Review

New Insights Into Pathophysiology, Diagnosis, and Treatment of Renovascular Hypertension

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Renovascular disease includes renal artery stenosis, renovascular hypertension, and azotemic renovascular disease (ischemic nephropathy). Renovascular hypertension is defined as an elevated blood pressure caused by renal hypoperfusion, usually resulting from anatomic stenosis of the renal artery and activation of the renin-angiotensin system. It accounts for 1% to 2 % of all cases of hypertension in the general population and 5.8 % of secondary hypertension, but it plays a major role in treatable causes of hypertension in the young individuals. Although renovascular stenosis is a common and progressive disease in patients with atherosclerosis, it is a relatively uncommon cause of hypertension in patients with mild hypertension. In contrast, renal artery stenosis is more frequent in certain high-risk populations.

Early diagnosis of renovascular hypertension and timely implementation of appropriate therapeutic procedures ensures optimum control of blood pressure, prevents ischemic nephropathy progression, and prevents the development of cardiovascular morbidity and mortality in the hypertensive patient population. As with most complex disorders, management decisions must be highly individualized for patients with renovascular disease. It is essential to consider renal arterial disease as one aspect of atherosclerotic disease.

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INTRODUCTION

Renovascular disease includes renal artery stenosis (RAS), renovascular hypertension (RVH), and azotemic renovascular disease (ischemic nephropathy). Renovascular hypertension that is the result of RAS is the most common reason of secondary hypertension (accounts for 1% to 2% of all cases of hypertension in the general population and 5.8% of secondary hypertension cases).[1] Different studies have shown that among the patients with mild to moderate hypertension, RVH accounts for nearly 1% of all reasons, whereas in severely hypertensive cases and those resistant to treatment, the prevalence of this complication rises significantly. In 2008, the American Heart Association defined significant stenosis as a decrease of at least 60% in luminal diameter of the renal artery, but RAS can be diagnosed when also narrowing of the diameter of a main renal artery by more than 70% or luminal narrowing by more than 50% is detected with a poststenotic dilatation.[2] This is important to emphasize that RVH and RAS are separate conditions; many cases with RAS can be find with normal blood pressure.

Renal artery stenosis can have different causes. Atherosclerosis accounts for nearly 90% of all RAS cases, and the rest of the 10% are thought to be caused by fibromascular dysplasia.[3,4] Other causes of RAS are very rare (Table 1).

ATHEROSCLEROTIC RENAL ARTERY STENOSIS

Atherosclerotic RAS is commonly seen in older

Table 1. Potential Causes of Renal Artery Stenosis

Lesion of renal artery or its branches
Aneurysm
Arteriolar nephrosclerosis
Arteritis (ie, polyarteritis nodosa, Takayasu arteritis, and Kawasaki disease)
Atherosclerosis
Arteriovenous malformation
Congenital narrowing
Dissection
Fibromuscular dysplasia
Thrombosis or embolism
Trauma
Renal parenchymal disease
Neoplasm (ie, carcinoma, sarcoma, Wilms tumor, and metastasis)
Obstructive uropathy
Ptosis of kidney
Pyelonephritis
Renal vein thromboembolism
Renal compression (page kidney)
Extrarenal mass (ie, aortic aneurysm, retroperitoneal hematoma or neoplasm, and peripelvic cyst)
Subcapsular hemorrhage
Rare diseases
Type 1 neurofibromatosis, tuberous sclerosis, pseudoxanthoma elasticum, Ehlers–Danlos syndrome, Alagille syndrome, Marfan syndrome, and Williams syndrome

population, and most of the time is the disease of patients older than 50 years of age, accompanying with disseminated atherosclerosis and peripheral or coronary vascular involvement. Indeed, left ventricular hypertrophy, ischemic heart disease, and kidney failure are common in this population as well.[5] From a hemodynamic point of view, a stenosis is significant when there is a demonstrable pressure gradient, because the pressure drop beyond the stenosis would begin intrarenal adaptive mechanisms, finally leading to renal ischemia and hypertension.[6]

Due to the variability of hospital populations and to a selection process, the frequency of RAS ranged from 12% to 53% in series examining fewer than 300 patients, and it was only 4% in a very large series (over 5000 patients) collected over an 8-year period.[7,8] In a systematic review that included 15879 patients, the prevalence of RAS among hypertensive patients who had undergone computed tomography-angiography, magnetic resonance imaging, or conventional angiography was 18%; however, it reached 33% in patients with aneurysm of the abdominal aorta.[9,10]

Stenosis due to atherosclerosis is often placed in the ostium and the first one-third of the main renal artery; however, this is remarkable that about half of the population of 60-year olds with normal blood pressure may have such a lesion in the proximal part of the renal artery. In the other words, atherosclerotic RAS can be found more commonly than RVH.

FIBROMUSCULAR DYSPLASIA

In about 10% of patients with RVH, the narrowing of the lumen is caused not by atherosclerosis but by the entity known as *fibromuscular dysplasia* (FMD). Patients are usually young and predominantly women between 30 and 50 years of age, and it is 4 times more common between women than men. Fibromuscular dysplasia is defined as an idiopathic, noninflammatory, and nonatherosclerotic disease of the vasculature basically involving renal arteries, and to some extent, carotid and vertebral arteries as well. The right renal artery is the leading site of FMD although a bilateral form is also probable in up to 40% of cases.

Fibromuscular dysplasia can be seen anatomically in 3 different types of medial, intimal, and adventitial or periarterial. The most common form of renal FMD is medial, which appears in approximately 805 to 90% of cases and has a classic angiographic "string-of beads" appearance due to aneurysmal dilatations separated by integrated

fibrosis plexus. The lesion usually is limited to the distal two-thirds of the renal artery; however, sometimes it can extend into the proximal portion. This lesion can be bilateral in 60% of the cases. Intimal FMD is the second most common (nearly 10%) presentation of FMD and is due to collagen deposition within the intimal layer. This is the most common form in children and young adults. It can even be progressive and cause ischemia and renal atrophy. In angiography, it can cause a unifocal lesion that results in a concentric or long tubular stenosis. Adventitial FMD is the least common (< 1%) presentation of FMD. It is usually due to hypertrophy of the connective tissue at the junction of the medial and adventitial layers of the renal artery. Indeed, huge amounts of elastic tissue are concentrated in the outer layer of media and cause perimedial fibrosis. These lesions can be unifocal and are found at the ostium, main trunk, or the branching of the renal arteries. This form of FMD is seen more commonly in early childhood and can terminate to high blood pressure and chronic kidney disease.[11,12]

The etiology of FMD is undetermined, although different aspects have been suggested. Environmental factors such as smoking have also been connected with FMD, but the precise link still seems to be uncertain. The superiority of right renal artery lesions implies a mechanical element because the right kidney is more mobile than the left one; the mechanism may contain compression of the vasa vasorum leading to ischaemia.[13] Radiology helps a lot in the diagnosis of FMD. In 2012, a new classification was built for FMD on the basis of angiographic appearance: multifocal form with 2 or more constrictive lesions in each vessel with or without string of beads appearance and unifocal form which manifests as 1 focal or tubular constriction. According to this study, other than the angiographic characteristics, clinical presentations were different among these two groups; unifocal form was more common in men, diagnosed at least 20 years earlier than multifocal lesions, and although less commonly appeared bilaterally, leading to higher blood pressures and more asymmetric kidneys.[14-22]

PATHOPHYSIOLOGY

Goldblatt first proposed that the direct cause of some forms of hypertension was hypersecretion of a pressor element secreted by the kidney in response to ischemia. Nowadays, we know it definitely as renin.[23] Goldblatt hypertension includes the 2-kidney-1-clip model, in which normal kidney would show pressure natriuresis, as well as the 1-kidney-1-clip model, in which all the kidney parenchyma would be affected by obstruction. Instantly after decreasing blood flow to 1 kidney, there was an increase in renin secretion rate, plasma renin activity (PRA), systemic angiotensin II, and systemic blood pressure.[24,25] The key role of the RAS in Goldblatt hypertension does not exclude other mechanisms from contribution in the creation of RVH. Prostaglandin inhibition in the existence of even concise increases in renin generation may cause hypertension, and it is shown that these autocoids have a main position in the compensation of the hypertension produced by angiotensin II in the Goldblatt experimental model.[26]

Transformed arachidonic acid metabolism has been shown in the clipped kidney of Goldblatt hypertension and helps to the beginning and preservation of hypertension. Moreover, angiotensin II causes the release of huge amounts of prostaglandin F2, 6-keto- prostaglandin F1, and thromboxane 2, suggesting a special enhancement of this vasoconstrictor eicosanoid by arterial constriction.[27,28]

A role for fluctuations in sympathetic tone in 2-kidney-1-clip model hypertension has also been proposed, which indicates that alteration of adrenergic systems may contribute to the expansion and prolongation of abnormal vascular responses in Goldblatt hypertension.[29,30] Angiotensin II also facilitates nonhemodynamic properties and has the ability to promote fibrosis through a number of mechanisms, including induction of collagen synthesis, inhibition of collagen-cleaving proteases, motivation of the excretion of platelet-derived growth factor, synthesis of nuclear factor-κB, and thus transforming growth factor-β, which is involved in many of procedures related to the progression of RVH, including cell cycle regulation, leading to hypertrophy or apoptosis, mitogen-activated protein kinases activation, inflammation, and extracellular matrix production. Mitogen-activated protein kinases activity is vital for inflammation and fibrosis development in stenotic kidneys in RAS, and it also can provoke monocyte chemoattractant protein-1.[31]

Increased monocyte chemoattractant protein-1 levels also fuel transforming growth factor-β production in glomerular cells, despite the lack of infiltrating inflammatory cells. Studies showed that monocyte chemoattractant protein-1 blockage would manifest as renal protection by reducing renal inflammation and the level of collagen deposition, thus maintaining the kidney in chronic RAS.[32]

Atrial natriuretic peptide is known to reduce vascular smooth muscle tone formerly constricted with angiotensin, but it also stops the secretion of renin and may lessen PRA. It has been proposed that atrial natriuretic peptide may somewhat avoid large rises in pressure in the early stages of hypertension.[33] Brain natriuretic peptide stimulates diuresis, natriuresis, and arterial vasodilation, and it antagonizes renin activity. Hypothetically, brain natriuretic peptide may be increased in patients with resistant hypertension and severe RAS.[34] Kalikrein is also increased in Goldblatt models. Because the kallikrein-kinin is a vasodilator diuretic system, it has been assumed that its role is to offer homeostatic protection against the RAS.[35,36]

CLINICAL MANIFESTATIONS OF RENOVASCULAR HYPERTENSION

Age of onset of hypertension in an individual under the age of 30 years or over the age of 55 years, particularly if hypertension is severe and requires 3 antihypertensive drugs to be controlled, is a strong clinical clue to RAS. Patients with a long history of mild hypertension, easily controlled with 1 or 2 drugs, who, especially later in life, develop severe and resistant hypertension, are likely to have developed atherosclerotic RAS. Grade 3 hypertensive retinopathy, malignant hypertension, and flash pulmonary edema all suggest RAS with or without RVH.[37-39] Clinical clues suggesting RAS are listed in Table 2.

Table 2. Diagnosis of Renovascular Hypertension

Clinical Clues
Age of onset of hypertension < 30 years or > 55 years
Abrupt onset of hypertension
Acceleration of previously well-controlled hypertension
Accelerated retinopathy
Acute kidney failure with use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers
Evidence of generalized atherosclerosis obliterans
Flash pulmonary edema
Hypertension refractory to an appropriate 3-drug regimen
Malignant hypertension
Systolic diastolic abdominal bruit

DIAGNOSTIC TESTS AND IMAGING

Indications

Before running any diagnostic evaluation, the clinician should consider this important point that whether or not revascularization would be necessary in case of finding any stricture. Any time that clinical suspicious is low for detecting renovascular disease, like in conceivably treated patients with stable kidney function and constantly hypertensive for many years, there is no need for further investigation of renovascular disease. It is better to consider more evaluation in hypertensive patients with a new rise in blood pressure (in very last weeks to months), nonresponders to medical treatment, those with severe or resistant hypertension, those with acute kidney failure on angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers, and patients with flush pulmonary edema.

Diagnostic tests for evaluation of RVH can be categorized in 3 groups: (1) functional and physiologic tests which evaluate the role of stenosis regarding to renin-angiotensin system, the sensitivity and specificity of which are strongly associated with the likelihood of RVH existence; (2) radiological diagnostic tests for evaluation of blood supply and percentage of stenosis; and (3) diagnostic tests which evaluate benefits of angiographic interventions. There is no single test or radiographic method which can definitely rule out RAS by its negative result.

Plasma Renin Activity

Because RVH probably results from renin hypersecretion, determining elevated circulating level of renin may help to detect those patients whose hypertension can be cured by a surgical revascularization. In 50% to 80% of RVH cases, PRA is actually high. However, PRA differs not only with physiological parameters such as blood volume, sodium load, and differences in unilateral versus bilateral disease, but also with age, race, sex, and comorbidities such as diabetes mellitus. This method has other major limitations, such as being affected by time of the day, body position (sitting versus lying down), state of water intake, and use of antihypertensive drugs and nonsteroidal anti-inflammatory drugs. Moreover, PRA test has

relatively low sensitivity and specificity (57% and 66%, respectively).[40]

Renin Provocation Test with Captopril

The captopril test is a noninvasive medical test that measures the change in renin plasma levels in response to administration of captopril. By administration of 20 mg to 50 mg of captopril 1 hour before checking plasma concentration of renin, it is possible to raise the predictive value of PRA. If the renin levels increase markedly or the baseline renin level is abnormally high, it means that test is positive. A patient with RAS would show an exaggerated increase in PRA value after the use of ACE inhibitors. Patients must have a normal salt intake. Additionally, 3 weeks prior to the test, the use of drugs that affect the PRA, such as ACE inhibitors, angiotensin receptor blockers (ARBs), diuretics, beta blockers, and direct renin blockers, should be stopped, whereas alpha blockers can be continued.[41] Renin provocation test with captopril is known to have lower sensitivity, specificity, and predictive value in comparison with captopril renography. Nowadays, it is not generally considered a useful test and more appropriate choices are accessible for diagnosis of RVH.

Bilateral Renal Veins Renin Level

The measurement of PRA in renal venous blood has become widely used to diagnose significant renal ischemia in RAS. A ratio of 1 to 1.5 between PRA measured in the renal vein on the affected side by RAS to the PRA from the contralateral renal vein denotes the presence of a functional RAS and anticipated response after revascularization is predictable.[41] Renal vein PRA is now used very rarely in diagnostic approaches to RVH and cannot be used as a suitable screening test in diagnosing RAS because of high false-positive and false-negative results reaching 67% in some studies.

Captopril Renography

The reason behind using captopril renography is reduction of glomerular filtration rate (GFR) in the affected kidney by RAS after using ACE inhibitors, against increased GFR in contralateral side. Captopril will reduce Angiotensin II, efferent arteriole vasoconstriction, and intraglomerular pressure in the affected kidney. By using captopril, low sensitivity and specificity of renal radionuclide scans can be partly overcome. The two most common radiolabelled pharmaceutical agents used are Tc99m-mercaptoacetyltriglycine and Tc99m-diethylenetriaminepentacetate. Mercaptoacetyltriglycine is a better diagnostic agent, particularly in patients with impaired kidney function.

The sensitivity of ACE inhibitor renography may be reduced in patients receiving ACE inhibitors. For this reason, short-acting ACE inhibitors, such as captopril, should not be used for 3 days before the study. Longer-acting ACE inhibitors should be withheld for 5 to 7 days. Angiotensin receptor blockers should also be discontinued before ACE inhibitor renography.[42] The volume depletion associated with chronic diuretic use may be the effect of ACE inhibition, leading to an increased risk of symptomatic hypotension; therefore, chronic diuretic administration should be stopped several days before the study. Interpretation of test results are as below:

Low probability. Normal findings on ACE inhibitor renography show a low probability (< 10%) for RVH.

Intermediate probability. Patients with an intermediate probability of disease are a small group with abnormal baseline findings, but the renography is unchanged after ACE inhibitor. The sensitivity of abnormal baseline findings that are unchanged after ACE inhibitor is quite high (> 90%), but the specificity is low.

High probability. The probability of RVH is considered high (> 90%) when marked changes of the renography curve occur after ACE inhibitor.

In high-risk patients for RVH, sensitivity and specificity of captopril renography is as high as greater than 90%, but in the low-risk group for having RVH and in patients with 2-sided RAS, the predictive value of this test somehow will decreased. Also, in cases with kidney failure (serum creatinine > 2 mg/mL), captopril renography shows low sensitivity and specificity.

This diagnostic test gives clinicians useful functional data but cannot specify any anatomical findings regarding to the place and number of renal artery lesions. A practical recommendation is to perform a captopril renography first, and if this scan shows any abnormality, then a second scan could be done without captopril. If this second nondrug scan shows normal results, this

indicates renal parenchymal disease otherwise a renovascular problem exists.

Color Doppler Ultrasonography

Color Doppler ultrasonography is a safe and noninvasive diagnostic technique for anatomical as well as functional evaluation of the renal arteries. It also can be used to select patients who are good candidates for successful revascularization and monitor renal arteries after revascularization for restenosis. Many experts believe that radiologic evaluation should be started with Doppler ultrasonography.[43] The criteria for RVH include peak systolic blood flow velocity greater than 180 cm/s, end-diastolic flow velocity greater than 50 cm/s, renoaortic ratio greater than 3.5, and reno-renal ratio greater than 4.0. Sensitivity and specificity of this test for detecting above 60% of RAS cases are 90 % and 69%, respectively.

Assessing the resistive index with ultrasonography has a prognostic value in RAS cases. Prognosis in patients with a resistive index higher than 80% is worse than cases with a resistive index less than 80%. Also the latter category responsiveness revascularization would be unsatisfactory.

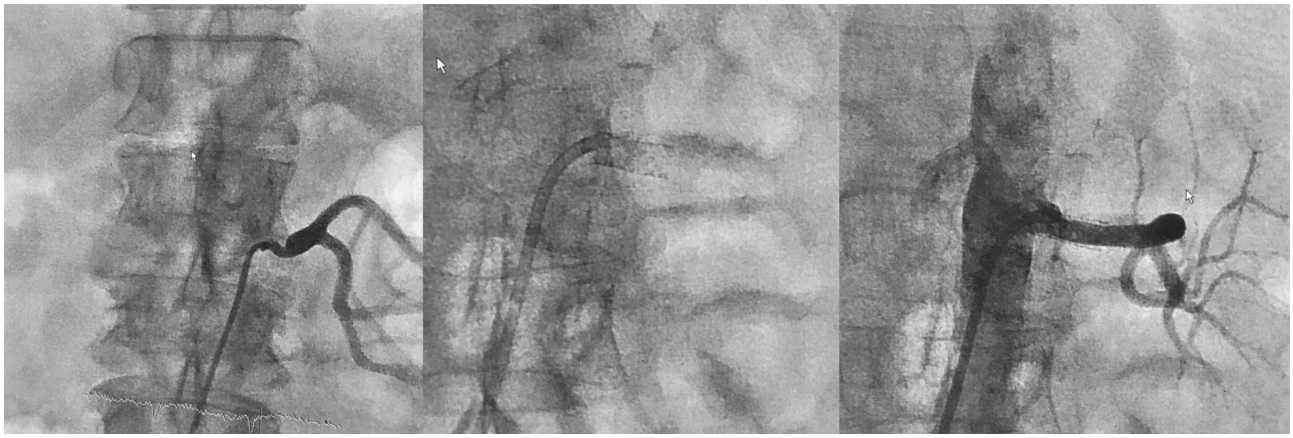
Limitations of Doppler ultrasonography are often related to insufficient evaluation of accessory renal arteries, especially in overweight individuals accompanying with being very operator-dependent modality.

Computed Tomography and Magnetic Resonance Angiography

Magnetic resonance and computed tomography angiography offer comprehensive images of the aorta and renal arteries, often permitting identification of multiple vessels, estimation of renal size, and anatomy. Magnetic resonance angiography is a very useful method for screening atherosclerotic renovascular disease but has limited value in diagnosing fibromuscular problems. Its sensitivity is reported to be around 95% in different studies. The main limitation of all forms of angiography is lack of information on renal flow or pressure distal to RAS. Because of the relationship between nephrogenic systemic fibrosis and gadolinium-based contrast agents, the United States Food and Drug Administration now notifies against using gadolinium-based contrast agents in patients with a GFR less than 30 mL/min/1.73 m^2; therefore, magnetic resonance angiography cannot be used in patients with impaired kidney function unless GFR has not still dropped to very low levels.[45]

Angiography

Intra-arterial digital subtraction angiography targets to confirm the diagnosis of RAS, evaluates the extent of intra-renal vascular disease, and recognizes associated aneurysmal or occlusive aortic disease therefore provides a gold standard of diagnostic approach to RAS. A major advantage of invasive imaging is that hemodynamiclly significant stenosis can be directly measured and treated immediately.[46] Being invasive, however, conventional catheter angiography has the highest risk including ionizing radiation and complications related to iodinated contrast and intervention, such as cholesterol emboli.[47,48] Angiography



Angiography shows severe proximal left renal artery stenosis at baseline (right side) and after placing the stent (middle), and final result of renal angioplasty (left side). The patient was a 50-year-old woman with uncontrolled hypertension, with 4 antihypertensive medications at maximum doses. After stenting, blood pressure was controlled with 1 medication and kidney function remained stable.

should be considered in a patient with a previous positive screening test who is a good candidate for revascularization or in a patient with high suspicious of RAS even though the computed tomography or magnetic resonance angiography shows normal results.

TREATMENT

Medical Treatment

Clinical data suggest that survival of patients with RVH is better when ACE inhibitors are part of therapy than when they are not. The clinical results and survival during medical therapy of high-grade RAS seem to be equivalent to those with revascularization when target blood pressures are reached. A main worry in the use of ACE inhibitors to overcome RVH is their potential capability to cause functional acute kidney failure. The mechanism of acute kidney failure relates to the inhibition of the compensatory mechanisms that develop beyond a stenotic lesion. Poststenotic reduction in renal perfusion pressures provokes renin and angiotensin II release, resulting in vasoconstriction of the efferent arteriole that preserves glomerular capillary filtration pressure. Administration of ACE inhibitors (or ARBs) and the subsequent relaxation of the efferent arteriole can reduce glomerular capillary hydrostatic pressure enough to cause a decrease in glomerular ultrafiltration. This loss of filtration produces a rise in serum creatinine.[49] As a result, it is essential that clinicians use attention when starting an ACE inhibitor in patients with known or suspected renal artery disease with close follow-up of kidney function and potassium levels. Observing a significant fall in GFR (usually defined as a 30% fall in calculated GFR or a rise in serum creatinine greater than 0.5 mg/dL) per se may be an indication to consider the need for renal revascularization.

In unilateral RAS, the affected kidney frequently has reduced filtration without measurable changes in creatinine. Changes in total GFR are minor, presumably because of a compensatory increase in GFR by the contralateral kidney. Clinically significant loss of GFR during treatment with ACE inhibitors happens in only a fraction of treated patients, usually in those with vascular stenosis that affects the entire functional renal mass (bilateral RAS or stenosis to a solitary kidney). Initial studies reported kidney failure in one-third to half of patients with either bilateral RAS or stenosis to a solitary kidney who received ACE inhibitors.[50] In a trial by Hollenberg and colleagues, 269 patients treated with the captopril reported a lower incidence of 136 (51%) patients with either bilateral RAS or stenosis to a solitary kidney and only 8 (5.8%) who developed progressive acute kidney failure within the first month of treatment.[51] The efficacy and safety of ACE inhibitors were examined in a randomized double-blinded study of 75 patients with RVH.[52] An increase in the serum creatinine level was observed in 10 patients (20%) in the ACE inhibitor group compared with 3% in the control group.

Taking all these together, ACE inhibitors usually can be used for treatment of RVH without important loss of GFR. Known risk factors that predispose to developing kidney failure during ACE inhibitor use include congestive heart failure, treatment with vasodilators or diuretics, and volume contraction. In current practice, the attention is on early recognition of probable risk factors for ACE inhibitor-induced renal side effects and close monitoring of this group of patients.

Lowering lipid levels, smoking cessation, and maintaining acceptable glucose levels all require consideration. Interestingly, recent studies have suggested that statins can lower the rate of progression to end-stage kidney disease as well as mortality and it is recommended to keep low-density lipoprotein cholesterol level to less than 70 mg/dL with using statins in all atherosclerotic renovascular cases.[53,54] Moreover, a recent pilot study showed that adding to the standard antihypertensive treatment after revascularization nebivolol, a new generation beta blocker that releases nitric oxide, improved GFR and proteinuria.[55]

Renal Revascularization

Interventional treatment includes conventional percutaneous transluminal renal angioplasty (PTRA) with or without stenting. Different studies showed more efficacy with stenting regarding restenosis after 6 months comparing with not using stents, although control of blood pressure was similar in both groups.

Conventional PTRA is considered the treatment of choice for patients with uncontrolled hypertension and FMD.[58] Indications for renal revascularization are summarized in Table 3.

Table3. Indications for Renal Revascularization

Resistant hypertension
Failure of medical therapy despite full dose of ≥ 3 drugs including diuretics
Progressive renal insufficiency
Recent rise in serum creatinine
Loss of glomerular filtration rate during antihypertensive therapy with angiotensin converting enzyme inhibitors or angiotensin receptor blockade
Evidence of preserved diastolic blood flow (low resistive index)
Recurrent 'flash' pulmonary edema unrelated to acute coronary syndrome
Refractory congestive heart failure with bilateral renal artery stenosis

In following situations, there would be no benefit of preforming revascularization for renal artery[54]: (1) resistive index measured from the blood flow curve through the segmental arteries > 0.8, which indicates high-grade fibrosis in the kidney due to chronic ischemic nephropathy; (2) advanced chronic kidney disease (GFR < 30 mL/min/1.73 m^2 or a serum creatinine > 3 mg/dL; and (3) patients with normal blood pressure and normal kidney function (silent RAS) or those with controlled high blood pressure after starting antihypertensive drugs.

Comparison of Angioplasty with Medical Treatment

Two randomized controlled trials compared PTRA to medical treatment with 6-month or longer follow-up. The study concluded that PTRA in unilateral renovascular disease has some drug sparing potential, but its efficacy for lowering blood pressure seems to be overestimated.[59] The DRASTIC trial showed no significant differences between the angioplasty and medical therapy.[60] The Angioplasty and Stenting for Renal Artery Lesions trial was one of the largest published randomized controlled trials to compare PTRA combined with medical therapy to medical therapy alone.[61] In 806 patients with RAS, differences in kidney function, blood pressure, kidney, and cardiovascular events, and mortality were all unimpressive. The decrease in kidney function over time was slightly but not statistically significantly slower in the revascularization group. The medical management group required a slightly higher number of antihypertensive drugs, reaching statistical but not clinical significance.

The stent placement and blood pressure and lipid lowering for the prevention of progression of kidney dysfunction caused by atherosclerosis directed to a 20% or greater decline in creatinine clearance in a multicener trial.[62] At 2 years, the primary endpoint had been reached in 16% of the stent group and 22% in the medication group, with no significant difference.[62]

The Cardiovascular Outcomes in Renal Atherosclerotic Lesions trial tested the hypothesis that stenting RAS greater than 60% (pressure gradient > 20 mm Hg) in patients with systolic hypertension reduced the incidence of cardiovascular and renal events.[63] Unlike other studies, the patients had difficult-to-control hypertension and systolic blood pressure of 155 mm Hg and higher, while on 2 or more drugs. No benefit was found in stenting with respect to the rate of the composite primary end point or any of its individual components, including death of cardiovascular or renal causes, stroke, myocardial infarction, congestive heart failure, progressive renal insufficiency, and the need for renal replacement therapy.

The RADAR is another ongoing multicenter trial to evaluate the clinical impact of PTRA on impaired kidney function in patients with 70% and greater RAS.[64] Three hundred patients were randomized to best medical treatment versus best medical treatment plus PTRA. The expected outcome of the study is a significant difference in the primary study end point, the difference between treatments in change of estimated GFR over 12 months. Results still are not released, but hopefully, the RADAR will help answer remaining concerns and questions.

Drug-eluting Stents and Distal Embolic Protection Devices

In the GREAT trial,[65] which compared sirolimus drug-eluting stents to bare metal stents in 102 patients, the relative risk reduction in angiographic binary renal artery in-stent restenosis was 50%, which was statistically insignificant (7% versus14%).

In-stent stenosis, binary restenosis rates, late lumen loss, and repeat revascularization were all lower in the drug-eluting stents group. At present, drug-eluting stents are manufactured solely for use in coronary vessels, and given the lack of outcome data, considerable expenses, and cost associated with postprocedure needs for long-term antiplatelet therapy with aspirin and clopidogrel, widespread use of drug-eluting stents is not recommended in RAS.

The contribution of distal embolization to worsening kidney function after stenting has grown interest in using embolic protection devices. A randomized phase II trial on 100 patients demonstrated no overall improvement in GFR with the use of a filter-based embolic protection devices, perhaps because of increased platelet aggregation or escaped renal atheroemboli associated with the device.[66]

Surgical Revascularization

Renal artery surgery offers major benefits for patients undergoing surgical repair of the aorta or nephrectomy and for patients with complex disease of the renal arteries, like aneurysms or failed angioplastic methods. Surgical procedures may include renal artery bypass grafting, end-arterectomy, or rarely extra-anatomic repair using anastomosis to the hepatic or splenic arteries. Thirty-day mortality rates range between 3.7% and 9.4% and is increased by the need for aortic reconstruction or bilateral renal bypass, severe preoperative azotemia, and the use of an aortic graft for aorto-renal bypass.[67] Fibromuscular dysplasia is not focal but diffuse and sometimes bilateral involvement of vessels so it seems that end-arterectomy is not the first-line choice for these cases. Taken together, end-arterectomy should be reserved for patients who cannot be treated otherwise.

CONCLUSIONS

Renovascular hypertension is defined as the elevation of arterial pressure precipitated by a hemodynamically significant stenosis of a renal artery (that is a stenosis greater than 75% of the vessel lumen or 50% with poststenotic dilation). The most prevalent mechanism underlying lesion of the renal arteries is atherosclerosis. This increases with age, especially in elderly patients with diabetes mellitus, hyperlipidemia, aortic occlusive disease, and lesions in the coronary artery. Atherosclerosis of the renal artery is a progressive disease that may cause ischemic renal disease, also known as ischemic nephropathy. Early diagnosis of RVH and timely application of appropriate therapeutic techniques certifies ideal control of blood pressure, prevents ischemic nephropathy progression and prevents the development of cardiovascular morbidity and mortality in the hypertensive patients. As with most complex disorders, management decisions must be highly individualized for patients with renovascular disease.

Regardless of how such patients are identified, close follow-up is essential to determine both the stability and recurrence of vascular lesions in the kidney. As long as blood pressure and kidney function are well maintained, expectant management appears to be completely correct. It must be understood, however, that acceleration of hypertension, kidney dysfunction, or target manifestations necessitates re-evaluation for both disease progression and recurrence.

CONFLICT OF INTEREST

None declared.

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