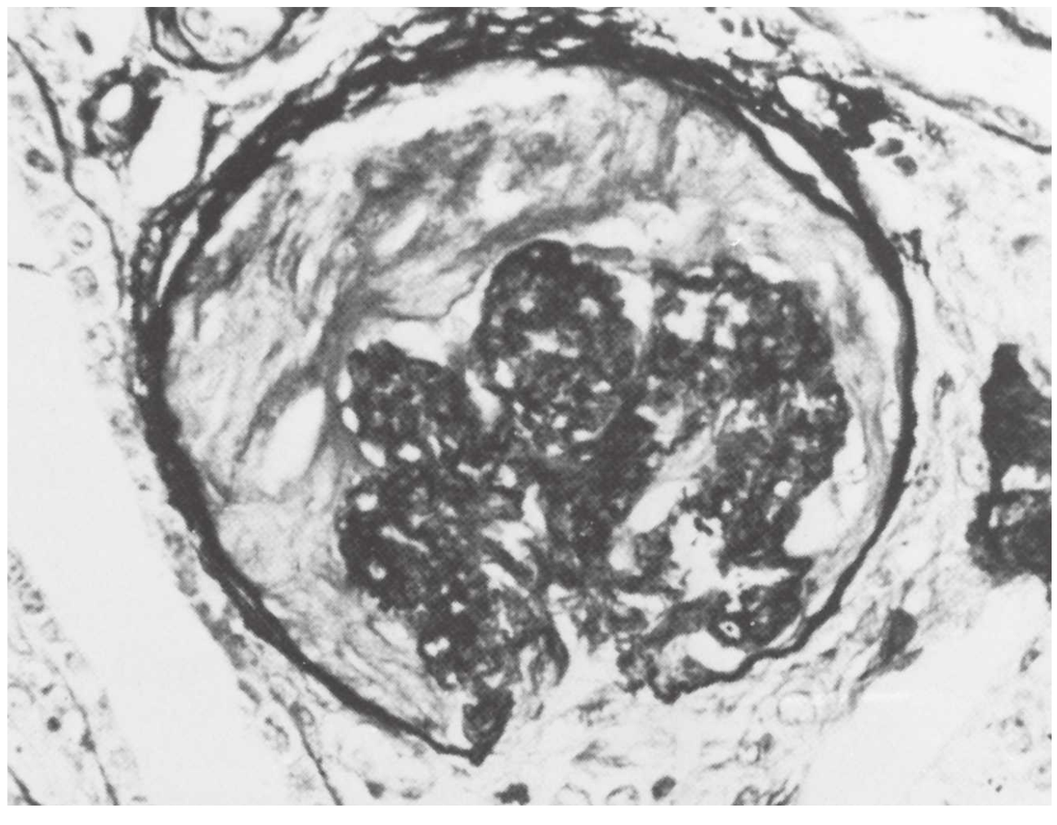


FIGURE 44.13 Glomerular obsolescence in malignant hypertension. The collapsed, avascular glomerular tuft consists predominantly of markedly convoluted basement membranes. The sclerosed tuft is partially enclosed within a collar of hyaline material filling Bowman's space. (Periodic acid–silver methenamine stain ×485.) (From Sinclair RA, Antonovych TT, Mostofi FK. Renal proliferative arteriopathies and associated glomerular changes: a light and electron microscopic study. *Hum Pathol.* 1976; 7:565, with permission.)

changes are not specific for malignant nephrosclerosis as they also can occur in scleroderma renal crisis, hemolytic–uremic syndrome, and even severe benign nephrosclerosis. However, the glomerular changes in malignant nephrosclerosis differ from the simple ischemic

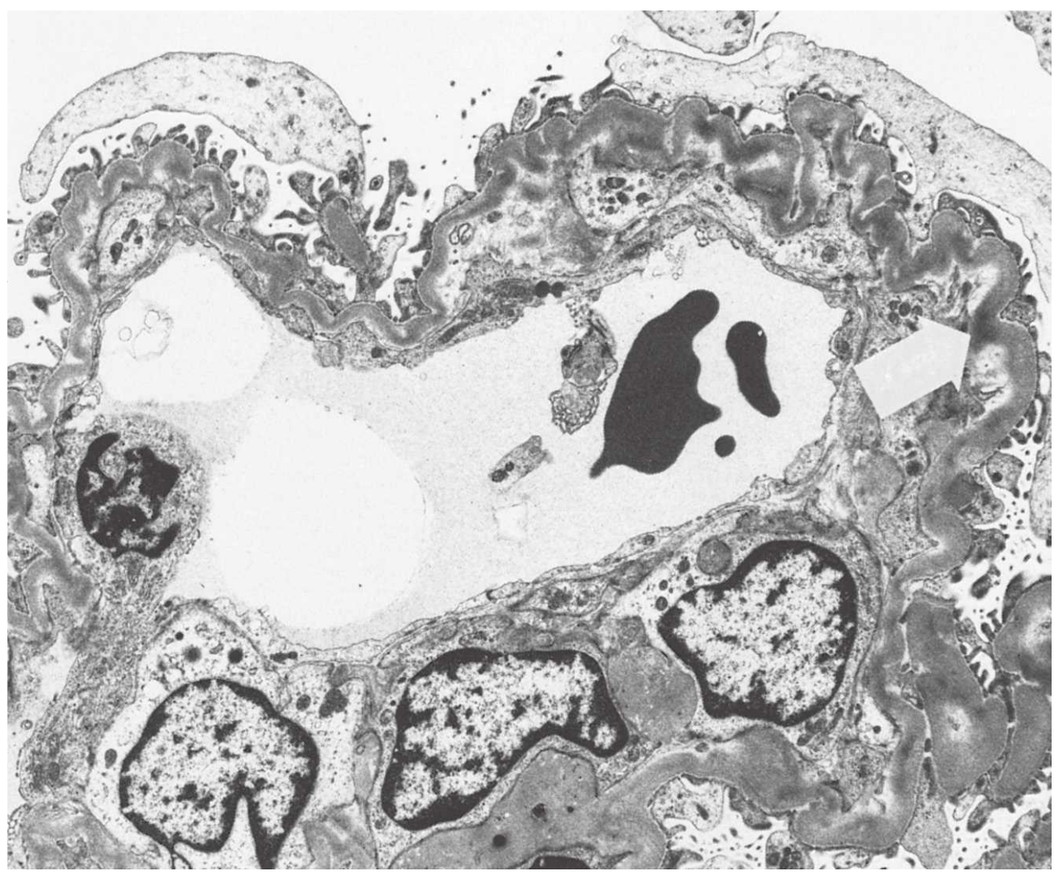


FIGURE 44.14 Accelerated glomerular obsolescence in malignant hypertension. The glomerular capillaries show striking basement membrane wrinkling (*arrow*) and some reduplication of the inner basement membrane. (Uranyl acetate and lead citrate ×4,250.) (From Jones DB. Arterial and glomerular lesions associated with severe hypertension: light and electron microscopic studies. *Lab Invest.* 1974; 31:303, with permission.)

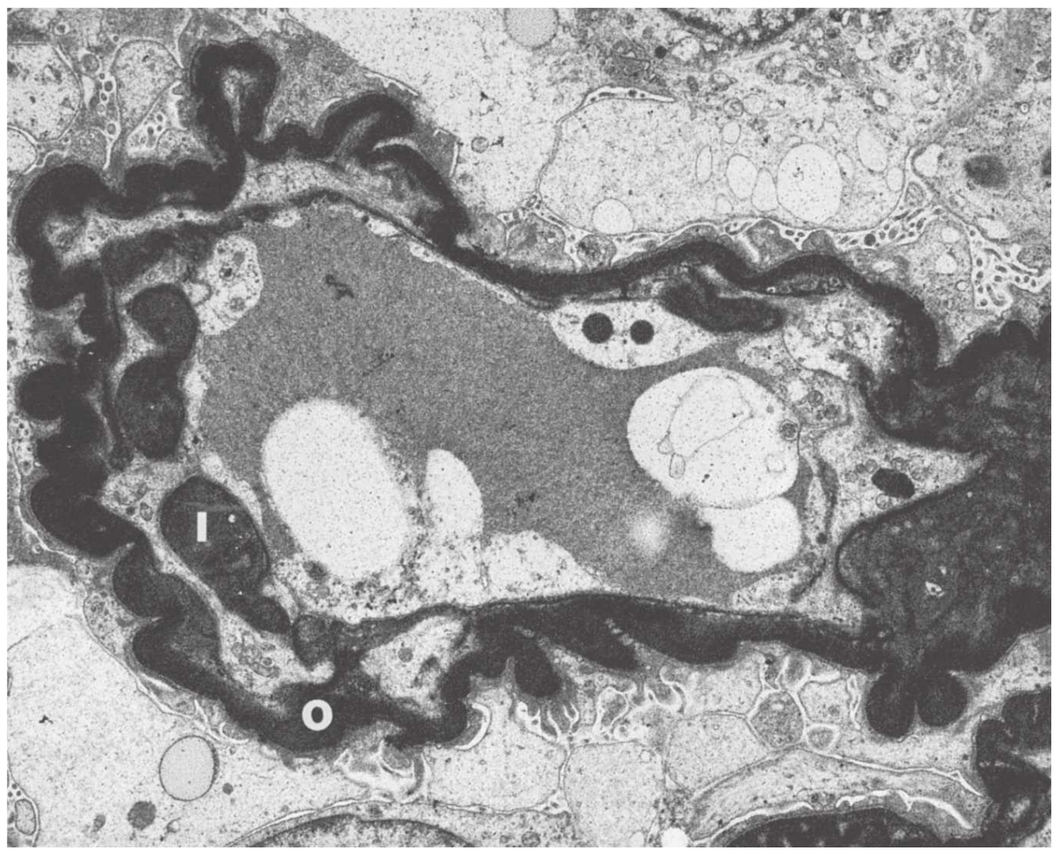


FIGURE 44.15 Accelerated glomerular obsolescence in malignant hypertension. The outer basement membrane (*O*) is thickened and wrinkled. There is a reduplicated inner basement membrane (*I*) with the capillary lumen still patent. (Uranyl acetate and lead citrate stain ×4,250.) (From Jones DB. Arterial and glomerular lesions associated with severe hypertension: light and electron microscopic studies. *Lab Invest.* 1974;31:303, with permission.)

obsolescence observed in benign hypertension. In addition to the wrinkled basement membrane observed in benign nephrosclerosis, there is constriction of the glomerular vascular bed in malignant nephrosclerosis due to the deposition of a new subendothelial layer of basement membrane material inside the original basement membrane (Fig. 44.15).[73] The new capillary lumen formed by this process is smaller, resulting in decreased blood volume in the ischemic glomerulus.

In malignant nephrosclerosis, the tubules may be atrophied and focally destroyed in areas supplied by severely narrowed arteries. Occasional tubules may be dilated and filled with eosinophilic cast material.[75] In the interstitium in these areas, there may be a fine reticular fibrosis and chronic inflammatory cells. In malignant hypertension, as in primary renal parenchymal diseases, renal insufficiency appears to correlate best with the degree of tubular atrophy.[70]

Immunofluorescence microscopy in patients with malignant nephrosclerosis has demonstrated deposition of gamma globulin, fibrinogen, albumin, and sometimes complement components in the walls of arterioles demonstrating fibrinoid necrosis by light microscopy.[81] Some of the glomeruli, especially those with focal necrosis, may contain immunoglobulin, albumin, and complement. Fibrinogen may be found diffusely along capillary basement membranes. Fibrinogen may also be found in the intima of interlobular arteries that by light microscopy show cellular or mucinous thickening.[76]

Striking juxtaglomerular hyperplasia has been reported in patients with malignant hypertension.[77] This ultrastructural finding is consistent with the hyperreninemic state often noted clinically.

Effective antihypertensive therapy may alter the pathology of malignant nephrosclerosis.[78–80] Within days, there may be resolution of fibrinoid necrosis, which leaves behind residual hyaline deposits in the arteriolar wall. In contrast to benign nephrosclerosis in which arteriolar hyaline change is often subendothelial, in treated malignant hypertension the hyaline material may be present throughout the entire vessel wall. Fibrosis of the arterioles with collagen replacement of the arteriolar muscle and elastica may also occur. Within several weeks after initiation of therapy, segmental fibrinoid necrosis in the glomeruli may also resolve, leaving behind an area of hyaline deposition that can mimic focal segmental glomerulosclerosis (FSGS). Furthermore, with treatment, in the intima of the interlobular arteries there may be an evolution from cellular hyperplasia to a more fibrous form of intimal thickening. A newly formed internal elastic lamina often separates this new collagen from the narrowed lumen. Heptinstall has postulated that the cellular lesion is an early finding implying active disease, whereas the acellular fibrotic lesion is a later process often reflecting a response to treatment.[75] These modifications in the interlobular arteries that occur following treatment may not be accompanied by any increase in the caliber of the lumen. Severely narrowed interlobular arteries often do not improve and the renal parenchyma distal to these arteries undergoes severe ischemic atrophy and scarring.[79] However, the nephrons supplied by interlobular arteries of normal caliber may undergo substantial hypertrophy following treatment of malignant hypertension. These histologic changes may explain the improvement in renal function that sometimes occurs in some patients following institution of antihypertensive therapy with resolution of malignant hypertension.

In summary, although fibrinoid necrosis was the hallmark of malignant nephrosclerosis in untreated patients at autopsy, it is now rarely observed. In treated patients with malignant hypertension or blacks with untreated malignant hypertension, closed renal biopsy most often reveals marked intimal hyperplasia of the interlobular arteries in association with accelerated glomerular obsolescence.[70,73]

Pathophysiology

Pathophysiology of Malignant Hypertension

The exact pathophysiologic mechanism underlying the transition from benign to malignant hypertension is not fully understood. The postulated pathogenesis of malignant hypertension is outlined in Figure 44.16. According to the pressure hypothesis, the development of fibrinoid necrosis and proliferative endarteritis is a direct consequence of the mechanical stress placed on vessel walls

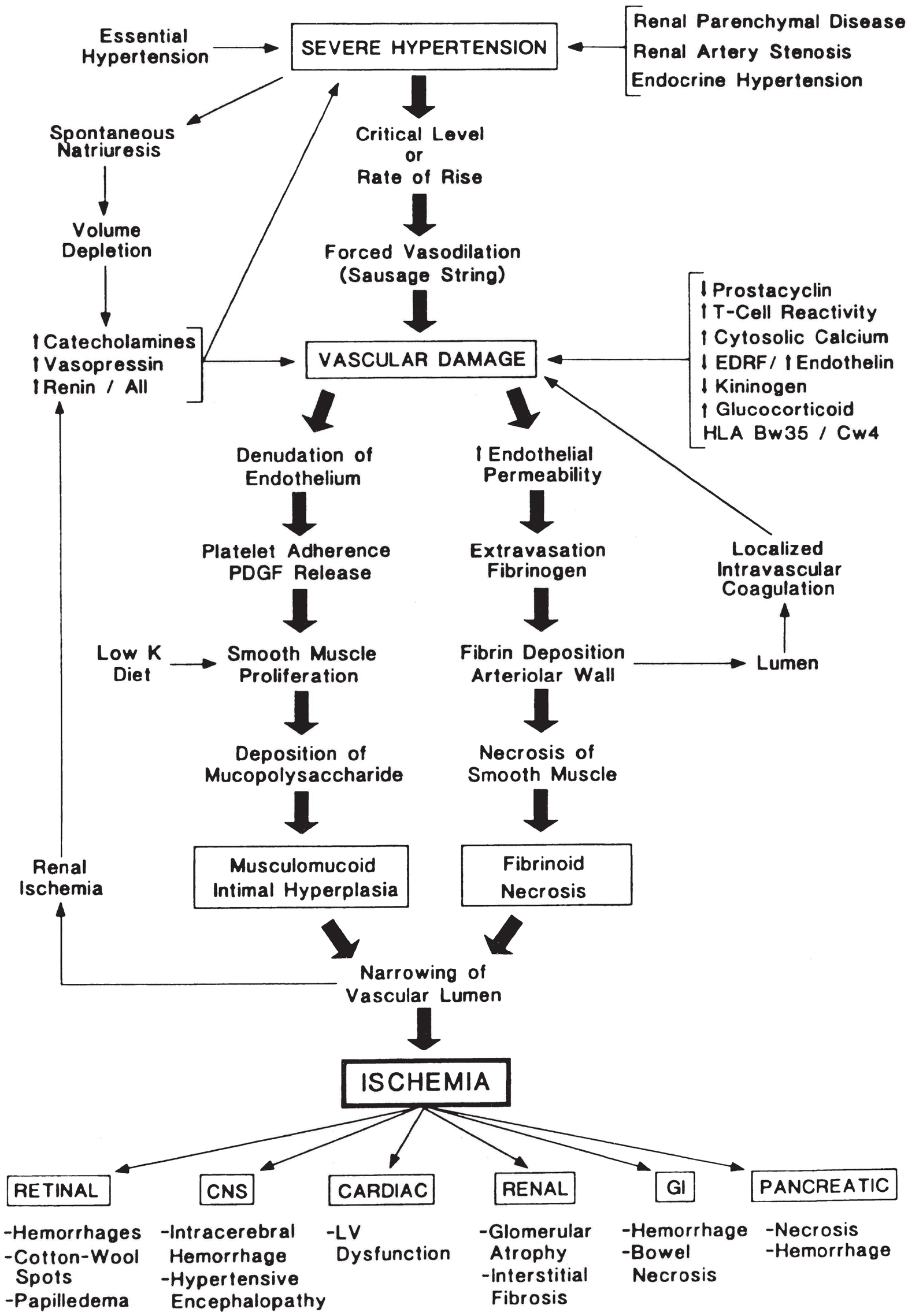


FIGURE 44.16 Pathophysiology of malignant hypertension. *AII,* angiotensin II; *EDRF,* endothelium-derived relaxing factor; *PDGF,* platelet-derived growth factor; *LV,* left ventricular.

by severe hypertension.[81] Undoubtedly, a marked increase in blood pressure is pivotal. Severe hypertension is the common element in malignant hypertension in humans and in each of the animal models of malignant hypertension. Moreover, reduction of the blood pressure leads to a resolution of the malignant phase regardless of the underlying etiology. Thus, a significant elevation of the blood pressure is necessary for the development and progression of malignant hypertension. The major issue is whether the mechanical stress of severe hypertension alone is sufficient to cause the transition from benign to malignant hypertension. Because there is considerable overlap in the levels of blood pressure seen in patients with benign and those with malignant hypertension, it is likely that severe hypertension alone is not sufficient to cause the malignant hypertension in all patients and that additional factor(s) probably participate. The vasculotoxic theory proposes that humoral factors interact with the hypertension-induced hemodynamic stress to cause the vascular damage observed in malignant hypertension.

These cofactors are not necessarily the same in every case. For example, activation of the renin–angiotensin axis may be important in some patients but not in others. In some patients, perhaps catecholamines, vasopressin, endothelin, or activation of the clotting cascade interact with hemodynamic stress to induce malignant hypertension. In several experimental models, spontaneous natriuresis appears to be the initiating event in the transition from benign to malignant hypertension.[82–84] In patients with malignant hypertension, an abrupt onset of weight loss early in the course of the disease has been reported. In the series of Kincaid-Smith et al.,[21] the onset of malignant hypertension often appeared suddenly. Despite minor increases in blood pressure, the patients became suddenly ill with weakness, wasting, and profound weight loss. The rapidity of the weight loss could only be explained by natriuresis-induced volume depletion and may be the human counterpart of the rat two-kidney, one-clip model of malignant hypertension in which spontaneous natriuresis is the inciting event.[82,83]

Pathophysiology of Hypertensive Neuroretinopathy

Retinal arteriolar vasculopathy in malignant hypertension leads to obliteration or rupture of vessels, resulting in striate hemorrhages, cotton-wool spots, and papilledema. Hypertensive neuroretinopathy is not simply the result of renal failure as hypertensive neuroretinopathy can clearly occur in malignant hypertension prior to the onset of clinically significant renal disease.[42] It also appears that hypertensive neuroretinopathy often occurs in the absence of increased intracranial pressure.[42]

The retinal circulation is under autoregulatory control and does not have a sympathetic nerve supply. As the systemic blood pressure increases, if autoregulation is intact, the retinal arterioles constrict to keep the retinal blood flow constant. The appearance of hypertensive neuroretinopathy implies that autoregulation has failed.[41]

Striate hemorrhages result from bleeding from superficial capillaries in the nerve fiber bundles near the optic disc. These capillaries originate from arterioles, so that when autoregulation fails, the high systemic pressure is transmitted directly to the capillaries. This leads to breaks in the continuity of the capillary endothelium with subsequent hemorrhage.[41]

Cotton-wool spots result from ischemic infarction of nerve fiber bundles due to arteriolar occlusion.[41] Fluorescein angiography demonstrates that cotton-wool spots are areas of retinal nonperfusion.[85] Embolization of pig retina with glass beads produces immediate intracellular edema followed by accumulation of mitochondria and other subcellular organelles in the ischemic nerve fibers.[87] It has been postulated that the normal axoplasmic flow of subcellular organelles is disrupted by ischemia such that accumulation of organelles in ischemic nerve fiber bundles results in a visible white patch.[53,54] Cotton-wool spots tend to distribute around the optic disc because the nerve fiber bundles are most dense in this region.

The pathogenesis of papilledema in malignant hypertension has been controversial. Papilledema may result from increased intracranial pressure. However, intracranial pressure is not always increased in malignant hypertension.[42] Papilledema has been produced in rhesus monkeys by occlusion of the long posterior ciliary artery, which supplies the optic disc.[88] Thus papilledema, like cotton-wool spots, most likely results from ischemia of nerve fibers in the optic disc.[87,88]

Treatment

Malignant hypertension must be treated expeditiously in order to prevent complications such as hypertensive encephalopathy, intracerebral hemorrhage, acute pulmonary edema, and renal failure. The hypertensive patient with hypertensive neuroretinopathy (hemorrhages, cotton-wool spots with or without papilledema) should be hospitalized for intensive medical therapy. Initiation of appropriate therapy should not be delayed pending extensive laboratory and roentgenographic examinations aimed at defining a potential underlying etiology. The workup for secondary causes should be deferred until the blood pressure has been controlled and the patient stabilized.

The traditional approach to patients with malignant hypertension has been the initiation of therapy with rapid-acting parenteral hypotensive agents such as sodium nitroprusside.[89] Table 44.4 lists the settings in which the use of

44.4 Indications for Parenteral Therapy in Malignant Hypertension

Patients unable to tolerate oral therapy due to intractable vomiting
Hypertensive encephalopathy
Rapidly failing vision
Intracerebral hemorrhage
Acute pulmonary edema
Acute myocardial infarction
Rapid deterioration of renal function
Acute pancreatitis
Gastrointestinal hemorrhage
Acute abdomen secondary to mesenteric vasculitis

parenteral antihypertensive agents is recommended for the initial management of malignant hypertension. In general, parenteral therapy should be utilized in patients who have evidence of acute end-organ damage or who are unable to tolerate oral medications.

The drug of choice for the management of patients with malignant hypertension requiring parenteral therapy is sodium nitroprusside.[90] Nicardipine and labetalol administered by continuous infusion are useful alternative agents.[90,91] The dopamine receptor (DA_1 selective) agonist fenoldopam may also be useful for parenteral treatment of malignant hypertension.[91,92] There are no absolute guidelines for the blood pressure goal during parenteral therapy. The theoretic risks of rapid reduction of blood pressure are discussed later in the section on the controversy over gradual versus rapid reduction of blood pressure. As a general rule, it is safe to initially reduce the mean arterial pressure by 20% or to a level of 160 to 170 mm Hg systolic and 100 to 110 mm Hg diastolic.[93] During the reduction of blood pressure with parenteral antihypertensives, the patient should be monitored closely for evidence of cerebral or myocardial hypoperfusion. The use of a short-acting agent such as sodium nitroprusside or fenoldopam has obvious advantages because the blood pressure can be stabilized quickly at a higher level if complications develop during rapid blood pressure reduction. If there is no evidence of vital organ hypoperfusion following this initial reduction of blood pressure, the diastolic blood pressure can gradually be lowered to 90 mm Hg over a period of 12 to 36 hours.

Oral antihypertensive agents should be initiated as soon as possible so that the duration of parenteral therapy can be minimized. However, a common error in the management of patients with malignant hypertension is the abrupt discontinuation of parenteral therapy immediately after oral therapy has been initiated. With this approach, severe rebound hypertension often develops before the oral antihypertensive regimen becomes effective. Ideally, oral antihypertensives should be initiated as soon as the patient has been stabilized and is able to tolerate medications by mouth. The nitroprusside infusion should be continued until the oral agents have taken effect and have been titrated to an effective dose. The nitroprusside or fenoldopam infusion can then be weaned as the oral regimen is gradually increased.

Although other agents may be effective in the long-term management of patients with malignant hypertension, the cornerstone of initial oral therapy should be an arteriolar vasodilator such as hydralazine, dihydropyridine calcium channel blocker, or minoxidil. Vasodilators may reflexively activate the adrenergic system and cause tachycardia with an increase in cardiac output, which may blunt the hypotensive response. Therefore, treatment with β-adrenergic blockers is usually also required. Direct-acting vasodilators also cause renal salt and water retention, fluid overload, and the development of pseudotolerance to the hypotensive effect of the drug. Thus, although diuretics may not be required for the initial management of patients with malignant hypertension (see later), they are usually required as a part of the long-term maintenance antihypertensive regimen. The regimen that follows has proved to be generally effective in the conversion from parenteral to oral therapy. After the blood pressure has been controlled with sodium nitroprusside and while the infusion is continued, hydralazine (50 mg) and beta-blocker are administered orally. As the oral agents become effective and the blood pressure declines, the nitroprusside infusion is tapered. Brief interruption of the infusion can be used to assess the hypotensive response to oral agents. If after 6 to 8 hours the diastolic blood pressure remains higher than 100 mm Hg, a second dose of hydralazine (100 mg) should be given. The beta blocker dose is increased as needed to maintain the heart rate in the 60 to 80 beats per minute range. If the blood pressure is not controlled with hydralazine at a dose of 100 mg twice daily, minoxidil should be substituted for hydralazine. The starting dose of minoxidil (2.5 mg) is increased by 2.5 to 5.0 mg every 6 to 8 hours until the blood pressure is adequately controlled. The usual effective dose is 5 to 10 mg twice daily. Treatment with a beta-blocker is recommended as for hydralazine. As the blood pressure is brought under control with oral agents, the sodium nitroprusside infusion is gradually weaned. When the convalescing patient is mobilized, upright blood pressure should be carefully monitored to avoid significant orthostatic hypotension. A diuretic, usually furosemide at a starting dose of 40 mg twice daily, is added to either the hydralazine or the minoxidil regimen when it becomes evident that salt and water retention is beginning to occur.

Volume Status and the Role of Diuretics

Routine parenteral diuretic therapy during the acute phase of treatment for malignant hypertension may actually be deleterious. Overdiuresis may result in deterioration of renal function due to superimposed prerenal azotemia. Moreover, volume depletion may activate the renin–angiotensin axis and other pressor hormone systems.

Even patients with malignant hypertension and pulmonary edema may not have an increase in total body salt and water content. Pulmonary congestion in this setting may result from an increase in left ventricular filling pressure due to a decrease in the compliance of the left ventricle (diastolic dysfunction) rather than an increase in left ventricular volume per se. With severe hypertension, the ventricle may become noncompliant due to the excessive workload imposed by the elevated systemic vascular resistance. As a result, left ventricular end-diastolic pressure (LVEDP) increases dramatically even though left ventricular end-diastolic volume may be near normal. With vasodilator therapy, the systemic vascular resistance decreases, left ventricular compliance improves, LVEDP decreases, and left ventricular end-diastolic volume may actually increase.[94] Despite the increase in left ventricular

end-diastolic volume, pulmonary congestion improves because of the reduction in pulmonary capillary pressure. Thus, even in patients with malignant hypertension complicated by pulmonary edema, afterload reduction rather than vigorous diuretic therapy should be the mainstay of initial therapy.

Some patients with malignant hypertension may actually benefit from a cautious trial of volume expansion. Intravascular volume depletion in patients with malignant hypertension should be considered in patients with exquisite sensitivity to vasodilator therapy manifest by a precipitous drop in blood pressure at relatively low infusion rates. Patients with malignant hypertension due to analgesic nephropathy are particularly prone to be severely volume-depleted at presentation due to the presence of chronic interstitial damage with a salt-wasting nephropathy.[17]

In summary, the need for diuretic therapy during the initial phase of treatment for malignant hypertension depends on an assessment of volume status. Unless obvious fluid overload is present, diuretics should not be given initially.

Management of Malignant Hypertension Complicated by Renal Insufficiency

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 occasionally precipitates oliguric acute renal failure, especially when the initial glomerular filtration rate is less than 20 mL per minute. However, this is not a contraindication to aggressive antihypertensive therapy aimed at normalization of the blood pressure. Control of hypertension protects other vital organs such as the brain and heart whose function cannot be replaced. Moreover, with tight blood pressure control, even patients who appear to have ESRD due to malignant nephrosclerosis have recovered renal function.[95–100]

In patients in whom aggressive control of hypertension precipitates the need for dialysis, dialysis is utilized to control serum chemistry values, treat uremia, and correct fluid overload. However, since dialysis alone rarely results in adequate control of blood pressure in patients with malignant hypertension, concomitant antihypertensive drug therapy is almost always required. A regimen with minoxidil and beta-blocker has proved to be particularly efficacious in this setting.[98,99]

Initial Oral Therapy

Although many patients with malignant hypertension require prompt treatment with parenteral antihypertensive agents, some patients may not yet have evidence of cerebral or cardiac complications, or rapidly deteriorating renal function and therefore do not require instantaneous control of the blood pressure.[89,101,102] These patients may be safely managed with an intensive oral regimen designed to bring the blood pressure under control over a period of 12 to 24 hours.

In patients with malignant hypertension, a multidrug oral regimen is often required to achieve adequate blood pressure control. The most useful combinations include a diuretic, a β-adrenergic blocker, and an arteriolar vasodilator. Minoxidil appears to be particularly well suited for the initial management of malignant hypertension that requires prompt but not immediate blood pressure reduction.[103–105] Alpert and Bauer[105] describe the use of a triple regimen of furosemide, beta-blocker, and minoxidil in nine patients with a diastolic blood pressure higher than 120 mm Hg. Seven of these patients had malignant hypertension. Furosemide (40 mg) and propranolol (40 mg) were given initially by mouth. Two hours later, if the diastolic pressure was higher than 120 mm Hg, a loading dose of minoxidil (20 mg) was administered. If the diastolic pressure was still over 100 mm Hg 4 hours after the loading dose, a booster dose of minoxidil was given. The amount of the booster dose was estimated based on the magnitude of the response to the loading dose. Maintenance therapy with minoxidil was begun with one half the sum of the loading and booster doses given twice daily, with adjustment of beta-blocker and diuretic doses as necessary for control of heart rate and fluid balance. Following the booster dose of minoxidil, a sustained decrease in blood pressure was seen in all patients. No overshoot hypotension or other adverse effects were encountered. During long-term therapy, the physicians were able to substitute hydralazine for minoxidil in five patients. However, the remaining four patients required chronic minoxidil therapy for adequate blood pressure control.[101]

Initial oral therapy with the dihydropyridine calcium channel blocker nifedipine has been shown to be effective in the management of malignant hypertension in black patients who did not require parenteral therapy for hypertensive encephalopathy or acute pulmonary edema.[102] No precipitous decreases in blood pressure or neurologic complications were encountered. However, despite adequate control of blood pressure during the first 24 hours with sustained-released nifedipine, all patients eventually required one or more additional drugs for long-term blood pressure control. Oral loading regimens with clonidine have been advocated in severe uncomplicated (urgent) hypertension.[106] However, there is limited information on the use of oral clonidine loading in the initial management of malignant hypertension. Clonidine loading can cause significant sedation, which may interfere with the assessment of potential neurologic complications during acute blood pressure reduction. Moreover, common side effects such as sedation and dry mouth can have a negative impact on compliance in patients treated with clonidine for the long term. Thus, oral clonidine loading regimens are not indicated for the initial management of malignant hypertension.

Long-Term Management

After the immediate crisis has resolved and the blood pressure has been brought under control with parenteral therapy, oral therapy, or both, lifelong surveillance of the blood pressure is essential. Close follow-up and aggressive treatment are mandatory because noncompliance or inadequate therapy may have devastating consequences. If blood pressure control becomes inadequate, malignant hypertension may recur even after years of successful antihypertensive therapy. In a study of the quality of care provided to patients with a history of malignant hypertension who subsequently died, only 27% of patients had an average treated diastolic blood pressure of less than 110 mm Hg.[107] Thus, meticulous long-term treatment of hypertension is imperative in patients with a history of malignant hypertension. Triple therapy with a diuretic, a beta-blocker, and a vasodilator is often required to achieve satisfactory blood pressure control.

Response to Therapy

In the absence of adequate blood pressure control, malignant hypertension has a uniformly poor prognosis. Without treatment, the 1-year mortality rate approaches 80% to 90%, and uremia is the most common cause of death.[21] However, since the introduction of potent antihypertensive agents, studies have shown that with control of blood pressure, dialysis-free survival can be substantially prolonged. A recent study of survival trends for patients with malignant hypertension (n = 446) over the last 40 years found that there was a significant improvement in 5-year survival from 32% prior to 1977 to 91% for patients diagnosed between 1997 and 2006.[25] Multivariate analysis revealed that age, decade of diagnosis of malignant hypertension, baseline creatinine, and follow-up systolic blood pressure were independent predictors of survival. In a another single-center retrospective analysis of 197 patients with malignant hypertension diagnosed in the period 1974 to 2007, renal damage at presentation was common (63%) but renal function improved or remained stable after diagnosis in the majority of patients.[26] The probability of renal survival was 84% and 72% after 5 and 10 years, respectively. The number of patients with malignant hypertension who improved or stabilized their renal function significantly increased in the second and third periods of the study (1987–2007). Diagnosis during the early study period (1974–1985), baseline renal function, proteinuria, and the presence of microhematuria were associated with an unfavorable outcome. However, by multivariate analysis, mean proteinuria during follow-up remained as the only significant risk factor (OR 2.72; 95% CI, 1.59–4.64). Renal survival for patients with mean protein excretion less than 0.5 g per 24 hours was 100% and 95% at 5 and 10 years, respectively.

The severity of renal impairment at the time of presentation with severe hypertension may also have prognostic significance.[108] Chronic kidney disease and acute kidney injury are common in patients hospitalized with severe hypertension. In the ongoing STAT trial, a U.S.-based, retrospective observational study of management practices and outcomes of patients with severe hypertension, both chronic kidney disease (CKD) and acute kidney injury (AKI) were common. AKI was a strong predictor of greater morbidity and cardiovascular mortality.[109]

Reversal of Hypertensive Neuroretinopathy

The funduscopic changes associated with hypertensive neuroretinopathy are reversible with control of blood pressure.[110] Striate hemorrhages cease to form as soon as the blood pressure is controlled. Clearance of existing hemorrhages takes 2 to 8 weeks. Cotton-wool spots may continue to form for several days after the blood pressure is controlled. The cellular (axonal) debris that comprises the cotton-wool spots is cleared away within 2 to 12 weeks. Hard exudates clear more slowly. A macular star may require more than a year to resolve completely. Papilledema often continues to increase during the first few days of treatment. However, in the majority of patients, it resolves slowly over several weeks. In contrast, the changes reflecting retinal arteriolosclerosis such as arteriolar narrowing, arteriovenous crossing defects, and changes in the light reflexes usually persist despite adequate blood pressure control.[110]

Evaluation for Secondary Causes

The various secondary causes of malignant hypertension were discussed previously in the section on etiologies of malignant hypertension. Whereas less than 5% of patients with benign hypertension have an underlying secondary cause of hypertension, malignant hypertension may be associated with a secondary cause in up to 50% of patients. For example, among patients with benign hypertension, the incidence of renovascular hypertension was less than 0.5%.[111] In contrast, there is a substantial incidence of renovascular hypertension (43% in whites, 7% in blacks) among patients with malignant hypertension.[18] Thus, after malignant hypertension has been treated successfully, the possibility of underlying renovascular hypertension should be investigated. Noninvasive screening tests such as radionuclide renal scans are of little value because of the high frequency of false-positive and false-negative results.[111] Renal arteriography is the procedure of choice to exclude the possibility of anatomic renal artery stenosis. The diagnosis and treatment of renovascular hypertension is discussed in detail in Chapter 42.

Pheochromocytoma is a rare cause of malignant hypertension. However, given the likelihood of surgical cure or amelioration of hypertension, pheochromocytoma should be considered if symptoms consistent with catecholamine excess persist following control of blood pressure. The approach to the diagnosis of pheochromocytoma is discussed in Chapter 43.

The role of renal biopsy in the diagnosis of possible underlying primary renal parenchymal disease in patients with malignant hypertension is controversial. In patients

presenting with malignant hypertension and renal failure, it may not be possible on clinical grounds to distinguish primary malignant hypertension from chronic glomerulonephritis or chronic interstitial nephritis with superimposed malignant nephrosclerosis. A renal biopsy may be required to make this distinction. When the kidneys appear small by ultrasonography, a biopsy is not indicated because it is unlikely that the results of the biopsy will alter therapy. In contrast, when the kidneys are normal in size, a renal biopsy may provide useful information. If primary malignant nephrosclerosis with ischemic but viable glomeruli is found, then intensive antihypertensive therapy may be associated with the eventual recovery of renal function, even after months of maintenance dialysis. Conversely, the finding of chronic glomerulonephritis or chronic interstitial nephritis with superimposed malignant nephrosclerosis suggests a less favorable long-term outcome.

Malignant hypertension can mimic acute glomerulonephritis or vasculitis. Patients can present with severe hypertension and oliguric acute renal failure with nephritic urinary sediment. In this setting, diagnostic renal biopsy is essential since acute glomerulonephritis or vasculitis may require specific therapy in addition to antihypertensive treatment.

Because uremia and severe hypertension predispose to serious hemorrhagic complications after renal biopsy, it is prudent to manage the patient with dialysis and blood pressure control for 1 to 3 weeks prior to performance of a percutaneous renal biopsy. Unfortunately, this delay in obtaining tissue may make the diagnosis of malignant nephrosclerosis more difficult because the lesions of fibrinoid necrosis may heal rapidly with the institution of antihypertensive treatment, leaving a residual hyaline or fibrous scar.[80] Moreover, given the sampling error inherent in closed renal biopsy, the patchy lesions of malignant nephrosclerosis might be missed. Thus, the diagnosis of malignant nephrosclerosis is often made on the basis of the findings of accelerated glomerular obsolescence and marked intimal hyperplasia of the arterioles.[73]

Benign Versus Malignant Hypertension

Since the original description by Volhard and Fahr,[35] two forms of essential hypertension have been recognized: benign and malignant. It is worth emphasizing that these two forms of hypertension should be conceptualized as distinct clinical and pathologic entities. In benign hypertension there is usually a long asymptomatic phase, with death resulting from complications of cerebrovascular disease, atherosclerotic disease, or congestive heart failure, rather than renal disease. In benign essential hypertension (i.e., without underlying primary renal disease or superimposition of malignant hypertension), ESRD seldom occurs.[112–115] In contrast, malignant hypertension left untreated uniformly progresses to ESRD.

There is much controversy in the field of hypertension regarding the frequency with which benign hypertension (benign arteriolar nephrosclerosis), in the absence of occult primary renal disease or superimposed malignant hypertension, causes ESRD. Recent reviews suggest that the number of patients reaching ESRD attributable to benign nephrosclerosis might have been significantly overestimated.[114,115] Goldring and Chasis[46] extensively evaluated renal function in a large group of patients with essential hypertension in the preantihypertensive treatment era. Most patients with long-standing essential hypertension had anatomic lesions in their kidneys consistent with hyaline arteriolar nephrosclerosis. Moreover, the majority had demonstrable renal abnormalities including abnormal urinalysis with hyaline and granular casts, low-grade proteinuria (less than 1 g per day), decreased tubular maximum for para-aminohippurate, decreased renal blood flow, normal to slightly decreased glomerular filtration rate, and increased filtration fraction. However, they found that ESRD rarely occurred in patients with benign hypertension. Among 150 hypertensive patients with ESRD, only one was found to have benign nephrosclerosis as the sole underlying etiology.[46] These authors concluded that in patients with benign hypertension, functional failure occurred earlier in the heart and brain than in the kidney and that death from renal failure without superimposed malignant hypertension was a rare event.

In contrast to these early reports, which were based principally on renal histologic findings at autopsy, in more recent series, "hypertensive nephrosclerosis" is listed as a common cause of ESRD, especially among African American patients. For example, blacks have a four- to eightfold elevation in the risk of hypertension-induced ESRD compared to whites.[116,117] The studies suggest that much of the excess risk of ESRD among blacks can be explained by an extraordinarily high rate of renal failure from hypertensive nephrosclerosis. On a national scale, an estimated 29% of blacks with ESRD have hypertension as the primary cause.[116] However, in these recent studies, classification of the causes of ESRD was based on clinical rather than histologic evidence. Furthermore, in these studies it was not clear whether the term hypertensive nephrosclerosis refers to benign or malignant nephrosclerosis. In the few available studies detailing the pathologic findings in blacks with ESRD due to hypertension, the characteristic findings have been those of malignant nephrosclerosis, namely, musculomucoid intimal hyperplasia of the interlobular arteries and accelerated glomerular obsolescence.[13] Moreover, there appears to be a racial bias with regard to the diagnosis of hypertensive nephrosclerosis. When nephrologists were asked to review identical case histories of patients with ESRD in which only the race of the patient was randomly assigned as either black or white, it was found that black patients were twice as likely as white patients to be labeled as having ESRD secondary to hypertensive nephrosclerosis.[118]

The relationship between essential hypertension and ESRD remains circumstantial despite the fact that these syndromes have long been associated in the medical literature.[115] Nephrologists credit essential hypertension as the cause of ESRD in 25% of patients initiating Medicare-supported renal

replacement therapy. Surprisingly, the widely held notion that benign hypertension with benign nephrosclerosis is a common cause of ESRD is difficult to support.[114,115,119] In contrast to the large body of literature relating mild to moderate benign hypertension to excessive cardiovascular morbidity, there is a dearth of information available regarding the corresponding risk of significant renal disease.[119] In available studies, serum creatinine levels infrequently increase in patients with long-standing mild to moderate hypertension. An analysis of the data from three large clinical trials in patients with essential hypertension revealed that advanced renal failure developed in less than 1% of 10,000 patients during the 4 to 6 years of follow-up.[120–122] Moreover, a very low incidence of clinically significant deterioration of renal function was also noted in the Hypertension Detection and Follow-up Program.[123] Another study of untreated patients with mild to moderate essential hypertension found only minor declines in glomerular filtration rate (1.6% per year) and renal blood flow (2.1% per year), which did not differ from the renal function decline associated with aging in normotensive individuals.[124] Even severe untreated hypertension (diastolic blood pressure, 120 to 150 mm Hg), in the absence of a malignant hypertension (hypertensive neuroretinopathy), caused only a minor decrement in glomerular filtration rate (1.7% per year).[124] Thus, hypertensive nephrosclerosis is commonly reported to Medicare as the cause of ESRD despite the fact that the risk of progressive renal dysfunction in clinical studies of patients with essential hypertension appears to be very low. This paradox could possibly be explained by the fact that the number of patients with essential hypertension is so large that even the small percentage at risk constitutes a relatively large number of patients who eventually develop ESRD. Long-term follow-up data from the Multiple Risk Factor Intervention Trial (MRFIT), in which over 322,000 men were screened for possible entry, support this hypothesis.[125] A direct correlation was found between the initial blood pressure and the risk of development of ESRD from any cause at 16-year follow-up. Nonetheless, the age-adjusted rate of ESRD in this group was only 0.34% at 16 years.

Patients classified as having hypertensive ESRD typically present with advanced disease, making the processes that initiated the renal disease difficult to discern. It has been proposed that many patients classified as having hypertensive nephrosclerosis actually have intrinsic renal parenchymal disease (often immunoglobulin A [IgA] nephropathy), unrecognized renal artery stenosis with ischemic nephropathy, unrecognized episodes of malignant hypertension, or primary renal microvascular disease.[114,115] At least among white patients with hypertension and renal impairment, if renal artery stenosis and malignant hypertension have been excluded, the most likely diagnosis is underlying primary renal parenchymal disease rather than benign nephrosclerosis.[126]

In contrast to these studies, a provocative study found that mild to moderate benign hypertension did cause renal insufficiency that progressed despite adequate blood pressure control.[127] However, since renal biopsies were not performed, the data do not exclude the possibility of occult primary renal parenchymal disease in patients demonstrating progressive renal insufficiency.[128]

In summary, although it is clear that malignant hypertension is a frequent cause of ESRD, especially among blacks, there remains considerable controversy regarding the commonly held belief that benign hypertension per se commonly causes ESRD. The critical issue that has yet to be resolved is why blacks constitute a disproportionately high percentage of patients with ESRD in the United States.[116] Epidemiologic studies suggest that essential hypertension occurs more frequently in blacks and is associated with more severe cardiovascular end-organ damage for any given level of blood pressure.[129] In angiographic studies of patients with mild to moderate essential hypertension and normal renal function, blacks tended to have more severe angiographic evidence of nephrosclerosis than did whites.[130] There are several other plausible explanations for the high frequency with which hypertensive nephrosclerosis is reported as a cause of ESRD in the black population. Since most of the available data are based on clinical diagnoses, there may be a tendency on the part of physicians to identify hypertension as the cause of ESRD given the known high prevalence of hypertension in blacks, even when a primary renal parenchymal disease cannot be excluded on clinical grounds.[119] Another possibility is that blacks with essential hypertension tend to develop more severe benign nephrosclerosis, which, unlike benign nephrosclerosis in whites, more often results in progressive renal insufficiency and ESRD.[115] Results from the African American Study of Kidney Disease (AASK) Trial indicate that benign nephrosclerosis can be accurately diagnosed in black patients with hypertension and renal insufficiency. A renal biopsy was performed in 39 nondiabetic black patients with chronic renal failure who did not have marked proteinuria (urine protein to creatinine ratio less than 2.0). Changes compatible with benign nephrosclerosis were seen in 38 patients. The remaining patient most likely had primary focal segmental glomerulosclerosis.[131] It is possible that genetic factors may increase the susceptibility of blacks to renal damage induced by benign hypertension. On the other hand, the AASK trial demonstrated that strict blood pressure control, including use of ACE inhibitors, failed to halt the progression of renal disease in these black patients with biopsy-proven hypertensive nephrosclerosis.[132] This finding suggests that the focal global glomerulosclerosis lesion identified in AASK trial participants may represent a form of primary renal disease rather than a primary consequence of hypertension-induced renal injury per se. Finally, it is possible that recurrent bouts of unrecognized or inadequately treated malignant hypertension are an underestimated cause of the high incidence of ESRD in minority populations. In this regard, a study of 100 patients admitted to an inner city hospital with a diagnosis of hypertensive emergency showed that two thirds had malignant hypertension based on funduscopic findings.[133] These patients were predominantly

young, male, black, or Hispanic individuals of lower socioeconomic status. At least 93% of these patients had been previously diagnosed as hypertensive, and at least 83% were aware of their diagnosis of hypertension. At least 87% were known to have received prior pharmacologic treatment for hypertension. However, no source of regular health care could be documented in 60% of patients. More than 50% were noted to have stopped their antihypertensive medications more than 30 days prior to admission and only 24% had taken any medication on the day of admission. If the overrepresentation of young blacks with ESRD is due to undiagnosed or inadequately treated malignant hypertension, this would have tremendous public health implications given that malignant hypertension is clearly preventable, and even significant renal dysfunction is potentially reversible with tight control of blood pressure.

HYPERTENSIVE ENCEPHALOPATHY

Most of the deleterious effects of hypertension on the brain are the result of long-standing mild to moderate elevations of blood pressure, including atherothrombotic infarction, lacunar infarction, and intracerebral hemorrhage. Occasionally, severe acute hypertension can produce dramatic and life-threatening cerebral complications. Hypertensive encephalopathy is an acute cerebral syndrome that develops in association with a sudden, sustained elevation of blood pressure.[56] It can occur with malignant hypertension or severe "benign" hypertension that is not accompanied by hypertensive neuroretinopathy. Hypertensive encephalopathy is a medical emergency that demands prompt diagnosis and rapid control of blood pressure to prevent irreversible brain damage or death. The clinical sine qua non of hypertensive encephalopathy is the prompt resolution of symptoms when the blood pressure is brought under control.

Clinical Presentation

The diagnosis of hypertensive encephalopathy is usually made on clinical grounds. The appearance of cerebral symptoms usually follows the sudden onset of hypertension in previously normotensive individuals or an abrupt increase in blood pressure in patients with chronic hypertension. The abrupt blood pressure elevation usually occurs 12 to 48 hours before the onset of symptoms, although this is often difficult to document. Symptoms may appear at lower levels of blood pressure in previously normotensive individuals compared to those with chronic hypertension. For example, in children with acute glomerulonephritis or pregnant women with eclampsia, hypertensive encephalopathy may occur when the blood pressure is no higher than 160/100 mm Hg.[134] However, the syndrome rarely occurs in chronically hypertensive individuals at pressures less than 200/120 mm Hg and may not occur until the blood pressure is more than 250/150 mm Hg.

The initial symptom of hypertensive encephalopathy is usually a severe, generalized headache that increases steadily in severity.[135] Unfortunately, headache is a nonspecific symptom, and even among patients with malignant hypertension, it does not necessarily imply CNS damage. Weakness, nausea, and vomiting (sometimes projectile) are often present. Neck stiffness is an occasional finding. Loss of vision is another common feature. Visual loss may be caused by the retinal edema and hemorrhages that accompany hypertensive neuroretinopathy or as the result of cortical (occipital) blindness.[136] Denial of visual loss or loss of vision in the presence of a normal light reflex suggests cortical blindness.

Altered mental status is a prominent clinical feature of hypertensive encephalopathy. Apathy, somnolence, and confusion are the initial manifestations that usually appear several hours to days after the onset of headache. If treatment is not instituted, coma and death can occur. Recurrent seizures are common, and they can be either focal or generalized.

There are numerous reports of transient focal neurologic disturbances in patients with hypertensive encephalopathy including fleeting paresthesias and numbness in the extremities, transient paralysis, and aphasia.[56,136] Thus, the presence of focal neurologic deficit in a patient with severe hypertension does not necessarily exclude the diagnosis of hypertensive encephalopathy.

Hypertensive neuroretinopathy (striate hemorrhages, cotton-wool spots, and papilledema) is present when hypertensive encephalopathy occurs in patients with malignant hypertension. However, it may be absent when hypertensive encephalopathy develops in the setting of acute glomerulonephritis, eclampsia, monoamine oxidase inhibitor–tyramine interactions, antihypertensive drug withdrawal syndromes, or pheochromocytoma.[134,136,137]

Many authors have cautioned that lumbar puncture should be avoided in patients with suspected hypertensive encephalopathy because of the risk of cerebellar herniation.[138] When performed, lumbar puncture has revealed elevated cerebrospinal fluid (CSF) pressure in most patients ranging from 230 to 560 mm of water.[136] CSF protein concentration is usually moderately elevated (48 to 90 mg per dL) but may be normal. The cell count is usually normal,[136] but neutrophilic pleocytosis has also been reported in hypertensive encephalopathy.[138]

Computed tomography (CT) and magnetic resonance imaging (MRI) reveal characteristic findings in hypertensive encephalopathy.[139–143] Abnormalities on imaging include areas of low white matter attenuation on CT scans and T1-weighted hypointense and T2-weighted hyperintense areas on MRI. These changes probably represent cerebral edema with increased water in the white matter. The most common location of the white matter abnormalities on neuroimaging is the posterior regions of the cerebral hemispheres. The multifocal abnormalities include both hemispheres and tend to be symmetric. Commonly involved areas in descending order of frequency include the occipital lobes, the posterior parietal lobes, and the posterior temporal lobes. The pons, the thalamus, and the cerebellum are occasionally involved. The term reversible posterior leukoencephalopathy syndrome

has been coined to describe patients with these typical radiographic findings and a reversible syndrome of headache, altered mental status, seizures, and loss of vision.[140] A reversible hypertensive brainstem encephalopathy with predominant involvement of the brainstem and relative sparing of supratentorial regions has also been reported.[143]

Etiologies

Although hypertensive encephalopathy can complicate malignant hypertension, not all patients with hypertensive encephalopathy have malignant hypertension. In fact, it most commonly occurs in previously normotensive individuals who experience sudden, severe hypertension (Table 44.5). The reported causes of hypertensive encephalopathy include acute glomerulonephritis,[134,135] eclampsia,[144,145] renovascular hypertension,[134] postcoronary artery bypass hypertension, clonidine withdrawal,[146] monoamine oxidase inhibitor–tyramine interactions,[147] pheochromocytoma,[148] phencyclidine (PCP) poisoning,[149] licorice ingestion,[150] phenylpropanolamine overdose,[151,152] acute renal artery occlusion,[136] acute lead poisoning,[136] immunosuppressive therapy with cyclosporine or tacrolimus for kidney, liver, or bone marrow transplantation,[153,154] chemotherapy for acute leukemia in children,[155] transplant renal artery stenosis or acute rejection,[156,157] and femoral lengthening procedures in children.[158] The preeclampsia–eclampsia syndrome has been hypothesized to reflect a subtype of hypertensive encephalopathy accompanied by impaired cerebral autoregulation and endothelial dysfunction.[137,141,144,145] The clinical and radiographic findings in patients with cyclosporine-induced neurotoxicity have been found to be identical to those seen in hypertensive encephalopathy.[154] The only major factor found to be associated with the neurotoxic effect of cyclosporine in all patients was hypertension. Subcortical edema, affecting the posterior regions of the brain, tends to resolve following reduction in blood pressure, with or without concomitant reduction in cyclosporine dose. Hypertensive encephalopathy may also occur in patients with acute or chronic spinal cord injuries if there is autonomic hyperreflexia due to bowel or bladder distention.[159,160] Acute elevation of blood pressure during recombinant human erythropoietin therapy occasionally results in hypertensive encephalopathy and seizures.[161] This complication is unrelated to the extent or rate of increase in hematocrit, but is associated with a rapid increase in blood pressure and may occur in previously normotensive patients. Scorpion envenomization results in stimulation of the autonomic nervous system and adrenals and in children can lead to severe hypertension and a clinical picture consistent with hypertensive encephalopathy.[162] Cocaine use can also induce a sudden increase in blood pressure accompanied by hypertensive encephalopathy.[163]

44.5 Etiologies of Hypertensive Encephalopathy

Malignant hypertension of any etiology
Acute glomerulonephritis
Eclampsia
Renovascular hypertension
Postcoronary artery bypass hypertension
Abrupt withdrawal of antihypertensive therapy
Monoamine oxidase inhibitor-tyramine interactions
Pheochromocytoma
Phencyclidine (PCP) poisoning
Phenylpropanolamine overdose
Recombinant erythropoietin therapy in dialysis patients
Scorpion envenomation, especially in children
Cocaine hydrochloride or alkaloidal (crack) cocaine
Acute renal artery occlusion
Acute lead poisoning in children
Cyclosporine-induced or tacrolimus-induced hypertension
Transplant renal artery stenosis or acute rejection
Femoral lengthening procedures
Acute or chronic spinal cord injuries

Pathogenesis

The breakthrough theory of autoregulation originally proposed by Lassen and Angoli[164] is the generally accepted view of the pathogenesis of hypertensive encephalopathy (Fig. 44.17). Under normal circumstances, there is autoregulation of the cerebral microcirculation such that, over a wide range of perfusion pressures, cerebral blood flow remains constant. It has been proposed that in the setting of a sudden, severe increase in blood pressure, autoregulatory vasoconstriction fails and there is forced vasodilation. The dilation is initially segmental (sausage-string pattern), but eventually becomes diffuse. The endothelium in the dilated segments becomes abnormally permeable, and there is extravasation of plasma components with the development of cerebral edema. This theory may explain the clinical observation that hypertensive encephalopathy develops at a much lower blood pressure in previously normotensive individuals than it does in those with chronic hypertension. With long-standing hypertension, structural changes and remodeling

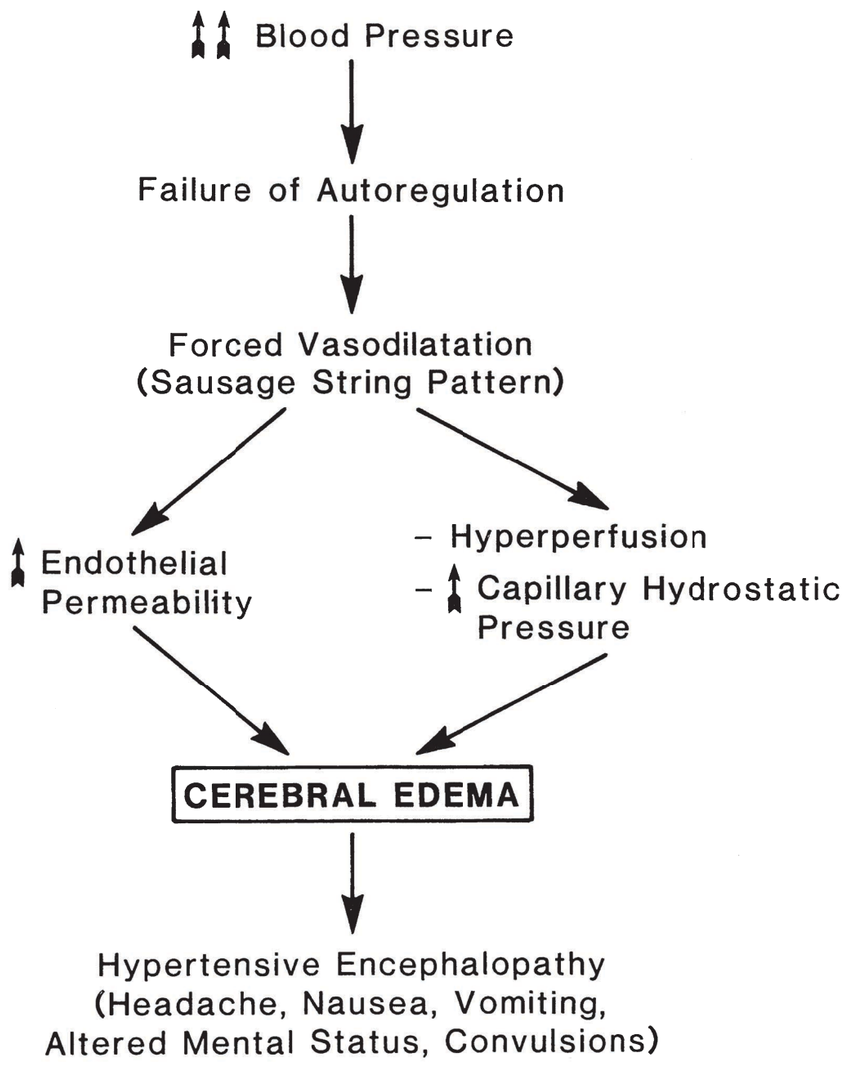


FIGURE 44.17 The breakthrough theory of hypertensive encephalopathy.

of the cerebral arterioles may lead to a shift in the autoregulatory curve such that much higher perfusion pressures can be tolerated before forced vasodilation and breakthrough of autoregulation occur.[165,166]

Treatment

The treatment of choice for hypertensive encephalopathy is prompt reduction of blood pressure. When the diagnosis of hypertensive encephalopathy seems likely, antihypertensive therapy should be initiated prior to obtaining the results of time-consuming laboratory and radiologic examinations. The goal of therapy, especially in the previously normotensive patient with acute hypertension, should be the reduction of blood pressure to normal or near-normal levels as quickly as possible.[134] Although cerebral blood flow could theoretically be jeopardized by failure of autoregulation during rapid reduction of blood pressure in patients with chronic hypertension, clinical experience has shown that the prompt reduction of blood pressure with the avoidance of frank hypotension is beneficial in patients with hypertensive encephalopathy.[134] 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 a rapid onset and short duration of action such as sodium nitroprusside, continuous infusion labetalol, or possibly fenoldopam should be utilized so that the blood pressure can be carefully titrated with close monitoring of the patient's neurologic status. There is some evidence that compared to labetalol, nitroprusside reduces systemic vascular resistance more than cerebral vascular resistance and could, therefore, result in shunting of blood from the brain.[167] The clinical sine qua non of hypertensive encephalopathy is a prompt clinical response to blood pressure reduction. Conversely, when antihypertensive therapy is associated with the development of new or progressive neurologic deficits, other diagnoses should be considered, and the blood pressure should be stabilized at a higher level.

In women with eclampsia, convulsions and other neurologic manifestations occur and are indistinguishable from those observed in nonpregnant individuals with hypertensive encephalopathy, except that in eclampsia they occur at a lower level of blood pressure.[145] Eclampsia is associated with extreme risk to both the mother and the fetus. Although delivery of the fetus is the definitive cure in most cases, rapid control of the blood pressure and encephalopathic manifestations is essential before the induction of labor or performance of a cesarean section.[137,144]

ACUTE HYPERTENSION COMPLICATING CEREBROVASCULAR ACCIDENT

The importance of hypertension as a risk factor for cerebrovascular accident is well established. The Framingham Study shows that regardless of gender or age, hypertension is associated with an increased incidence of ischemic and hemorrhagic stroke.[168] Several prospective, randomized clinical trials demonstrate that long-term antihypertensive drug therapy results in a significant reduction in morbidity and mortality from cerebrovascular accident.[169] Despite the proven benefits of blood pressure control in the prevention of stroke, the role of treatment of hypertension in the acute phase of stroke remains controversial. Whether antihypertensive therapy is indicated depends not only on the magnitude of the blood pressure elevation, but also on the type of cerebrovascular accident. It should be emphasized that the management of hypertension accompanying cerebral infarction is different from that for hypertension complicating either intracerebral hemorrhage or subarachnoid hemorrhage.

Cerebral Infarction

In the cerebral circulation, the sites of predilection for atherosclerosis are the bifurcations of the common carotid arteries, the carotid siphons, the origins of the vertebral and basilar arteries, the circle of Willis, and the proximal parts of the cerebral arteries.[170] Cerebral infarction can result from partial or complete occlusion of an artery by a plaque or embolization of atherothrombotic debris from a plaque. The atherothromboembolic infarcts produced by one of these mechanisms typically involve the cerebral or cerebellar cortex or the pons.[170] In contrast, hypertension-induced lipohyalinosis of the small penetrating cerebral end arteries is the principal cause of the small, deep lacunar infarcts that occur in the basal ganglia, pons, thalamus, cerebellum, and deep hemispheric white matter.[170]

Hypertension is common in the setting of acute cerebral infarction. In a series of 334 consecutive patients admitted for acute stroke, the blood pressure was elevated in 84% of the patients on the day of admission. Even without specific antihypertensive treatment, the blood pressure decreased spontaneously by an average of 20 mm Hg systolic and 10 mm Hg diastolic in the 10 days following the acute event.[171] This early elevation in blood pressure most likely represents a physiologic response to brain ischemia. Decreases in blood pressure accompany recovery of brain function.

Because of the known benefits of antihypertensive therapy with regard to stroke prevention, it has been assumed that reduction in blood pressure would benefit patients with acute cerebral infarction. Unfortunately, because treatment of hypertension in this setting has never been evaluated in a prospective, randomized trial, there are no good data to guide management. Moreover, there is no evidence to suggest that rapid reduction of blood pressure is beneficial. In fact, several cases have been reported in which worsening of the patient's neurologic status was apparently precipitated by emergency treatment of hypertension.[172,173] The rationale for not treating hypertension in acute ischemic strokes is based on concerns regarding impairment in autoregulation of cerebral blood flow in this setting.[173,174] In normal individuals, cerebral blood flow is maintained constant at mean arterial pressures ranging between 60 and 120 mm Hg. However, in patients with chronic hypertension as well as older adult patients, the curve is shifted such that the lower limit of autoregulation occurs at a higher mean arterial pressure. Furthermore, there is evidence that local autoregulation of cerebral blood flow is disturbed in the so-called ischemic penumbra that surrounds an area of acute infarction.[173,174] Without intact autoregulation, the regional blood flow becomes critically dependent on the perfusion pressure. Thus, to some extent, the presence of hypertension may be beneficial in the setting of acute cerebral infarction, whereas reduction of blood pressure may cause a regional decrease in blood flow with extension of the infarct.

The recently published SCAST trial examined whether careful blood pressure reduction with the angiotensin-receptor blocker candesartan is beneficial in the treatment of patients with acute stroke accompanied by elevated blood pressure.[175] Participants were recruited from 146 centers in nine northern European countries. Patients older than 18 years with acute stroke (ischemic or hemorrhagic) and systolic blood pressure of 140 mm Hg or higher were initiated on study drug or placebo therapy within 30 hours of onset of symptoms. Patients were randomly allocated to candesartan ($n = 1017$) or placebo treatment ($n = 1012$) for 7 days, with doses increasing from 4 mg on day 1 to 16 mg on days 3 to 7. There were two coprimary outcome variables: the composite endpoint of vascular death, myocardial infarction, or stroke within the first 6 months; and the functional outcome at 6 months. During the 7-day treatment period, blood pressures were significantly lower in the candesartan group (147/82 mm Hg, standard deviation [SD] 23/14 mm Hg) compared to the placebo group (152/84 mm Hg, SD 22/14 mm Hg; $P < .0001$). During the 6 months of follow-up, the risk of the composite vascular endpoint did not differ between treatment groups (candesartan, 120 events, versus placebo, 111 events; adjusted hazard ratio 1.09, 95% CI 0.84–1.41; $P = .52$). Analysis of functional outcomes suggested a higher risk of poor outcomes in the candesartan group (adjusted common OR 1.17, 95% CI 1.00–1.38; $P = .048$, not significant at $P \leq .025$ level). The observed effects were similar for all prespecified secondary endpoints including death from any cause, vascular death, ischemic stroke, hemorrhagic stroke, stroke progression, myocardial infarction, symptomatic hypotension, and renal failure. The authors conclude that there was no indication that careful blood pressure reduction with candesartan in the setting of acute stroke is beneficial; if anything, the evidence suggested a harmful effect of blood pressure reduction.

A recent metaregression analysis of the differences in on-treatment blood pressure and odds ratio for outcomes after acute stroke has been performed.[176] In an analysis of 37 trials involving 9008 patients, a U or J shaped relationship was identified amongst on-treatment blood pressure differences and early or 90-day death rates. Although large increases in blood pressure were associated with worse outcomes, modest reductions in blood pressure were beneficial in this large observational study.

Because there is no evidence that mild to moderate hypertension has a deleterious effect on the outcome of cerebral infarction during the acute stage, it is probably wise 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 over the first week without specific therapy.[171] On the other hand, if hypertension persists for more than 3 weeks in a patient with a completed stroke, gradual reduction of blood pressure into the normal range can be accomplished safely. The goal of long-term antihypertensive treatment in hypertensive stroke survivors is the prevention of stroke recurrence. The benefits of antihypertensive therapy in secondary stroke prevention are uncertain, but large clinical trials are in progress that should provide helpful guidelines for clinical practice.

Although benign neglect of mild to moderate hypertension is prudent in the setting of acute cerebral infarction, there may be certain indications for active treatment of hypertension. When the diastolic blood pressure is sustained at more than 130 mm Hg, many authorities recommend cautious reduction of the systolic blood pressure to 160 to 170 mm Hg and diastolic to 100 to 110 mm Hg with a short-acting parenteral agent such as sodium nitroprusside.[173,177–179] Stroke accompanied by other hypertensive crises such as acute myocardial ischemia or left ventricular dysfunction with acute pulmonary edema is also an indication for cautious blood pressure reduction.[173,178] Stroke due to carotid occlusion caused by aortic dissection mandates aggressive blood pressure reduction to prevent propagation of the dissection.[173,178] In some patients with severe hypertension,

it may be impossible to distinguish between hypertensive encephalopathy and cerebral infarction on clinical grounds. Because rapid lowering of the blood pressure may be life-saving in the patient with hypertensive encephalopathy, a cautious diagnostic trial of blood pressure reduction with a short-acting parenteral antihypertensive agent, such as sodium nitroprusside, may be indicated.[178] In patients who have suffered a stroke and require anticoagulation therapy, moderate control of severe hypertension into the 160 to 170 mm Hg systolic and 100 to 110 mm Hg diastolic range may also be prudent. In the severely hypertensive patient with progressing stroke in whom continued deterioration is believed to be secondary to concomitant cerebral edema, cautious blood pressure reduction may be warranted. Appropriate management of such patients may require continuous intracranial as well as intra-arterial pressure monitoring so that cerebral perfusion pressure can be optimized.[178]

It has been demonstrated that sodium nitroprusside, given at a dose that reduced mean arterial pressure by 10 mm Hg, significantly inhibited platelet aggregation and adhesion molecule expression and improved regional cerebral blood flow in patients with acute ischemic stroke.[180] These findings were attributed to beneficial effects of nitric oxide on platelet function and local vasodilation in the area of the ischemic penumbra.

In the setting of acute cerebral infarction, hypertension tends to be very labile and exquisitely sensitive to hypotensive therapy. Even modest doses of oral antihypertensive agents may cause profound and devastating overshoot hypotension.[172] Antihypertensive treatment, when indicated, should be initiated with extreme caution using small doses of short-acting agents such as sodium nitroprusside. Use of oral or sublingual nifedipine may be associated with overshoot hypotension resulting in extension of the infarct and is contraindicated for the treatment of hypertension accompanying acute cerebral infarction. Oral clonidine loading is also contraindicated because it may induce overshoot hypotension or lead to sedation, which will interfere with assessment of mental status. It had been proposed that there the calcium channel blocker nimodipine, which is a cerebral vasodilator, might theoretically minimize arterial spasm and therefore improve cerebral ischemia. However, a large controlled clinical trial demonstrated no improvement in outcome in patients with thrombotic stroke treated with nimodipine when compared to placebo treatment.[181]

Intracerebral Hemorrhage

Hypertension is a major risk factor for intracerebral hemorrhage. The small-diameter, penetrating cerebral end arteries are especially vulnerable to the deleterious effects of hypertension because they arise directly from the main arterial trunks.[170] The most common sites of hypertension-associated hemorrhage include the basal ganglia, pons, thalamus, cerebellum, and deep hemispheric white matter.[182] Lacunar infarcts arise from the same vessels and are similarly distributed.

Hypertensive hemorrhage most often occurs in patients older than 50 years of age. Intracerebral hemorrhage characteristically begins abruptly with headache and vomiting followed by steadily increasing focal neurologic deficits and alteration of consciousness.[182] More than 90% of hemorrhages rupture through brain parenchyma into the ventricles, producing a bloody CSF.[182] Patients presenting with acute intracerebral hemorrhage invariably have elevated blood pressure. In fact, the finding of a normal or low blood pressure makes the diagnosis of intracerebral hemorrhage unlikely.[182] In contrast to cerebral infarction, the blood pressure does not tend to decrease spontaneously during the first week after the event.[171] Once the hemorrhage has occurred, 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, it is most often due to herniation caused by the expanding hematoma and surrounding edema.

Small hemorrhages, which may be clinically indistinguishable from cerebral infarction, probably require no specific therapy.[170] The issue of treatment of hypertension in the setting of a large (greater than 3 cm) intracerebral hemorrhage is controversial. There is almost always a rise in intracranial pressure accompanied by a reflex increase in systemic blood pressure.[171] Because cerebral perfusion pressure is a function of the difference between systemic arterial pressure and intracranial pressure, reduction of blood pressure may compromise cerebral perfusion. Furthermore, the hematoma impairs the local autoregulatory response in the surrounding area of marginal ischemia.[173] Because there is no good evidence that persistent hypertension promotes further bleeding, some authorities strongly advise against treating hypertension in patients with intracerebral hemorrhage.[172] On the other hand, cerebral vasogenic edema may develop as a consequence of an abrupt, severe increase in blood pressure,[170] and treatment of hypertension may be beneficial by virtue of a reduction in cerebral edema and intracranial pressure. Thus, in deciding to treat hypertension, a precarious balance must be struck between prevention of cerebral edema on the one hand, and deleterious reduction of cerebral blood flow on the other. In a study of eight patients with intracerebral hemorrhage treated with trimethaphan, cerebral blood flow measurements revealed that the cerebral autoregulation curve was intact but shifted such that the lower limit of autoregulation was at 80% of the initial level of blood pressure.[183] Thus, a 20% decrease in mean arterial pressure should be considered the maximal reduction of blood pressure during the acute stage. Active treatment of the blood pressure should only be undertaken in the intensive care environment where intracranial pressure and intra-arterial pressure can be closely monitored.[170,184]

Although current specific therapeutic guidelines for blood pressure treatment in intracerebral hemorrhage are not based on strong evidence, a large ongoing therapeutic trial has reported on the value of intensive blood pressure reduction in acute cerebral hemorrhage—the INTERACT Trial.[184] Patients with acute hemorrhage were randomized

within 6 hours to targeted systolic blood pressure of 140 mm Hg (intensive group) or to targeted systolic blood pressure of 180 mm Hg (guideline group). The primary endpoint was hematoma growth at 24 hours. At 24 hours the achieved blood pressure was 146 mm Hg in the intensive group and 157 mm Hg in the guideline group. Hematoma growth was reduced in the intensive group with an absolute risk reduction of 8% ($P < .05$). There were no differences in adverse events between the two groups. The authors concluded that early blood pressure lowering in hemorrhagic stroke is feasible, safe, and reduces hematoma growth. It will be important to determine if these results yield better functional outcomes in further larger trials.

The drug of choice for the management of hypertension in the setting of intracerebral hemorrhage is a matter of debate. Sodium nitroprusside has traditionally been regarded as the best agent because its brief duration of action allows for rapid titration with avoidance of the catastrophic consequence of sustained overshoot hypotension.[179] However, concern has been expressed that because sodium nitroprusside causes an increase in venous capacitance as well as cerebral arterial vasodilation, the resulting increase in cerebral blood volume may cause a further elevation of intracranial pressure.[185,186] Other cerebral vasodilators such as intravenous nitroglycerin, hydralazine, or calcium channel blockers also can cause potentially deleterious elevations of intracranial pressure in patients with compromised intracranial compliance due to intracranial disease.[186] Because labetalol and urapidil (a postsynaptic α-receptor blocker) may not alter intracranial pressure, they have been recommended for treatment of hypertension in patients undergoing neurosurgery.[186] Unfortunately, these agents have the potential to cause overshoot hypotension, which may be difficult to quickly reverse. Thus, despite the theoretic risk of elevation of intracranial pressure, sodium nitroprusside remains the treatment of choice when severe hypertension must be treated in the patient with intracerebral hemorrhage because its brief duration of action allows for cautious, graded blood pressure reduction, which can be quickly reversed if the patient's neurologic status deteriorates or a further increase in intracranial pressure occurs. Of interest, some patients with cerebral infarction or hemorrhage have extreme elevations of catecholamine levels that may render hypertension refractory to sodium nitroprusside in the absence of concomitant beta-blocker therapy.[187]

A recent prospective randomized trial compared safety and efficacy of intravenous nicardipine and sodium nitroprusside drip for control of hypertension in the neurosurgical intensive care unit in patients with subarachnoid hemorrhage or intracerebral hemorrhage.[188] One hundred and sixty-three patients were randomized including 89 in the sodium nitroprusside group and 74 in the nicardipine group. Both drugs proved safe and effective for control of hypertension. However, patients randomized to nicardipine had fewer dose adjustments per day: 5.7 versus 8.8 in the nitroprusside group ($P = .0012$). There were fewer additional medications per day to maintain blood pressure control in the nicardipine group: 1.4 versus 1.9 ($P = .043$). Moreover, blood pressure control was similar in the two groups: 66% versus 69% of the time within study-defined parameters for nicardipine versus nifedipine respectively ($P =$ not significant).

Another recent study compared the clinical outcomes between patients with intracerebral hemorrhage treated with different antihypertensive medications during the first 24 hours after admission.[189] Analysis of the Premier database, a nationally representative hospital discharge database, was used to compare discharge outcomes, length of stay, and cost of hospitalization between groups of patients with intracerebral hemorrhage who were treated with either intravenous nicardipine or nitroprusside infusion. Logistic and linear regression analyses were performed to adjust for baseline risk of mortality between the two groups. A total of 12,767 admissions with primary diagnosis of intracerebral hemorrhage were identified. Nicardipine was administered in 926 patients (7.3%) and nitroprusside was administered in 530 (4.3%). There were no differences in baseline disease severity or risk of mortality between the two groups. After adjustment for baseline risk of mortality, the risk of in-hospital mortality was higher among patients treated with nitroprusside compared with nicardipine (OR 1.7, 95% CI 1.3–2.2). There was no difference in length of stay or total hospital costs in the multivariate analysis. The authors conclude that nicardipine compared with nitroprusside during the first 24 hours after intracerebral hemorrhage was associated with a significantly reduced risk of in-hospital mortality.

Cerebellar hemorrhage represents a neurosurgical emergency requiring prompt diagnosis and treatment.[170] Typically, patients complain of the sudden onset of dizziness, nausea, vomiting, headache, and difficulty walking. Truncal ataxia, nystagmus, and ipsilateral sixth nerve paresis may be present. If the process continues unchecked, brainstem compression or herniation produces progressive stupor and coma. The untreated mortality is extremely high. The diagnosis can usually be confirmed by computerized tomography. Treatment consists of emergency suboccipital craniotomy with evacuation of the hematoma.[170]

Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) accounts for less than 10% of all cerebrovascular accidents. Rupture of a congenital aneurysm is the most common cause. Rupture is heralded by the sudden onset of a profound headache and is often followed by brief syncope. If the mass of the hemorrhage is large, patients rapidly become comatose. As the hemorrhage diffuses throughout the subarachnoid space, the patient may awaken and experience headache, nausea, vomiting, and seizures. Within 24 hours, nuchal rigidity and other meningeal signs develop. Initially, neurologic findings are nonfocal. CT can be used to confirm the diagnosis.

Recurrent hemorrhage is a potential complication associated with high mortality. Whether treatment of hypertension after SAH reduces the risk of recurrent bleeding or

improves prognosis is uncertain. In the setting of elevated intracranial pressure or cerebral arterial vasospasm, hypertension may actually be protective because it helps to maintain cerebral perfusion pressure. Thus, reduction of the blood pressure could conceivably result in aggravation of cerebral vasospasm and ischemia.

Early surgical repair of the aneurysm has reduced the incidence of rebleeding in patients with SAH. In fact, delayed cerebral ischemia due to cerebral arterial vasospasm has been found to be the most important cause of morbidity and mortality in patients who survive the initial hemorrhage.[190] Vasospasm, which is probably caused by the irritating effects of blood in the subarachnoid space closely opposed to the large arteries, usually develops 4 to 12 days after the acute hemorrhage. Symptoms include a gradual deterioration of the level of consciousness, accompanied by focal neurologic deficits.

Surgical clipping of the aneurysm is usually undertaken as soon as possible to prevent rebleeding.[190,191] There is conflicting evidence as to whether or not postoperative treatment with intravascular volume expansion, in conjunction with deliberate induction of arterial hypertension using dopamine or dobutamine, may be an effective means of reversing the ischemic neurologic deficits caused by cerebral vasospasm.[192,193]

Nimodipine, a 1,4-dihydropyridine calcium channel blocker, has been approved for the prevention and treatment of delayed cerebral ischemia caused by subarachnoid hemorrhage from ruptured congenital aneurysms. Nimodipine is highly lipid-soluble and readily crosses the blood–brain barrier.[194] It dilates cerebral blood vessels at concentrations lower than those required for dilation of the peripheral vasculature.[194] Thus, it may dilate intracerebral vessels at doses that do not result in a significant reduction in mean arterial pressure. Furthermore, inhibition of calcium uptake by neurons may also protect against ischemic injury at the cellular level, independent of an effect on cerebral blood flow.[194] Nimodipine has been shown, in randomized, placebo-controlled trials, to reduce the severity of neurologic deficits resulting from vasospasm in patients who have had a recent SAH.[194–196] The recommended dosage is 60 mg orally every 4 hours for 21 consecutive days beginning within 96 hours of the SAH. The liquid content of the capsules can be given through a nasogastric tube in unconscious patients. The optimal timing of surgery in nimodipine-treated patients has not yet been defined.

CATECHOLAMINE-RELATED HYPERTENSIVE CRISES

Hypertensive Crises with Pheochromocytoma

The diagnosis and treatment of pheochromocytoma are discussed in detail in Chapter 43. The comments here are restricted to treatment of hypertensive crises in patients with pheochromocytoma, with emphasis on the perioperative management of hypertension. In the majority of patients, pheochromocytoma causes sustained hypertension that occasionally enters the malignant phase. In roughly 30% of patients, paroxysmal hypertension is present. Paroxysms usually occur spontaneously and consist of severe hypertension, headache, profuse diaphoresis, pallor of the face, coldness of the hands and feet, palpitations, and abdominal discomfort. Marked elevation of blood pressure can lead to intracerebral hemorrhage, hypertensive encephalopathy, or acute pulmonary edema.[198] Prompt reduction of blood pressure is mandatory to prevent these life-threatening complications. Although the nonselective α-adrenergic receptor blocker phentolamine is often cited as the treatment of choice for pheochromocytoma-related hypertensive crises, sodium nitroprusside is equally effective.[198,199] Phentolamine is given in 5- to 10-mg intravenous boluses every 5 minutes as necessary to control blood pressure. Given its short duration of action, a continuous infusion of phentolamine can also be utilized. After the blood pressure has been controlled with sodium nitroprusside or phentolamine, intravenous β-adrenergic receptor blockers such as esmolol and metoprolol can 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.

Skillful preoperative management of blood pressure and volume status is clearly a prerequisite to successful surgical intervention.[198–200]Usually, the nonselective α-blocker phenoxybenzamine is administered for 1 to 2 weeks prior to elective surgery. The initial dose of 10 mg twice daily is increased every other day until normotension, accompanied by moderate (15 mm Hg) asymptomatic orthostatic hypertension, has been attained and paroxysms are well controlled.[199,200] The last dose of phenoxybenzamine is usually administered at 10 PM on the evening before surgery. After adequate α-blockade has been achieved, oral beta-blocker therapy can be initiated if needed to control tachycardia. Oral or intravenous beta-blockers should never be administered before adequate α-adrenergic blockade has been achieved. Administration of a beta-blocker to patients with catecholamine-secreting tumors can lead to severe hypertension with acute pulmonary edema as the result of intense α-adrenergic-mediated vasoconstriction that is no longer opposed by β-adrenergic vasodilatory stimuli. Prazosin, a selective α_1-antagonist, has been used for preoperative management of hypertension.[201] However, hypertensive crises responsive to low-dose phenoxybenzamine have been observed in patients receiving apparently adequate α-blockade with prazosin.[202] Labetalol has also been advocated for the preoperative management of hypertension in patients with pheochromocytoma.[203] However, hypertensive crises precipitated by the use of labetalol have been reported.[204] The paradoxical increase in blood pressure is due to the fact that labetalol exhibits more potent β-blockade than α-blockade.

Careful attention to volume status is imperative in the preoperative period.[199,200] Alleviation of the chronic state of catecholamine-induced vasoconstriction by α-blockade results in increases in both arterial and venous capacitance. Preoperative volume expansion guided by measurements of central venous pressure or pulmonary capillary wedge pressure has been advocated to reduce the severity of intraoperative hypotension.[200] However, other authors maintain that a high-salt diet or infusions of crystalloid are usually not necessary in the majority of patients during the preoperative period because treatment with α-adrenergic blockade for 1 to 2 weeks alleviates the chronic state of vasoconstriction and allows for spontaneous restoration of normal plasma volume.[198] Moreover, caution has been advised if intravenous fluids are administered during the preoperative period because pulmonary edema can occur if an underlying catecholamine-induced cardiomyopathy is present.[198]

Cardiac status should be evaluated carefully in the preoperative period. Approximately 25% of patients with catecholamine-secreting tumors have some degree of cardiomyopathy with biventricular dysfunction caused either by a direct toxic effect of catecholamines on the myocardium or indirectly by chronic hypertension.[206] This catecholamine-induced cardiomyopathy is associated with an increased risk of sudden death from arrhythmias, as well as increased surgical risk. Thus, preoperative evaluation should include echocardiography to assess ventricular function. The cardiomyopathy is usually reversible with adequate preoperative chronic adrenergic blockade. Surgical intervention should generally be deferred until serial echocardiograms confirm that ventricular function has improved in response to treatment with adrenergic blocking drugs.

During surgery, rapid and wide fluctuation in blood pressure should be anticipated.[199] Adequate premedication should be used to minimize the risk of sympathetic activation during endotracheal intubation and induction of anesthesia. Diazepam and short-acting barbiturates are the agents of choice for premedication.[199] Droperidol, phenothiazines, and morphine are contraindicated because they can cause catecholamine release. Atropine should be avoided because its vagolytic effect results in tachycardia in the setting of high-circulating catecholamine levels.

Careful intraoperative monitoring of intraarterial blood pressure, cardiac output, pulmonary capillary wedge pressure, and systemic vascular resistance is required to manage rapid swings in blood pressure.[199] Despite adequate preoperative α-blockade with phenoxybenzamine, severe hypertension can occur during intubation or intraoperatively due to catecholamine release during tumor manipulation. Although intermittent bolus phentolamine has been advocated in this setting, prolonged α-blockade may predispose to significant hypotension following tumor devascularization.[199] Therefore, sodium nitroprusside, with its immediate onset and short duration of action, is the agent of choice for controlling acute hypertension during pheochromocytoma surgery.[199] Infusions of esmolol can be used for short-term control of arrhythmias.[198,199]

At the opposite end of the spectrum, severe intraoperative hypotension can occur. Hypotension or even frank shock can supervene following isolation of tumor venous drainage from the circulation, with a resultant abrupt decrease in circulating catecholamine levels. This hypotension is caused by a precipitous reduction in vascular tone, which can be aggravated further by operative blood loss, downregulation of adrenergic receptors in response to chronic increases in catecholamines, α-adrenergic blockade, or impaired heart rate response resulting from β-adrenergic blocking drugs.[199] Volume expansion with crystalloid, colloid, or blood as needed is the recommended treatment for intraoperative hypotension. Volume repletion should be guided by measurements of pulmonary capillary wedge pressure and cardiac output. Pressors should only be employed when hypotension is unresponsive to adequate volume repletion.[199] The risk of hypotension due to hypovolemia extends into the postoperative period during which close monitoring of volume status is essential. In the postoperative period, required volume replacement not uncommonly exceeds measured fluid losses.[199]

Hypertensive Crises Secondary to Withdrawal of Antihypertensive Therapy

Abrupt discontinuation of high doses of centrally acting antihypertensive agents such as clonidine,[205] methyldopa,[206] and guanabenz[205,207] can produce a withdrawal syndrome characterized by sympathetic overactivity.[208] Symptoms consisting of headache, nausea, restlessness, agitation, insomnia, and tremor usually begin 12 to 72 hours after discontinuation of the drug. Occasionally, this withdrawal syndrome is accompanied by a rapid increase in blood pressure to above pretreatment levels (overshoot hypertension).[209] The abrupt rise in blood pressure can precipitate a hypertensive crisis with hypertensive encephalopathy or acute pulmonary edema.

The symptoms that develop following cessation of centrally acting α-receptor agonists are suggestive of sympathetic overactivity. It has been postulated that the syndrome may be related to excessive circulating catecholamine levels.[208] Because the antihypertensive action of central α-agonists is due to a reduction in catecholamine release from nerve terminals, abrupt discontinuation may provoke a sudden catecholamine surge. Increased plasma and urine catecholamine levels have been found after abrupt discontinuation of high-dose clonidine. The renin–angiotensin system may also be involved in withdrawal phenomenon. As clonidine and methyldopa suppress PRA, it is possible that a rebound increase in PRA and angiotensin II could mediate the hypertensive overshoot following drug withdrawal.[210]

In general, withdrawal symptoms or rebound hypertension occur only after cessation of large doses of drugs. Withdrawal symptoms rarely appear after discontinuation of clonidine in doses less than 1.2 mg per day.[211] The average dose of guanabenz in the reported cases of withdrawal syndrome was 48 mg per day.[207] However, the withdrawal syndrome can occasionally be precipitated by cessation of lower

doses of drugs. This is especially apt to occur in patients with underlying renal insufficiency or renovascular hypertension.[210] Patients treated with beta-blockers may be predisposed to develop severe hypertension during withdrawal of centrally acting α-agonists.[212] Beta-adrenergic receptor blockade inhibits the vasodilatory effect of β_2-receptors on the peripheral vasculature, leaving vasoconstrictor α_1-receptors unopposed.

Treatment of antihypertensive drug withdrawal syndromes should be individualized. In patients with generalized symptoms of sympathetic overactivity but without excessive blood pressure elevation, reinstitution of the previously administered drug is usually all that is required.[210] However, if the withdrawal syndrome is associated with severe hypertension, hypertensive encephalopathy, or acute pulmonary edema, rapid control of blood pressure with parenteral antihypertensive agents is imperative. Sodium nitroprusside or phentolamine should be used for the management of these hypertensive crises. After the blood pressure is controlled with parenteral agents, oral clonidine, guanabenz, or methyldopa should be restarted. The offending drug should then be gradually withdrawn with close monitoring for withdrawal symptoms and rebound hypertension. Another oral antihypertensive regimen, preferably without a beta-blocker, should be initiated simultaneously.

THE CONTROVERSY OVER GRADUAL VERSUS RAPID REDUCTION OF BLOOD PRESSURE

Some authors have cautioned against rapid lowering of blood pressure in patients with hypertensive crises and have recommended a more gradual reduction of blood pressure.[213,214] The case for gradual reduction of blood pressure is based largely on the finding of altered autoregulation of cerebral blood flow in hypertensive patients and scattered case reports of serious neurologic sequelae resulting from overly aggressive reduction of blood pressure in patients with severe hypertension or hypertensive crises.[215–221]

In both hypertensive and normotensive individuals, cerebral blood flow is maintained constant, at approximately 50 mL/minute/100 g of brain tissue, over a wide range of perfusion pressures, by virtue of various intrinsic and neurohumoral autoregulatory mechanisms. The lower limit of cerebral blood flow autoregulation is the blood pressure below which autoregulatory vasodilation becomes maximal and cerebral blood flow decreases. In normotensive subjects, the lower limit of autoregulation is a mean arterial pressure of 60 to 70 mm Hg. In chronically hypertensive patients, the lower limit of autoregulation is shifted so that autoregulation fails and cerebral blood flow decreases at a higher blood pressure than in normotensive individuals.[222,223] This effect may be the result of hypertension-induced changes in the cerebral arterioles. In animal models, chronic hypertension causes hypertrophy of the walls of cerebral vessels with a reduction in internal diameter. Moreover, during chronic hypertension, cerebral arterioles undergo structural remodeling, which results in a smaller external diameter and encroachment on the vascular lumen.[224]

On the one hand, these structural changes are protective in that the thickened cerebral arterioles are able to maintain constant cerebral blood flow at a higher perfusion pressure than would be tolerated by normotensive individuals. In this regard, in chronically hypertensive individuals, the mean arterial pressure at which autoregulatory vasoconstriction gives way to pressure-induced forced vasodilation and hyperperfusion—that is, the upper limit of cerebral blood flow autoregulation—is shifted to a higher level compared to the upper limit in normotensive individuals (see discussion of breakthrough theory in the above section on hypertensive encephalopathy). However, as a consequence of these structural changes, the arterioles are not able to dilate fully at low mean arterial pressures, which could predispose hypertensive patients to cerebral ischemia if the blood pressure is lowered excessively.

Fortunately, with long-term control of blood pressure these changes in cerebral arterioles appear to be at least partially reversible given the observation that patients with previously severe but adequately treated hypertension have a lower limit of autoregulation, which is shifted toward the range for normotensive subjects (Table 44.6).[222]

The upward shift in the autoregulatory curve in patients with chronic hypertension is one of the major arguments put forward by those who favor gradual reduction of blood pressure in patients with hypertensive crises.[222] However, the clinical importance and therapeutic implications of this shift in the autoregulatory curve may have been overemphasized. The demonstration of hypertensive adaptation of cerebral autoregulation should not be interpreted to mean that acute reduction of blood pressure in hypertensive crises is unwise. In the various hypertensive crises in which rapid reduction of blood pressure is indicated (see later), the proven benefits of acute reduction of blood pressure (i.e., decreased risk of intracerebral hemorrhage, hypertensive encephalopathy, or acute pulmonary edema) clearly outweigh the theoretic risk of blood pressure reduction (i.e., possible cerebral ischemia).

In practice, moderate, controlled reduction of blood pressure in hypertensive crises rarely causes cerebral ischemia. This clinical observation may be explained by the fact that even though the autoregulatory curve is shifted toward a higher blood pressure in chronically hypertensive patients, there is still a considerable difference between the presenting blood pressure and the lower limit of autoregulation (Table 44.6). Strandgaard[223] has studied the autoregulation of cerebral blood flow during controlled hypotension produced with trimethaphan and a 25-degree head-up tilt in 13 patients with untreated or ineffectively treated hypertension. At least eight of these patients had grade III or grade IV changes on funduscopy consistent with the diagnosis of malignant hypertension. The control groups included nine patients who had been severely hypertensive in the past but whose blood pressure was effectively controlled at the time of the study, and 10 normotensive subjects. Baseline

44.6 Autoregulation of Cerebral Blood Flow During Trimethaphan-Induced Hypotension[a]

Group	MAP (mm Hg)		Percent of Resting MAP %	
	Resting Level	Autoregulation	Tolerated MAP	Autoregulation	Tolerated
Uncontrolled severe hypertensives (n = 13)	145 ± 17	113 ± 17[b,c]	65 ± 10[b]	79 ± 10	45 ± 6
Controlled hypertensives (n = 9)	116 ± 18	96 ± 17	53 ± 18	72 ± 29	46 ± 16
Normotensives (n = 10)	98 ± 10	73 ± 9	43 ± 8	74 ± 12	45 ± 12

[a]Values given as mean ± SD.
[b]$P < .01$ for difference between normotensives and uncontrolled hypertensives.
[c]$P < .01$ for difference between controlled and uncontrolled hypertensives.
MAP, mean arterial pressure.
Adapted from Gifford RW Jr. Effect of reducing elevated blood pressure on cerebral circulation. Hypertension. 1983;5[Suppl III]:III-17, with permission.)

mean arterial pressures in the three groups were 145 ± 17, 116 ± 18, and 98 ± 10 mm Hg, respectively (Table 44.6). The lower limit of mean arterial pressure at which autoregulation of cerebral blood flow failed was 113 ± 17 mm Hg in uncontrolled hypertensives, 96 ± 17 mm Hg in controlled hypertensives, and 73 ± 9 mm Hg in normotensive individuals. Although the absolute level at which autoregulation failed differed substantially in the three groups, the percentage reduction of mean arterial pressure at which autoregulation failed was similar. The mean arterial pressure at the lower limit of autoregulation was 79 ± 10% of the resting mean arterial pressure in the uncontrolled hypertensives, 72 ± 29% in the controlled hypertensive group, and 74 ± 12% in the normotensive group. Thus, a reduction in mean arterial pressure of approximately 20% to 25% from the baseline level was required in each group to reach the lower limit of autoregulation. Therefore, even in uncontrolled hypertensive patients, there was a considerable safety margin before the limit of autoregulation was reached. Another important observation from this study was that symptoms of cerebral hypoperfusion did not occur until the blood pressure was reduced substantially below the lower limit of autoregulation.[223] Studies have shown that with normal cerebral blood flow, oxygen extraction is not maximal because oxygen saturation in the jugular venous blood at rest is normally 60% to 70%. Thus, even when the mean arterial pressure is reduced below the lower limit of autoregulation, cerebral metabolism can be maintained and ischemia prevented by increasing oxygen extraction from the blood. The lowest tolerated blood pressure, which was defined as the level at which mild symptoms of brain hypoperfusion were encountered (yawning, nausea, and hyperventilation with hypocapnia), was 65 ± 10 mm Hg in patients with uncontrolled hypertension, 53 ± 18 mm Hg in patients with controlled hypertension, and 43 ± 8 mm Hg in normotensive subjects. These values were 45 ± 6%, 46 ± 16%, and 45 ± 12% of the resting baseline mean arterial pressures, respectively. Thus, symptoms of cerebral hypoperfusion did not occur until the mean arterial pressure was reduced by an average of 55% from the resting level (Table 44.6).

In summary, with regard to the shift in cerebral autoregulation in chronically hypertensive patients, there is a therapeutic threshold above which the blood pressure can be reduced safely in patients with hypertensive crises who require immediate control of hypertension. Strandgaard concludes that the upward shift in cerebral autoregulation should not be taken as a warning against aggressive antihypertensive therapy in hypertensive crises. It merely implies that the initial treatment should be aimed at partial reduction but not complete normalization of blood pressure.[222,223]

The second argument used to support the recommendation for gradual reduction of blood pressure is based on case reports of the occurrence of acute neurologic sequelae during rapid blood pressure reduction in the treatment of severe hypertension or hypertensive crises.[215–221]

Franklin reviews 19 reported cases of neurologic complications following aggressive antihypertensive therapy.[93] The average age of the patients was 36 years. All had evidence of severe antecedent hypertension with an average mean arterial pressure of 188 ± 19 mm Hg. Malignant hypertension, based on the finding of hypertensive neuroretinopathy, was present in 79% and hypertensive encephalopathy was present in 53% of these patients. Aggressive antihypertensive treatment resulted in a reduction of mean arterial pressure to 84 ± 18 mm Hg. This represented a 56% decrease from the baseline blood pressure level, a level clearly below the predicted autoregulatory range for hypertensive patients. The time course of blood pressure reduction was

within minutes in 26% and over hours in 74% of patients. However, the most critical factor in the development of neurologic sequelae was the long duration of drug-induced overshoot hypotension, which varied from a period of hours to days. Neurologic complications consisted of permanent blindness in 47%, coma in 32%, pyramidal tract signs in 32%, residual neurologic deficits after therapy in 58%, and death in three patients. The majority of these patients (80%) had received a large intravenous bolus of diazoxide. Three patients received no parenteral agents but had sustained hypotension induced with multiple oral agents. Franklin concludes that rather than the rapidity with which blood pressure was reduced, the duration of excessive hypotension was the factor that correlated best with the development of neurologic complications.

In summary, the data suggest that in the treatment of patients with hypertensive crises who require prompt control of blood pressure, potent parenteral agents can be used safely if excessive lowering of blood pressure is avoided. The studies of Strandgaard suggest that autoregulation of cerebral blood flow can be maintained in hypertensive patients as long as the mean arterial pressure is not reduced below 120 mm Hg.[222,223] This value is two standard deviations above the average mean arterial pressure at which patients in the reported series developed neurologic sequelae.

In general, an initial blood pressure reduction to 160 to 170 mm Hg systolic and 100 to 110 mm Hg diastolic or to a mean arterial pressure of 120 to 130 mm Hg can be safely accomplished in patients who require immediate control of blood pressure in the setting of hypertensive crises.[93] Alternatively, the initial antihypertensive therapy can be individualized based on the pretreatment level of blood pressure. In the individual patient, reduction of the mean arterial pressure by 20% should be the initial therapeutic goal. At this level, the blood pressure should still be above the predicted autoregulatory lower limit. Once this goal is obtained, the patient should be carefully evaluated for evidence of cerebral hypoperfusion. Further reduction of blood pressure can then be undertaken if necessary in a controlled fashion based on the overall status of the patient. In previously normotensive individuals in whom acute hypertensive crises develop, such as patients with acute glomerulonephritis complicated by hypertensive encephalopathy, eclampsia, and autonomic hyperreflexia, the autoregulatory curve may not yet be shifted and the initial goal of therapy will often be normalization of the blood pressure.

The use of potent parenteral agents with a rapid onset and short duration of action, such as sodium nitroprusside, has obvious advantages. If overshoot hypotension or neurologic sequelae develop, they can be quickly reversed by allowing the blood pressure to stabilize at a higher level. Agents with a long duration of action all have an inherent disadvantage in that excessive reduction of blood pressure cannot be easily reversed. Thus, diazoxide, labetalol, minoxidil, hydralazine, converting enzyme inhibitors, calcium channel blockers, and central α-agonists should be used with extreme caution in patients requiring rapid blood pressure reduction in order to avoid prolonged overshoot hypotension.

Although in the great majority of hypertensive patients, cautious blood pressure reduction can be undertaken without a significant risk of causing cerebral hypoperfusion, it should be noted that there is one clinical setting in which there is a significant risk of causing cerebral ischemia even with moderate blood pressure reduction. In patients with acute cerebral infarction, because of failure of autoregulation in the surrounding marginally ischemic zone, even moderate blood pressure reduction can be detrimental. Therefore, in acute cerebral infarction, the aforementioned considerations regarding the general safety of acute blood pressure reduction do not apply. The management of hypertension complicating acute cerebral infarction is outlined in the section entitled Hypertension Complicating Cerebrovascular Accident.

PHARMACOLOGY OF DRUGS USEFUL IN THE TREATMENT OF HYPERTENSIVE CRISES

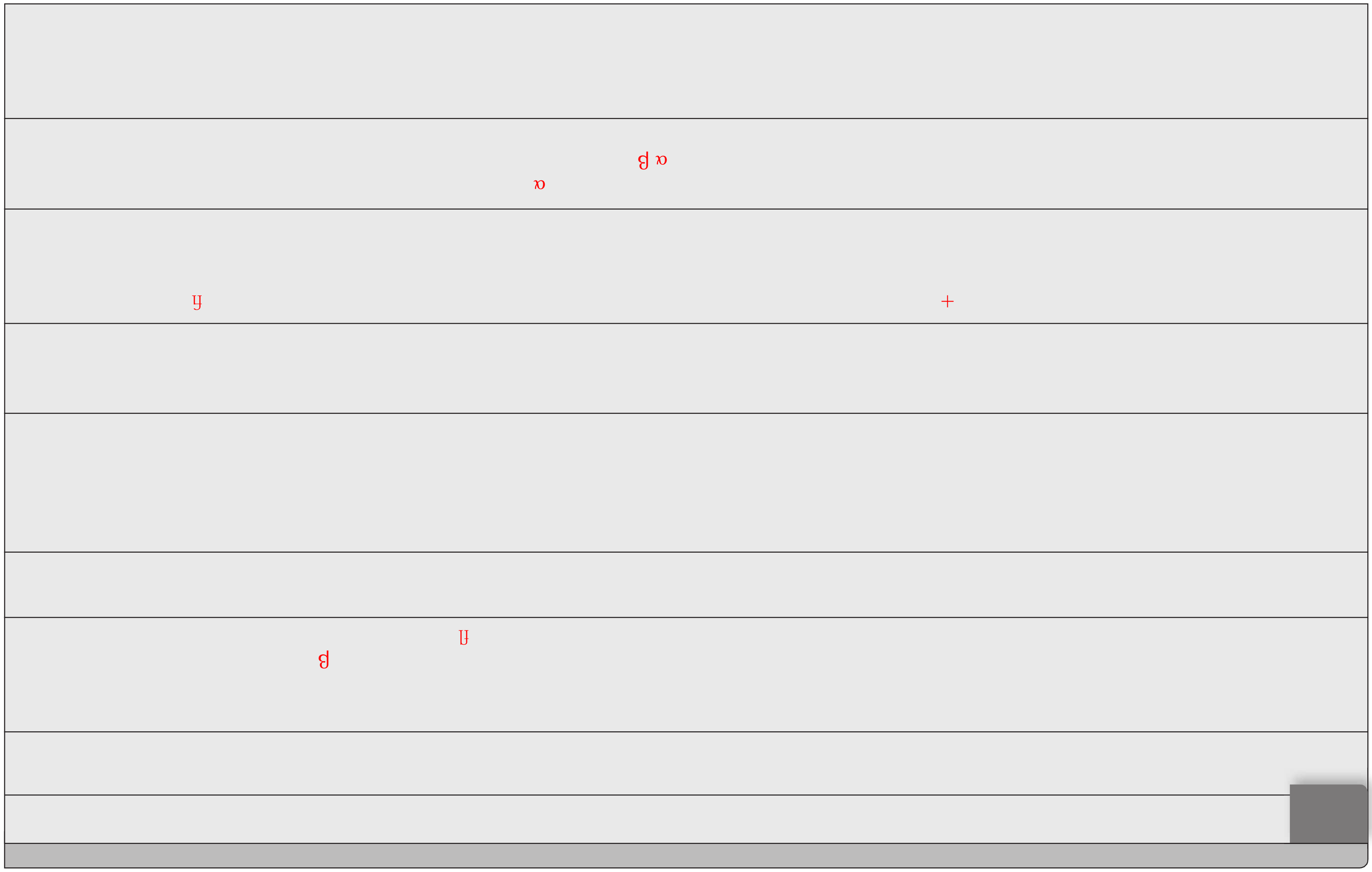
The pharmacopeia of parenteral vasodilators and adrenergic blockers available for the treatment of hypertensive crises is outlined in Table 44.7. Preferred parenteral agents for the treatment of selected hypertensive crises are detailed in Table 44.8.

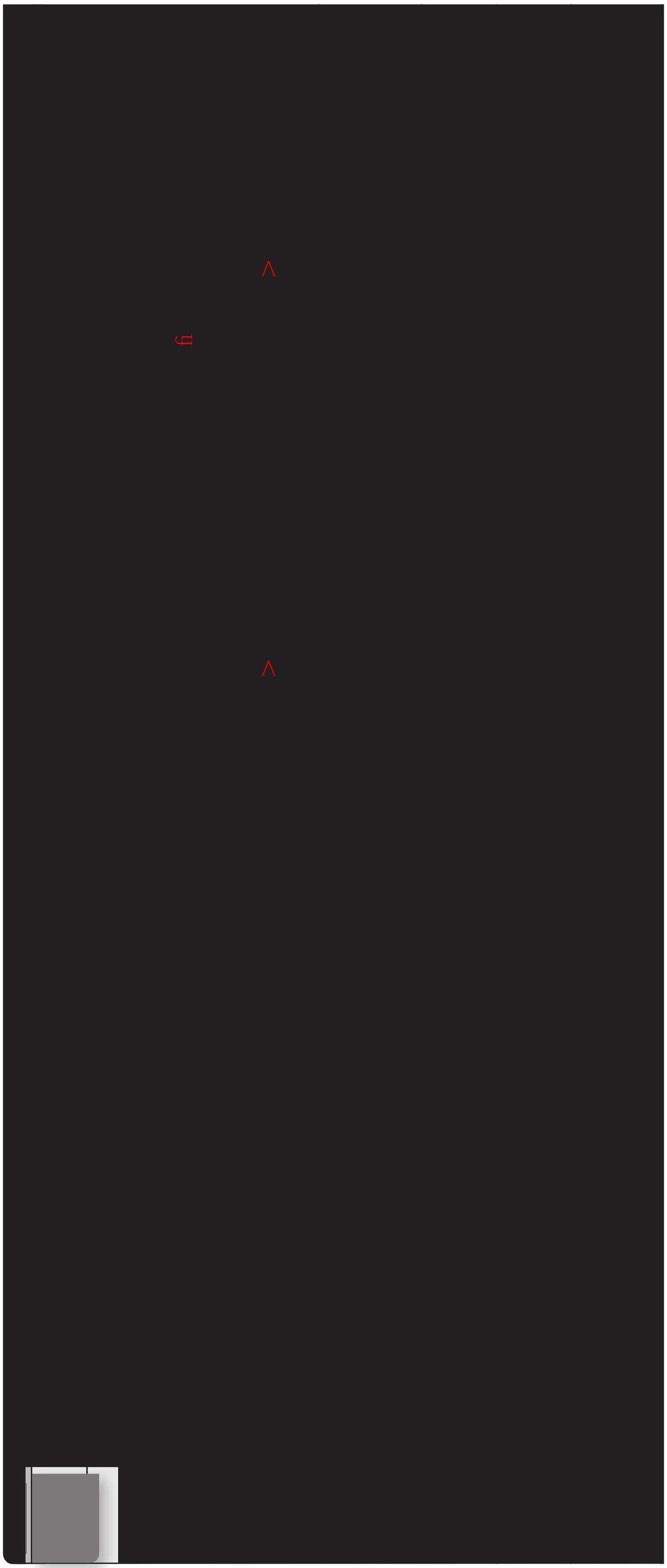
Sodium Nitroprusside

In 1929, intravenous administration of the color indicator sodium nitroprusside was reported to lower blood pressure.[225] Nonetheless, concern that the hypotensive action of the drug was related to the release of cyanide led to a delay in the introduction of the drug. In 1955, intravenous infusion of sodium nitroprusside was shown to be a safe and effective method for achieving short-term blood pressure control.[226] However, it was not until 1974 that sodium nitroprusside (Nipride) was approved for clinical use. Over the ensuing decades, it has remained the drug of choice for the management of virtually all hypertensive crises. Sodium nitroprusside is useful for the management of hypertensive crises due to malignant hypertension, pheochromocytoma, and other catecholamine-related hypertensive crises, hypertensive encephalopathy, acute pulmonary edema, intracerebral hemorrhage, aortic dissection (in combination with a beta-blocker), and perioperative hypertension.[227]

Mechanism of Action

Sodium nitroprusside is a potent intravenous hypotensive agent with an immediate onset and brief duration of action. The site of action is the vascular smooth muscle. It has no direct effect on the myocardium, although it may indirectly affect cardiac performance through alterations in systemic hemodynamics. In therapeutic doses it has no effect on





duodenal or uterine smooth muscle.[226] It has no direct CNS effect. Sodium nitroprusside causes vasodilation of both arteriolar resistance vessels and venous capacitance vessels. Its hypotensive action is the result of a decrease in systemic vascular resistance. Venodilation results in a decrease in venous return; hence, preload is reduced. The combined decrease in preload and afterload reduces left ventricular wall tension and myocardial oxygen demand.

The net effect of sodium nitroprusside on cardiac output and heart rate depends on the intrinsic state of the myocardium.[227] In the absence of congestive heart failure, venodilation and preload reduction can result in a small decrease in cardiac output with a reflex increase in sympathetic tone and heart rate.In contrast, in patients with left ventricular dysfunction and elevated left ventricular end-diastolic volume or pressure, sodium nitroprusside causes an increase in stroke volume and cardiac output as the result of a reduction in afterload and impedance to left ventricular ejection. There is usually a reduction in heart rate as the result of improved cardiac performance.[228–230]

The cellular mechanism of action of nitroprusside has been well defined.[231,232] Nitroprusside is an iron coordination complex with five cyanide moieties and a nitroso group. The action of sodium nitroprusside, as well as that of other nitrogen oxide-containing vasodilators, is mediated by a reaction with cysteine to form nitrosocysteine and other short-acting S-nitrosothiols. Nitrosocysteine, a potent activator of guanylate cyclase, causes cyclic guanosine monophosphate accumulation and relaxation of vascular smooth muscle.

Pharmacokinetics

The hypotensive effect of sodium nitroprusside appears within seconds and is immediately reversible when the infusion is stopped. It is rapidly metabolized, with a reported half-life of 3 to 4 minutes. Cyanide is formed, as a short-lived intermediate product, by direct combination of sodium nitroprusside with sulfhydryl groups in red cells and tissues.[226] 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 unchanged by the kidney with a half-life of 1 week in patients with normal renal function.[227]

Dosage and Administration

The contents of a 50-mg sodium nitroprusside vial should be dissolved in 2 mL of dextrose in water. No other diluent should be used. The stock solution is diluted in 250 mL of dextrose in water to yield a concentration of 200 μg/mL. The container is immediately wrapped in aluminum foil to prevent decomposition on exposure to light. A small portion of the tubing can be left uncovered to observe the solution for color changes during administration. The freshly prepared solution has a faint brownish tint. The nitroprusside molecule reacts with a wide variety of organic and inorganic substances to yield highly colored reaction products. Therefore, the infusion fluid should not be used as a vehicle for the delivery of other drugs. If a color change occurs, the solution should be replaced. Regardless, the solution should be changed every 24 hours.

In patients who are not taking other antihypertensive agents, the average effective dose is 3.0 μg/kg/minute (range, 0.5 to 10.0 μg/kg/minute). The initial infusion rate should be 0.5 μg/kg/minute. The flow rate should be increased in increments of 1 μg/kg/minute every 2 to 3 minutes until the desired hypotensive response is obtained. The solution should be administered by infusion pump or microdrip regulator to allow for precise measurement of flow rate. The blood pressure should be monitored every 30 to 60 seconds during the initial titration and every 15 minutes thereafter. To avoid excessive accumulation of thiocyanate and the risk of cyanide toxicity, the infusion rate should not be increased above 10 μg/kg/minute. Sodium nitroprusside failures are extremely rare, and tachyphylaxis does not occur. Concomitant oral antihypertensive agents should be initiated as soon as possible and the sodium nitroprusside infusion weaned as it becomes effective.

Adequate facilities, equipment, and personnel must be available for close monitoring of blood pressure during sodium nitroprusside administration. Auscultatory or oscillometric pressure is usually adequate, so that intra-arterial pressure monitoring is not routinely required. However, in hypertensive patients with acute myocardial infarction or acute pulmonary edema, hemodynamic monitoring may be required for assessment of left ventricular filling pressure and cardiac output.[227]

Adverse Effects

Nitroprusside is the most effective parenteral agent for the management of hypertensive crises. When properly administered in an intensive care unit setting, it is very safe and clinically significant adverse reactions are uncommon. Overshoot hypotension can result from accidental bolus infusion, faulty infusion equipment, or failure to frequently monitor the blood pressure. However, the hypotensive action is evanescent and hypotension can be reversed easily by slowing or discontinuing the infusion.

The most frequent side effects include anorexia, nausea, vomiting, abdominal cramps, diaphoresis, headache, apprehension, restlessness, and palpitations. Most of these adverse reactions result from rapid blood pressure reduction per se and they usually disappear if the infusion is slowed.

Thiocyanate accumulation and toxicity can occur when a high-dose or prolonged infusion is required, especially in the setting of renal insufficiency. When these factors are present, thiocyanate levels should be monitored and the infusion reduced or discontinued if the plasma level exceeds 10 mg per dL. Thiocyanate toxicity is rare in patients with normal renal function requiring less than 3 μg/kg/minute for less than 72 hours. Symptoms of thiocyanate toxicity include fatigue, anorexia, weakness, tinnitus, blurred vision, and disorientation, which may progress to frank organic

psychosis with hallucinations. Seizures have also been reported. Treatment consists of discontinuing the infusion. Thiocyanate is also efficiently removed by both peritoneal dialysis and hemodialysis.[227]

Cyanide poisoning is a very rare complication of sodium nitroprusside use. Since hepatic clearance of cyanide may be deficient in patients with severe liver disease and in rare conditions such as Leber's optic atrophy or tobacco amblyopia,[233] the use of sodium nitroprusside is contraindicated in these settings. Most of the reported deaths from cyanide poisoning occurred when very high doses of nitroprusside (20 μg/kg/minute) were required for the control of refractory hypertension or in normotensive patients in whom very large doses were used to induce deliberate surgical hypotension.[234,235] The cyanide ion combines with cytochrome c and inhibits aerobic metabolism so that lactic acidosis results. Cyanide toxicity most often occurs within the first 6 to 8 hours of therapy. Cyanide toxicity should be considered if there appears to be increased tolerance to the drug. Tachyphylaxis and an increased anion gap metabolic acidosis are the most reliable early signs of cyanide toxicity. Other signs include the smell of bitter almonds on the breath, anxiety, headache, stiffness of the lower jaw, dyspnea, and widely dilated pupils. Coma, seizures, and death may follow. Occult cyanide toxicity has been reported in patients who are treated with prolonged low-dose infusion of sodium nitroprusside following cardiac surgery. Treatment of cyanide toxicity consists of amyl nitrite inhalation, and sodium nitrite, thiosulfate, and hydroxocobalamin infusions.[236]

The safe use of sodium nitroprusside during pregnancy has not been established. In animals, nitroprusside readily crosses the placenta. In a study of eight normotensive gravid ewes, five required high doses of nitroprusside (mean, 25 μg/kg/minute) to reduce blood pressure by 20% for 1 hour.[237] Among these five animals, a marked accumulation of maternal cyanide occurred. Fetal blood levels of cyanide were even higher and all of these fetuses died. However, in the other three ewes, hypotension was achieved with low doses of sodium nitroprusside (less than 1 μg/kg/minute). In this group, all of the fetuses survived and umbilical cord blood cyanide levels were low.

When sodium nitroprusside was used to achieve normotension for 50 minutes in ewes with norepinephrine-induced hypertension, the mean infusion rate required to control blood pressure was only 2.3 μg/kg/minute, and no fetal or maternal deaths occurred.[238] Neither maternal nor fetal blood samples contained more than 50 μg per L of cyanide (toxic levels in humans, 5,000 μg per L).

There are some reports on the safe use of sodium nitroprusside for hypertensive crises in pregnant women.[239,241] It has been recommended that the use of sodium nitroprusside for hypertensive crises during pregnancy be restricted to patients who are unresponsive to intravenous hydralazine or diazoxide.[242] When nitroprusside is required, it should only be used briefly to manage the acute crisis, and delivery should be performed as quickly as possible.

In summary, sodium nitroprusside has several characteristics that make it nearly the ideal drug for the short-term management of hypertensive crises. These include rapid onset of action, immediate reversibility, specific effects on resistance and capacitance vessels with no direct effect on the myocardium or CNS, lack of tachyphylaxis, and high potency. It is also a very safe drug when used appropriately. It is the most useful and consistently effective drug available for parenteral use in the treatment of hypertensive crises.

Fenoldopam

Fenoldopam is a selective dopamine receptor (DA_1) agonist. Recent studies have shown that intravenous fenoldopam, when used in the setting of hypertensive crises or perioperative hypertension, can safely lower blood pressure while maintaining or improving renal function.[243] Fenoldopam, a benazepine derivative of dopamine, was initially developed as an oral agent for the treatment of hypertension, renal insufficiency, and congestive heart failure. However, it was eventually withdrawn from development because of poor oral bioavailability. When subsequent studies demonstrated that intravenous fenoldopam exhibited a short-half life and predictable pharmacokinetics and dose-response characteristics, it was subsequently evaluated as a potential alternative to sodium nitroprusside for parenteral treatment of hypertension. Intravenous fenoldopam mesylate (Corlopam) was approved by the U.S. Food and Drug Administration (FDA) in 1997 for use in hypertension when oral therapy is not feasible or possible and for use in patients with severe hypertension, with or without target-organ damage.

Pharmacology and Pharmacokinetics

Fenoldopam selectively binds to DA_1 receptors and functions as a dopamine agonist. It does not bind to DA_2 receptors or β-adrenergic receptors. Fenoldopam is also an α-adrenergic receptor antagonist with greater activity at α_2 than α_1 receptors. However, this activity is observed only at higher concentrations than those required for activation of DA_1 receptors and it is unlikely that α-adrenoreceptor antagonism contributes to the hemodynamic and renal effects of therapeutic doses of fenoldopam. Peripheral DA_1 receptors are located postsynaptically in the systemic and renal vasculature, and at various sites in the nephron and GI tract. These receptors mediate systemic, renal, and mesenteric vasodilation. Fenoldopam exerts its hypotensive effect by decreasing systemic vascular resistance. Unlike sodium nitroprusside, it also increases renal blood flow and causes a natriuresis and diuresis. It is six times as potent as dopamine in causing renal vasodilation. In patients with severe hypertension, intravenous infusion of fenoldopam significantly increases renal blood flow, and decreases renal vascular resistance with a significant increase in creatinine clearance, urine flow rate, and sodium excretion.[244] Because of its selective receptor binding characteristics, fenoldopam exhibits minimal adrenergic effects. Although DA_1 receptors are present in the

CNS, fenoldopam does not have any direct CNS effect because it does not cross the blood–brain barrier. Fenoldopam is metabolized in the liver to a variety of nontoxic methyl, sulfate, and glucuronide metabolites. There are two principal inactive metabolites, 7- and 8-methoxy-fenoldopam, that are eliminated by the kidney (80%) and in the feces (20%). Less than 1% is excreted unchanged in the urine; therefore, dosage adjustment is not required in the setting of renal insufficiency. Moreover, pharmacokinetic parameters do not appear to be significantly altered in the setting of hepatic insufficiency.[244] Fenoldopam is not metabolized by the cytochrome P 450 system and has no major drug–drug interactions although concomitant acetaminophen administration may increase fenoldopam levels by 30% to 70%. Following intravenous administration, the onset of action is within 10 minutes, and the half-life is 9.8 minutes. There is no evidence of rebound hypertension after stopping the infusion. The volume of distribution is 0.6 L per kg.

Dosage and Administration

Fenoldopam is available in 5-mL ampules at a concentration of 10 mg per mL. Following dilution, the solution, which is light stable, can be used for up to 24 hours. For the treatment of severe hypertension or hypertensive crises, fenoldopam is administered by continuous infusion with an initial dose of 0.1 μg/kg/minute. The infusion may be increased in increments of 0.1 μg/kg/minute every 20 minutes until the target blood pressure is achieved. The maximum recommended dosage is 1.7 μg/kg/minute. The average infusion rate required is 0.25 to 0.5 μg/kg/minute. Mean plasma fenoldopam levels after a 2-hour infusion at 0.5 μg/kg/minute is between 13 to 50 ng per mL. When the desired response has been achieved, fenoldopam infusion may be discontinued gradually or abruptly, as rebound elevation of blood pressure has not been observed. Oral antihypertensive medications may be started as the fenoldopam infusion is weaned.

Adverse Effects

Adverse events attributed to fenoldopam in the treatment of hypertensive emergencies and urgencies were generally mild, occurred within the first 24 hours, and were related to the vasodilatory action of the drug.[244] Headache was reported in 11% to 36% of patients, flushing in 7% to 11%, nausea in 20%, and dizziness in 10%. Asymptomatic ST-segment abnormalities occurred in 6% to 33% of patients. The etiology of these nonspecific ST- and T-wave abnormalities, which are similar to those seen with the use of other vasodilators, is unknown. They appear to be a benign phenomenon related to blood pressure lowering with alterations in myocardial repolarization rather than an indication of subclinical myocardial ischemia.[244] Less frequently reported adverse events included palpitations, transient hypotension, asthenia, and sinus bradycardia. Fenoldopam, unlike sodium nitroprusside, produced a reversible, dose-related increase in intraocular pressure and should be used with caution in patients with glaucoma. In comparative trials, the adverse event profiles of fenoldopam and sodium nitroprusside were generally similar, although fenoldopam may be associated with a lower incidence of transient hypotension than sodium nitroprusside.

Use for Treatment of Hypertensive Crises

Fenoldopam has been compared mostly with sodium nitroprusside in patients with acute severe hypertension (either severe uncomplicated hypertension or true hypertensive crises).[243,245,246] Treatment with fenoldopam or sodium nitroprusside reduced mean diastolic blood pressure to a similar extent and to goal levels in most patients.[244] The time to achievement of goal blood pressure was similar to that with sodium nitroprusside. There was no evidence of rebound hypertension following cessation of either drug. There was no evidence of tolerance to the antihypertensive effect of either drug during maintenance infusion. In patients with hypertension following noncardiac surgery or coronary artery bypass grafting, fenoldopam and sodium nitroprusside were equally efficacious in lowering blood pressure.[247,248]

The efficacy, safety, and cost of sodium nitroprusside versus fenoldopam has been compared in a retrospective analysis of consecutive patients with hypertensive crises admitted to a level 1 trauma center and treated with nitroprusside (n = 21) or fenoldopam (n = 22).[246] Neither the mean pretreatment mean arterial pressure (nitroprusside 168 ± 19; fenoldopam 163 ± 9; P = .45), time to reach MAP goal (3.6, range 0.4 to 30 hours vs. 4.0, range 1 to 22 hours; P = .5), nor the duration of infusion (18, range 0.7 to 113 hours vs. 18, range 3 to 74 hours; P = .45) differed between the treatment groups. Time to imitation of oral antihypertensive therapy was similar between nitroprusside (4.5, range 0.5 to 22 hours) and fenoldopam (6.5, range 1 to 100 hours) treated patients (P = .45). Change in creatinine clearance and the incidence of tachycardia did not differ between the two groups. No symptoms of cyanide toxicity were detected in nitroprusside-treated patients. Cost of therapy was less with nitroprusside ($2.66, range $1.68 to $3.48) than with fenoldopam ($567, range $199 to $6,675 dollars). Thus, treatment of hypertensive crises with fenoldopam appears to result in patient outcomes equal to those with nitroprusside but at substantially higher cost.

Additional studies are needed to compare fenoldopam and sodium nitroprusside in the treatment of true hypertensive crises. Because fenoldopam preferentially dilates the renal vasculature, it has theoretical advantages in the treatment of patients with severe hypertension associated with renal impairment. Moreover, fenoldopam is not associated with the risk of toxicity from thiocyanate accumulation or cyanide. It is possible that it may also offer advantages in patients in whom cross clamping of the aorta above the level of the renal arteries is required.

Esmolol Hydrochloride

Pharmacology and Pharmacokinetics

Esmolol hydrochloride is a $beta_1$-selective (cardioselective) adrenergic receptor blocking agent with rapid onset of action and a very short duration of action. At therapeutic doses it has no significant intrinsic sympathomimetic activity. Elimination half-life after intravenous infusion is approximately 9 minutes. Esmolol inhibits $beta_1$ receptors located chiefly in cardiac muscle, but this preferential effect is not absolute and at higher doses it begins to inhibit $beta_2$ receptors located chiefly in the bronchial and vascular smooth muscle. Esmolol hydrochloride is rapidly metabolized by hydrolysis of the ester linkage by the esterases in the cytosol of red blood cells. Total body clearance is about 20 L/kg/hour which is greater than cardiac output, thus metabolism is not limited by the rate of hepatic or renal blood flow. Esmolol at doses of 200 μg/kg/minute produces reductions in heart rate, systolic blood pressure, rate-pressure product, left and right ventricular ejection fraction, and cardiac index.

Dosage and Administration

Esmolol hydrochloride is supplied as ready-to-use 10-mL vials containing 100 mg per 10 mL (10 mg per mL) and 250-mL bags containing 2,500 mg per 250 mL (10 mg per mL) and double strength vials containing 100 mg per 5 mL (20 mg per mL) and double strength bags containing 2,000 mg per 100 mL (20 mg per mL). Esmolol hydrochloride is titrated based on ventricular rate response and blood pressure. An initial loading dose of 500 μg per kg is infused over 1 minute followed by a maintenance infusion of 50 μg/kg/minute for 4 minutes. If adequate therapeutic response is not observed within 5 minutes, repeat the same loading dose and follow with a maintenance infusion increased to 100 μg/kg/minute. Higher maintenance infusion rates (250–300 μg/kg/minute) may be required for adequate control of blood pressure in up to one third of patients with postoperative hypertensive crises. In the absence of loading doses, constant infusion of any given maintenance dose reaches pharmacokinetic and pharmacodynamics steady-state in about 30 minutes. Maintenance infusions (with or without loading doses) may be continued for as long as 24 hours.

Adverse Effects

Adverse reaction rates are based on use of esmolol hydrochloride in clinical trials involving nearly 1000 patients with supraventricular tachycardia or intraoperative and postoperative hypertension enrolled in clinical trials. Symptomatic hypotension with diaphoresis and dizziness was the most common side effect occurring in 12% of patients. Asymptomatic hypotension occurred in about 25% of patients. Pallor, flushing, bradycardia with heart rate less than 50 beats per minute, chest pain, syncope, pulmonary edema, and heart block have each been reported in less than 1% of treated patients. Bronchospasm, wheezing, and dyspnea were reported in less than 1% of patients.

Use for Treatment of Hypertensive Crises

Esmolol hydrochloride is indicated for treatment of tachycardia and hypertension that occur during induction of anesthesia and tracheal intubation, during surgery, on emergence from anesthesia, and in the postoperative period. Esmolol hydrochloride may also be useful in conjunction with sodium nitroprusside to achieve blood pressure reduction and reduction in heart rate and dV/dP in patients with dissecting aortic aneurysm.

Intravenous Nitroglycerin

Intravenous nitroglycerin is particularly useful for the management of hypertension complicating acute myocardial infarction and hypertension occurring after coronary artery bypass. Nitroglycerin causes relaxation of vascular smooth muscle. The predominant effect at lower doses is venodilation. At higher doses, both venous and arterial dilation occur in a dose-dependent fashion.[249] As with nitroprusside, the effects of intravenous nitroglycerin on stroke volume and cardiac output vary, depending on the presence or absence of left ventricular dysfunction. In patients without heart failure, the reduction in preload usually predominates and stroke volume falls. In contrast, in patients with left ventricular systolic dysfunction, the decrease in afterload results in a decrease in the impedance to left ventricular ejection such that stroke volume is maintained despite a reduction in preload.

For the treatment of hypertension complicating acute myocardial infarction or postcardiac bypass hypertension, nitroglycerin may have an advantage over sodium nitroprusside.[250] Nitroglycerin and nitroprusside have different effects on regional myocardial blood flow.[251–253] Although both drugs dilate coronary vessels, nitroglycerin has a predominant effect on large coronary conductance arteries, including intercoronary collaterals, and relatively little effect on small resistance arterioles. This phenomenon is explained by the fact that coronary resistance vessels less than 100 microns in diameter cannot convert nitrates to nitric oxide such that there is preferential dilation of the larger epicardial collateral vessels.[254] In contrast, sodium nitroprusside predominantly dilates the resistance vessels and has less effect on intercoronary collaterals. In the setting of regional myocardial ischemia, resistance vessels in the ischemic region are already maximally dilated. Thus, sodium nitroprusside may dilate resistance vessels in nonischemic areas and shunt blood away from ischemic areas (coronary steal). Nitroglycerin, by predominantly dilating conductance vessels, improves blood flow to the ischemic region. Given the potentially deleterious effect of nitroprusside on regional myocardial blood flow, it has been recommended that intravenous nitroglycerin be used in preference to nitroprusside for the treatment of hypertension with left ventricular dysfunction in association with acute myocardial infarction.[250]

Nitrates produce vasodilation through the formation of nitric oxide (endothelium-derived relaxing factor), which

activates guanylate cyclase.[250] There appears to be tight coupling between the cyclic guanosine monophosphate (cGMP) production and smooth muscle relaxation. A cGMP-dependent protein kinase is stimulated, resulting in alterations in the phosphorylation of various proteins in smooth muscle. Dephosphorylation of the light chain of myosin leads to smooth muscle relaxation.[256]

Intravenous nitroglycerin has a rapid onset and brief duration of action with a half-life of 1 to 4 minutes. It is metabolized in the liver by a glutathione-dependent organic nitrate reductase. Intravenous nitroglycerin is supplied in 10-mL bottles containing 50 mg, which should be diluted in 5% dextrose in water or 0.9% sodium chloride. Usually one bottle is diluted in a 250 mL volume to yield a final concentration of 200 μg per mL. Nitroglycerin interacts with many types of plastic. Thus, the drug should be diluted only in glass parenteral solution bottles. Special infusion sets that have been developed absorb fewer nitroglycerins than standard polyvinyl chloride tubing. The initial infusion rate should not exceed 5 μg per minute. The dose is titrated in 5 μg per minute increments every 3 to 5 minutes until the desired hypotensive response is achieved. There is no standard optimal dose of nitroglycerin. There tends to be great variability in response from patient to patient. Blood pressure should be monitored every 30 seconds during the titration phase and every 15 minutes thereafter. As with nitroprusside, close monitoring in an intensive care unit setting is required. In the setting of acute myocardial infarction, monitoring of cardiac output and left ventricular filling pressure is essential.

Intravenous nitroglycerin has also been recommended for the management of the potentially dangerous posttreatment hypertensive response that inevitably follows electroconvulsive therapy.[257]

Labetalol

Intravenous labetalol may be of value in a variety of hypertensive crises including malignant hypertension, hypertensive encephalopathy,[258] aortic dissection,[259] and hypertensive crises during pregnancy.[259]

Labetalol has selective α_1- and nonselective beta-blocking properties.[260,261] The ratio of beta- to α-blocking potency is 7:1 for intravenous labetalol. The acute antihypertensive effect after intravenous administration appears to be caused by a decrease in systemic vascular resistance without an appreciable change in cardiac output.[261] However, when used in the treatment of hypertension following open heart surgery, labetalol causes a significant reduction in cardiac output.[262] The beta-blocking effect offsets the baroreceptor-mediated sympathetic response to hypotension. Thus, heart rate remains unchanged or decreases slightly.

After intravenous bolus injection, the full antihypertensive effect occurs within 5 to 10 minutes, and the blood pressure gradually rises to pretreatment levels over 16 to 18 hours. The duration of action, defined as the time from the last injection until the diastolic blood pressure rises 10 mm Hg above the nadir pressure, ranges from 2.0 to 6.5 hours. The major route of elimination is via glycuronide conjugation in the liver. Thus, the labetalol dose must be decreased in patients with liver dysfunction but need not be modified in patients with renal failure.

Labetalol is supplied in 20-mL ampules containing 100 mg of drug. It is usually administered by repeated mini-bolus injections through an intravenous line. The initial dose is 20 mg (4 mL) injected slowly over a 2-minute period. The maximum hypotensive response usually occurs within 5 minutes of the injection. If the desired hypotensive response is not obtained after 10 minutes, a 40-mg bolus is administered over 2 minutes. Additional injections of 40 to 80 mg can be given at 10-minute intervals until the desired hypotensive response is obtained or the maximum total dose of 300 mg has been given.

Labetalol can also be given by continuous infusion. The contents of two ampules (200 mg, 40 mL) are added to 160 mL of diluent to yield a volume of 200 mL with a final concentration of 1 mg per mL. The infusion is begun at 2 mg per minute. The infusion is continued until the desired response is obtained and then discontinued. Again, the maximum total dose of 300 mg should not be exceeded. Continuous infusion may be preferable to bolus therapy in patients at risk for ischemic complications due to overshoot hypotension.

After the blood pressure is controlled with either the mini-bolus or the continuous infusion technique, oral therapy can be initiated with labetalol as soon as the supine diastolic pressure increases by 10 mm Hg above the minimum obtained with parenteral therapy. The initial oral dose is 200 mg. Thereafter the oral dose is titrated beginning at 200 mg twice daily and increased to 600 mg twice daily as required. The addition of a diuretic often enhances the long-term blood pressure response.

As with other parenteral antihypertensive agents, intravenous labetalol can cause precipitous hypotension, which can result in cerebral ischemia. Exaggerated hypotensive responses are usually reported when the initial injection is large (1.5 to 2.0 mg per kg); however, overshoot hypotension can also develop with either the mini-bolus or the continuous infusion technique. Chronically hypertensive patients sometimes develop paradoxical hypertension in response to volume depletion.[263] In this setting treatment with labetalol leads to reduction in systemic vascular resistance leading to sustained overshoot hypotension. Thus, before labetalol is used to treat a patient with postoperative hypertension and tachycardia, the possibility of physiologic tachycardia due to volume depletion should be considered.

Other side effects of labetalol are related to its nonselective beta-blocking properties. It should be avoided in patients with severe sinus bradycardia, heart block greater than first degree, bronchial asthma, or congestive heart failure.

Oral labetalol has been used safely for treatment of hypertensive crises of pregnancy.[264] However, intravenous labetalol should be used with caution because it has been associated with evidence of neonatal β-adrenergic blockade such as hypoglycemia, bradycardia, and hypotension.[265]

Labetalol can cause a significant reduction in cardiac index when used in the setting of hypertension after open heart surgery.[262] The hypotensive action of the drug in this setting appears to result from a decrease in cardiac output rather than from a decrease in systemic vascular resistance. Thus, labetalol should be avoided after open heart surgery, a setting in which nitroglycerin or sodium nitroprusside is preferred for management of hypertension.

Although there are reports of preoperative management of pheochromocytoma with labetalol,[266] beta-blockade can result in exacerbation of hypertension if α-blockade is incomplete. In this regard, there have been reports of paradoxical hypertension when labetalol was used to treat pheochromocytoma.[267] Therefore, routine use of labetalol for the preoperative management of pheochromocytoma is not recommended.

Several deaths have been reported to the FDA with use of parenteral labetalol injection to treat intraoperative hypertension (including cases where it is used to control intraoperative bleeding).

Although intravenous labetalol has been recommended as an effective agent for the treatment of severe acute hypertension in patients with chronic renal failure,[268] life-threatening hyperkalemia has been reported in patients with renal failure that received intravenous labetalol for the treatment of hypertensive crises.[269,270] Beta-adrenergic stimulation is known to shift potassium into cells and beta-agonists have been proposed as acute therapy for hyperkalemia in dialysis patients. Conversely, hyperkalemia may be caused by nonselective beta-blockers through inhibition of Na-K-ATPase with decreased cellular uptake of potassium, independent of effects on insulin or aldosterone.[271] Thus, labetalol and other nonselective beta-blockers should probably be avoided for the acute management of postoperative hypertension and other hypertensive crises in patients with renal failure.

In summary, although intravenous labetalol has been used to treat a variety of hypertensive crises, its long duration of action and beta-blocking properties are potential disadvantages. Slow continuous infusion may be preferred over intravenous bolus therapy to minimize the risk of sustained overshoot hypotension. For this reason, sodium nitroprusside or nicardipine usually represents more logical choices for the acute management of patients with hypertensive crises requiring parenteral therapy.

Phentolamine

Phentolamine is useful in the management of catecholamine-related hypertensive crises including pheochromocytoma, monoamine oxidase (MAO) inhibitor–tyramine interactions, and clonidine, methyldopa, or guanabenz withdrawal reactions. It is not consistently effective in other hypertensive crises. In fact, phentolamine has largely been replaced by sodium nitroprusside in the management of catecholamine-related hypertensive crises.

Phentolamine is a nonselective α-adrenergic blocking agent that competitively inhibits the effect of norepinephrine on vascular smooth muscle α_1-receptors. It does not have beta-blocking activity and therefore does not block the cardiac effects associated with β_1-receptor activation by catecholamines. Phentolamine produces dilation of both arteriolar resistance vessels and venous capacitance vessels.[273]

The intravenous injection of 1 to 5 mg produces a hypotensive effect within 2 to 3 minutes; however, the duration of action may be only 15 to 30 minutes, so that frequent dosing is required to control blood pressure. Phentolamine is supplied in ampules containing 5 mg. The initial dose should be 1 mg. Subsequent boluses of 1 to 5 mg are administered up to a total dose of 20 to 30 mg or until the blood pressure is controlled. After the desired blood pressure is achieved, intermittent injections are given as necessary to maintain the response.

Side effects due to phentolamine are common. Tachycardia and arrhythmias can occur due to β-adrenergic cardiac stimuli that are not blocked by phentolamine. GI side effects include abdominal pain, nausea, vomiting, and diarrhea. Exacerbation of peptic ulcer disease can occur, so phentolamine should be used with caution in patients with a history of gastritis or peptic ulcer disease.

Hydralazine

In the past, parenteral hydralazine was often used for the treatment of hypertensive crises. Most obstetricians still consider hydralazine to be the drug of choice for the management of hypertensive crises during pregnancy.[273] However, aside from its use during pregnancy, hydralazine has largely been replaced by other agents in the treatment of hypertensive crises.

The hypotensive response to either intramuscular or intravenous hydralazine is unpredictable. The onset of action occurs 10 to 30 minutes after a parenteral dose. The duration of action is 3 to 9 hours. The dose and frequency of administration needed to control the blood pressure are highly variable.[274] Profound and sustained hypotension can occur with an intravenous dose as low as 10 mg. Hydralazine is a direct-acting arteriolar vasodilator. It causes reflex activation of the adrenergic nervous system.[274] Because venous capacitance vessels are not affected, venous return is maintained. In association with activation of the adrenergic system, there are increases in heart rate and stroke volume.[274] Hydralazine is contraindicated in the treatment of aortic dissection because the increase in myocardial contractility can result in propagation of the dissection. It is also contraindicated in patients with ischemic heart disease because the increased myocardial oxygen demand can precipitate angina or myocardial infarction.

Parenteral hydralazine is still used in acute hypertensive crises of pregnancy. In the majority of patients, hydralazine reduces the blood pressure to acceptable levels and is well tolerated by both mother and fetus, despite reflex activation of the adrenergic system.[273] Dosing guidelines for the use of parenteral hydralazine during pregnancy are well established.[273] Because maternal hypertension helps to maintain placental perfusion, there is concern that aggressive treatment aimed at normalization of blood pressure might

further compromise placental perfusion to the detriment of the fetus. Therefore, hydralazine treatment is usually instituted only if the diastolic blood pressure is more than 110 mm Hg and the goal of therapy is a diastolic pressure in the 90 to 100 mm Hg range. After an initial intravenous dose of 5 mg, additional 5- to 10-mg doses are administered every 15 to 20 minutes until the desired response is obtained. Because preeclampsia is associated with intravascular volume depletion, it is important to initiate therapy with a low dose to avoid overshoot hypotension. Intramuscular injection of hydralazine is unsatisfactory because the onset of action and magnitude of response are unpredictable.

Calcium Channel Blockers

Intravenous nicardipine has been reported to be effective in the acute treatment of severe hypertension in both adults and children.[275–277] It may be useful in the management of postoperative hypertension in both cardiac and noncardiac patients.[277] Intravenous nicardipine is also effective in preventing circulatory responses to laryngoscopy and tracheal intubation in hypertensive patients.[278] Safe use of nicardipine in preeclamptic patients has also been reported.[279]

Nicardipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium into vascular smooth muscle, resulting in vasodilation with a decrease in systemic vascular resistance. The effect on heart rate is dependent on the intrinsic state of the myocardium. In patients with intact systolic function, reflex increases in heart rate may occur in response to blood pressure reduction. In patients with impaired left ventricular function, cardiac output may increase in response to afterload reduction.

Compared to other parenteral medications available for the treatment of hypertensive crises, the pharmacokinetic properties of nicardipine (as well as other calcium channel blockers) are unfavorable. The currently available dihydropyridine calcium channel blockers have very long half-lives. The beta half-life of nicardipine is 40 minutes, whereas its gamma half-life is approximately 13 hours. Because about 14% of the drug is eliminated during the gamma phase, the hypotensive effect is prolonged. Discontinuation of the infusion is followed by a 50% reduction in the hypotensive action within 30 minutes but a gradually decreasing antihypertensive effect may last for about 50 hours. Thus, nicardipine may not be the best choice for true hypertensive crises in which moment-to-moment titration of the blood pressure is the desired therapeutic goal.

In the past, nimodipine had been recommended for the treatment of patients undergoing cardiac valve replacement to decrease the incidence of postoperative neurologic sequelae by increasing cerebral blood flow and protecting against anoxic brain cell damage. However, a recent placebo controlled trial of oral nimodipine following cardiac valve replacement was terminated prematurely because of a lack of evidence of benefit of nimodipine and an unexpected increase in the death rate of patients treated with nimodipine compared to placebo.[280] The higher mortality rate was attributed to an increased risk of major bleeding in patients treated with nimodipine. Excess bleeding in patients treated with calcium channel blockers may be explained by the combination of vasodilation and the antiplatelet action of calcium antagonists.

The clinical use of nifedipine for severe uncomplicated hypertension and hypertensive crises has been reviewed.[281,282] Nifedipine produces a prompt fall in systemic arterial pressure after a single oral dose. The antihypertensive effect results from arteriolar vasodilation with a decrease in systemic vascular resistance. Nifedipine produces a prompt reduction in systolic, diastolic, and mean arterial pressures of about 25% below the baseline value in most patients.[282]

The major acute side effects of nifedipine include a burning sensation in the face and legs, facial flushing, headache, and palpitations. Overshoot hypotension has been observed, especially in hypovolemic patients or patients pretreated with diuretics.[283,284] Exaggerated hypotension can cause myocardial ischemia in patients with underlying coronary atherosclerosis.[285]

Oral nifedipine may be useful in the management of patients with malignant hypertension who do not have an absolute indication for parenteral antihypertensive therapy. However, in patients with hypertensive crises requiring careful titration of the hypotensive response, the prolonged duration of action and the potential risk of overshoot hypotension with nifedipine are major disadvantages. Sodium nitroprusside is clearly preferable for the management of true hypertensive crises. The role of nifedipine in the acute treatment of severe uncomplicated hypertension in the emergency room setting prior to discharge is discussed in the section entitled Severe Uncomplicated Hypertension.

Minoxidil

Minoxidil is a potent antihypertensive agent that is available only for oral use. In combination with a potent diuretic and a beta-blocker, it is very useful in the control of hypertension refractory to conventional antihypertensive regimens. The efficacy of a triple drug regimen with minoxidil in the management of the patient with malignant hypertension and azotemia has already been discussed. Minoxidil is often employed for the long-term control of blood pressure in patients with malignant hypertension after initial control of the blood pressure with parenteral medications. Furthermore, in patients with malignant hypertension not requiring immediate blood pressure reduction, an oral triple drug regimen consisting of minoxidil, a beta-blocker, and a loop diuretic can effectively control the blood pressure over a period of hours to days and thereby eliminate the need for parenteral antihypertensive therapy (see Treatment subsection under Malignant Hypertension earlier in this chapter).

Minoxidil is a direct-acting arteriolar vasodilator. Its antihypertensive effect results from a decrease in systemic vascular resistance.[286] It has no effect on venous capacitance vessels. The hypotensive response to minoxidil is accompanied by a baroreceptor-mediated reflex increase in

sympathetic tone, which results in an increase in heart rate, contractility, and cardiac output. Unopposed, the cardiac output may increase threefold to fourfold and attenuate the fall in blood pressure.[286,287] The resulting increase in myocardial oxygen demand may precipitate ischemia in patients with limited coronary reserve. For this reason minoxidil is usually given concomitantly with a β-adrenergic blocking drug.

As with other peripheral vasodilators, minoxidil induces profound renal salt and water retention.[286] This fluid retention is probably related to the hypotensive effect of the drug. A similar antinatriuresis occurs with both hydralazine and diazoxide. Minoxidil causes more fluid retention because it is a more potent arteriolar vasodilator. Several factors enhance renal salt and water retention.[287] Decreased peritubular capillary pressure is a potent stimulus for salt and water reabsorption in the proximal tubule. Increased adrenergic tone also enhances proximal tubular salt and water reabsorption. Like other vasodilators, minoxidil increases renin release, which leads to increased aldosterone production and enhanced distal tubular sodium reabsorption.[287] Pseudotachyphylaxis to the original hypotensive effect of minoxidil can occur if either beta-blockade or diuretic therapy is inadequate.

The serum half-life of minoxidil is 4.5 hours; however, the duration of action is longer than the half-life would predict.[287] After oral administration, the antihypertensive effect begins within 30 to 60 minutes, reaches a maximum in 2 to 4 hours, and slowly abates over the next 12 to 18 hours. The prolonged hypotensive effect is probably due to persistent binding of minoxidil at the site of action in vascular smooth muscle. About 15% of the parent compound is excreted in the urine, whereas the remainder is metabolized in the liver by glucuronide conjugation.[287]

Although the serum half-life is 4 hours, the persistent hypotensive effect allows for a twice daily dosing schedule. Prior to the initiation of minoxidil, all other antihypertensives except diuretics and beta-blockers should be discontinued. Minoxidil is started at a dose of 2.5 mg twice daily and increased in 5-mg per day increments every 2 to 3 days until the desired response is obtained. The usual effective dose is 10 to 40 mg per day. The doses of loop diuretic and beta-blocker are titrated to maintain dry weight and prevent tachycardia, respectively.

When more rapid control of arterial pressure is required, incremental changes in minoxidil dosage can be made every 6 hours. The initial 2.5-mg dose is doubled every 6 hours up to a maximum dose of 20 mg, or until the desired response is obtained. The effective dose should then be administered every 12 hours and the dose of diuretic and beta-blocker titrated as necessary.[287]

The dose of beta-blocker required to prevent reflex tachycardia in patients treated with minoxidil is often in excess of the usual beta-blocking dose. This is because the sympathetic nervous system is activated by minoxidil and beta-blockers compete with catecholamines for receptor binding.[287] The dose of beta-blocker should be titrated to maintain resting heart rate at 70 to 80 beats per minute.

In general, thiazide diuretics are not potent enough to counteract minoxidil-induced antinatriuresis, especially if renal insufficiency is present. The starting dose of furosemide is 40 mg twice daily. However, a dose of 300 to 400 mg per day may be required to prevent fluid retention and maintain dry weight.

The most common side effects of minoxidil are related to its pharmacologic properties. Fluid retention can lead to weight gain, edema, anasarca, congestive heart failure, and pericardial effusion. With inadequate beta-blockade, reflex sympathetic stimulation can lead to angina or myocardial infarction in patients with underlying coronary disease. Electrocardiographic changes following the initiation of minoxidil have been reported. In more than 90% of patients flattening or inversion of T waves develops.[287] Although often marked, these changes do not necessarily indicate myocardial ischemia, and they usually resolve with continued therapy.[286,287]

Pericardial effusion has been reported with minoxidil treatment; however, progression to cardiac tamponade is rare. The cause of the effusion is unknown, but it occurs most commonly in patients with renal failure, collagen vascular diseases, or inadequate diuretic therapy. A hemodynamically insignificant effusion is not necessarily a reason to discontinue minoxidil, but the patient should be treated aggressively with diuretics and followed closely for signs of tamponade.[286,287] Patients on dialysis should have a trial of intensive daily dialysis to achieve and maintain dry weight.

Reversible hypertrichosis of the face, back, and arms occurs in almost all patients taking minoxidil and is the most frequent reason for discontinuation of the drug, especially among female patients. Calcium thioglycolate depilatory agents and shaving are used to control this cosmetic side effect.

Triple therapy with minoxidil, a beta-blocker, and a loop diuretic is often dramatically effective in the long-term management of malignant hypertension, even when conventional antihypertensive regimens are unsuccessful or produce intolerable side effects.[288]

SEVERE UNCOMPLICATED HYPERTENSION

The benefits of acute reduction of blood pressure in the setting of true hypertensive crises are obvious. Fortunately, hypertensive crises are relatively rare events that never affect the vast majority of hypertensive patients. Another type of presentation that is more common than true hypertensive crisis is the patient who presents with severe hypertension (diastolic blood pressure greater than 115 mm Hg) in the absence of the hypertensive neuroretinopathy or other acute end-organ damage that would signify a true crisis. This entity, which is known as severe uncomplicated hypertension, is very common in the emergency department setting. In a recent study of severe uncomplicated hypertension treated in an emergency room, 60% of the patients were

entirely asymptomatic and had presented for prescription refills or routine blood pressure checks, or were found to have elevated blood pressure during routine examinations. The other 40% presented with nonspecific symptoms such as headache, dizziness, and weakness in the absence of evidence of acute end-organ dysfunction.[289]

In the past, this entity has been referred to as urgent hypertension, reflecting the widely accepted notion that acute reduction of blood pressure, over a few hours prior to discharge from the emergency room, was essential to minimize the risk of short-term complications from the severe hypertension.[290] Commonly used treatment regimens include oral clonidine loading, or sublingual nifedipine given to acutely reduce the blood pressure prior to initiation of a maintenance antihypertensive regimen.[289,290]

In recent years, however, the urgency of treatment in patients with severe uncomplicated hypertension has been questioned.[3,5,291] Although it is clear that in comparison to patients with mild or moderate hypertension, patients with severe uncomplicated hypertension are at increased long-term risk of cardiovascular complications,[292] they are generally not in any immediate danger of an untoward event. The argument supporting the acute reduction of blood pressure is based on the following assumptions: (1) it is important to reduce blood pressure immediately to avoid complications; (2) oral antihypertensive loading prior to initiation of maintenance therapy produces improved immediate and long-term blood pressure control; and (3) there are no adverse consequences of this form of treatment.[3] Two classical studies provided some useful information regarding the need to reduce blood pressure immediately with the aim of preventing hypertensive complications. In the Veterans Administration Cooperative Study of patients with severe hypertension,[293] there were 70 untreated patients who had no evidence of malignant hypertension or significant end-organ dysfunction despite the presence of diastolic blood pressures averaging 121 mm Hg. Among these patients, 27 experienced morbid events at an average of 11 ± 8 months into follow-up. The earliest morbid event occurred after 2 months. Likewise, a similar study in Baltimore showed that among 42 untreated patients with severe but uncomplicated hypertension, 19 patients experienced morbid events (congestive heart failure, onset of malignant hypertension, cerebrovascular accident, or evidence of declining renal function) at a mean of 12 ± 7 months into follow-up. The earliest morbid event occurred at 2 months.[293] These data suggest that patients who have severe but uncomplicated hypertension need not be exposed to the risk of "urgent" blood pressure reduction in the emergency room setting because hypertensive complications tend to occur over a matter of months to years rather than hours to days.

Another study addressed the question of whether antihypertensive loading prior to the initiation of maintenance therapy improves or hastens blood pressure control.[5] Sixty-four asymptomatic patients with severe hypertension were randomized to treatment with hourly doses of clonidine followed by clonidine and thiazide diuretic maintenance therapy, or an initial dose of clonidine followed by hourly placebo and then subsequent maintenance therapy, or initiation of maintenance therapy without prior antihypertensive loading. There was no difference between the first two groups with regard to the time required to achieve acceptable blood pressure control during loading therapy. Furthermore, there were no differences between the three groups with regard to adequacy of blood pressure control at 24 hours or 1 week. The authors conclude that sustained blood pressure control resulted solely from maintenance therapy and that the time to adequate control and eventual level of blood pressure were independent of the administration of an initial loading dose. They suggest that the common practice of acute oral antihypertensive loading to treat severe, asymptomatic hypertension should be reconsidered.[5] In this regard, a study of 32 patients with severe uncomplicated hypertension found that a significant decrease in blood pressure frequently occurred in the emergency department even before pharmacologic intervention was initiated. The mean arterial pressure decreased by 6% without treatment within 1 hour after the initial blood pressure reading.[294] The authors suggest that given a short period of observation, many patients with severe uncomplicated hypertension will experience a decrease in blood pressure to mildly or moderately hypertensive levels, which would clearly make acute blood pressure reduction with an antihypertensive loading regimen unnecessary.

Although generally safe, the oral antihypertensive loading regimens occasionally cause significant adverse effects. Sublingual nifedipine can produce severe headache and profound overshoot hypotension.[284] The marked blood pressure reduction can exacerbate underlying ischemic heart disease, resulting in angina or myocardial infarction. It has even been suggested that a moratorium be placed on the use of sublingual nifedipine for the treatment of severe uncomplicated hypertension.[295] Loading doses of clonidine cause sedation in 60% of patients and some of these patients are difficult to awaken and require assistance in returning home.[289] Furthermore, the recommended conversion from the oral loading dose to a twice-daily dose of clonidine may represent special problems in the treatment of patients with severe uncomplicated hypertension. Clonidine produces a number of common side effects including dry mouth, drowsiness, and constipation, which may interfere with long-term compliance with medical therapy. The risk of hypertensive rebound on abrupt discontinuation of clonidine[290] should also be considered since many patients with this form of hypertension are noncompliant with medical therapy.[5]

Although the acute reduction of blood pressure in patients with severe uncomplicated hypertension with sublingual nifedipine or oral clonidine loading regimens has become the de facto standard of care in the acute care setting, this practice is often an emotional response on the part of the treating physician to the dramatic elevation of blood pressure. This aggressive approach may also be motivated

by fear of medicolegal repercussions in the unlikely event that an untoward hypertensive complication occurs shortly after the emergency room visit. Although observing and documenting the dramatic fall in blood pressure prior to discharge is a satisfying therapeutic maneuver, there is no scientific basis for this approach and it is unclear if even the small but definite risks of acute blood pressure reduction are justified. There is, at present, no literature to support the notion of an absolute level of blood pressure above which the acute reduction of blood pressure is mandatory before the patient can be discharged from the acute care setting. For asymptomatic patients with severe uncomplicated hypertension, acute reduction of blood pressure in the emergency room is often counterproductive because it can produce untoward symptoms that render the patient less likely to comply with long-term drug therapy. Because the available data suggest that the risks to the patient are not immediate, therapeutic intervention should focus on tailoring an effective, well-tolerated maintenance antihypertensive regimen with emphasis on patient education to enhance long-term compliance.[5] Therefore, oral antihypertensive loading in this setting is of little value. If the patient has simply run out of medications, reinstitution of the previous regimen should suffice. If the patient is thought to be compliant with an existing drug regimen, a sensible change in therapy such as an increase in a suboptimal dosage of an existing drug or the addition of a drug of another class is appropriate. Addition of a low dose of a thiazide diuretic as a second-step agent to existing monotherapy with converting enzyme inhibitor, calcium channel blocker, beta-blocker, or central α_2-agonist is often efficacious. Another essential goal of the intervention should be to arrange for 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 follow-up visits to modify drug regimens and reinforce the importance of lifelong compliance with therapy. Although less dramatic than acute reduction of blood pressure in the emergency room, this type of approach to the treatment of this chronic disease is more likely to prevent long-term hypertensive complications as well as recurrent episodes of severe uncomplicated hypertension.

A recent multicenter study evaluated the level of adherence to current guidelines that recommend that patients in the emergency department with severely elevated blood pressure be evaluated for target organ damage (to exclude hypertensive crisis requiring immediate blood pressure reduction), have their outpatient medical regimen adjusted, and be instructed to follow-up promptly for reassessment.[296] This observational study was conducted during 1 week at four urban academic emergency departments. Severely elevated blood pressure was defined as systolic blood pressure greater than or equal to 180 mm Hg or diastolic blood pressure greater than or equal to 110 mm Hg on at least one measurement. Among 423 patients with severely elevated blood pressure, serum chemistry was obtained in 73%, ECG in 53%, chest radiograph in 46%, urinalysis in 43%, and funduscopic examination to exclude malignant hypertension in 36%. All recommended studies were performed in only 6% of patients. Acute reduction of blood pressure with oral medications was undertaken in 36% of patients and intravenous antihypertensive agents were given to 4% of patients. Modification of the outpatient antihypertensive regimen was documented in only 19% of discharged patients. The authors conclude that the majority of emergency department patients with severely elevated blood pressure do not receive the evaluation, medical regimen modification, and discharge instructions advised by current guidelines.

Finally, an important entity that can masquerade as severe uncomplicated hypertension deserves special mention. Pseudohypertension is a condition in which indirect measurement of arterial pressure using a cuff sphygmomanometer is artificially high in comparison to direct intra-arterial pressure measurements.[297] Failure to recognize pseudohypertension can result in unwarranted and sometimes frankly dangerous treatment. Pseudohypertension can result from Mönckeberg's medial calcification, advanced atherosclerosis with widespread calcification of intimal plaques, or azotemic arteriopathy (metastatic vascular calcification in patients with ESRD).[297] In these entities, stiffening of the arterial wall may prevent its collapse by externally applied pressure, resulting in artificially high indirect blood pressure readings affecting both systolic and diastolic measurements. Pseudohypertension should be suspected in the patient with severe hypertension in the absence of significant target-organ damage. The presence of a positive Osler's maneuver, in which the radial or brachial artery remains clearly palpable despite being made pulseless by proximal inflation of a cuff above systolic blood pressure, is an important physical examination finding that should suggest the diagnosis.[298] Roentgenograms of the extremities will often reveal calcified vessels.[297] However, the diagnosis can only be made definitively by direct measurement of intra-arterial pressure. If unrecognized, pseudohypertension may result in unwarranted treatment. Patients with pseudohypertension are often older adults and therefore may have critical limitation of blood flow to the brain or heart such that inappropriate blood pressure reduction may precipitate life-threatening ischemic events.[297]

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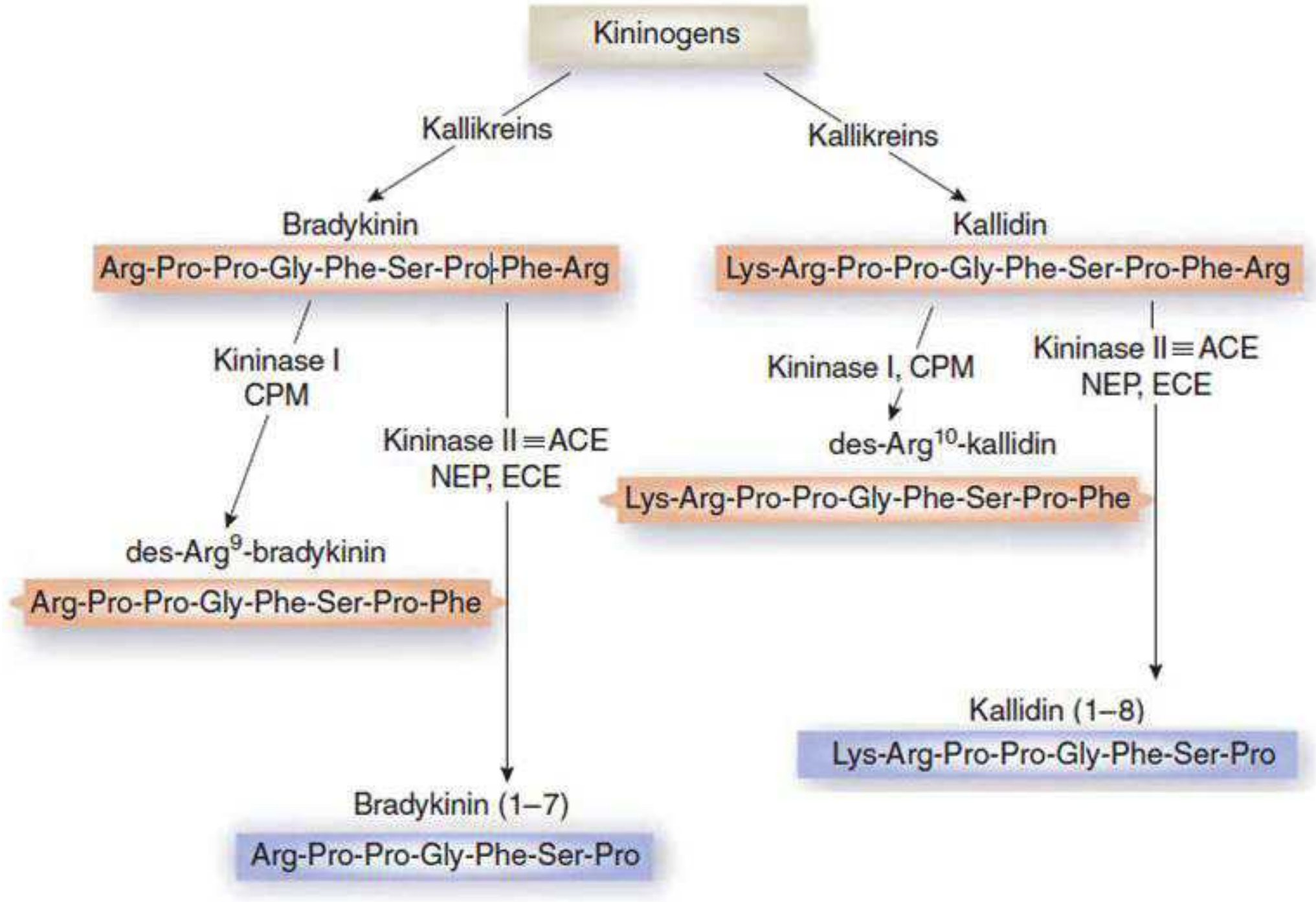


FIGURE 8.5

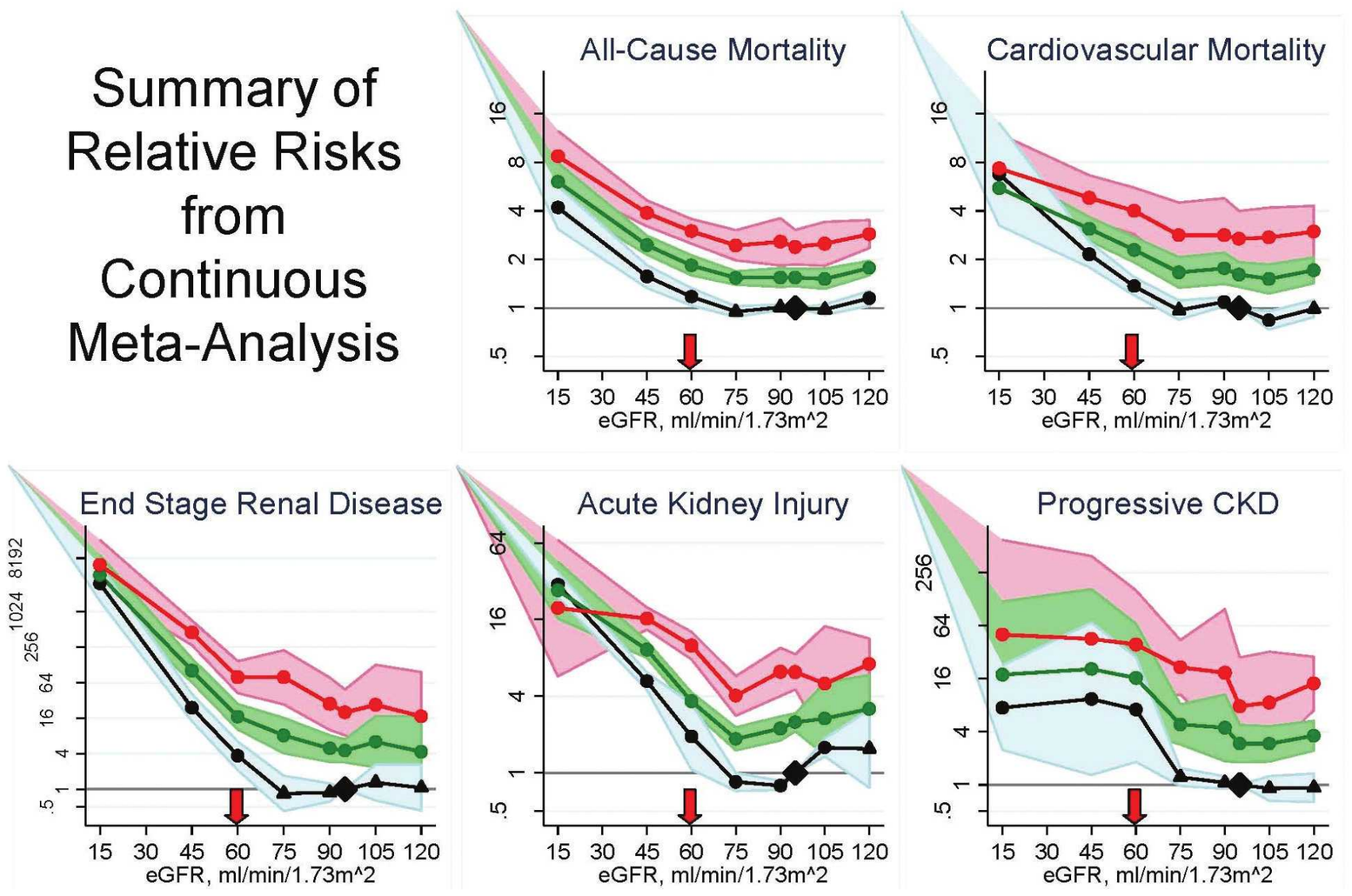


FIGURE 9.2

Summary of Relative Risks from Categorical Meta-Analysis

(dipstick included [-, ±, +, ≥++])

All-Cause Mortality

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR > 105	1.1	1.5	2.2	5.0
eGFR 90-105	Ref	1.4	1.5	3.1
eGFR 75-90	1.0	1.3	1.7	2.3
eGFR 60-75	1.0	1.4	1.8	2.7
eGFR 45-60	1.3	1.7	2.2	3.6
eGFR 30-45	1.9	2.3	3.3	4.9
eGFR 15-30	5.3	3.6	4.7	6.6

Cardiovascular Mortality

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR > 105	0.9	1.3	2.3	2.1
eGFR 90-105	Ref	1.5	1.7	3.7
eGFR 75-90	1.0	1.3	1.6	3.7
eGFR 60-75	1.1	1.4	2.0	4.1
eGFR 45-60	1.5	2.2	2.8	4.3
eGFR 30-45	2.2	2.7	3.4	5.2
eGFR 15-30	14	7.9	4.8	8.1

Kidney Failure (ESRD)

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR > 105	Ref	Ref	7.8	18
eGFR 90-105	Ref	Ref	11	20
eGFR 75-90	Ref	Ref	3.8	48
eGFR 60-75	Ref	Ref	7.4	67
eGFR 45-60	5.2	22	40	147
eGFR 30-45	56	74	294	763
eGFR 15-30	433	1044	1056	2286

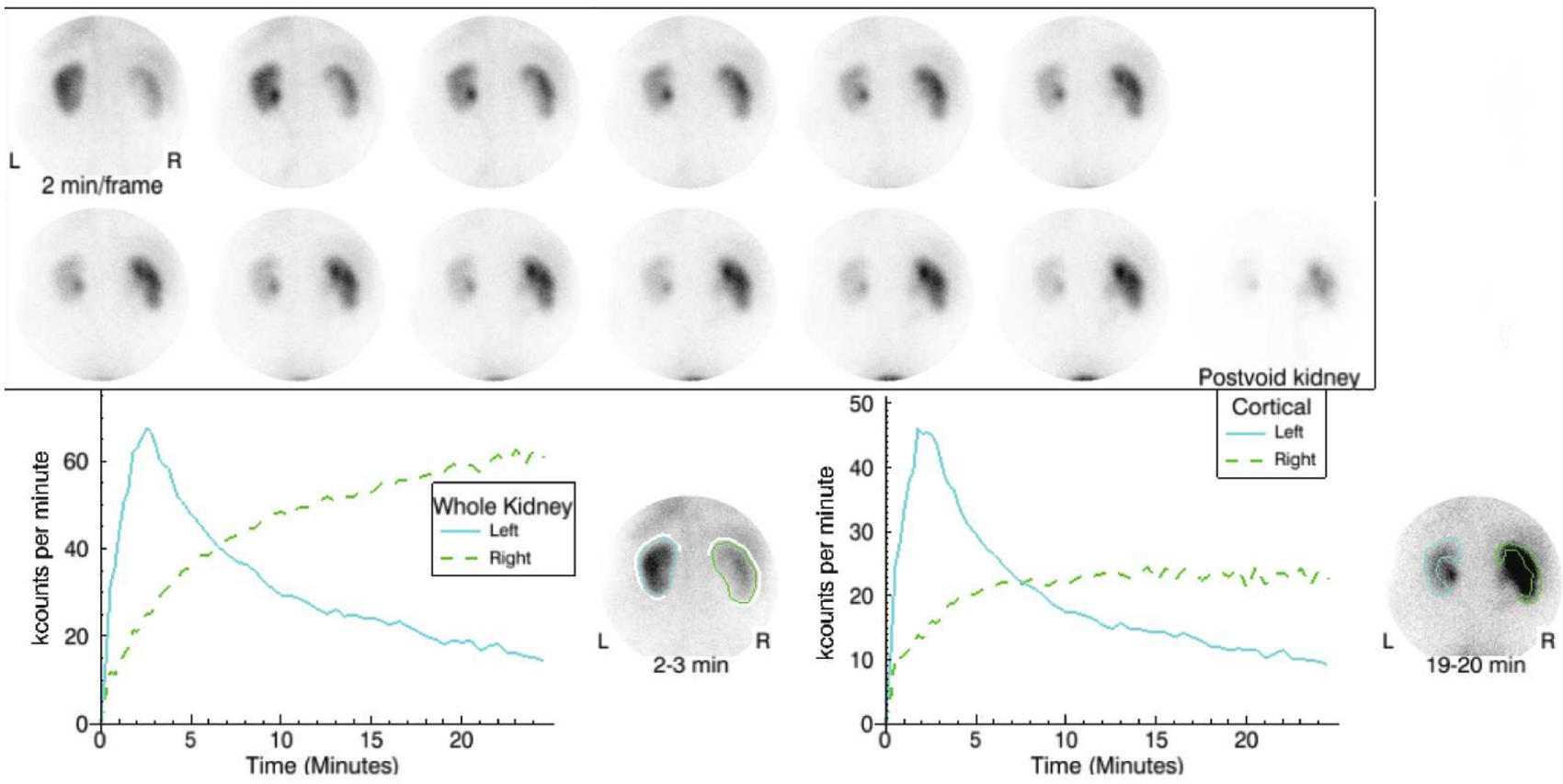
Acute Kidney Injury (AKI)

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR > 105	Ref	Ref	2.7	8.4
eGFR 90-105	Ref	Ref	2.4	5.8
eGFR 75-90	Ref	Ref	2.5	4.1
eGFR 60-75	Ref	Ref	3.3	6.4
eGFR 45-60	2.2	4.9	6.4	5.9
eGFR 30-45	7.3	10	12	20
eGFR 15-30	17	17	21	29

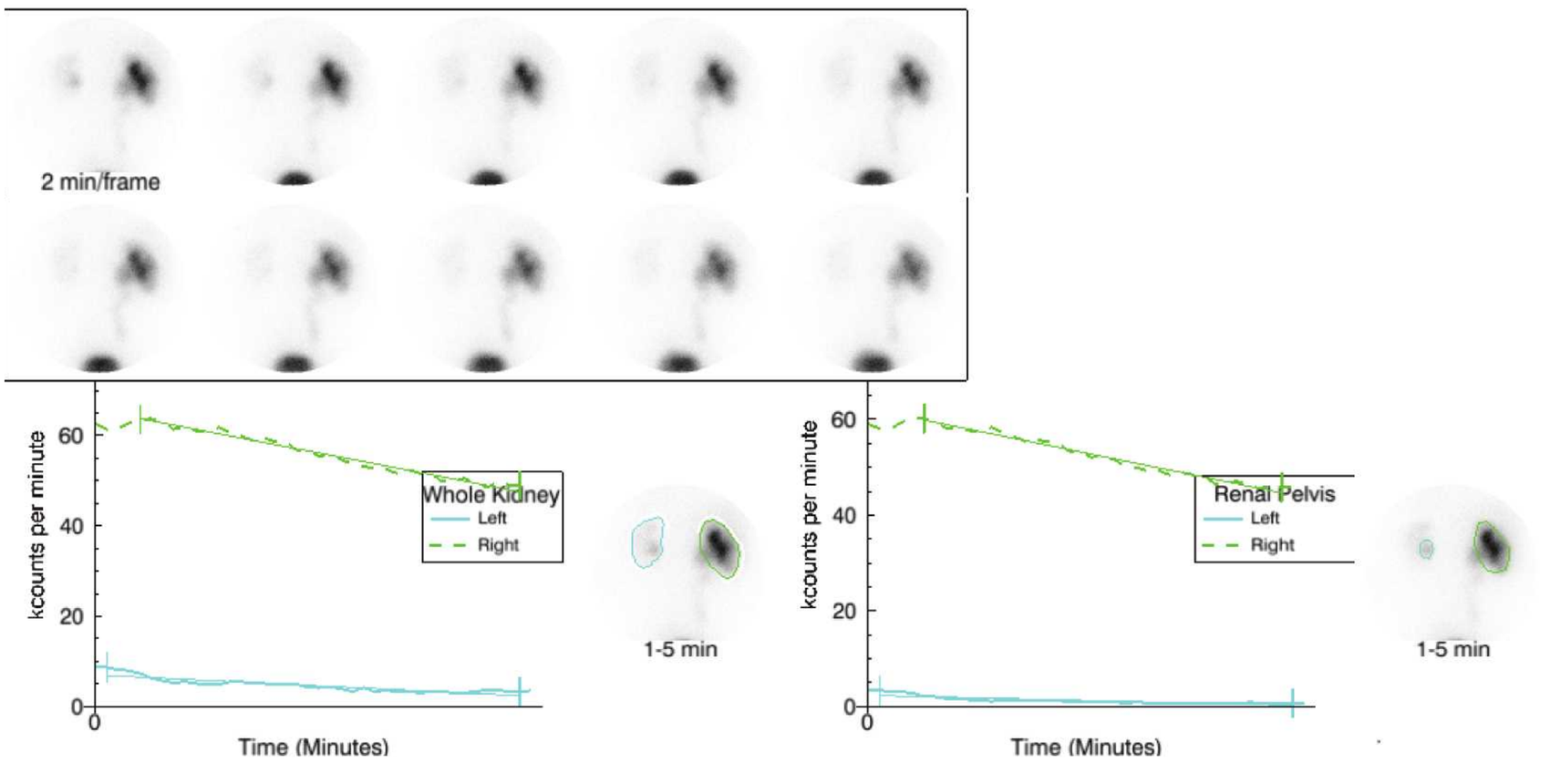
Progressive CKD

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR > 105	Ref	Ref	0.4	3.0
eGFR 90-105	Ref	Ref	0.9	3.3
eGFR 75-90	Ref	Ref	1.9	5.0
eGFR 60-75	Ref	Ref	3.2	8.1
eGFR 45-60	3.1	4.0	9.4	57
eGFR 30-45	3.0	19	15	22
eGFR 15-30	4.0	12	21	7.7

FIGURE 9.3

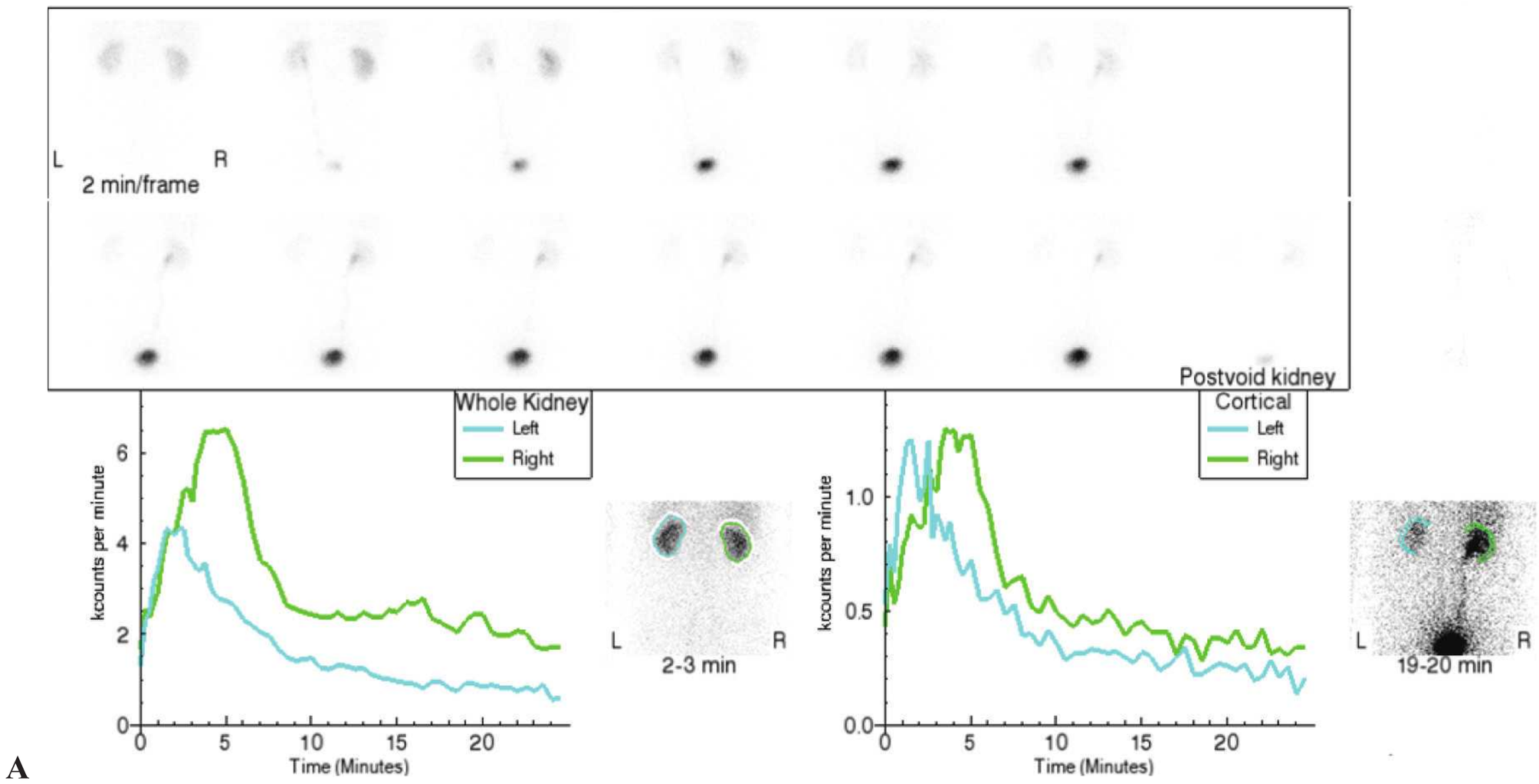


A

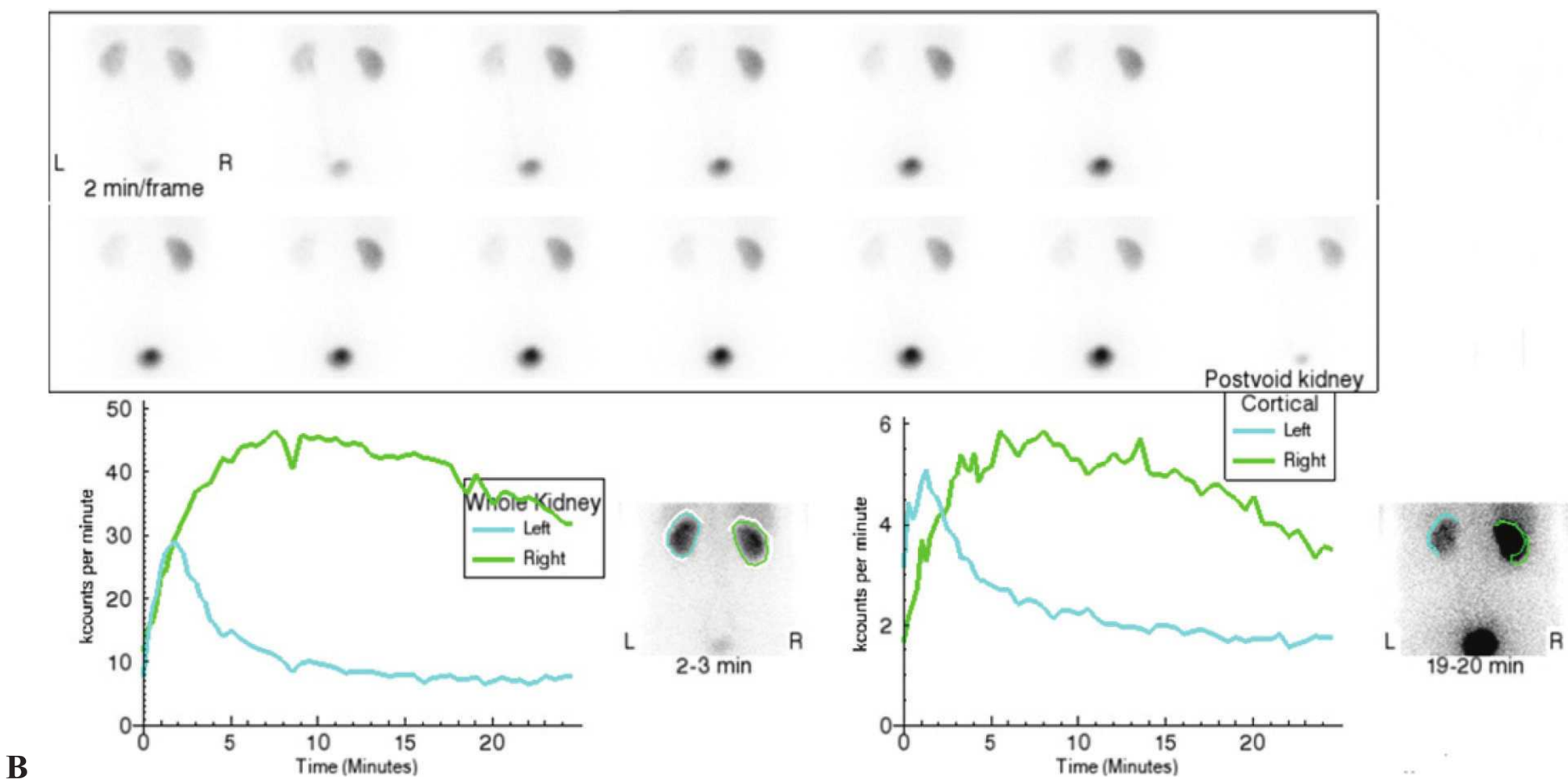


B

FIGURE 10.37A,B



A



B

FIGURE 10.38A,B

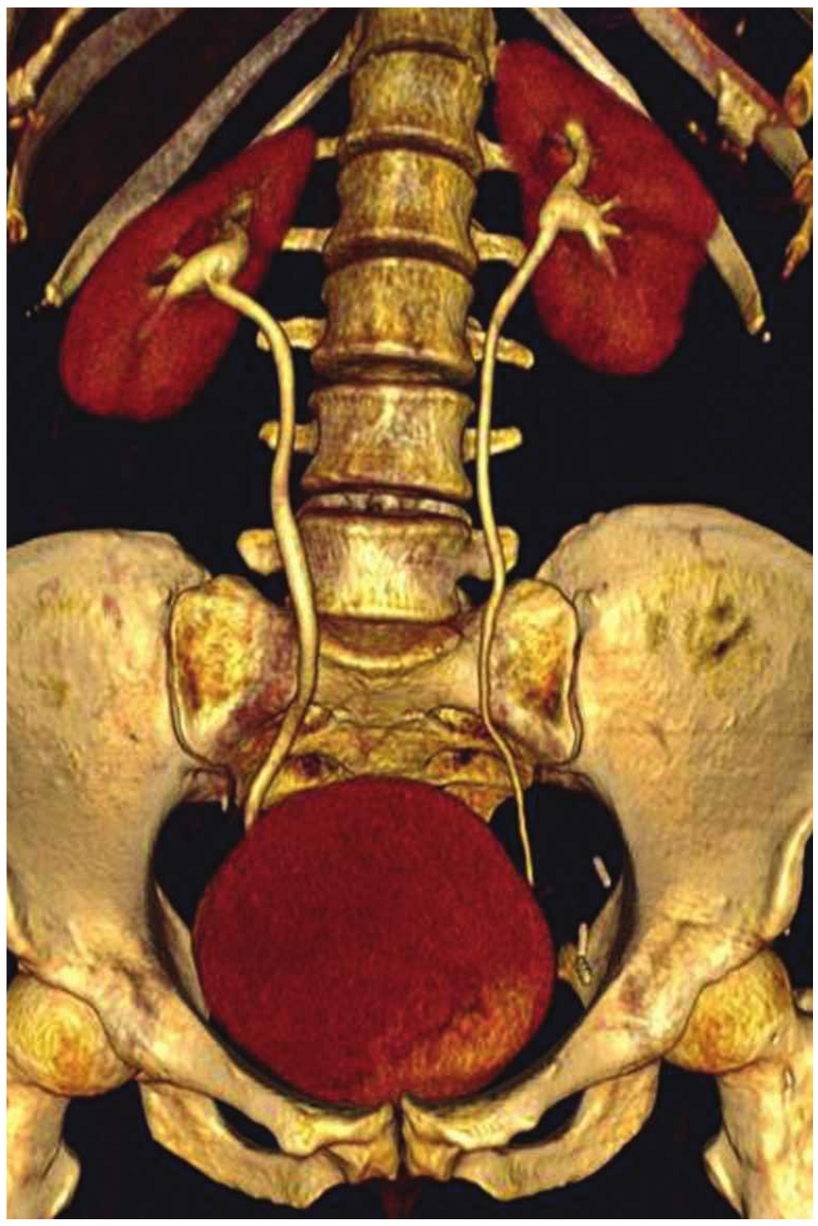
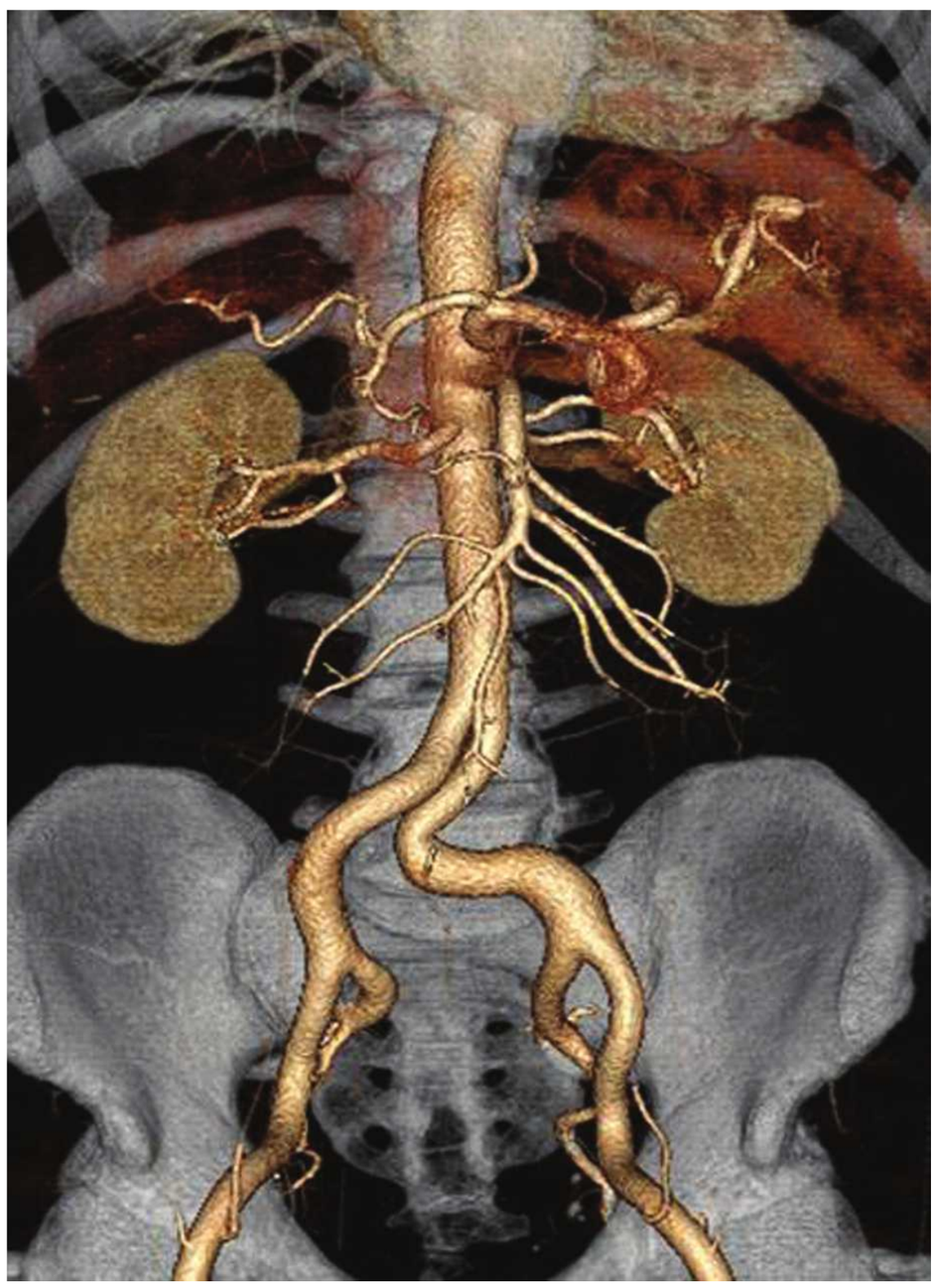


FIGURE 11.1B



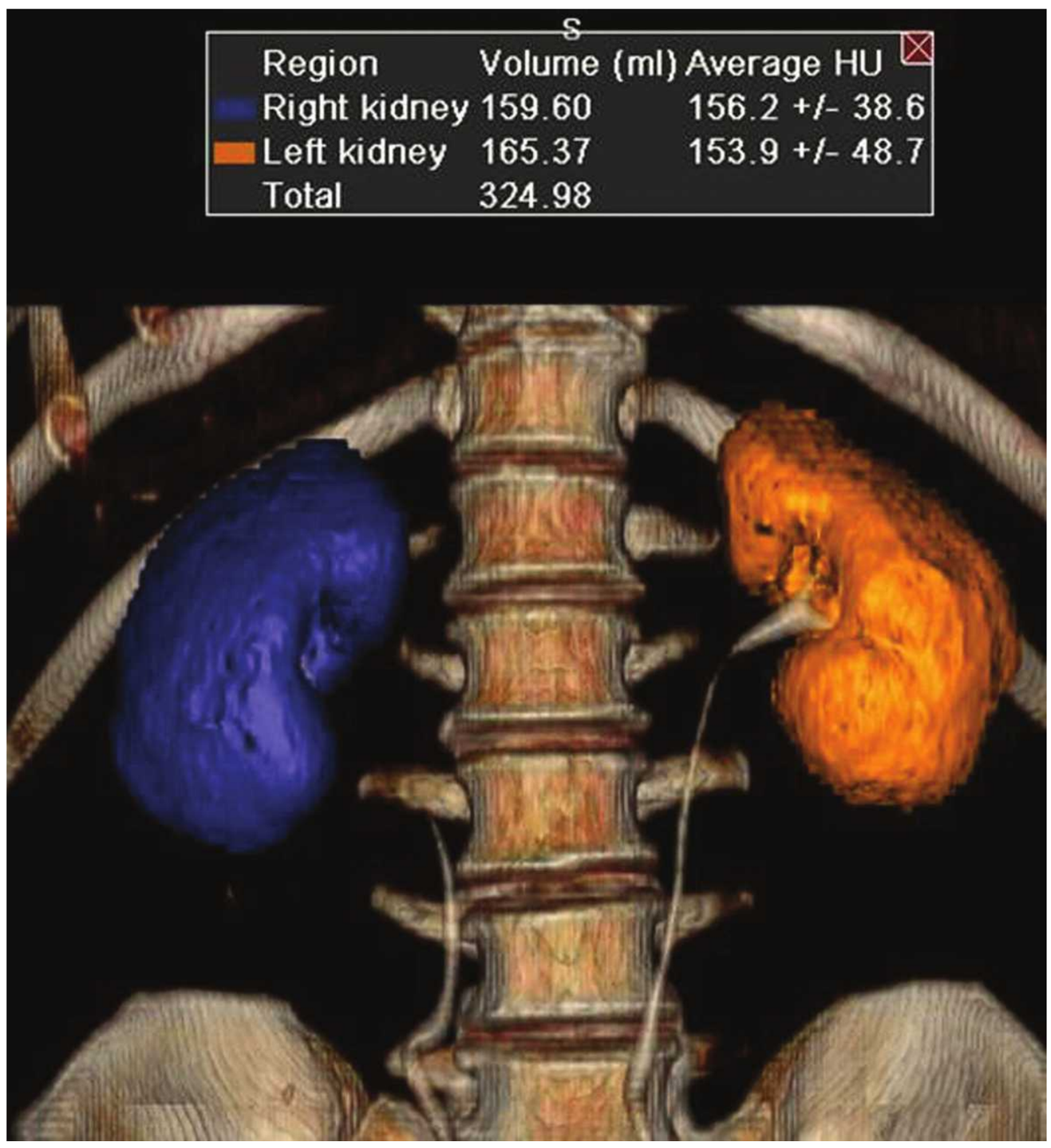
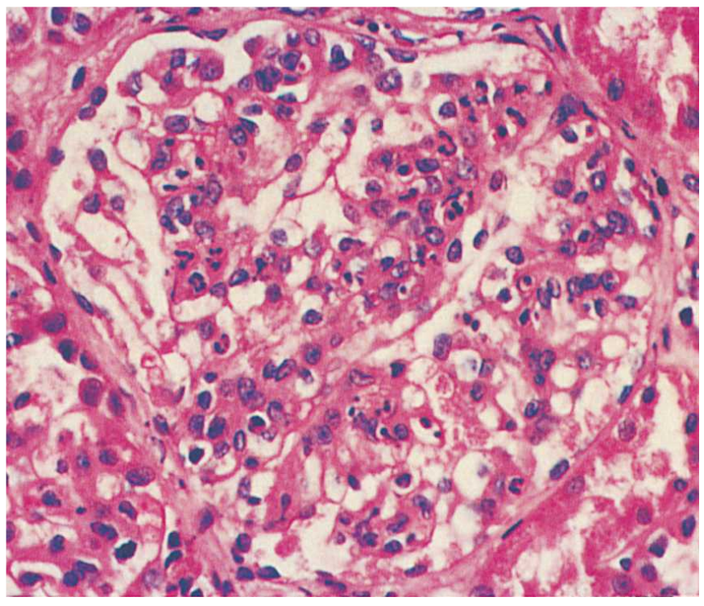
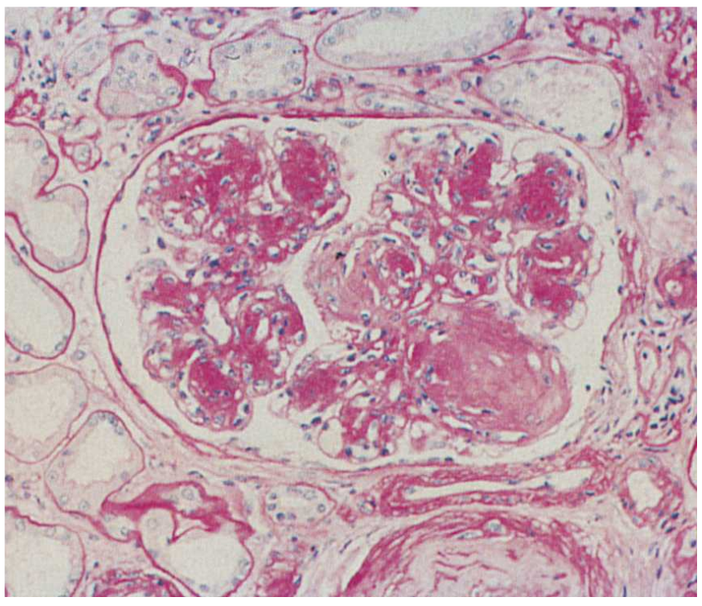
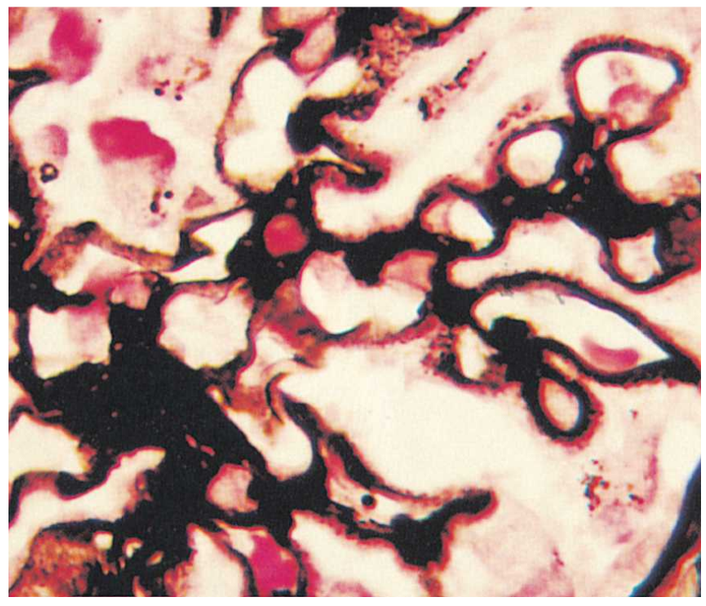


FIGURE 11.2A,C

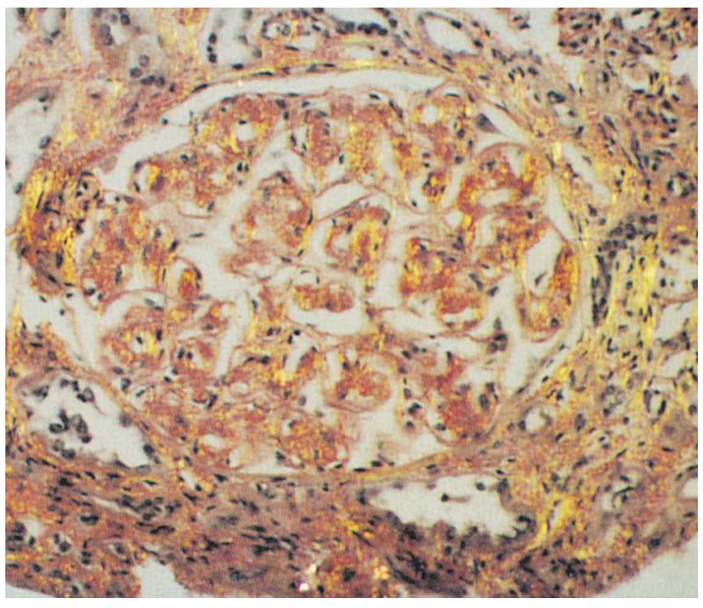


A,B

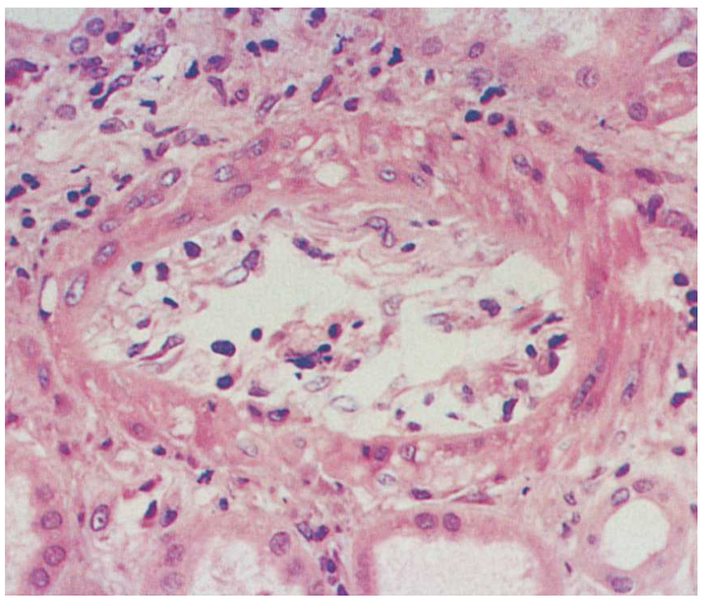


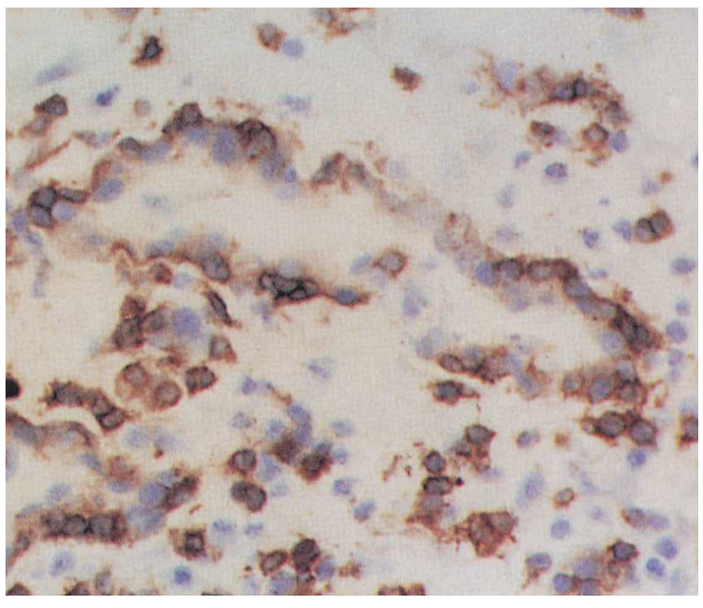


C



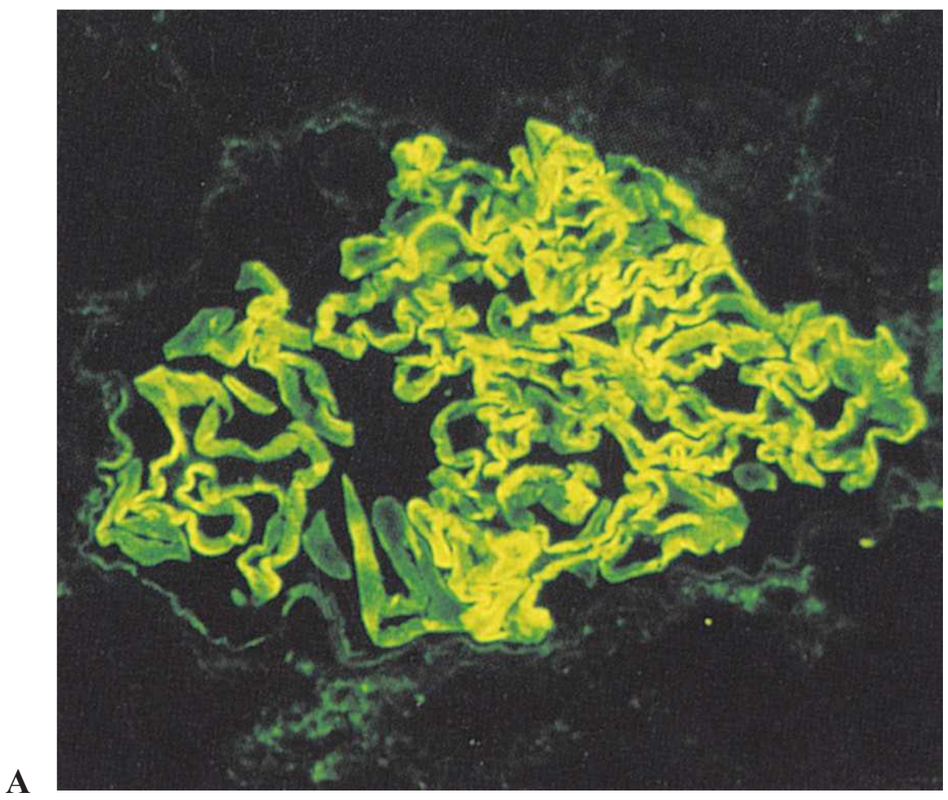
D,E



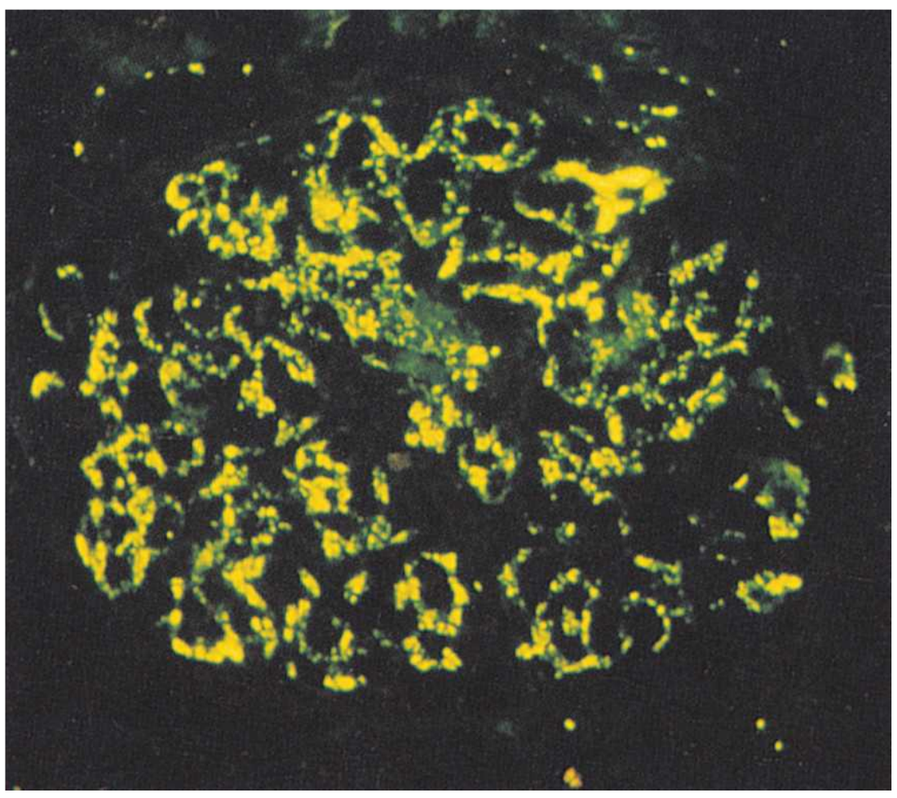


F

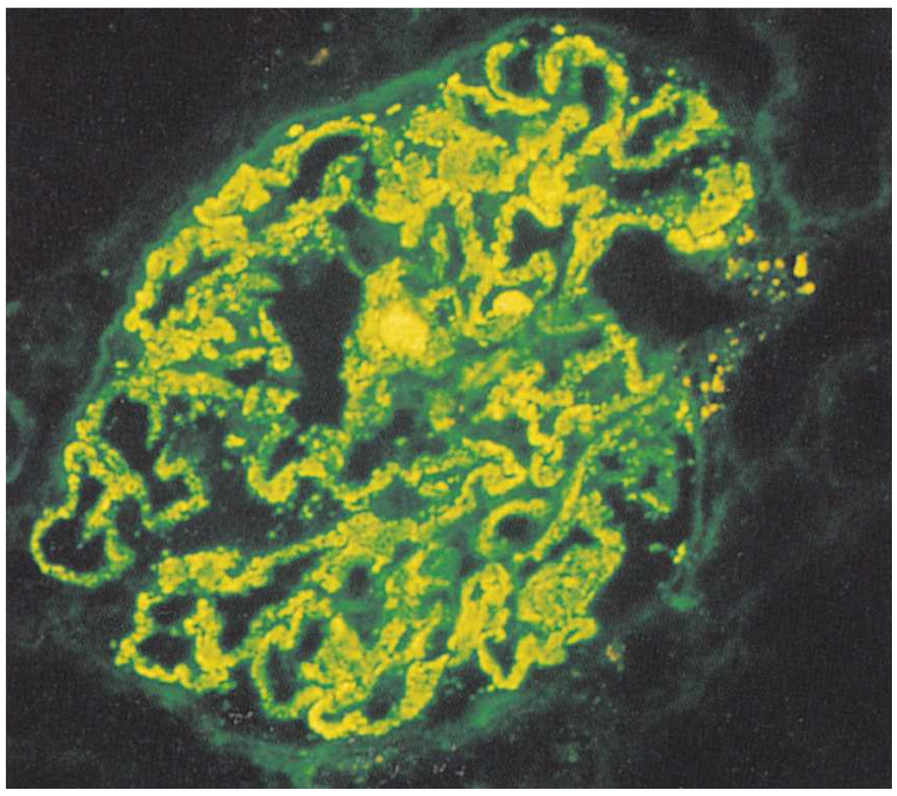
FIGURE 13.4



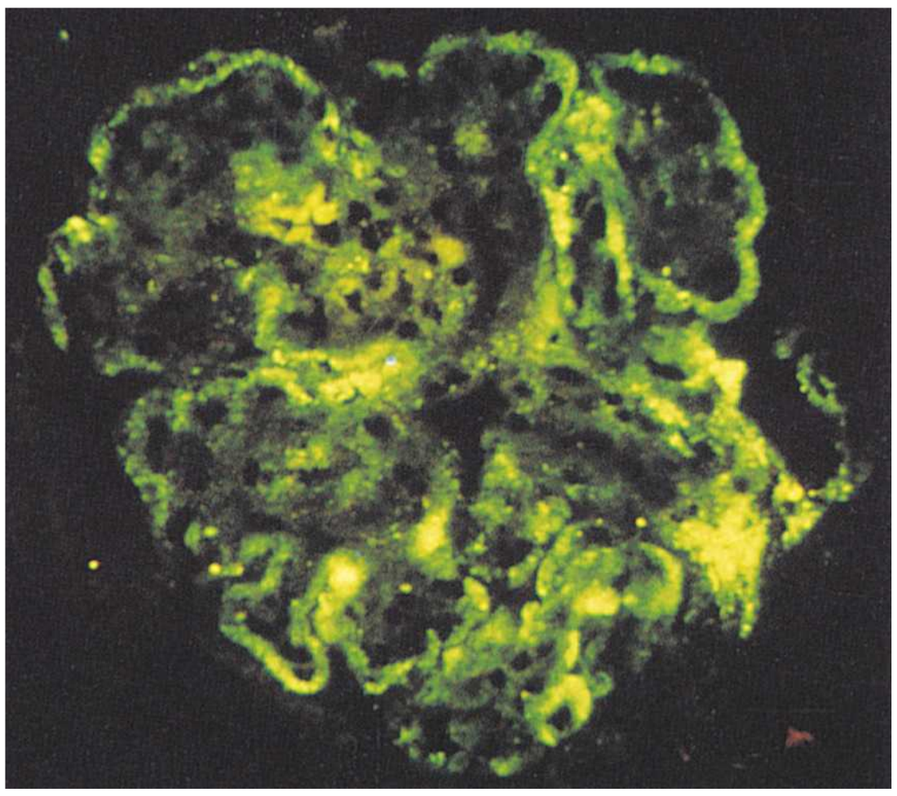
A



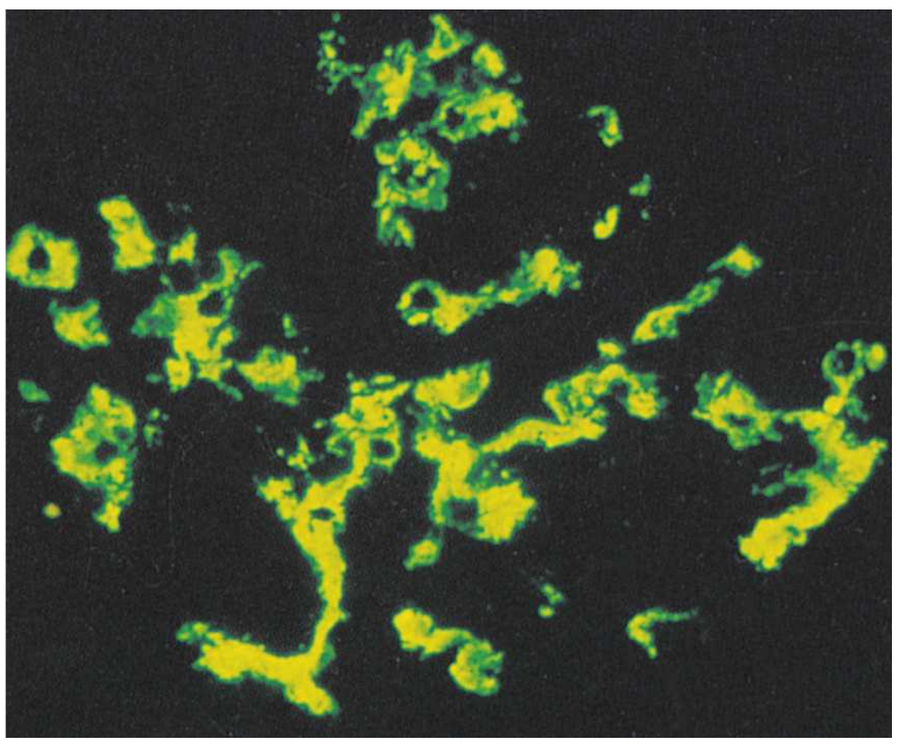
B



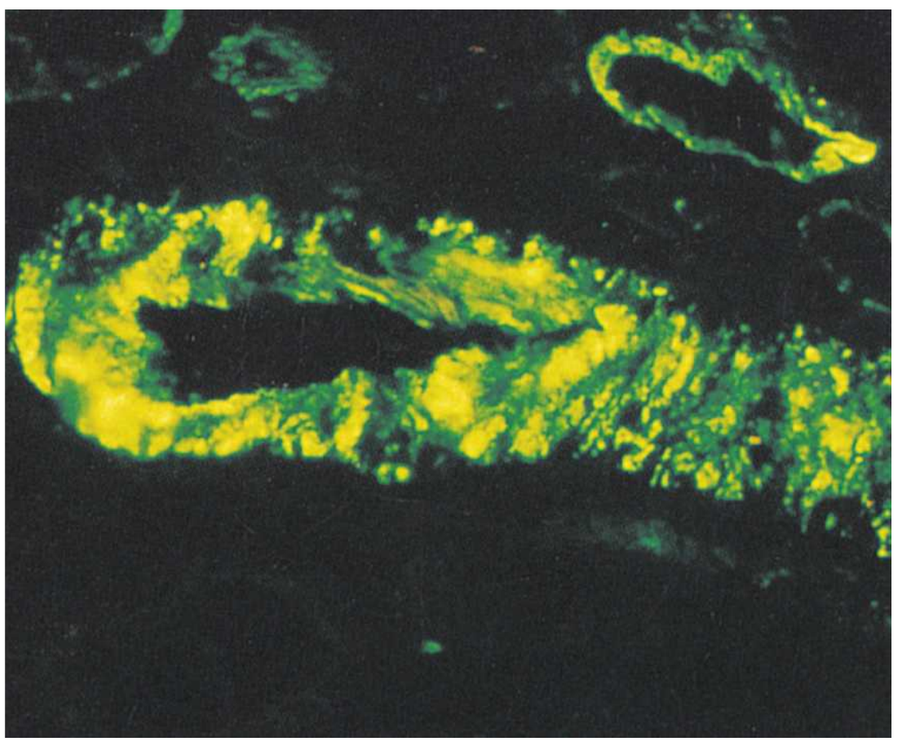
C



D



E



F

FIGURE 13.22 A,F

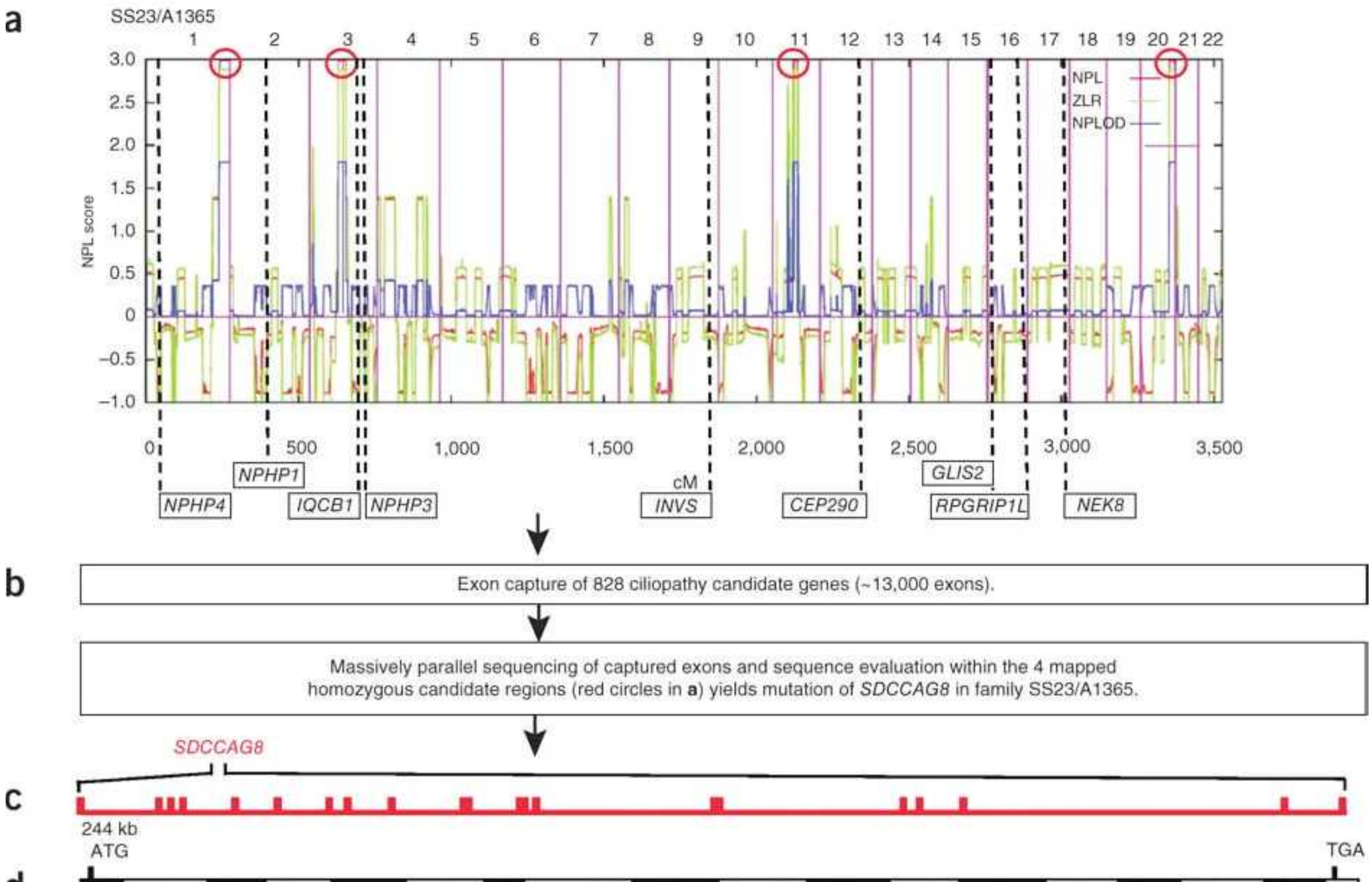

a
SS23/A1365
NPL score
NPL
ZLR
NPLOD
cM
NPHP4
NPHP1
IQCB1
NPHP3
INVS
CEP290
GLIS2
RPGRIP1L
NEK8
b
Exon capture of 828 ciliopathy candidate genes (~13,000 exons).
Massively parallel sequencing of captured exons and sequence evaluation within the 4 mapped homozygous candidate regions (red circles in a) yields mutation of SDCCAG8 in family SS23/A1365.
c
SDCCAG8
244 kb
ATG
TGA
d
2,142 bp
< Deletion >
e
NGD
NLS
CC1
CC2
CC3
CC4
CC5
CC6
CC7
CC8
713 aa
PN
PC
Gln_rich (PS50322)
f
F159
Δ exon 5–7
FII.22
679A>T
(K227X)
FI.2
740+356C>T
(ESE loss)
A2290
1068+1G>A
(splice)
SS-F336
1339-40insG
(447fsX463)
SS23/A1365
1420delG
(E474fsX493)
F1054
1796T>G
(L599X)
F195
1946-1949
delGTGT
(C649fsX658)
Control
F159-21
F159-22
Exon 8
Exon 5
Exon 6
Exon 8
Exon 8
Exon 7

FIGURE 14.1

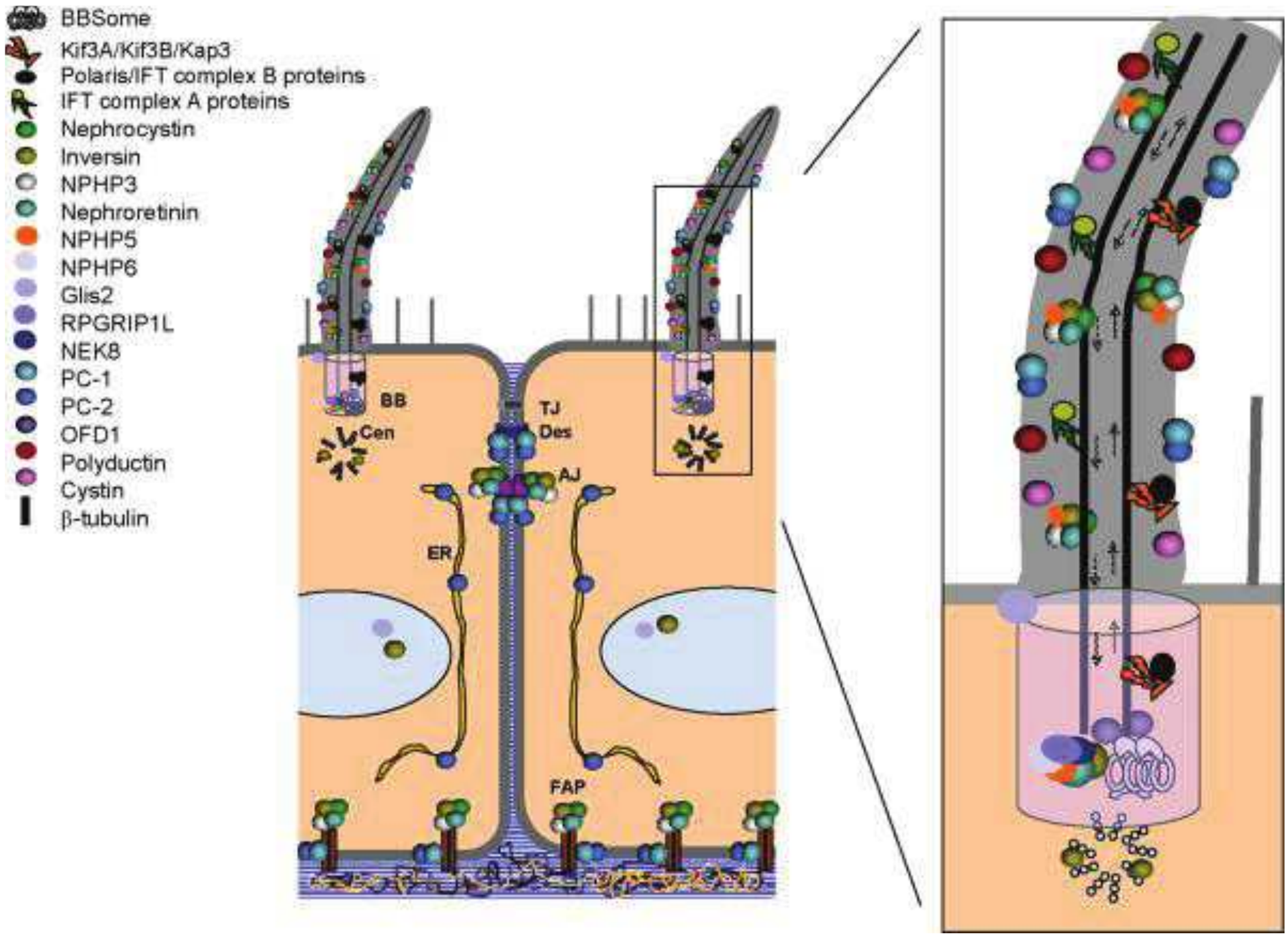


FIGURE 14.7

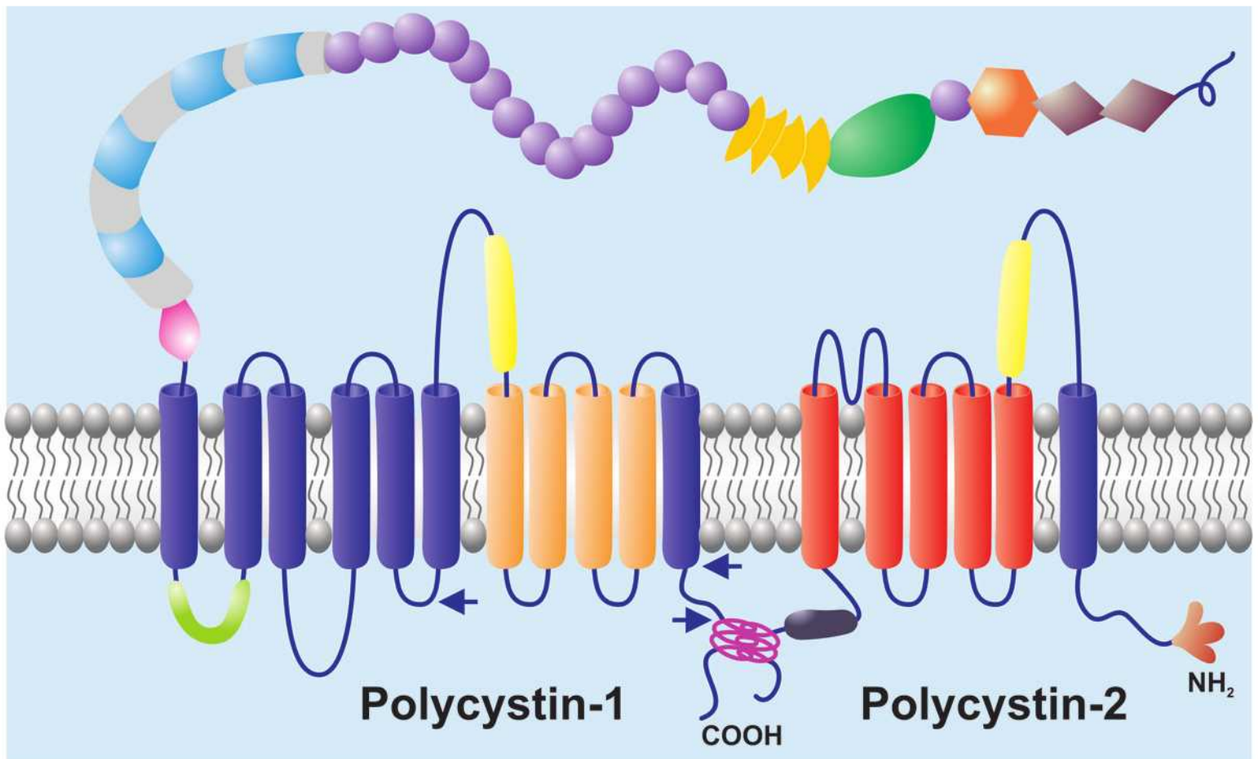


FIGURE 16.2

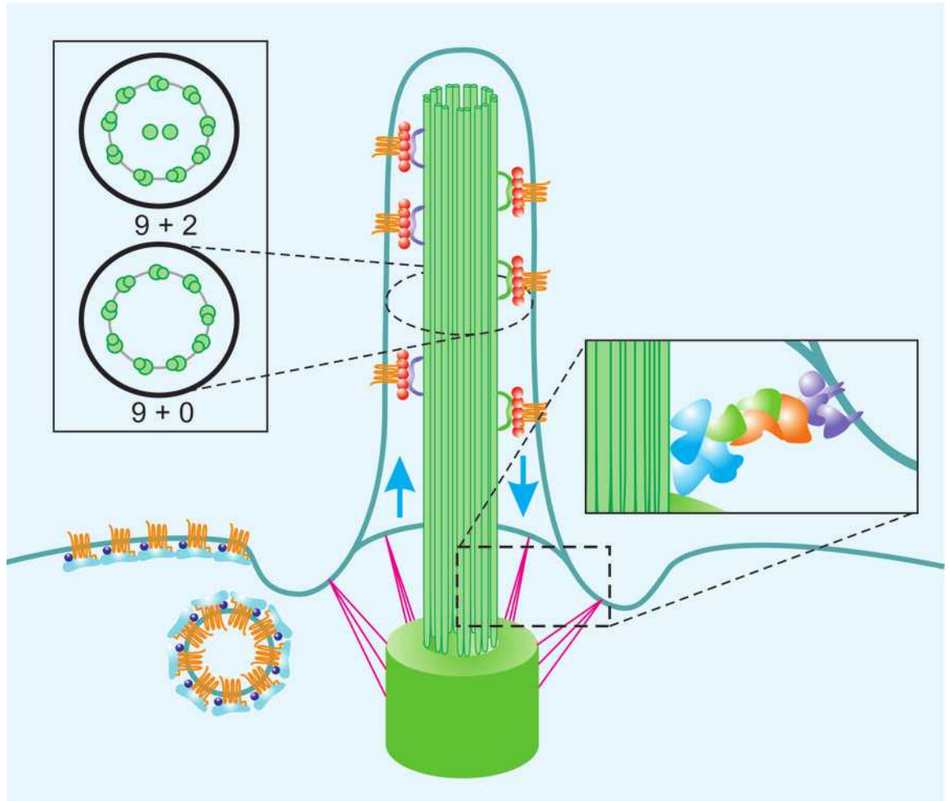


FIGURE 16.5

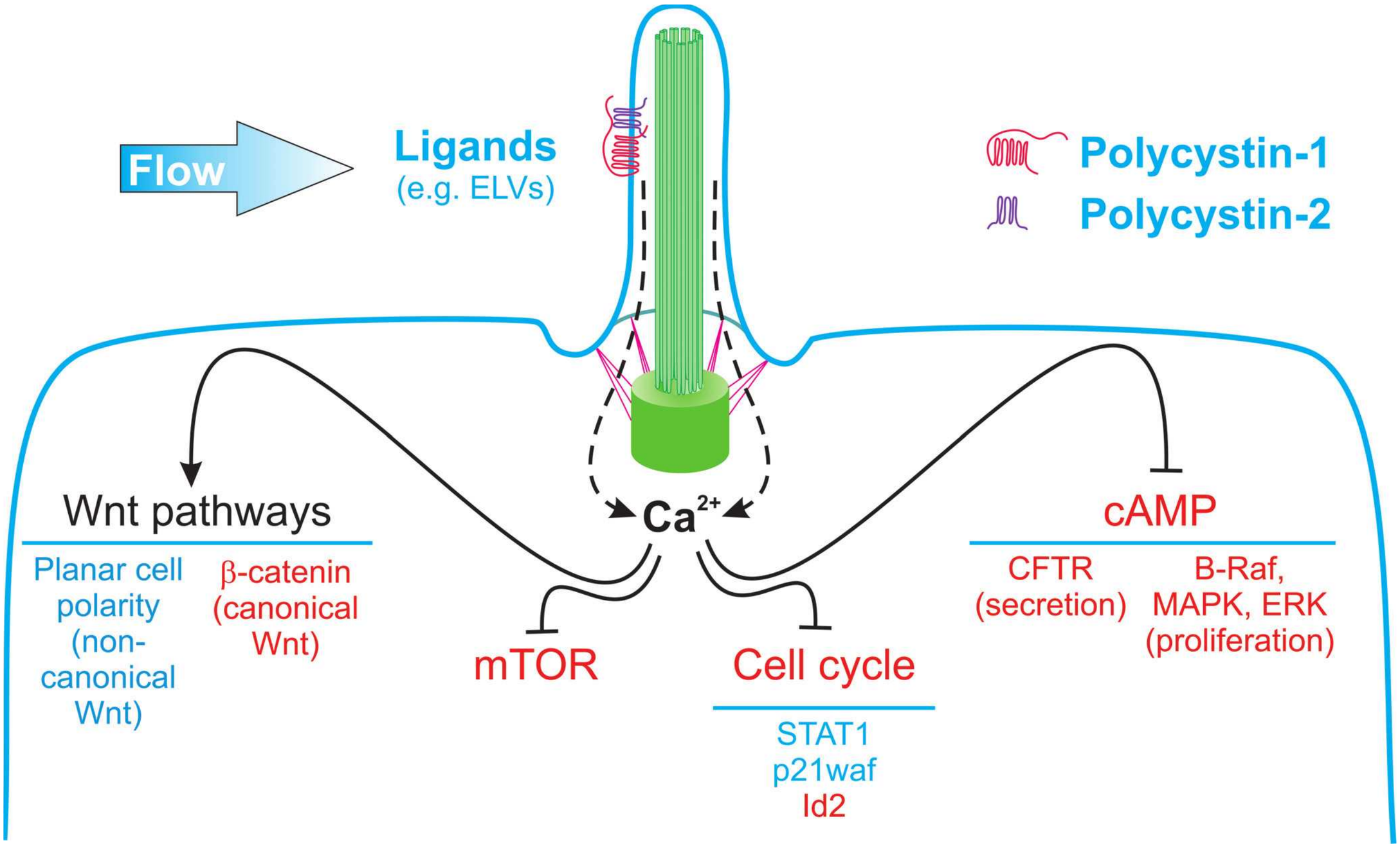


FIGURE 16.6

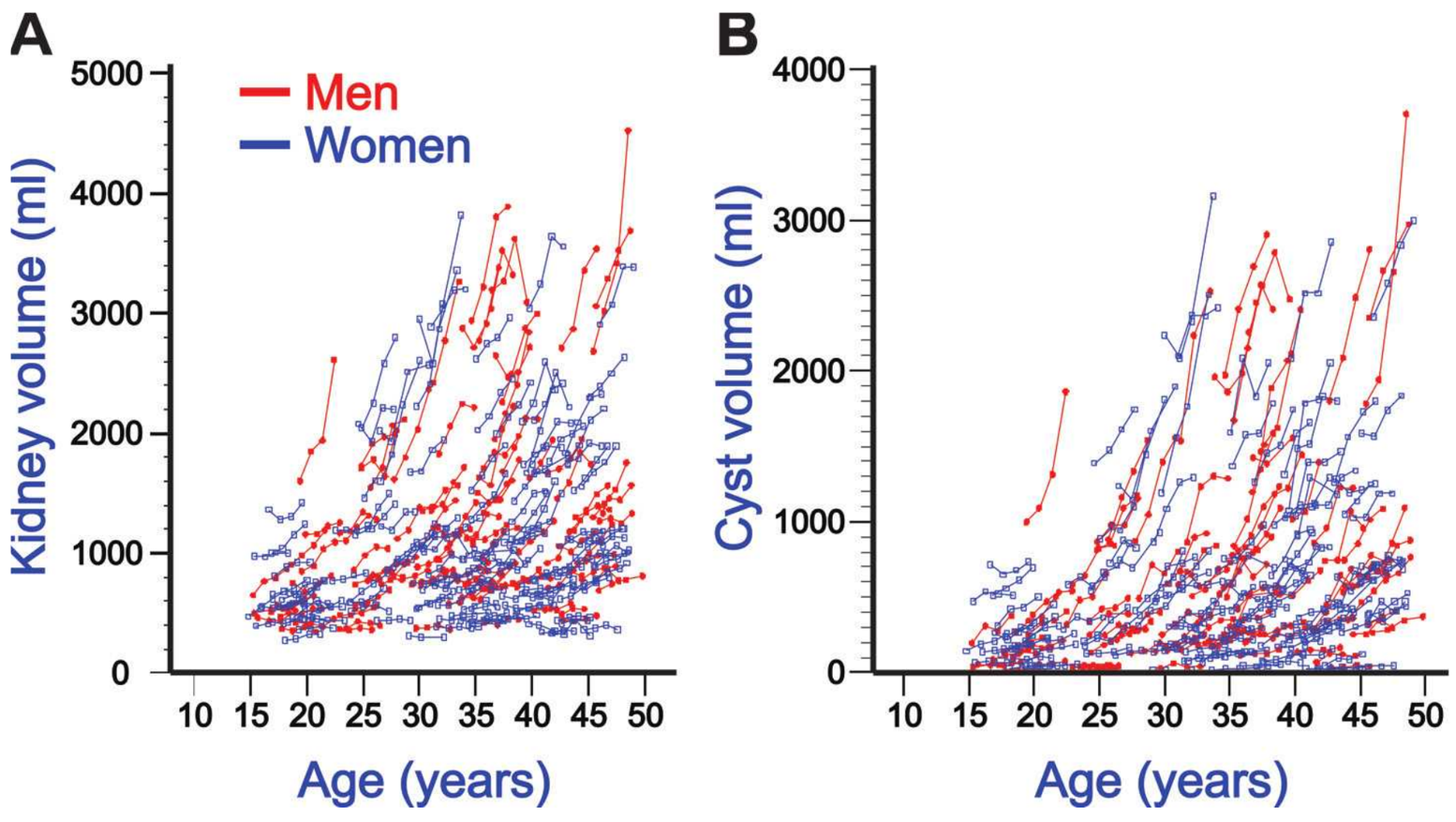


FIGURE 16.9

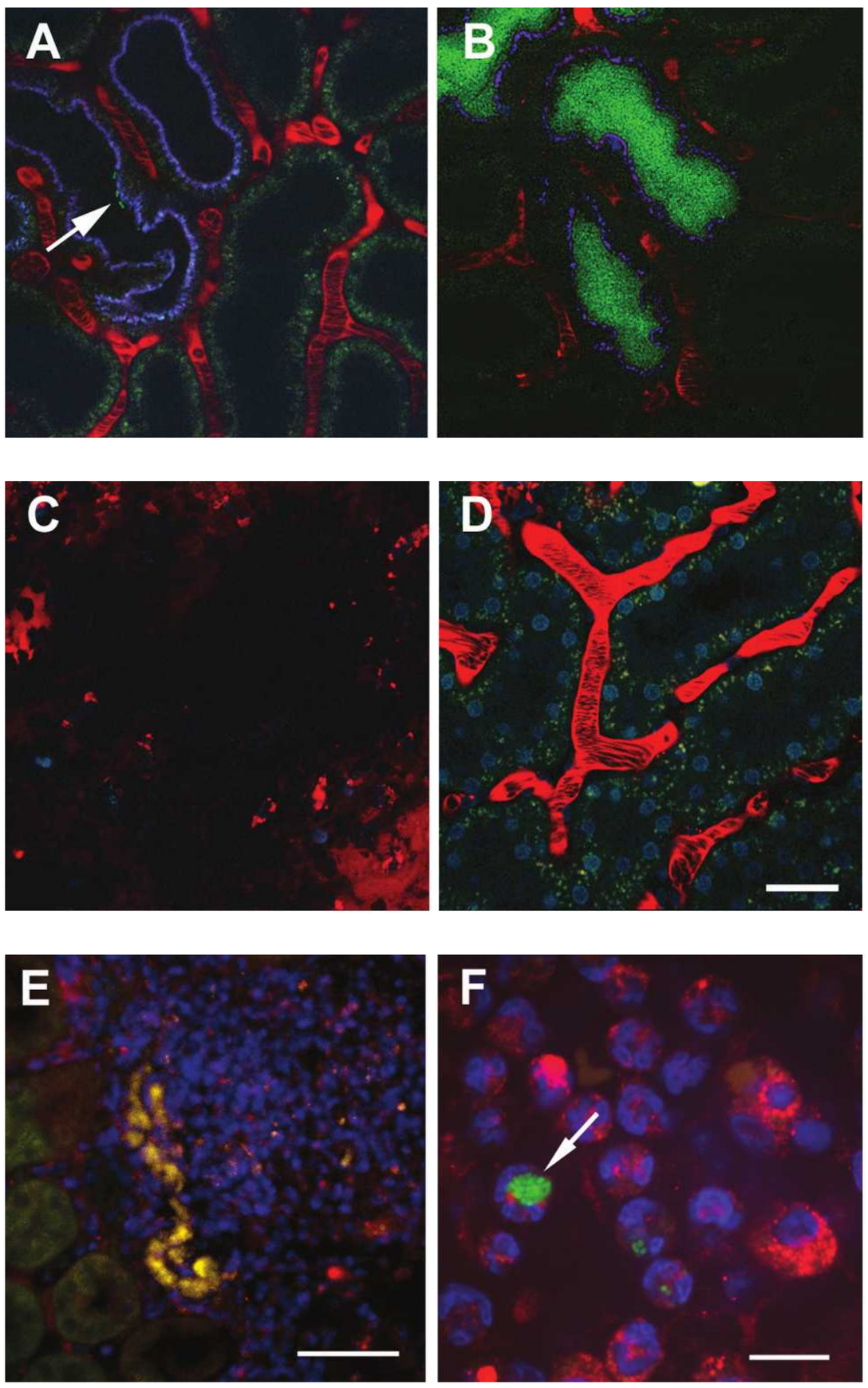


FIGURE 21.1

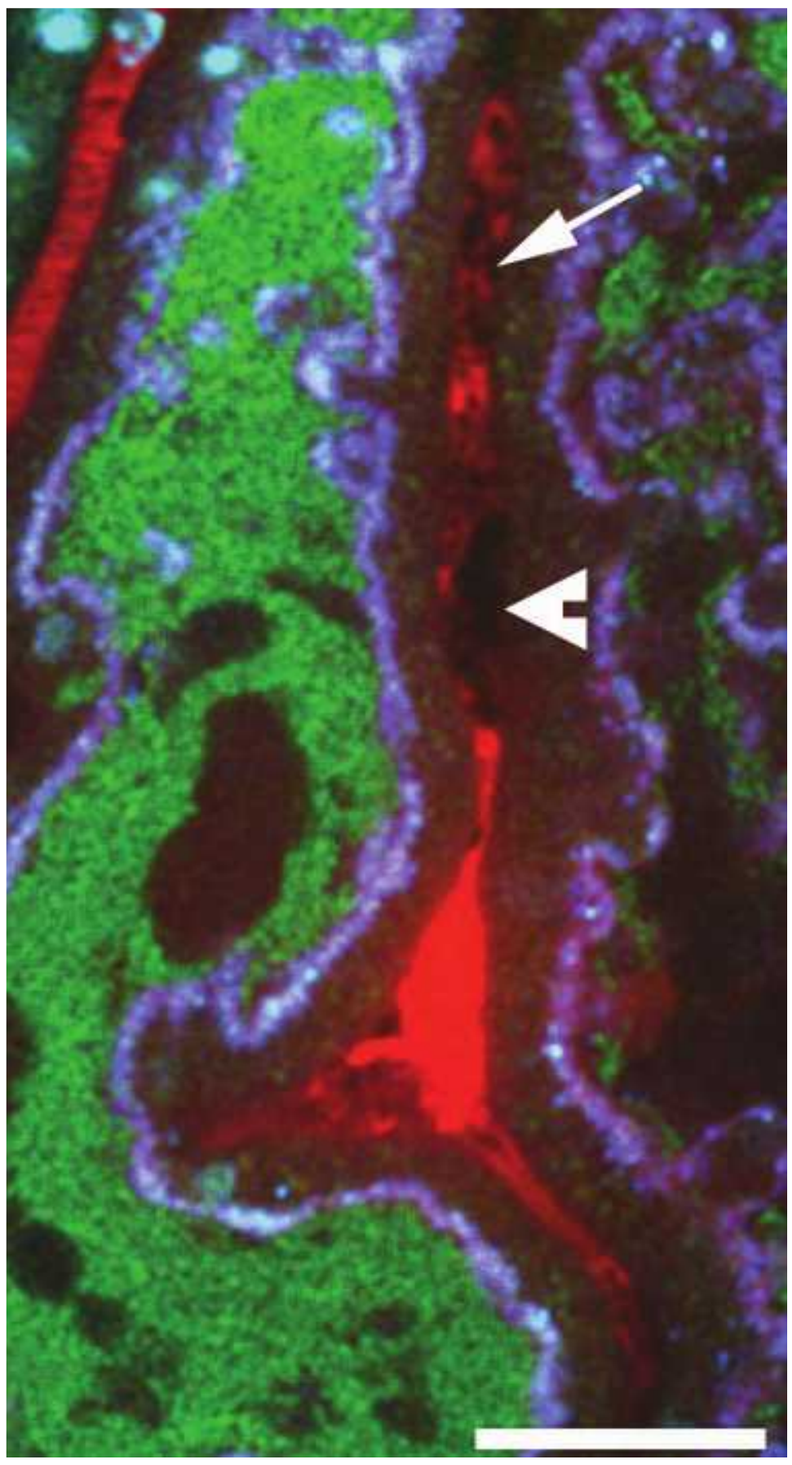


FIGURE 21.2

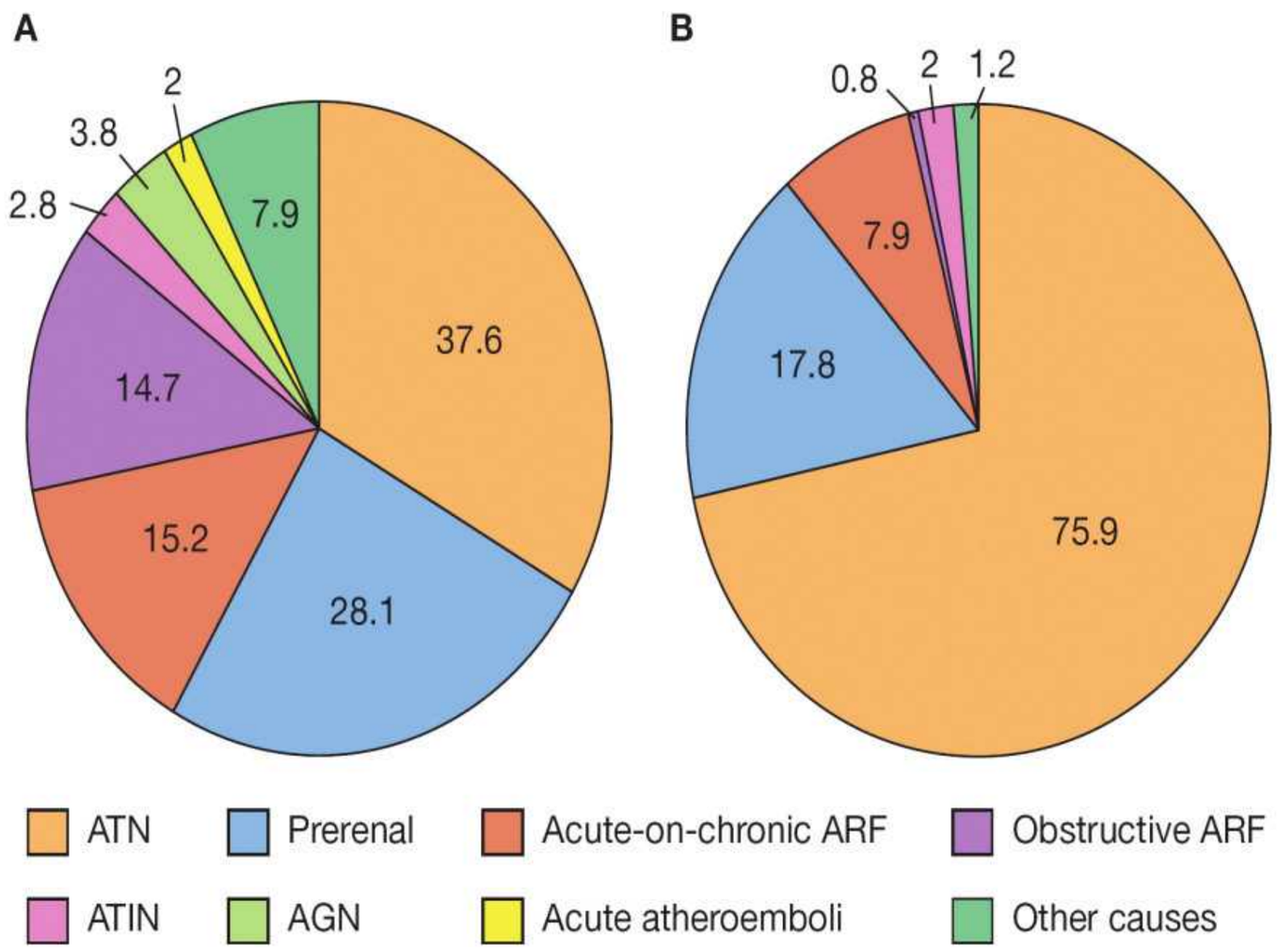


FIGURE 28.7

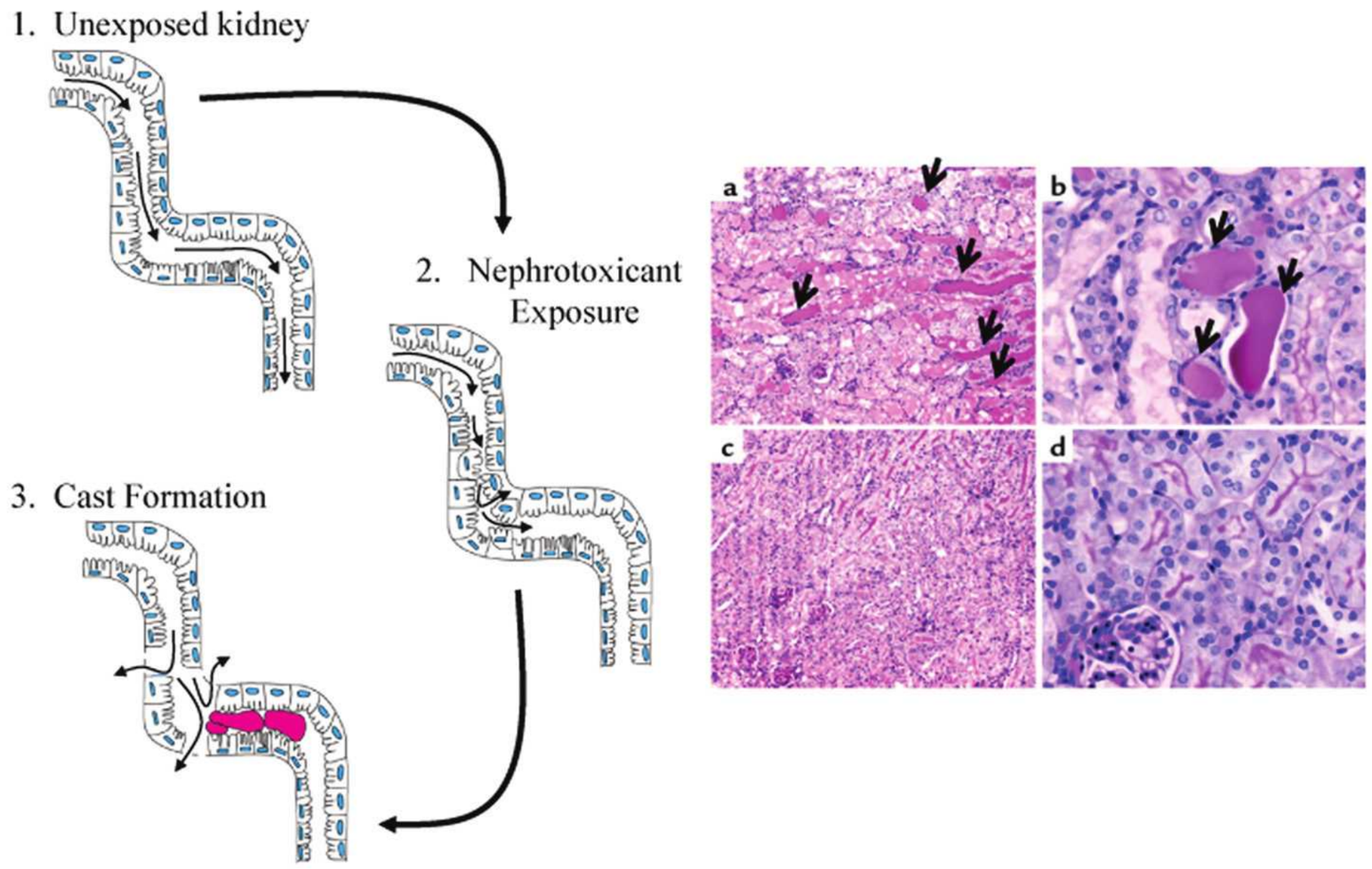


FIGURE 30.1

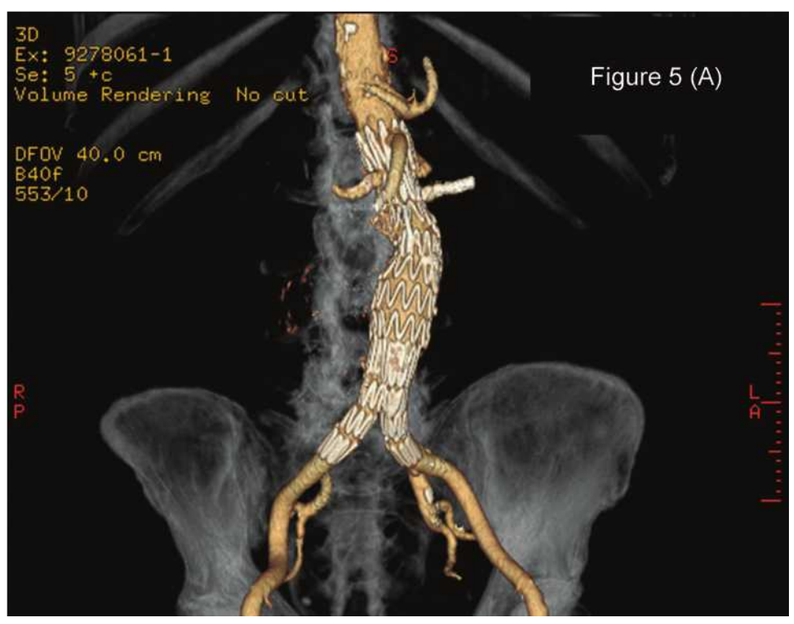
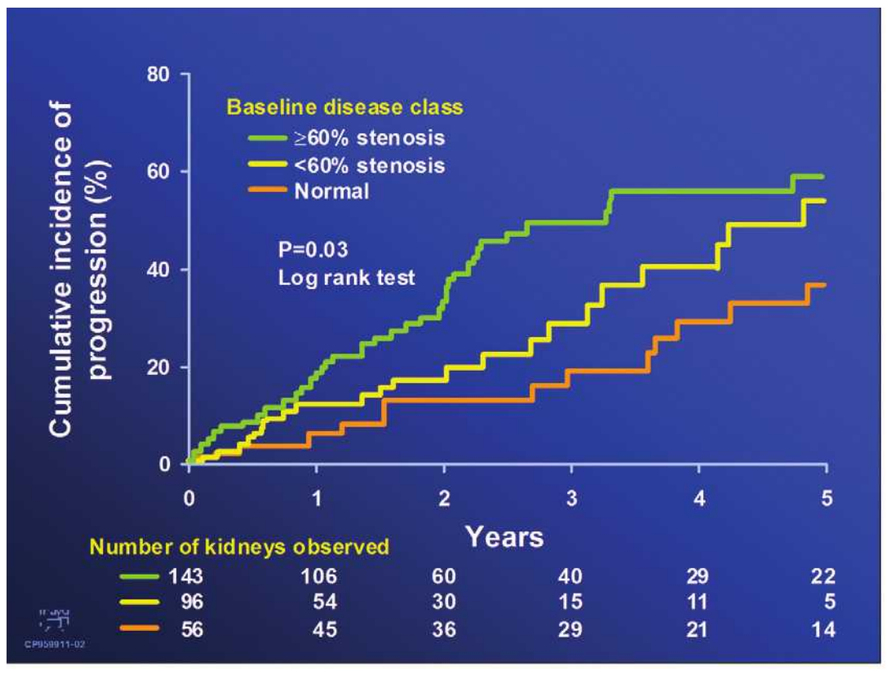


FIGURE 42.5A

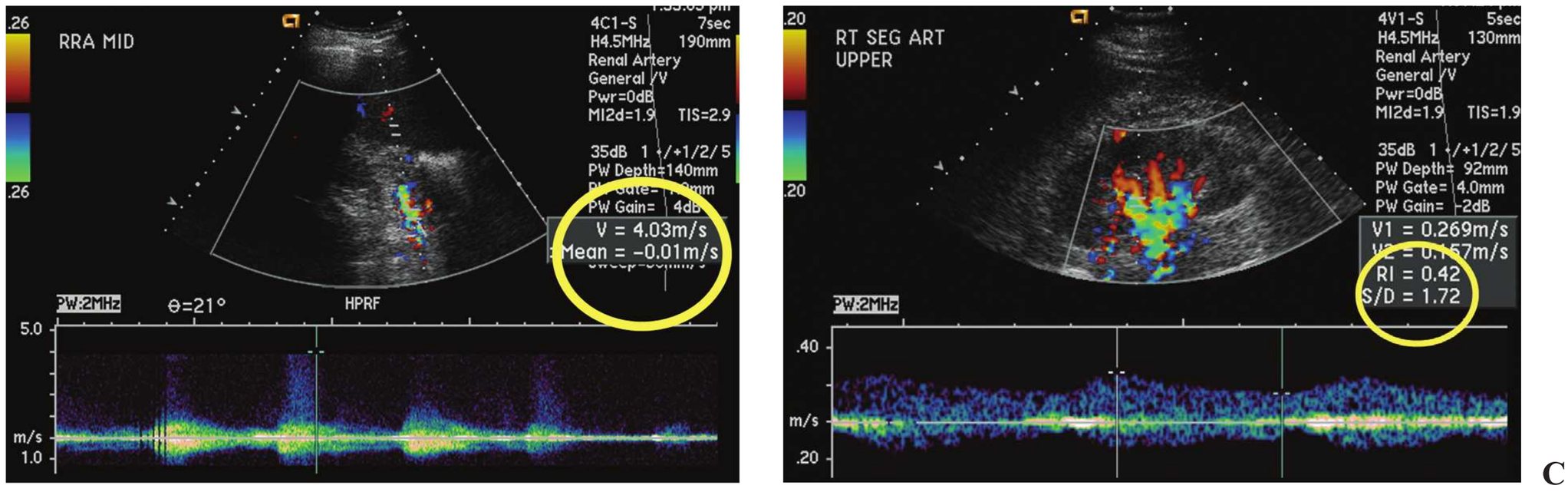


N=170 patients with study of 295 renal arteries by serial duplex scans between 1990 and 1997.

Total Occlusion: 9/295 arteries (3%)

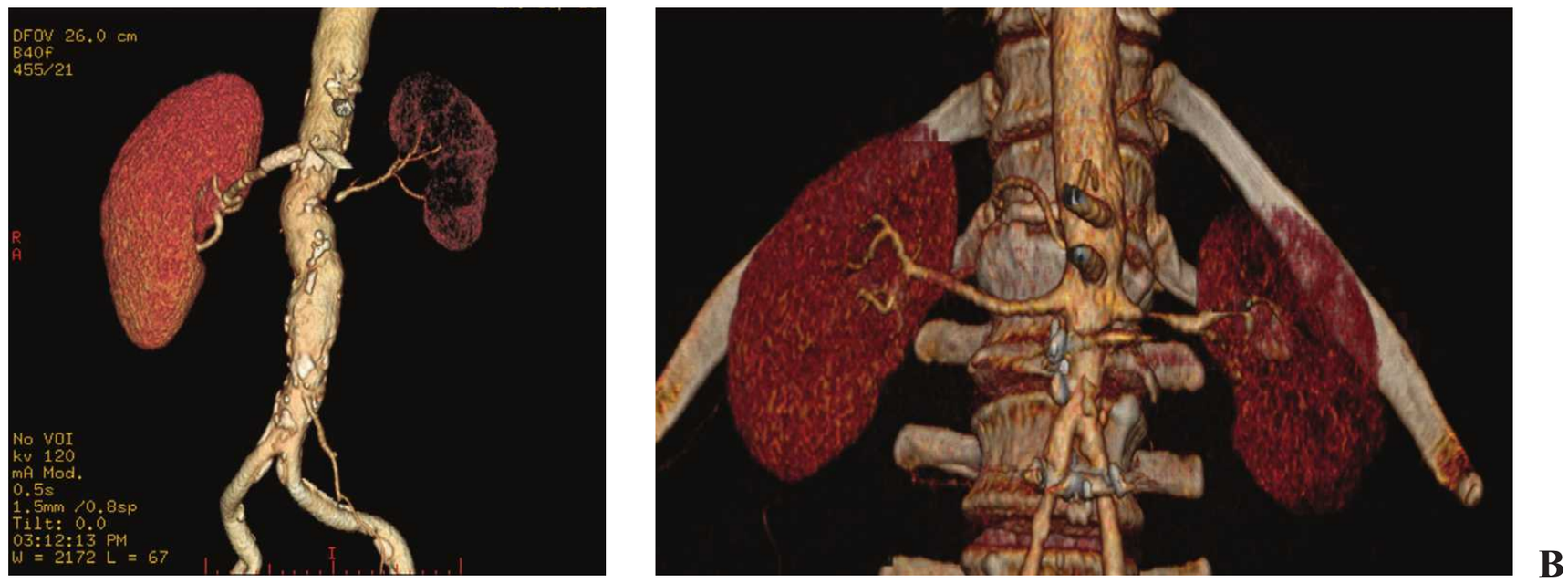
Caps, et. al. : Circulation 98: 2866-2872, 1998

FIGURE 42.6



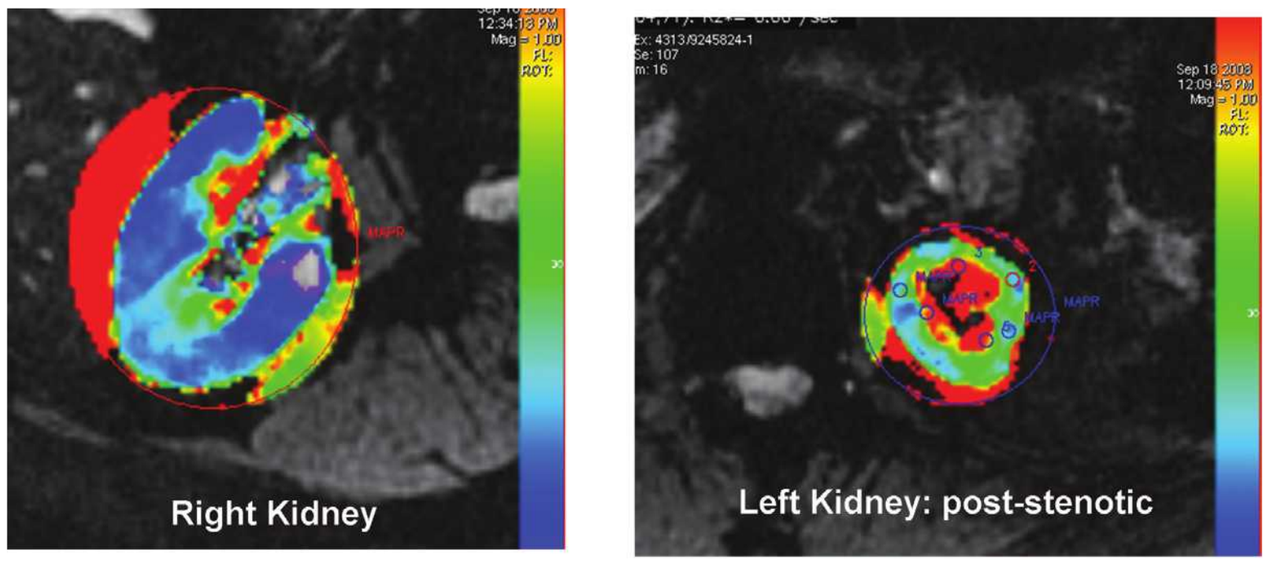
B C

FIGURE 42.13B,C



A B

FIGURE 42.16A,B



B C

FIGURE 42.18B,C