Renovascular Hypertension

Background

Renovascular hypertension (RVHT) reflects the causal relation between anatomically evident arterial occlusive disease and elevated blood pressure. The coexistence of renal arterial vascular (ie, renovascular) disease and hypertension roughly defines this type of nonessential hypertension. More specific diagnoses are made retrospectively when hypertension improves after intravascular intervention.[1]

Since Goldblatt's seminal experiment in 1934, RVHT has increasingly been recognized as an important cause of clinically atypical hypertension and chronic kidney disease, the latter by virtue of renal ischemia. RVHT is the clinical consequence of activation of the renin-angiotensin-aldosterone system (RAAS).

Renal artery occlusion creates ischemia, which triggers the release of renin and a secondary elevation in blood pressure. Hyperreninemia promotes conversion of angiotensin I to angiotensin II, causing severe vasoconstriction and aldosterone release. The ensuing cascade of events varies, depending on the presence of a functioning contralateral kidney.

When two kidneys are present, aldosterone-mediated sodium and water retention is handled properly by the nonstenotic kidney, precluding volume from contributing to the angiotensin II–mediated hypertension. By contrast, a solitary ischemic kidney has little or no capacity for sodium and water excretion; hence, volume plays an additive role in the hypertension.

At present, no sufficiently accurate, noninvasive, radiologic, or serologic screening test is available that, if negative, completely excludes the presence of renal artery stenosis (RAS). Current guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) advocate screening for RAS only when a corrective procedure will be considered if renovascular disease is detected.[2]

When the history is highly suggestive and no risk of radiocontrast-mediated renal injury is present, intra-arterial digital subtraction angiography (DSA) or conventional angiography (renal arteriography) is the appropriate initial test. When a moderate suspicion of renovascular disease exists, spiral computed tomography (CT), magnetic resonance angiography (MRA), or duplex ultrasonography should be performed, depending on availability and local experience.

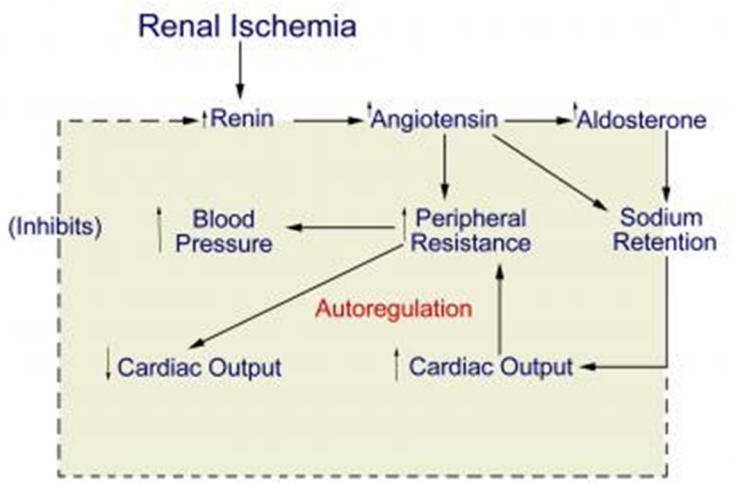
Antihypertensive drug therapy is indicated. Optimal blood pressure control plays an essential role in the therapeutic management of RVHT; however, aggressive control of other risk factors for atherosclerosis also is crucial. Cessation of smoking is important for its positive impact on the cardiovascular risk profile in patients with hypertension. Similarly, antidyslipidemic therapy for those patients with hyperlipidemia likely provides benefit in atherosclerotic RVHT.

The invasive and surgical options for treatment of RVHT include percutaneous transluminal angioplasty (PTA), surgical revascularization, and nephrectomy. Intravascular stents dmay be placed during angioplasty, although research has called the clinical benefit of this into question.

Patient education regarding hypertension should include information about the clinical features associated with RVHT (see Presentation) and about the importance of good blood pressure control.

Pathophysiology

The chief pathophysiologic mechanism underlying RVHT involves activation of both limbs of the RAAS and depends on the presence or absence of a contralateral kidney (see the image below).



Proposed pathogenesis of renovascular hypertension.

Unilateral renal ischemia initiates hypersecretion of renin, which accelerates conversion of angiotensin I to angiotensin II and enhances adrenal release of aldosterone. The result is profound angiotensin-mediated vasoconstriction and aldosterone-induced sodium and water retention.

In the two-kidney one-clip model, where the clinical correlate is unilateral renal artery disease, sodium and water handling via pressure diuresis of the contralateral kidney may be sufficient to prevent a volume component to the hypertension. In the setting of a solitary kidney (experimentally, the one-kidney one-clip model), sodium and water handling is compromised, sodium and water retention ensues, and volume-mediated hypertension occurs.

In unilateral RAS, renin production is increased in the ischemic kidney but suppressed in the unaffected nonstenotic kidney, which lacks the same ischemic stimulus. Consequently, when two kidneys are present with a unilateral stenosis (two-kidney one-clip model), hyperreninemia persists and blood pressure remains elevated because of an angiotensin II–induced vasoconstrictive effect. Renin production decreases in the contralateral kidney, a pressure diuresis ensues, and hypertension is maintained by high levels of angiotensin II.

A solitary kidney rendered ischemic by RAS is unable to achieve the pressure diuresis required to handle the aldosterone-induced sodium and water retention. The resultant volume expansion contributes to the elevation in blood pressure and also suppresses the production of renin by the stenotic kidney.

The sympathetic nervous system does not appear to play a role in perpetuating elevated blood pressure in the two-kidney one-clip model of RVHT. Evidence for a role in the one-kidney one-clip model of RVHT has been presented but is not clear or definitive.

Stages in development of renovascular hypertension

The evolution of RVHT has been described as having the following three stages or phases:

- Renin-angiotensin–dependent phase
- Salt-retention phase
- Systemic renin-angiotensin–independent phase

In the first phase, the immediate rise in blood pressure is a direct consequence of hyperreninemia. Over days to weeks, blood pressure remains elevated, but the course and presence of hyperreninemia vary with the presence and function of the contralateral kidney. The mechanism by which hypertension is produced in patients with renovascular disease thus changes over time and varies with the state of sodium balance.

When the contralateral kidney is functional, volume expansion is avoided and renin levels remain high. The two kidneys are in opposition; the stenotic kidney avidly retains sodium and produces excess renin in response to renal ischemia, while the nonstenotic kidney excretes sodium and water to maintain euvolemia and renin production decreases. The end result is systemic hypertension that is mediated by both renin and angiotensin.

In the second phase, in the setting of an ischemic solitary kidney, sodium and water retention, together with the vasopressor effects of angiotensin II, act to maintain renal perfusion pressure. The

stimulus to produce renin is stifled, and renin levels fall. Hypertension becomes less dependent on angiotensin II and predominantly results from volume expansion. Thus, perfusion pressure is restored at the expense of systemic hypertension and volume overload.

If blood flow is restored during these first two phases and renal perfusion is reinstated, blood pressure soon returns to a normal level. If renal hypoperfusion persists and the third phase is reached, restoration of renal blood flow may not normalize blood pressure, presumably because of secondary irreversible vascular or renal parenchymal disease.

In the third phase, hypertension often is unremitting, persisting well after the removal of the stenosis. Recalcitrant hypertension in this setting likely represents the presence of ischemic nephropathy in either or both kidneys; patients in whom stenoses were not hemodynamically significant initially also may have persistent hypertension.

RAAS and control of intrarenal hemodynamics

Angiotensin II exerts a vasoconstrictive effect on both afferent and efferent arterioles, but because the efferent arteriole has a smaller basal diameter, the increase in efferent resistance exceeds that the increase in afferent resistance. Afferent vasoconstriction is further minimized by angiotensin II–mediated release of vasodilatory prostaglandins and nitric oxide. In addition, angiotensin II can constrict the glomerular mesangium, thereby reducing the surface area available for filtration.

The net effect of angiotensin II on filtration invokes the opposing factors of reduced renal blood flow and mesangial surface area (causing a decrease in filtration) and the increase in glomerular capillary pressure (which tends to increase filtration). The end result depends on the clinical setting in which it occurs.

In the healthy kidney, a fall in systemic blood pressure activates the RAAS, which triggers a decrease in renal blood flow secondary to increased renal vascular (afferent) resistance. The preferential increase in efferent resistance mediated by angiotensin II results in increased glomerular capillary hydraulic pressure, which maintains the glomerular filtration rate (GFR).

In the ischemic kidney with reduced afferent blood flow, intraglomerular pressure and glomerular filtration are maintained by and depend upon angiotensin II–mediated efferent vasoconstriction. In this setting, removal of the efferent vasoconstrictive effect by angiotensin blockade, as achieved by angiotensin-converting enzyme (ACE) inhibitors, results in a decrease in intraglomerular pressure and GFR.

Thus, in patients with renovascular disease, particularly those with bilateral RAS or those with a stenotic renal artery to a single kidney, ACE inhibitors may cause a deterioration of renal function and azotemia. The propensity for angiotensin receptor blockers (ARBs) to affect GFR adversely is based on similar pathophysiology. It should be kept in mind that an acute decline in renal function in this setting is reversible once the ACE inhibitor (or the ARB) is discontinued.

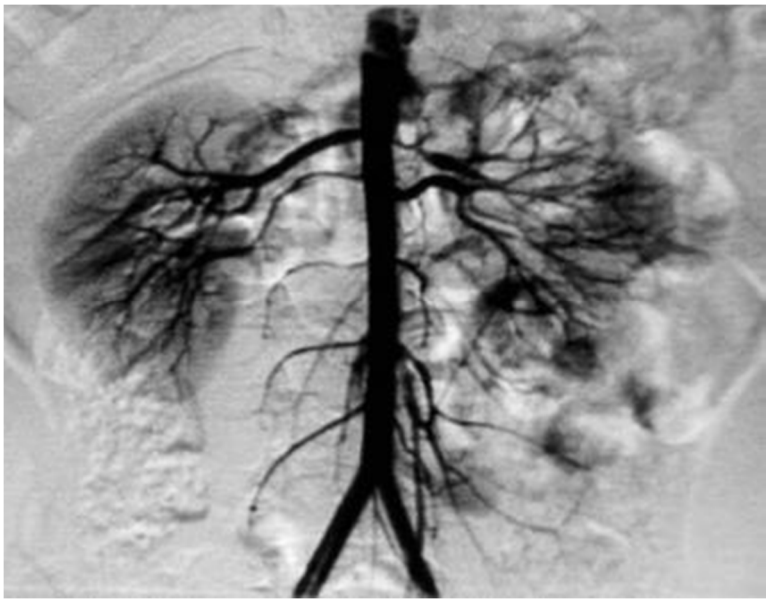
Manifestations

In adults, renovascular disease tends to appear at different times and affects the sexes differently. Atherosclerotic disease affects mainly the proximal third of the main renal artery and is most common among older men. Fibromuscular dysplasia (FMD) involves the distal two thirds and branches of the renal arteries and is most common among younger women. Midaortic syndrome is considered a variant of FMD. Neurofibromatosis may be seen.

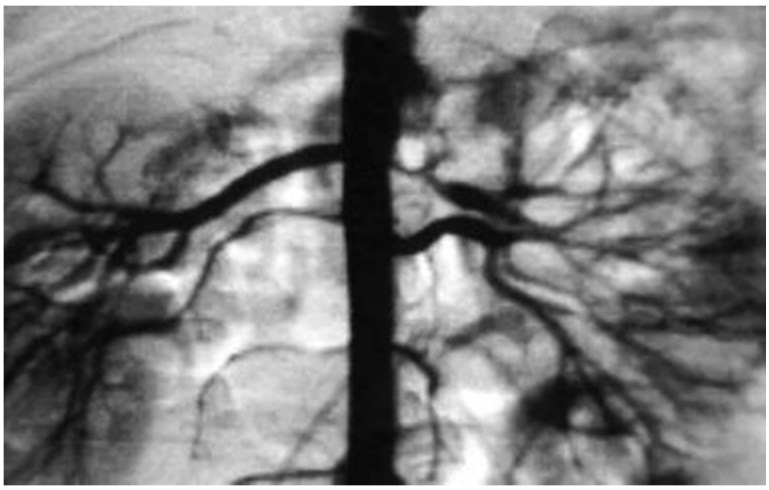
Fibromuscular dysplasia

FMD involves fibrous or muscular hypertrophy of the vessel tunica media with fibrous intimal hyperplasia; accordingly, it is sometimes referred to as fibromuscular hyperplasia. Often, poststenotic dilatation is also present. The process may range from mild occlusion to complete occlusion of the vessel. On radiographs, FMD produces the classic string-of-beads appearance less often in children than in adults; rather, it tends to show short discrete or longer tubular segments of stenosis.

The most common site of stenosis is the orifice of the renal artery at its origin in the aortic wall (see the images below). The next most common location is within the main renal artery, and the segmental arteries are the least common site of stenosis. Total occlusion most often occurs at the orifice of the renal artery.



Aortogram of 4-year-old child with renovascular hypertension caused by stenosis of left renal artery. Note that left kidney has 2 renal arteries and that artery to superior pole has stenosis.



Close-up view of aortogram of 4-year-old child. Stenotic lesion begins at ostium of left superior renal artery. This lesion was caused by fibromuscular dysplasia and did not respond well to balloon angioplasty.

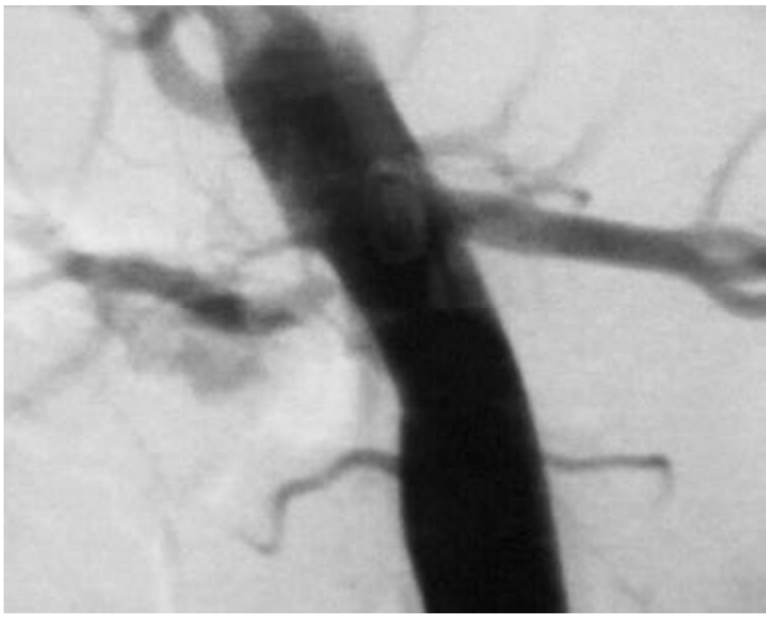
FMD may be either unilateral or bilateral, but the inciting event is unknown. Some have suggested an autoimmune origin. In 1995, Stanley proposed that the lesion forms as a developmental disease in the muscular layer, which is followed by intimal hyperplasia from the abnormal flow through the constricted lumen.[3]

Midaortic syndrome

In midaortic syndrome, vascular involvement extends beyond the renal artery. Aortic narrowing is present, often extending from the aortic hiatus to just above the inferior mesenteric artery (IMA). One or both of the renal arteries are usually involved, and the celiac artery and the superior mesenteric artery (SMA) may be narrowed. Midaortic syndrome may result in total renal artery occlusion, with perfusion dependent on collateral circulation. Extensive collateralization from the IMA and a Riolan arcade may exist. Renal artery stenosis is usually bilateral.

Neurofibromatosis

Hypertension in patients with neurofibromatosis is often essential, but some patients also present with RVHT (see the image below). These patients have a pattern of RAS similar to that observed in FMD. However, involvement of the intrarenal arteries and arterioles may also exist. Neurofibromatosis usually involves the renal arteries of both kidneys.



Aortogram of 8-year-old child with neurofibromatosis and renovascular hypertension caused by right renal artery stenosis.

Etiology

The term renovascular hypertension implies that the cause of the elevated blood pressure is decreased arterial inflow to the kidneys. Overall, approximately two thirds of RVHT cases are caused by atherosclerotic disease, and one third are caused by FMD or other congenital disorders. Other clinical entities that may be associated with RVHT include the following:

- Cholesterol embolic disease
- Acute arterial thrombosis or embolism
- Aortic dissection
- Renal arterial trauma
- Arterial aneurysm
- Arteriovenous malformation of the renal artery
- Polyarteritis nodosa

In children, congenital disorders that may lead to RVHT include arterial hypoplasia (as observed in multicystic renal dysplasia), neurofibromatosis, and Williams syndrome. Tumors and other masses may impinge on the renal vasculature. Trauma, irradiation, vessel anastomosis in transplantation, and thrombosis all may lead to constriction of vessels and the resulting hypertension. The most common cause of RVHT in newborns is a thrombosis or embolization related to umbilical artery catheterization.

Trauma or kidney transplantation can lead to scarring or anastomotic lesions that produce renovascular constriction. Although Takayasu arteritis and Kawasaki disease occasionally lead to FMD, the cause of FMD is not always known. Radiation therapy for tumors in the renal area may lead to renovascular hypertension.

Prenatal detection of multicystic renal dysplasia by means of screening ultrasonography is common. These lesions are rarely bilateral and are usually associated with ipsilateral ureteral atresia. Hypertension and recurrent infections can result from this condition.

Epidemiology

United States statistics

RVHT is the most common type of secondary hypertension, accounting for 1-5% of cases in unselected populations and as many as 30% of cases in selected populations. The prevalence may be up to 60% in patients older than 70 years.

The incidence of hypertension in children is reported to be 1-5%, and that in adolescents may be as high as 10%. In children, unlike adults, 70-80% of hypertension may be secondary hypertension, which is often correctable. Of secondary hypertension cases in children, 5-25% have a renovascular etiology.

RVHT is common in children and is second only to coarctation of the aorta as a surgically correctable cause of hypertension. With improved screening for coarctation in younger children, RVHT may become the most common cause of surgically correctable hypertension.

International statistics

The prevalence of RVHT internationally is not clear, but it likely accounts for the sole etiology in a relatively small percentage of unselected patients with hypertension. Significant geographic differences in the overall prevalence of RVHT have not been reported, though the etiology does appear to vary geographically.

In the western hemisphere, FMD is the most common cause of pediatric renovascular hypertension. Reports from Asia identify arteritis, either aortoarteritis or Takayasu arteritis, as the most common cause of renovascular hypertension in children. One study in south Asia found that 87% of the patients presenting with renovascular hypertension had arteritis.[4] A report from South Africa also indicated that Takayasu arteritis was the most important cause of renovascular hypertension in nonwhite children.

Age-related demographics

The onset of RVHT tends to occur in patients younger than 30 years or older than 50 years. Systemic hypertension is less common in children than in adults, but the incidence of hypertension in children is approximately 1-5%. The presence of hypertension in younger children is usually indicative of an underlying disease process (secondary hypertension). In children, approximately 5-25% of secondary hypertension is attributed to renovascular disease.

In children, the prevalence of renovascular disease as the cause of hypertension is inversely related to age. In other words, younger children are more likely to have hypertension that is due to renovascular disease. In children younger than 5 years, the incidence of potentially surgically correctable hypertension is close to 80%. This incidence drops to 40-45% in children aged 6-10 years. In children aged 11-20 years, a 20% incidence of surgically correctable hypertension is observed.

Sex-related demographics

RVHT is most common in younger women and older men. Younger women develop RVHT most commonly from FMD affecting the distal two thirds and branches of the renal arteries. Older men develop RVHT most often from atherosclerotic disease affecting mainly the proximal third of the main renal artery. In children, multiple studies have failed to demonstrate any clear sex difference with regard to the prevalence of RVHT.

Race-related demographics

Overall, RVHT and RAS are less common in the black population than in the white population. Blood pressure has been shown to be higher in black children than in white children, but the difference has not been deemed clinically significant. When adjusted for height, much of this difference is eliminated. RVHT is less common among older black children than among adolescent whites, but the prevalence is actually higher in young black children.

Prognosis

The prognosis of patients with RVHT is difficult to ascertain and varies with the extent of the occlusive phenomena, the sensitivity of the individual to antihypertensive therapy, and the efficacy of surgical repair or angioplasty. In patients with hypertension, the presence of atherosclerotic renal artery disease is a strong predictor of increased mortality relative to the general population. RVHT in the setting of renal dysfunction is associated with the greatest mortality.

Although the actual mortality of untreated renovascular hypertension has not been reported, in part because effective treatments are available, the prognosis is clearly poor. The severity of the hypertension places considerable of strain on target organs and can lead to death. Fortunately, most renovascular disease is correctable with surgical treatment or invasive intervention.

For 35% of patients, PTA yields normal blood pressures. Another one third of patients have decreased blood pressures. Unfortunately, a high rate of recurrence of hypertension and vascular stenosis appears to be observed in patients treated with PTA.

Surgical revascularization provides a very good prognosis for patients with renovascular hypertension. Approximately 70% of patients become normotensive without requiring additional pharmacologic treatment. Another 25% have reduced hypertension that can usually be resolved with the addition of medical therapy. Thus, fewer than 5% of patients appear refractory to revascularization. Some patients may experience resolution of their hypertension after nephrectomy.

Successful surgical intervention is expected to offer patients a normal lifespan without complications. Children who undergo surgical revascularization appear to do well for at least 16 years postoperatively. They are able to participate in active sports and similar vigorous activities without problems. Further long-term follow-up is needed to determine the durability of these reconstructions and the actual life potential of these children.

History

Patients with renovascular hypertension (RVHT) may be asymptomatic, and the hypertension may be discovered during routine examination or preparation for surgical treatment of another problem. In most pediatric studies, more than one half of children who were found to be hypertensive were asymptomatic, or their hypertension was discovered during a routine examination. When symptoms are present, they are nonspecific and are often related to the organ systems most affected by hypertension.

The most common symptom of RVHT seems to be headache. Other neurologic symptoms include altered mental status, vision changes, vomiting, seizures, coma, encephalopathy, hyperexcitability, and hyperirritability. Symptoms of congestive heart failure (eg, decreased energy, edema, and shortness of breath) may also develop. In patients with abdominal aortic narrowing, claudication may be present. Some children have anorexia, and infants or young children often present with failure to thrive. Occasionally, patients have oliguric renal failure.

Clinical risk factors for RVHT include the following:

- A history of hypertension with azotemia (serum creatinine level >1.5 mg/dL) and modest proteinuria (levels <1.5 g/day)
- Progressive renal insufficiency
- Accelerated or malignant hypertension
- Severe hypertension (diastolic blood pressure >120 mm Hg)
- Hypertension with an asymmetric kidney
- Paradoxical worsening of hypertension with diuretic therapy
- Hypertension refractory to standard therapy

The following are common findings from the history:

- Onset of hypertension occurring in patients younger than 30 years without risk factors
- Abrupt onset of severe (stage II) hypertension (greater than 160/100 mm Hg in patients older than 55 years)
- Severe or resistant hypertension despite appropriately dosed multidrug (>3 agents) antihypertensive therapy
- Abrupt increase in blood pressure over previously stable baseline in patients with previously well-controlled essential hypertension, as well as patients with known renal artery stenosis (RAS)
- Negative family history for hypertension
- Smoking tobacco products
- Acute sustained rise in serum creatinine levels with angiotensin-converting enzyme (ACE) inhibitor therapy
- Unprovoked hypokalemia (serum potassium level <3.6 mEq/L, often associated with metabolic alkalosis)
- Symptoms of atherosclerotic disease at other sites, in the presence of moderate-to-severe hypertension, particularly in patients older than 50 years
- Recurrent pulmonary edema in the setting of moderate-to-severe hypertension

- Moderate-to-severe hypertension in a patient with an unexplained atrophic kidney, significantly asymmetric kidneys (>1.5 cm difference), or diffuse atherosclerosis

Physical Examination

Findings suggestive of long-standing hypertension may or may not be evident upon physical examination. Such findings may include the following:

- Recurrent flash pulmonary edema or unexplained episodes of congestive heart failure
- Advanced funduscopic changes
- Abdominal bruit – A clear abdominal bruit is heard in 46% of patients with RVHT, as well as in 9% of patients with essential hypertension; however, innocent bruits are common in younger individuals; systolic-diastolic bruits in combination with hypertension are suggestive of RVHT

Upon physical examination, pediatric patients have a blood pressure elevation above the 95th percentile for their age, sex, and height. Generally, children with blood pressures higher than 140/100 mm Hg are thought to be more likely to have secondary hypertension, and RVHT is more likely in children with higher blood pressure.

Eye examination may reveal retinopathy and retinal hemorrhages. Patients with heart failure may present with tachypnea, cardiomegaly, and vasomotor instability leading to mottling and acrocyanosis. Lower-extremity pulses may be diminished with aortic coarctation, whether thoracic or abdominal.

An enlarged liver may be palpated, and an abdominal bruit may be auscultated. Patients with tumors impinging on renal vasculature may present with an abdominal mass in the area of the kidney. Rarely, signs or symptoms of visceral artery involvement are present because of the extensive collateralization that occurs.

Café-au-lait macules are classic findings in the presentation of neurofibromatosis. Patients with neurofibromatosis may also have macrocephaly, neurofibromas, dermal neurofibromas, and axillary freckling.

Complications

RVHT can develop into chronic hypertension, and patients usually present with malignant hypertension. If left untreated, this can produce serious consequences, including coma and death. Chronic hypertension can damage blood vessels, leading to such pathology as plaques, aneurysms, claudication, and dissection.

The main comorbidity of RVHT is directly related to its capacity to lead to end-organ damage. Neurologic manifestations are often the presenting symptoms because severe hypertension can lead to retinopathy, headaches, dizziness, confusion, seizures, and stroke. The heart is frequently affected because increased afterload leads to congestive heart failure and ventricular hypertrophy.

Renovascular hypertension may also damage the kidneys, especially when significant stenosis of the perfusing vessels is present. Although they are rare, oliguric renal failure and ischemic kidneys have been reported with renovascular disease.

Finally, RVHT is often associated with failure to thrive in young children.

Diagnostic Considerations

Clues to the presence of renovascular hypertension (RVHT) that might lead to serious complications (eg, stroke, renal failure, and cardiac decompensation) include the following:

- Recurrent and otherwise unexplained flash pulmonary edema or heart failure
- Recalcitrant hypertension that previously was controlled easily
- Hypertension that abruptly becomes more difficult to control and requires increased antihypertensive agents
- Slowly increasing serum creatinine levels, signifying the evolution of ischemic nephropathy

In addition to the conditions listed in the differential diagnosis, other problems to be considered include the following:

- Adrenal tumor
- Aldosteronoma
- Aortic insufficiency
- Arterial hypoplasia
- Cushing disease
- Cushing syndrome
- Essential hypertension
- Fibromuscular dysplasia
- Increased intracranial pressure
- Intracranial mass
- Irradiation
- Moyamoya disease
- Other nonessential forms of hypertension
- Renal cyst
- Renal failure
- Renal hypoplasia
- Renal parenchymal disease
- Retinopathy
- Stroke
- Thrombosis
- Umbilical catheter embolism

Approach Considerations

It is useful to determine the clinical risks for renovascular hypertension (RVHT) before embarking on an extensive workup that may not be productive or cost-effective. Patients in whom a definitive noninvasive or invasive workup is indicated are those in whom suggestive clinical features have been identified in the course of the history and physical examination (see Presentation).

At present, no sufficiently accurate, noninvasive, radiologic, or serologic screening test is available that, if negative, completely excludes the presence of renal artery stenosis (RAS). Current guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) advocate screening for RAS only for patients in whom a corrective procedure would be considered if renovascular disease were detected.[2]

Guidelines from the ACC/AHA and the European Society of Cardiology (ESC) recommend performing diagnostic studies to identify RAS in patients with any of the following[2, 6]:

- Onset of hypertension before the age of 30
- Onset of severe hypertension after the age of 55
- Accelerated hypertension (sudden and persistent worsening of previously controlled hypertension)
- Resistant hypertension (failure of blood-pressure control despite full doses of an appropriate three-drug regimen including a diuretic)
- Malignant hypertension (hypertension with coexistent end-organ damage; ie, acute kidney injury, flash pulmonary edema, hypertensive left ventricular failure, aortic dissection, new visual or neurological disturbance, and/or advanced retinopathy)
- New azotemia or worsening renal function after the administration of an angiotensin-converting enzyme (AC)E inhibitor or an angiotensin receptor blocker (ARB)
- Unexplained atrophic kidney or size discrepancy of greater than 1.5 cm between the kidneys
- Unexplained renal failure

The ACC/AHA guidelines also include patients with sudden, unexplained pulmonary edema in its class I recommendations.[2] The ESC has additional recommendation for patients with hypertension and abdominal bruit as well as those with hypertension and hypokalemia in particular when receiving thiazide diuretics.[6]

Various laboratory studies are mentioned (see below), largely for historical background, but these are no longer universally considered useful as screening tests. Therefore, the clinical index of suspicion remains the primary determinant of the degree of evaluation that is indicated for RVHT.

As a screening test for RAS, the ACC/AHA guidelines recommend duplex ultrasonography.[2] The advantages of duplex ultrasonography include lack of radiation, high sensitivity and specificity, low expense, and ability to be repeated without risk or discomfort to the patient.[7]

Other recommended screening tests include computed tomographic angiography, in patients with normal renal function, and magnetic resonance angiography. When the results of noninvasive screening tests are inconclusive and the clinical index of suspicion is high, catheterangiography is recommended to establish the diagnosis of RAS.[2] In patients at risk, carbon dioxide angiography can determine the presence of a stenosis, and the risk associated with radiocontrast angiography is imposed only on those individuals most likely to benefit.

Tests that are not recommended for RAS screening include captopril renal scintigraphy, selective renal vein renin measurements, plasma renin activity, and measurement of plasma renin activity after captopril administration (the captopril test).[2]

Basic Laboratory Studies

The 2004 fourth report from the National High Blood Pressure Education Program (NHBPEP) Working Group on Children and Adolescents recommends the following initial tests in children with hypertension[8]:

- Complete blood count (CBC)
- Urinalysis
- Urine culture (all girls, selected boys)
- Serum electrolyte levels (sodium, potassium, chloride, and total carbon dioxide)
- Blood urea nitrogen (BUN) levels
- Serum creatinine levels

In addition, a fasting lipid panel and fasting glucose level are recommended for the following[8]:

- Overweight patients whose blood pressure is at the 90th–94 th percentile
- All patients with blood pressure at the 95th percentile or higher
- Patients with a family history of hypertension or cardiovascular disease
- Children with chronic renal disease

Renal function test results frequently yield normal results in children with renovascular disease, even when the lesions are bilateral. Findings on a 24-hour urine study should also be within the reference range in renovascular hypertension.

The CBC, serum electrolyte levels, BUN levels, and serum creatinine levels should indicate whether a pattern of renal function impairment or a pattern of aldosteronoma is present.

Measure a 24-hour urine sample for electrolytes, creatinine, vanillylmandelic acid, catecholamines, 17-hydroxy steroids, and 17-keto steroids. Normal results should rule out the possibility of a medullary or cortical tumor.

The erythrocyte sedimentation rate (ESR) is a good indicator of active arteritis.

One study found that nearly 90% of renal artery disease was detected when patients were pretreated with furosemide. However, these findings can also be misleading, especially in bilateral disease.

Assessment of Renin Release

Plasma renin activity

The baseline plasma renin activity (PRA) is elevated in 50-80% of patients with RVHT. Renin levels may be increased or decreased by all antihypertensive agents. Nonsteroidal anti-inflammatory drugs (NSAIDs) decrease plasma renin levels. Measuring the rise in the PRA 1 hour after administering 25-50 mg of captopril can increase the predictive value of the test. Patients with RAS have an exaggerated increase in PRA, perhaps due to removal of the normal suppressive effect of high angiotensin II levels on renin secretion in the stenotic kidney.

The sensitivity and specificity of studies of the captopril renin test are 75-100% and 60-95%, respectively. Limitations include the need to discontinue antihypertensive medications that can affect the

PRA (eg, ACE inhibitors, beta-blockers, and diuretics), the low sensitivity, and the somewhat decreased predictive value when compared to a renogram after ACE inhibition.

Although elevation of peripheral or renal vein PRA has been used to diagnose unilateral renal disease and predict surgical curability, an elevated plasma renin level does not establish the cause of hypertension, and levels that are within the reference range do not rule out renovascular disease.

Renal vein renin ratio

Renal vein renin measurements compare renin release from the 2 kidneys and are used to predict the potential success of surgical revascularization. Renin secretion is increased in the ischemic kidney but is suppressed in the contralateral kidney is suppressed, as evidenced by the similar levels of renin measured in the renal artery (infrarenal inferior vena cava) and the renal vein.

The ratio of the measurement from the ischemic kidney to the measurement from the contralateral kidney is the renal vein renin ratio. A ratio higher than 1.5 constitutes a positive test result and is suggestive of functionally important renovascular disease. Volume depletion exaggerates reduced renal perfusion and may increase the renal vein renin ratio in asymmetric disease.

Fewer than 10% of healthy patients have a renal vein renin ratio higher than 1.5, and less than 20% have a ratio lower than 1.1. It has been suggested that the accuracy of these measurements can be enhanced by prior administration of an angiotensin-converting enzyme (ACE) inhibitor, which will increase renin secretion on the affected side.

False-negative and false-positive results are common. Although more than 90% of patients with unilateral RAS and lateralizing renin values respond positively to angioplasty or surgery, about 50% of those with nonlateralizing findings also benefit from correction of the stenosis.

As a result, most physicians rely on the clinical index of suspicion rather than on renal vein renin measurements to estimate the physiologic significance of a stenotic lesion. An exception may occur in patients with bilateral RAS, in whom renal vein renin measurements can be used to determine the side that most contributes to the hypertension.

Angiography

When renovascular hypertension is suspected, the standard diagnostic study is renal arteriography. Because this is a highly invasive procedure, it is frequently necessary to perform less specific tests to refine the level of suspicion for renovascular disease before submitting the patient to this test. Some consider intra-arterial DSA to be equally acceptable as a standard.

MRA, CT angiography, and spiral angiography are newer studies that hold considerable promise for diagnosis and evaluation of RVHT. However, they have not yet been investigated sufficiently to permit recommendation of their use in children with renovascular disease. At present, interpretation of the images is technically difficult, and the usefulness of these modalities appears limited to imaging of main vessels.

Renal arteriography

Selective renal arteriography is still widely considered the standard for diagnosis of RVHT. Renal arteriography is necessary whenever surgery or percutaneous transluminal angioplasty is anticipated. Adding DSA technology to renal arteriography requires one half the volume of dilute contrast medium that standard arteriography requires, while yielding comparable results. Use abdominal pressure and glucagon to prevent bowel motion and gas from affecting the image quality.

Digital subtraction angiography

Intra-arterial DSA is now often recommended as an initial test in this setting. Because intra-arterial DSA requires less radiocontrast (25-50 mL) than conventional angiography (100 mL), it is preferred for patients with compromised renal function. RAS of 70% or more or stenosis of 50% with poststenotic dilatation is considered hemodynamically significant.

Intravenous (IV) DSA has also been suggested for identification of renovascular disease. It is less invasive than intra-arterial DSA but requires more radiocontrast. Yield depends on the skill of the

individual interpreting the radiograph, and image quality is diminished by interference from patient or intestinal motion or gas (which can be reduced by abdominal pressure and glucagon), as well as by overlying vessels and poor cardiac output. Compared with arterial studies, IV DSA has a sensitivity and specificity of 90% or less and thus is not commonly used.

Carbon dioxide angiography

Carbon dioxide digital angiography is used as an effective alternative to radiocontrast angiography in patients with renal insufficiency. Carbon dioxide angiography allows gross assessment of the presence of a stenotic lesion. If angioplasty or surgical intervention is to be carried out, subsequent traditional radiocontrast angiography is required to outline the lesions; however, carbon dioxide angiography allows patients to be identified without the risk of dye-related renal injury.

Magnetic resonance angiography

MRA is increasingly reported to provide better results than noninvasive screening procedures. Studies indicate that 3-dimensional MRA with gadolinium-based contrast agents (which are potentially nephrotoxic) has a sensitivity of 96-100% and a specificity of 71-96% for the detection of a main RAS of greater than 50% (see the image below).[9, 10]

Limitations of MRA include relatively high cost and restricted availability. Contraindications to MRA include reduced renal function (estimated glomerular filtration rate [GFR] below 30 mL/min), claustrophobia, and patients with a metallic implant (eg, a pacemaker or surgical clip). The risk-to-benefit ratio should be carefully considered in patients with moderately reduced renal function (estimated GFR, 30-60 mL/min).

Blood oxygen level-dependent MRI

Blood oxygen level-dependent (BOLD-MRI) is a new technique that uses the contrasting paramagnetic properties of oxyhemoglobin and deoxyhemoglobin to depict tissue oxygenation without the need for contrast material. The magnetic rate of relaxation (R2) correlates positively with deoxyhemoglobin levels to measure tissue oxygenation and thus can detect ischemia. Images are obtained at baseline and following administration of an agent that decreases renal oxygen consumption, such as furosemide. Poststenotic kidneys that appear normal on imaging despite high-grade RAS (ie, viable kidney) display a greater-than-normal decrease in R2 after administration of furosemide. Larger studies are needed to confirm the role of BOLD-MRI in identifying patients mostly likely to benefit from revascularization.[11]

Spiral CT with angiography

Spiral CT using small amounts of IV contrast (ie, CT angiography) combines the diagnostic accuracy of arteriography with the lower risk of renal injury of DSA.

The sensitivity and specificity of spiral CT for detecting RAS are approximately 98% and 94%, respectively. In patients with a plasma creatinine concentration higher than 1.7 mg/dL (150 µmol/L), the accuracy is lower (93% sensitivity, 81% specificity), possibly as a consequence of reduced renal blood flow.

Doppler Ultrasonography

Many authors believe that diagnostic imaging should begin with Doppler ultrasonography of the kidneys and abdomen, which is useful in identifying renal disease and abdominal masses. This technique potentially can detect both unilateral and bilateral disease and also can be used to detect recurrent stenosis in patients previously treated with angioplasty or surgery. It should be kept in mind, however, that renal ultrasonographic findings are insufficient to rule out the need for angiography.

Doppler ultrasonography provides both anatomic and functional assessment of the renal arteries. Direct visualization of the main renal arteries (B-mode imaging) is combined with measurement (via Doppler) of intrarenal pressures and velocities (by waveform) to achieve a sensitivity of 72-92% for detecting RAS of 70% or greater.

Doppler ultrasonographic evaluation of renal resistance indices (1 – end diastolic velocity/maximum systolic velocity × 100) can be used to classify patients as potential responders or nonresponders to intervention (ie, a renal resistance index exceeding 80% implies a low likelihood that correction of the stenosis will eventuate in improved blood pressure control or renal function).

Important disadvantages of this modality include the possibility that bowel gas can interfere with direct visualization of the renal arteries (50-90% of the time). Doppler measurements are hampered very infrequently (0-2%). Furthermore, this modality is time-consuming to perform (requiring approximately 2 hours) and is a technically difficult procedure with a steep learning curve, making success highly operator-dependent.

Renogram

Because of its high false-negative rate (20-25%), the nonstimulated renal scan has limited efficacy and is not universally recommended as a screening test. The predictive value of radioisotope scanning, however, can be enhanced by the administration of captopril orally (25-50 mg) 1 hour before the isotope is injected. Decreased function after treatment with captopril indicates a high likelihood of renovascular stenosis. If the scan findings remain normal, renovascular disease is not ruled out.

Intravenous Pyelography

IV pyelography (IVP) is mentioned primarily because of its historical significance. It has a sensitivity of only 75-80%; thus, a negative test result cannot exclude RVHT reliably. Furthermore, it is often unhelpful when bilateral disease is present; bilateral disease can be missed if a small difference exists between the 2 kidneys. Major findings on IVP that suggest unilateral ischemia include decreased renal size and delayed caliceal appearance time in comparison with the contralateral kidney. Results of IVP are often inaccurate in children.

Other Studies

Chest radiography and echocardiography may be helpful in differentiating left ventricular failure from chronic hypertension.

Because many of the lesions in FMD occur at the renal artery orifice, obtaining a good histologic sample is frequently difficult. Evaluation of stenotic lesions invariably reveals the characteristic FMD in the medial or perimedial muscular layers, associated with varying degrees of intimal hyperplasia.

Approach Considerations

Antihypertensive drug therapy is indicated. Optimal blood pressure control plays an essential role in the therapeutic management of renovascular hypertension (RVHT); however, aggressive control of other risk factors for atherosclerosis is also crucial. Cessation of smoking is important for its positive impact on the cardiovascular risk profile in patients with hypertension. Similarly, antidyslipidemic therapy for those patients with hyperlipidemia likely provides benefit in atherosclerotic RVHT.

Progression of atherosclerotic stenosis may occur in as many as one third of patients, and the sequelae of ongoing ischemia to the stenotic kidney are a theoretical concern. Furthermore, normalization of blood pressure may be associated with reduced renal perfusion pressures, and renal function may deteriorate despite good blood pressure control.

Definitive therapy for the underlying cause must be considered in order to avoid the development of ischemic nephropathy.[12] Intervention to treat hemodynamically significant stenoses has been presumed to offer clinical benefit; however, trials comparing renal artery revascularization with medical management do not unequivocally favor surgical over medical intervention.[13]

The invasive and surgical options for treatment of renovascular hypertension include the following:

- Percutaneous transluminal angioplasty (PTA)
- Surgical revascularization
- Nephrectomy

Catheter-based radiofrequency denervation of the renal arteries has entered clinical use in many countries as a treatment for resistant hypertension. The SYMPLICITY HTN-3 trial, a randomized in 535 patients with severe resistant hypertension, found that catheter-based radiofrequency denervation of the

renal arteries was safe but did not result in a significant reduction of systolic blood pressure 6 months post-procedure, as compared with a sham control.[14] However, subsequent reviews have shown that renal denervation was not effectively or consistently achieved in the trial.[15]

The patient should be transferred to a tertiary care medical facility whenever the need for invasive or surgical treatments has been established and the current treating facility is not equipped for such procedures.

Inpatient care usually is necessary for the management of hypertensive urgencies or emergencies associated with RVHT. Timely diagnosis of RVHT and early intervention are required to prevent further ischemic end-organ damage to the kidney and other organs.

Pharmacologic Therapy

Hypertensive patients should receive antihypertensive medication. In children with severe hypertension, it may be necessary to initiate medical treatment before a definitive diagnosis is obtained.

RVHT is often refractory to medical treatment. Because current approaches to renal artery dilation and surgical revascularization yield excellent results, these procedures are generally considered the treatments of choice in preference to life-long antihypertensive medication. However, attempts to control the patient's blood pressure in preparation for surgical intervention should always be made. In particular, it is advisable to defer surgery until manifestations of malignant hypertension are relieved.

All classes of antihypertensive medications are used to treat RVHT; however, the most effective therapy is with an angiotensin-converting enzyme (ACE) inhibitor, which minimizes the ischemia-induced rise in angiotensin production. Because hypertension may be dependent on angiotensin II, antihypertensives that inhibit renin or angiotensin II are used widely.

An ACE inhibitor markedly decreases blood flow through the stenotic kidney; thus, in patients with a solitary kidney or bilateral renovascular disease, blood pressure may fall rapidly, with an ensuing deterioration in renal function. Although this deterioration usually is reversible upon discontinuance of the medication, ACE inhibitors are generally avoided until definitive therapy has been attempted. There has been less clinical experience with angiotensin receptor blockers (ARBs), but these agents appear to be as effective as ACE inhibitors in experimental models.

Certainly, any patients with RVHT who are treated with ACE inhibitors or ARBs should have their serum creatinine levels monitored, and therapy should be discontinued if their creatinine levels rise significantly. In patients without hemodynamically significant renal artery disease, a serum creatinine increase of up to 35% above baseline with an ACE or an ARB is considered acceptable and is not a reason to withhold treatment unless hyperkalemia develops.

Both beta blockers and diuretics also are used, the latter often in conjunction with ACE inhibitors. Diuretics enhance sodium and water diuresis, thereby eliminating the volume-mediated component of RVHT. Calcium channel blockers may provide equally good control of hypertension while presumably causing less impairment of the function of the ischemic kidney than ACE inhibitors do. Nitroprusside and phenoxybenzamine are useful in the short-term management of malignant hypertension before surgery.

The selective aldosterone inhibitor eplerenone is also available for the treatment of hypertension. This agent selectively blocks aldosterone at the mineralocorticoid receptors in both epithelial tissues (eg, kidney) and nonepithelial tissues (eg, heart, blood vessels, and brain), thereby decreasing blood pressure and sodium reabsorption. The adult dosage is 50 mg/day orally, which may be increased after 4 weeks to a dosage not exceeding 100 mg/day. Contraindications include the following:

- Documented hypersensitivity
- Hyperkalemia
- Coadministration with drugs causing increased potassium
- Type 2 diabetes with microalbuminuria
- Moderate-to-severe renal insufficiency (ie, creatinine clearance less than 50 mL/min or serum creatinine level higher than 2 mg/dL in males or 1.8 mg/dL in females)

Because eplerenone is a cytochrome P-450 (CYP450) 3A4 substrate, potent CYP3A4 inhibitors (eg, ketoconazole) increase serum levels of the drug about 5-fold, whereas less potent CYP3A4 inhibitors (eg,

erythromycin, saquinavir, verapamil, and fluconazole) increase serum levels about 2-fold. Grapefruit juice increases serum eplerenone levels by about 25%.

Coadministration of eplerenone with potassium supplements, salt substitutes, or drugs known to increase serum potassium (eg, amiloride, spironolactone, triamterene, ACE inhibitors, and ARBs) increases the risk of hyperkalemia. Eplerenone may cause hyperkalemia, headache, or dizziness. Caution is advised in patients with hepatic insufficiency.

Percutaneous Transluminal Angioplasty

PTA is a therapeutic nonsurgical procedure involving expansion of a small balloon on a special vascular catheter to dilate narrow areas in a blood vessel. Up to 10 atm of pressure is generally used to expand the balloon, and more than 1 dilation may be required to achieve the desired effect. PTA is cheaper and less invasive than surgical revascularization and can be performed at the time of angiography. If patients are refractory to treatment or if restenosis develops, surgical revascularization can still be performed.

Outcomes appear to be significantly better in patients whose lesions result from fibromuscular dysplasia (FMD) than they are in persons whose lesions are associated with atherosclerotic stenosis: Cure was reported in 50-85% of patients in the former group and 8-20% of patients in the latter group.

The results of PTRA in patients with bilateral renal artery disease have been relatively poor, suggesting that surgical intervention should be a strong consideration in this setting. In patients with diffuse atherosclerosis, the complication rate is relatively high with either surgery or angioplasty; medical therapy may be preferred in this setting.

Renal stents

Placement of intravascular stents during angioplasty (see the images below) may be helpful in preventing restenosis and managing RVHT. Data suggest that stenting may prove useful in patients with ostial disease, those who develop restenosis after PTRA, or those with complications resulting from PTRA (eg, dissection). Primary renal artery stenting in patients with atherosclerotic RAS has a high rate of technical success and a low rate of complications.[19, 20]

The Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial—a randomized, unblinded trial in 806 patients with atherosclerotic renovascular disease that compared revascularization plus medical therapy with medical therapy alone—found substantial risks but no evidence of a worthwhile clinical benefit from revascularization. Over a 5-year period, the two patient groups showed no statistically significant difference in systolic blood pressure or in the rate of progression of renal impairment, renal or major cardiovascular events, or death.

Other cases in which renal artery stenting generally represents appropriate care after a trial of optimal medical therapy include the following[7]:

- Patients with accelerated or resistant hypertension (failure of ≥3 maximally tolerated medications including the use of a diuretic)
- Global renal ischemia (bilateral RAS or severe RAS in a solitary functioning kidney)
- Hypertension with medication intolerance

Complications

The rate at which complications of PTRA develop varies among physicians, but potential adverse consequences are known to include thrombosis, vascular or renal perforation, and tearing or dissection of the vessel wall. Restenosis appears to occur approximately 25% of the time.

Surgical Revascularization

The goal of surgical revascularization is correction of RVHT with preservation of renal function. Reports have shown that more than 90% of patients are cured or experience improvement of their hypertension with surgical revascularization. Preservation of a functional kidney is especially important because of the high rate of bilateral disease in children.

In patients with FMD, the cure rate is as high as 80%, and morbidity is low; however, these results are not significantly better than what can be achieved by means of PTRA with less morbidity, mortality, cost, and inconvenience.

In patients with diffuse atherosclerosis, the complication rate is relatively high with surgical revascularization, as with angioplasty; thus medical therapy may be preferable.

Diet

Placing all patients who are hypertensive on a low-salt diet is recommended. In patients with RVHT, this is unlikely to correct the systemic hypertension, but it may assist in managing the hypertension until more definitive therapy can be performed. It certainly does not hurt patients.

In addition, efforts should be made to keep patients well hydrated; dehydration may lead to decreased renal perfusion or increased renin release.

Prevention

Atherosclerotic RAS is now recognized as an important and fast-growing cause of end-stage renal disease. Because this form of renal failure can be prevented by performing an operation or angioplasty, it is important to identify patients who may be at risk for renal ischemia as a result of atherosclerosis. Even when renal function is impaired, relief of the stenosis, if achieved early enough, may result in dramatic improvement.

Factors that should prompt evaluation for renal artery disease include the following:

- Clinically atypical course of hypertension developing in people older than 50 years
- Difficulty in controlling long-standing hypertension that previously was easy to control
- Increase in creatinine level after administration of an ACE inhibitor

Deterioration of renal function in the setting of diffuse atherosclerosis without proteinuria or known renal parenchymal disease, even in the absence of hypertension, is highly suggestive of renovascular disease.

Consultations

The need for consultation depends on the degree of end-organ damage. If a patient has had chronic hypertension that led to heart failure, referral to a pediatric cardiologist should be considered. Likewise, a patient presenting with neurologic symptoms may need to see a neurologist or neurosurgeon before surgical treatment is started.

Once a diagnosis of RVHT is made, prompt treatment of the disease is the best protection against further end-organ damage.

Long-Term Monitoring

In addition to diagnosis and treatment of hypertension, renal function must be assessed and followed so that any renal dysfunction can be recognized at an early stage, allowing definitive intervention (when appropriate) to be initiated promptly.

Because long-term outcomes have not yet been determined, sequential blood pressure measurements should be monitored indefinitely. In some patients with unilateral disease, contralateral stenosis has been reported to develop as late as 14 years after treatment. In addition, stenosis of the graft or thrombosis may occur up to 2 years postoperatively.

Approximately 25% of patients who undergo surgical treatment still require some drug therapy to maintain blood pressure measurements within the reference range.

Medication Summary

Medical treatment of renovascular hypertension (RVHT) may be necessary to control blood pressure until surgery can be performed. Attempts should be made to reduce the blood pressure before surgery so as to improve the likelihood of a good surgical outcome. Afterward, medical treatment is necessary 25-30% of the time to provide complete resolution of improved or refractory hypertension.

Adrenergic receptor blockers and diuretics are the preferred agents. Arterial dilators are also useful in the preoperative management of malignant hypertension. Calcium channel blockers do not seem to be as widely used, and angiotensin-converting enzyme (ACE) inhibitors are generally avoided because of their potential to compromise renal function.

ACE Inhibitors

Class Summary

ACE inhibitors have been used by some in the control of RVHT. These agents minimize an ischemia-induced rise in angiotensin production. Because hypertension may be dependent on angiotensin II, antihypertensives that inhibit renin or angiotensin II are used widely. All drugs in this class have similar action and adverse effects. In particular, ACE inhibitors increase the risk of decreased renal function. Although this increased risk is usually reversible, the use of these agents is generally avoided until definitive therapy has been attempted.

Renal blood flow is maintained by a balance between angiotensin-II–induced vasoconstriction and prostaglandin-mediated vasodilation. With ACE inhibitors, kidney perfusion is increased and renal vascular resistance decreased. ACE inhibitors induce vasodilation in both afferent and efferent arterioles. The glomerular filtration rate (GFR) generally increases. However, in hypoperfusion states (eg, renal artery stenosis (RAS), aggressive diuresis, and decompensated congestive heart failure), GFR may fall because of unopposed prostaglandin vasodilation.

Captopril

Captopril, the most commonly used ACE inhibitor, prevents conversion of angiotensin I to angiotensin II (a potent vasoconstrictor), resulting in lower aldosterone secretion. It is excreted primarily by the kidney.

Enalapril (Vasotec)

Enalapril is a competitive ACE inhibitor that reduces angiotensin II levels and decreases aldosterone secretion.

Lisinopril (Zestril, Prinivil)

Lisinopril prevents conversion of angiotensin I to angiotensin II, resulting in decreased aldosterone secretion.

Angiotensin Receptor Blockers (ARBs)

Class Summary

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system (RAAS) and plays an important role in the pathophysiology of hypertension. Besides being a potent vasoconstrictor, angiotensin II stimulates aldosterone secretion by the adrenal gland; thus, angiotensin receptor blockers (ARBs) decrease systemic vascular resistance without a marked change in heart rate by blocking the effects of angiotensin II.

Type I angiotensin receptors are found in many tissues, including vascular smooth muscle and the adrenal gland. Type II angiotensin receptors also are found in many tissues, although their relationship to cardiovascular hemostasis is not known. The affinity of ARBs for the type I angiotensin receptor is approximately 1000 times greater than that for the type II angiotensin receptor.

In general, ARBs do not inhibit ACE, other hormone receptors, or ion channels. They interfere with the binding of formed angiotensin II to its endogenous receptor. Experience with using ARBs to treat RVHT is still limited. Losartan and valsartan are specific and selective nonpeptide ARBs that block the vasoconstricting and aldosterone-secreting effects of angiotensin II.

Other ARBs have been approved by the US Food and Drug Administration (FDA), including olmesartan (Benicar). Olmesartan is initiated at a dosage of 20 mg/day orally, which may be increased to 40 mg/day after 2 weeks if further blood pressure reduction is required.

Losartan (Cozaar)

Losartan is appropriate for patients unable to tolerate ACE inhibitors. It may induce a more complete inhibition of the RAAS than ACE inhibitors do, it does not affect the response to bradykinin, and it is less likely to be associated with cough and angioedema. Compared to the ACE inhibitors (eg, captopril and enalapril), losartan is associated with a lower incidence of drug-induced cough, rash, and taste disturbances.

Valsartan (Diovan)

Valsartan is appropriate for patients unable to tolerate ACE inhibitors. It may induce a more complete inhibition of the RAAS than ACE inhibitors do, it does not affect the response to bradykinin, and it is less likely to be associated with cough and angioedema. Compared to the ACE inhibitors (eg, captopril and enalapril), losartan is associated with a lower incidence of drug-induced cough, rash, and taste disturbances.

Blockers, Beta-1 Selective

Class Summary

Adrenergic blockers (both alpha-adrenergic and beta-adrenergic) compete with adrenergic neurotransmitters (eg, catecholamines) for binding at sympathetic receptor sites. They tend to be some of the most effective medicines for prolonged treatment of RVHT.

At low doses, alpha-adrenergic receptor blockers may be used as monotherapy in the treatment of hypertension. At higher doses, they may cause sodium and fluid to accumulate. As a result, concurrent diuretic therapy may be required to maintain the hypotensive effects of the alpha-receptor blockers.

Atenolol and metoprolol, in low doses, selectively block $beta_1$ -adrenergic receptors in the heart and vascular smooth muscle. Pharmacodynamic consequences of $beta_1$ -receptor blockade include decreases in (1) resting and exercise heart rate, (2) cardiac output, and (3) systolic and diastolic blood pressure. Like all selective adrenergic antagonists, they lose their selectivity for the $beta_1$ receptor higher doses and can competitively block $beta_2$ -adrenergic receptors in the bronchial and vascular smooth muscles, potentially causing bronchospasm.

Actions that generally make beta blockers useful in treating hypertension include a negative chronotropic effect that decreases the heart rate at rest and after exercise, a negative inotropic effect that decreases cardiac output, reduction of sympathetic outflow from the central nervous system (CNS), and suppression of renin release from the kidneys. Thus, beta blockers affect blood pressure via multiple mechanisms.

Metoprolol (Lopressor, Toprol-XL)

Selective beta1-adrenergic receptor blocker that decreases automaticity of contractions. During IV administration, carefully monitor blood pressure, heart rate, and ECG.

Atenolol (Tenormin)

Atenolol selectively blocks beta1 receptors, with little or no effect on beta2 types.

Beta-Blockers, Nonselective

Class Summary

Although selective $beta_1$ -blockers (eg, metoprolol) are preferred over nonselective agents in patients with asthma or pulmonary conditions in which acute bronchospasm would put them at risk (eg, chronic obstructive pulmonary disease [COPD], emphysema, or bronchitis), all beta-blockers should be used with caution in these patients, particularly with high-dose therapy.

Propranolol (Inderal, InnoPran XL)

Propranolol is a beta-adrenergic blocking agent. Renin release is enhanced by beta-receptor activation, and chronic beta blockade consistently suppresses plasma renin activity. Propranolol has membrane-stabilizing activity and decreases the automaticity of contractions. It is not suitable for emergency treatment of hypertension and should not be administered IV in hypertensive emergencies.

Labetalol (Trandate)

Labetalol blocks beta1-adrenergic, alpha-adrenergic, and beta2-adrenergic receptor sites.

Alpha Blockers, Antihypertensives

Class Summary

At low doses, alpha-adrenergic receptor blockers may be used as monotherapy in the treatment of hypertension. At higher doses, they may cause sodium and fluid to accumulate. As a result, concurrent diuretic therapy may be required to maintain the hypotensive effects of alpha-receptor blockers.

Phentolamine

Phentolamine is an alpha1- and alpha2-adrenergic blocking agent that antagonizes the action of circulating epinephrine and norepinephrine, reducing the hypertension that results from catecholamine's effects on the alpha-receptors.

Phenoxybenzamine (Dibenzyline)

Phenoxybenzamine is a noncompetitive alpha-adrenergic blocker. It is a long-acting adrenergic alpha-receptor blocker that can produce and maintain a chemical sympathectomy. Phenoxybenzamine hydrochloride lowers supine and upright blood pressure. It does not affect the parasympathetic nervous system.

Prazosin (Minipress)

Prazosin is an alpha blocker. It decreases arterial tone by allowing peripheral postsynaptic blockade.

Calcium Channel Blockers

Class Summary

Calcium channel blockers provide control of hypertension associated with less impairment of function of the ischemic kidney. It has been suggested that they may have beneficial long-term effects, but this remains uncertain.

Calcium channel blockers inhibit influx of extracellular calcium across both myocardial and vascular smooth muscle cell membranes. Serum calcium levels remain unchanged. The resultant decrease in intracellular calcium inhibits the contractile processes of myocardial smooth muscle cells, resulting in dilation of coronary and systemic arteries and improved oxygen delivery to myocardial tissue. In addition, total peripheral resistance, systemic blood pressure, and afterload are decreased.

Diltiazem (Cardizem CD, Dilacor XR, Tiazac)

Diltiazem is similar to verapamil in that it inhibits the influx of extracellular calcium across both the myocardial and vascular smooth muscle cell membranes.

Verapamil (Calan, Verelan, Covera-HS)

During depolarization, verapamil inhibits calcium ions from entering slow channels or voltage-sensitive areas of the vascular smooth muscle and myocardium.

Nifedipine (Adalat, Procardia, Procardia XL)

Nifedipine relaxes coronary smooth muscle and produces coronary vasodilation, which, in turn, improves myocardial oxygen delivery. Sublingual administration is generally safe, despite theoretical concerns.

Diuretics, Other

Class Summary

Diuretics promote excretion of water and electrolytes by the kidneys. They are used to treat heart failure or hepatic, renal, or pulmonary disease when sodium and water retention has resulted in edema or

ascites. They may be used as monotherapy or combination therapy to treat hypertension. Thiazide diuretics are preferred.

Diuretics are used only as an adjunct to other medications for RVHT, especially during acute hypertensive crises. Furosemide is especially effective in managing pulmonary edema associated with hypertensive crises and may be particularly useful in patients unresponsive to other diuretics or those who have severe renal impairment.

Furosemide (Lasix)

Furosemide primarily appears to inhibit reabsorption of sodium and chloride in the ascending limb of the loop of Henle. These effects increase urinary excretion of sodium, chloride, and water, resulting in profound diuresis. Renal vasodilation occurs after administration of furosemide. Renal vascular resistance decreases, and renal blood flow is enhanced.

Hydrochlorothiazide (Microzide)

Hydrochlorothiazide inhibits reabsorption of sodium in distal tubules, causing increased excretion of sodium and water and potassium and hydrogen ions.

Bumetanide

Bumetanide increases excretion of water by interfering with the chloride-binding cotransport system; this, in turn, inhibits sodium and chloride reabsorption in the ascending loop of Henle. Bumetanide does not appear to act in the distal renal tubule.

Vasodilators

Class Summary

Arterial vasodilators are effective in reducing hypertension and may be useful in the short-term management of RVHT before surgical treatment. Nitroprusside is especially useful for this purpose.

Nitroprusside (Nitropress)

Nitroprusside produces vasodilation and increases the inotropic activity of the heart. At higher dosages, it may exacerbate myocardial ischemia by increasing the heart rate. It is mainly used when a patient presents with a hypertensive emergency secondary to RVHT.

Cardiovascular, Other

Class Summary

Renin inhibitors constitute the newest class of antihypertensive drugs. They act by disrupting the RAAS feedback loop.

Aliskiren (Tekturna)

Aliskiren is a direct renin inhibitor. It decreases plasma renin activity and inhibits the conversion of angiotensinogen to angiotensin I (thus also decreasing angiotensin II) and thereby disrupts the RAAS feedback loop. Aliskiren is indicated for treatment of hypertension, either alone or in combination with other antihypertensive drugs.