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ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Asso ciation Task Force on Clinical Practice Guidelines. Hypertension 71:e13, 2018. Wright JT Jr. et al: SPRINT revisited: Updated results and implications. PART 6 Disorders of the Cardiovascular System Hypertension 78:1701, 2021. Stephen C. Textor*

Renovascular Disease The renal vasculature is unusually complex with high arteriolar flow to the cortex in excess of metabolic requirements, consistent with its primary function as a filtering organ. After delivering blood to cortical glomeruli, the postglomerular circulation supplies deeper medullary segments that support energy-dependent solute transport at multiple levels of the renal tubule. These postglomerular vessels deliver less blood and, coupled with high oxygen consumption, leave the deeper medullary regions at the margin of hypoxemia. Vascular disorders that commonly threaten the blood supply of the kidney include largevessel atherosclerosis, fibromuscular diseases, and embolic disorders. Microvascular injury, including inflammatory and primary hema tologic disorders, is described in Chap. 329. MECHANISMS OF VASCULAR INJURY

AND HYPERTENSION The glomerular capillary endothelium shares susceptibility to oxidative stress, pressure injury, and inflammation with other vascular territo ries. Endothelial injury can be manifest by urinary albumin excretion (UAE), which is predictive of systemic atherosclerotic disease events. Increased UAE may develop years before cardiovascular events. UAE and the risk of cardiovascular events are both reduced with pharmaco logic therapy such as antihypertensive drugs and statins. Experimen tal studies demonstrate functional changes and rarefaction of renal microvessels under conditions of accelerated atherosclerosis and/or compromise of proximal perfusion pressures with large-vessel disease (Fig. 289-1). Large-vessel renal artery occlusive disease can result from multiple conditions, including extrinsic compression of the vessel, intimal dis section, aortic stent graft placement, fibromuscular dysplasia (FMD), or, most commonly, atherosclerotic disease. Any disorder that reduces perfusion pressure to the kidney can activate mechanisms that tend to restore renal pressures at the expense of developing systemic hyper tension. Because restoration of perfusion pressures can reverse these pathways, renovascular disease is considered a specifically treatable “secondary” cause of hypertension. Renal artery stenosis is common, usually gradually progressive, and often has only minor hemodynamic effects.

FMD is reported in 3–5% of normal subjects presenting as potential kidney donors without hypertension. It may present clinically with hypertension in younger individuals (between age 15 and 50), most often women. FMD does not often threaten kidney function, but sometimes produces total occlu sion and can be associated with renal artery aneurysms. Atheroscle rotic renal artery stenosis (ARAS) is common in the general population (6.8% of a community-based sample above age 65). The prevalence increases with age and for patients with other vascular conditions such as coronary artery disease (18–23%) and/or peripheral aortic or lower *Deceased

extremity disease (>30%). If untreated, ARAS progresses in nearly 50% of cases over a 5-year period, sometimes to total occlusion. Intensive treatment of arterial blood pressure and statin therapy can slow these rates and improve clinical outcomes. Critical levels of stenosis (usually >70–80% luminal obstruction) lead to a reduction in perfusion pressure that activates the reninangiotensin system, reduces sodium excretion, and activates sympa thetic adrenergic pathways. These events lead to systemic hypertension characterized by angiotensin dependence in the early stages, widely varying pressures, loss of circadian blood pressure (BP) rhythms, and accelerated target organ injury, including left ventricular hypertrophy and renal fibrosis. Renovascular hypertension can be treated with agents that block the renin-angiotensin system and other drugs that modify these pressor pathways. It can also be treated with restoration of renal blood flow by either endovascular or surgical revasculariza tion. Most patients require continued antihypertensive drug therapy due to preexisting hypertension and because revascularization alone rarely lowers BP to normal. ARAS and systemic hypertension tend to affect both the postste notic and contralateral kidneys, reducing overall glomerular filtration rate (GFR) in ARAS. When kidney function is threatened by largevessel disease primarily, it has been labeled ischemic nephropathy. Moderately reduced blood flow that develops gradually is associated with reduced GFR and limited oxygen consumption with preserved tissue oxygenation. Hence, kidney function often remains reduced but stable during medical therapy, sometimes for years. With more advanced disease, reductions in cortical perfusion and overt tissue hypoxia develop. Unlike FMD, ARAS develops in patients with other risk factors for atherosclerosis and is commonly superimposed upon preexisting small-vessel disease in the kidney resulting from hyperten sion, aging, and diabetes. Nearly 85% of patients considered for renal revascularization have stage 3–5 chronic kidney disease (CKD) with estimated GFR <60 mL/min per 1.73 m2. The presence of ARAS is a strong predictor of morbidity- and mortality-related cardiovascular events, independent of whether renal revascularization is undertaken. DIAGNOSIS OF RENOVASCULAR DISEASE Diagnostic approaches to renovascular disease necessarily include evaluation of the kidney vasculature and depend on the specific clini cal questions to be addressed. Noninvasive characterization of the renal vasculature may be achieved by several techniques, summarized in Table 289-1. Although activation of the renin-angiotensin system is a key step in developing renovascular hypertension, it is transient. Levels of renin activity are therefore subject to timing, the effects of drugs, and sodium intake, and do not reliably predict the response to vascular therapy. Peak systolic renal artery velocities by Doppler ultrasound

> 200 cm/s generally predict lesions with more than >60% vessel lumen occlusion, although some treatment trials have required velocity >300 cm/s to avoid false positives. The renal resistive index has predictive value regarding the viability of

> the kidney. It remains operator- and institution-dependent, however. Contrast-enhanced computed tomog raphy (CT) with vascular reconstruction provides excellent vascular images and functional assessment but carries a small risk of contrast toxicity. It provides a more reliable evaluation of accessory vessels and the distal vasculature than duplex or magnetic resonance imaging (MRI). Magnetic resonance angiography (MRA) is less often used than previously, as gadolinium contrast has been associated with neph rogenic systemic fibrosis particularly in patients with reduced GFR. Captopril-enhanced renography has a strong negative predictive value when entirely normal. TREATMENT Renal Artery Stenosis While restoring renal blood flow and perfusion seems intuitively beneficial for high-grade occlusive lesions, revascularization proce dures also pose hazards and expense. Patients with FMD are com monly younger females with otherwise normal vessels and a long

Cortex Medulla Normal MV proliferation (early atherosclerosis) MV rarefaction (chronic renal ischemia) FIGURE 289-1 Examples of micro-CT images from vessels defined by radiopaque casts injected into the renal vasculature. These illustrate the complex, dense cortical capillary network supplying the kidney cortex that can either proliferate or succumb to rarefaction under the influence of atherosclerosis and/or occlusive disease. Changes in blood supply are followed by tubulointerstitial fibrosis and loss of kidney function. MV, microvascular. (Reproduced with permission from LO Lerman, AR Chade. Angiogenesis in the kidney: A new therapeutic target? Curr Opin Nephrol Hypertens 18:160, 2009.) life expectancy. These patients often respond well to percutaneous renal artery angioplasty. If BP can be controlled to goal levels and kidney function remains stable in patients with ARAS, it may be argued that medical therapy with follow-up for disease progression is equally effective over periods of 3–5 years. Multiple prospective randomized controlled trials for individuals with moderate stenosis have failed to identify compelling additional benefits for interven tional revascularization procedures regarding short-term results of BP and renal function. Studies of cardiovascular outcomes, includ ing stroke, congestive heart failure, myocardial infarction, and end-stage renal failure, suggest a small mortality benefit for stented patients without proteinuria. Medical therapy should include block ade of the renin-angiotensin system, attainment of goal BPs, cessa tion of tobacco, statins, and aspirin. Follow-up requires surveillance for progressive occlusion manifest by worsening renal function TABLE 289-1 Summary of Imaging Modalities for Evaluating the Kidney Vasculature Perfusion Studies to Assess Differential Renal Blood Flow Captopril renography with technetium-99m mertiatide (99mTc MAG3) Captopril-mediated fall in filtration pressure amplifies differences in renal perfusion Normal study excludes renovascular hypertension Vascular Studies to Evaluate the Renal Arteries Duplex ultrasonography Shows the renal arteries and measures flow velocity as a means of assessing the severity of stenosis Inexpensive; widely available, suitable for follow-up studies Computed tomographic angiography Shows the renal arteries and perirenal aorta Provides excellent images; stents do not cause artifacts Magnetic resonance angiography Shows the renal arteries and perirenal aorta Not nephrotoxic, but concerns for gadolinium toxicity exclude use in GFR <30 mL/min/1.73 m2; provides excellent images Intraarterial angiography Shows location and severity of vascular lesion Considered “gold standard” for diagnosis of large-vessel disease, usually performed simultaneous with planned intervention Abbreviation: GFR, glomerular filtration rate.

CHAPTER 289 Renovascular Disease and/or loss of BP control. Renal revascularization should be consid ered for patients with rapidly progressive clinical syndromes, failing medical therapy, and/or developing additional complications. Techniques of renal revascularization are improving. With expe rienced operators, major complications occur in <5% of cases, including renal artery dissection, capsular perforation, hemorrhage, and occasional atheroembolic disease. Although not common, atheroembolic disease can be catastrophic and accelerate both hypertension and kidney failure, precisely the events that revascu larization is intended to prevent. Although renal blood flow usually can be restored by endovascular stenting, recovery of renal function is limited to ~25% of cases, with no change in 50% and some dete rioration evident in others. Patients with rapid loss of kidney func tion, sometimes associated with antihypertensive drug therapy, or with vascular disease affecting the entire functioning kidney mass Multiple limitations in patients with advanced atherosclerosis or creatinine >2.0 mg/dL (177 µmol/L) Heavily dependent on operator's experience; less useful than invasive angiography for the diagnosis of fibromuscular dysplasia and abnormalities in accessory renal arteries Expensive, moderate volume of contrast required Expensive; gadolinium excluded in renal failure, unable to visualize stented vessels Expensive, associated hazard of atheroemboli, contrast toxicity, procedure-related complications, e.g., dissection

TABLE 289-2 Clinical Factors That Determine the Role of Revascularization in Addition to Medical Therapy for Renal Artery Stenosis Factors Favoring Medical Therapy with Revascularization for Renal Artery Stenosis PART 6 Disorders of the Cardiovascular System • Progressive decline in GFR during treatment of systemic hypertension • Failure to achieve adequate blood pressure control with optimal medical therapy (medical failure) • Rapid or recurrent decline in the GFR in association with a reduction in systemic pressure • Decline in the GFR during therapy with ACE inhibitors or ARBs • Recurrent congestive heart failure in a patient in whom left ventricular dysfunction does not fully explain the cause Factors Favoring Medical Therapy and Surveillance of Renal Artery Disease • Controlled blood pressure with stable renal function (e.g., stable renal insufficiency) • Stable renal artery stenosis without progression on surveillance studies (e.g., serial duplex ultrasound) • Advanced age and/or limited life expectancy • Extensive comorbidity that make revascularization too risky • High risk for or previous experience with atheroembolic disease • Other concomitant renal parenchymal diseases that cause progressive renal dysfunction (e.g., interstitial nephritis, diabetic nephropathy), particularly with proteinuria Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; GFR, glomerular filtration rate. are more likely to recover function after restoring blood flow. When hypertension is refractory to effective therapy, revascularization offers real benefits. Table 289-2 summarizes currently accepted guidelines for considering renal revascularization in addition to optimal medical therapy. ATHEROEMBOLIC RENAL DISEASE Emboli to the kidneys arise most frequently as a result of cholesterol crystals breaking free of atherosclerotic vascular plaque and lodging in downstream microvessels. Most clinical atheroembolic events follow angiographic procedures, often of the coronary vessels. It has been argued that nearly all arterial interventional procedures lead to plaque fracture and release of microemboli, but clinical manifestations develop only in a fraction of these. The incidence of clinical atheroemboli has been increasing with more vascular procedures and longer life spans. Atheroembolic renal disease is suspected in >3% of elderly subjects with end-stage renal disease (ESRD) and is likely underdiagnosed. It is more frequent in males with a history of diabetes, hypertension, and ischemic cardiac disease. Atheroemboli in the kidney are strongly associated with aortic aneurysmal disease and renal artery stenosis. Most clinically

evident cases can be linked to precipitating events, such as angiography, vascular surgery, anticoagulation with heparin, thrombolytic therapy, or trauma. Clinical manifestations of this syndrome commonly develop between 1 and 14 days after an inciting event and may continue to develop for weeks thereafter. Systemic embolic disease manifestations, such as fever, abdominal pain, and weight loss, are present in less than half of patients, although cutaneous manifestations including livedo reticularis and localized toe gangrene may be more common. Wors ening hypertension and deteriorating kidney function are common, sometimes reaching a malignant phase. Progressive renal failure can occur and require dialytic support. These cases often develop after a stuttering onset over many weeks and have an ominous prognosis. Mor tality rate after 1 year exceeds 38%, and although some may eventually recover sufficiently to no longer require dialysis, many do not. Beyond the clinical manifestations above, laboratory findings include rising creatinine, transient eosinophilia (60–80%), elevated sedimentation rate, and hypocomplementemia (15%). Establishing this diagnosis can be difficult and is often by exclusion. Definitive diagnosis depends on kidney biopsy demonstrating microvessel occlusion with

cholesterol crystals that leave a “cleft” in the vessel. Biopsies obtained from patients undergoing surgical revascularization of the kidney indicate that silent cholesterol emboli are frequently present before any further manipulation is performed. No effective therapy is available for atheroembolic disease once it has developed. Withdrawal of anticoagulation is recommended. Late recovery of kidney function after supportive measures sometimes occurs, and statin therapy may improve outcome. The role of embolic protection devices in the renal circulation during angiography is unclear, but a few prospective trials have failed to demonstrate major benefits. The effect of such devices is limited to distal protection during the endovascular procedure, and they offer no protection from embolic debris developing after removal. THROMBOEMBOLIC RENAL DISEASE Thrombotic occlusion of renal vessels or branch arteries can lead to declining renal function and hypertension. It is difficult to diagnose and is often overlooked, especially in elderly patients. Thrombosis can develop as a result of local vessel abnormalities, such as local dissec tion, trauma, inflammatory vasculitis, or systemic infections, such as COVID-19. Local microdissections sometimes lead to patchy, transient areas of infarctions labeled “segmental arteriolar mediolysis.” Although hypercoagulability conditions sometimes present as renal artery throm bosis, this is rare. It can also derive from distant embolic events, e.g., the left atrium in patients with atrial fibrillation or from fat emboli originat ing from traumatized tissue, most commonly large bone fractures. Car diac sources include vegetations from subacute bacterial endocarditis. Systemic emboli to the kidneys may also arise from the venous circula tion if right-to-left shunting occurs, e.g., through a patent foramen ovale. Clinical manifestations vary depending on the rapidity of onset and extent of occlusion. Acute arterial thrombosis may produce flank pain, fever, leukocytosis, nausea, and vomiting. If kidney infarction results, enzymes such as lactate dehydrogenase (LDH) rise transiently to extreme levels. If both kidneys are affected, renal function will decline precipitously with a drop in urine output. If a single kidney is involved, renal functional changes may be minor. Hypertension related to sud den release of renin from ischemic tissue can develop rapidly, as long as some viable tissue in the “peri-infarct” border zone remains. If the infarct zone demarcates precisely, the rise in BP and renin activity may resolve. Diagnosis of renal infarction may be established by vascular imaging with CT angiography, MRI, or arteriography (Fig. 289-2). ■ ■MANAGEMENT OF ARTERIAL THROMBOSIS OF THE KIDNEY Options for interventions of newly detected arterial occlusion include surgical reconstruction, anticoagulation, thrombolytic therapy, endo vascular procedures, and supportive care, particularly antihypertensive drug therapy. Application of these

methods depends on the patient’s overall condition, the precipitating factors (e.g., local trauma or sys temic illness), the magnitude of renal tissue and function at risk, and the likelihood of recurrent events in the future. For unilateral disease, for example, arterial dissection with thrombosis and supportive care with anticoagulation may suffice. Acute, bilateral occlusion is potentially catastrophic, producing anuric renal failure. Depending on the precipi tating event, surgical or thrombolytic therapies can sometimes restore kidney viability if undertaken early in the course of the acute event. MICROVASCULAR INJURY ASSOCIATED WITH HYPERTENSION ■ ■ARTERIOLONEPHROSCLEROSIS “Malignant” Hypertension Although BP rises with age, it has long been recognized that some individuals develop rapidly progressive BP elevations with target organ injury including retinal hemorrhages, encephalopathy, and declining kidney function. Pla cebo arms during the early controlled trials of hypertension therapy identified progression to severe levels in 20% of subjects over 5 years. If untreated, patients with target organ injury including papilledema

A B FIGURE 289-2 A. CT angiogram illustrating loss of circulation to the upper pole of the right kidney in a patient with fibromuscular disease and a renal artery aneurysm. Activation of the renin-angiotensin system produced rapidly developing hypertension. B. Angiogram illustrating high-grade renal artery stenosis affecting the left kidney. This lesion is often part of widespread atherosclerosis and sometimes is an extension of aortic plaque. This lesion develops in older individuals with preexisting atherosclerotic risk factors. and declining kidney function suffered mortality rates in excess of 50% over 6–12 months, hence the designation “malignant.” Postmor tem studies of such patients identified vascular lesions, designated “fibrinoid necrosis,” with breakdown of the vessel wall, deposition of eosinophilic material including fibrin, and a perivascular cellular infiltrate. A separate lesion was identified in the larger interlobu lar arteries in many patients with hyperplastic proliferation of the vascular wall cellular elements, deposition of collagen, and separa tion of layers, designated the “onionskin” lesion. For many of these

 patients, fibrinoid necrosis led to obliteration of glomeruli and loss of tubular structures. Progressive kidney failure ensued and, without dialysis support, led to early mortality in untreated malignant-phase hypertension. These vascular changes could develop with pressurerelated injury from a variety of hypertensive pathways, including but not limited to activation of the renin-angiotensin system and severe vasospasm associated with catecholamine release. Occasionally, endothelial injury is sufficient to induce microangiopathic hemolysis, as discussed below.

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