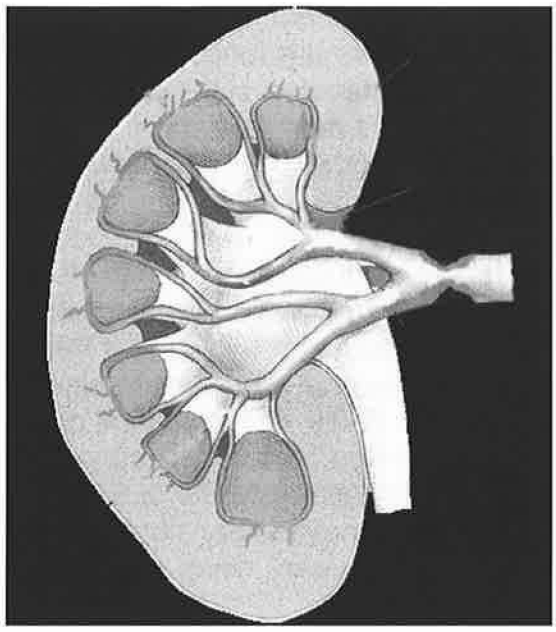
Internal Medicine Grand Rounds

Renal Artery Stenosis and Hypertension: Current Diagnostic and Therapeutic Dilemma



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1. Definition and Epidemiology

Renovascular hypertension (RVH) is a common cause of secondary hypertension, accounting for 1-7% of all hypertensive patients [1]. The minimal degree of stenosis that reduces renal perfusion in humans is not known but, in dogs, diameter stenosis of > 70% is needed to decrease renal blood flow and increase the systemic arterial pressure [2]. Diameter stenosis between 50-70% is also considered to be significant stenosis by some investigators, if the systolic pressure gradient across the lesion is more than 20 mmHg based on canine studies [3]. Because there are currently no clinical tests that can precisely assess the functional significance of a given stenosis, the diagnosis of renovascular hypertension still relies heavily on clinical presentation *expo facto* and the BP response to revascularization. However, such reliance may still lead to inaccurate interpretation as lack of BP responses to revascularization may occur in some patients with renovascular hypertension who develop irreversible contralateral or ipsilateral renal parenchymal injury.

The main pathology found in most cases of RVH is atherosclerosis, accounting for 70–90% of patients and usually involves the ostium and proximal one-third of the main renal artery. Fibromuscular dysplasia (FMD) is a form of vascular diseases that affects the intima, media, and adventitia seen predominantly in young adults and is responsible for 10–30% of cases of RVH. The incidence of atherosclerotic renovascular hypertension is increasing in the United States, reflecting the increased life expectancy and the aging of our population. According to the U.S. Renal Data System database, the incidence of ESRD related to renovascular diseases has doubled over the past decade (from 2.9 to 6.1 per million per year), rising at a faster rate than ESRD related to other causes such as diabetes mellitus [4].

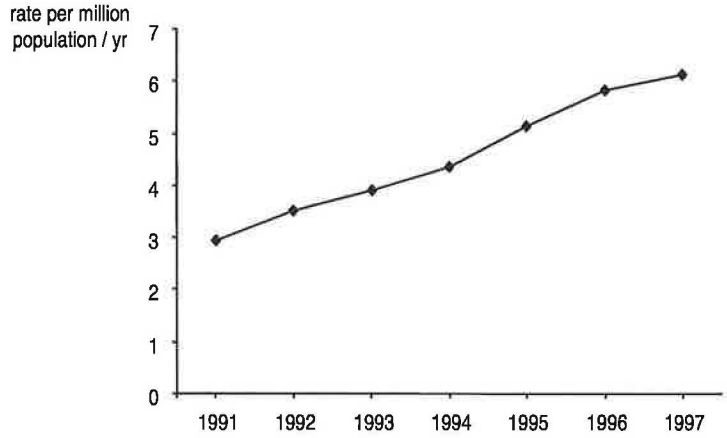


Figure 1: Adjusted incidence rate of ESRD due to renovascular disease, U.S. Renal Data System database.

It is estimated that 15-20% of elderly patients who enter dialysis program have atherosclerotic renal artery stenosis as a contributing factor [5,6]. The prevalence of renovascular hypertension is thought to be lower in African Americans than Caucasians [7,8]. However, this is an incorrect notion based on the captopril renogram. Angiographic studies have not confirmed such an ethnic difference [9,10].

Atherosclerotic renovascular disease may lead to deterioration in renal function, "ischemic nephropathy". Chronic underperfusion is thought to be the main mechanism

leading to renal atrophy. However, the hypothesis is questioned by study in humans indicating that less than 10% of oxygen delivered to the kidneys is needed to maintain normal physiologic function [11]. Because renal dysfunction and atrophy is rarely seen with fibromuscular dysplasia, additional mechanisms such as repetitive episodes of atheroembolism in the ipsilateral or contralateral kidney or renal parenchymal damage from long-standing hypertension [12,13] may contribute to renal dysfunction in the patients with atherosclerotic renovascular disease. Consequently, the term "ischemic nephropathy" is somewhat misleading and several investigators have proposed to rename this clinical entity as "azotemic renovascular disease".

It is important to emphasize that not all patients with renal artery stenosis subsequently develop hypertension or renal dysfunction. A population-based Cardiovascular Health Study in the elderly reported prevalence of renovascular disease of 6.8%, based on Doppler ultrasonography, but only 53% of these subjects were hypertensive [14]. In most angiographic studies, prevalence of incidental renovascular disease was reported to be between 15-30% in patients undergoing abdominal aortogram or coronary angiogram. Only half of these patients have hypertension or renal dysfunction [15,16]. One-third of elderly patients with congestive heart failure were found to have a stenotic renal artery disease, but only one-third of these have hypertension [17]. Thus, renal artery stenosis should not be used synonymously with renovascular hypertension or ischemic nephropathy.

2. Natural History and Prognosis

Atherosclerotic renal artery stenosis tends to be progressive over time. The 3-year incidence of renal atrophy is 10-20% [18], doubling of serum creatinine is 15% [19], and progression to end-stage renal disease is 7-10% [19-21]. Patients with more severe disease are more susceptible to have ipsilateral renal atrophy but those with high systolic blood pressure are also at increased risk of renal atrophy in both ipsilateral and contralateral kidneys, independent of severity of stenosis [18]. Thus, the presence of renal artery stenosis does not necessarily protect the kidney against harmful effects of systemic hypertension. Because renal function is influenced by many factors other than renal perfusion, it is usually difficult to show a correlation between the severity of the renal artery lesion with either baseline renal function or the subsequent decline in renal function [21,22].

Once renal dysfunction develops, the prognosis of patients with renovascular disease is poor. Death rates increase from 5%/year in those with preserved renal function to 15-20%/year in those with severe renal failure [21]. Elderly patients who develop ESRD have a very poor prognosis with 2-year survival rate of 50% [20] and 10-year survival rate of only 5% [6]. The major causes of death in these patients are myocardial infarction, stroke, and congestive heart failure [19,21], reflecting generalized atherosclerosis in the coronary, carotid, and peripheral vascular beds [23].

Fibromuscular dysplasia is also a progressive disease with evidence of worsening stenosis, aneurysm formation, or development of new FMD lesion up to one third of patients over the period of 5 years [24,25].

3. Pathogenesis

Analogous to human unilateral renovascular hypertension, animals with 2-kidney, one-clip (2K, 1C) model of Goldblatt hypertension have high levels of plasma renin early on. Increased production of renin from ischemic kidney leads to increased production of angiotensin II and aldosterone causing increased BP. Exposure of the contralateral kidney to high BP over time leads to glomerular hypertrophy, hyperfiltration, and pressure natriuresis [26]. Thus, the animals maintain a high-renin state with normal extracellular volume. Other factors that contribute to the development of this hypertension include angiotensin II-stimulated release of vasoconstrictor prostaglandins [27], and reactive oxygen species [28], resulting in impairment in endothelium-dependent vasodilation, and the stimulated central sympathetic outflow by an action of angiotensin II in the central nervous system [29].

In the late phase of Goldblatt hypertension, the contralateral kidneys develop glomerular fibrosis and irreversible renal injury. Reduction in glomerular filtration rate (GFR) in both ipsilateral and contralateral kidneys leads to an expanded plasma volume, which suppresses plasma renin activity. Removal of the clip leads to resolution of hypertension early on. In the late stages, however, hypertension persists despite removal of the clip and resolves only after removal of the contralateral kidney, indicating that contralateral kidney damage from long-standing hypertension is important in maintenance of hypertension [30].

Analogous to the clinical condition of unilateral stenosis of a solitary functioning kidney or bilateral renovascular hypertension, animals with 1-kidney, one-clip (1K, 1C) model of Goldblatt hypertension have an expanded plasma volume with normal or low plasma renin levels. ACE inhibitors and ARB have minimal effect on BP in this low renin condition [31,32].

The Goldblatt model of renovascular hypertension alone may not adequately explain natural history of patients with atherosclerotic renal artery stenosis because mechanical constriction of the renal artery, rather than luminal obstruction by atherosclerotic plaque, was the cause of stenosis. One recent study in swine model indicated that diet-induced hypercholesterolemia stimulated production of tissue fibrogenic cytokines such as TGF-beta and NF-kB and promoted a variety of renal injury such as interstitial fibrosis, tubular atrophy, and glomerulosclerosis beyond injury caused by renal artery stenosis alone [33].

4. Diagnosis

Angiography is still the gold standard for diagnosis of renal artery stenosis. Because technique is more invasive, procedure is typically reserved for patients in whom revascularization are planned. Atherosclerotic RAS usually involve the ostial or proximal portion of the artery in patients with concomitant coronary, carotid, or peripheral vascular diseases. Fibromuscular dysplasia usually involves the middle or distal artery segments with "string of beads" appearance in women between the age of 15-50. Because pathology in FMD is composed of multiple sequential narrowing of the lumen, assessment of severity of stenosis can be problematic and may require assessment of pressure gradient across the lesion. Noninvasive tests that can be used for diagnosis of RAS are the following:

4.1 Captopril Renal Scintigraphy

Renal perfusion can be assessed by radionuclide imaging study before and 1-2 hours after administration of oral captopril or intravenous enalaprilat. The radiopharmaceuticals commonly used in this test are technitium-99m (^{99m} Tc) diethylenediaminepentaacetic acid (DTPA) and ^{99m} Tc mercaptoacetyltriglycine (MAG_3). DTPA is purely filtered by the glomerulus and therefore, renal uptake of DTPA is proportional to GFR. MAG_3 is cleared mostly by the proximal tubules and its renal uptake provides estimate of renal plasma flow. In the presence of renovascular hypertension, the uptake and clearance of radiopharmaceuticals are normal at baseline but becomes significantly reduced after captopril, which antagonizes the action of angiotensin II at the efferent arterioles causing an acute fall in renal perfusion distal to stenosis. Recent meta-analysis [34] and a large-scale single center experience [35] indicate that the test has a low-to-moderate sensitivity of 65-75% with specificity of 80-90% in detecting renal artery stenosis. The test is less accurate in patients with renal insufficiency and bilateral renal artery stenosis. It is reportedly less reliable in low renin hypertension [10], which is common in the elderly [12]. In many observational studies, positive captopril renal scintigraphy is reported to be highly predictive of successful control of hypertension after revascularization with a positive predictive value of 90-100% [36-39]. However, data from recent prospective randomized studies challenge this concept. One study of patients with ostial atherosclerotic renal artery stenosis and positive captopril renography showed that the hypertension control was improved in only one-half of patients undergoing renal angioplasty or stenting [40]. The Dutch Renal Artery Stenosis Interventional Cooperative (DRASTIC) study [41] demonstrated that, in the group of patients who were randomized to receive angioplasty, the presence of an abnormal captopril renogram did not predict BP response over the 12 months follow-up. There were no differences in either BP or doses of antihypertensive medication between patients with normal scintigraphy vs. those with abnormal scintigraphy at entry (figure 2).

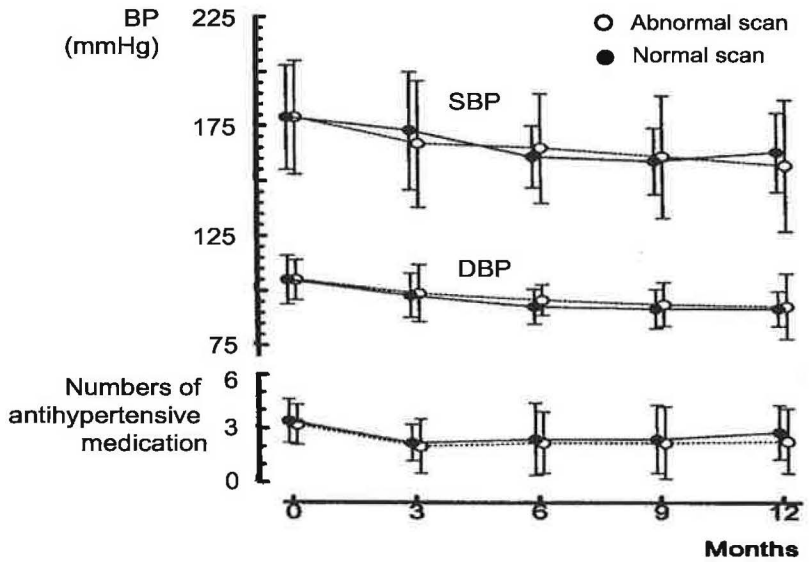


Figure 2: Failure of captopril renography in predicting BP response to percutaneous renal angioplasty in the DRASTIC study. The systolic BP, diastolic BP, and number of antihypertensive medications were identical among the group of patients with or without abnormal scan prior to intervention

4.2 Selective Renal Blood Flow Studies

Nuclear imaging with technetium mertiatide or technetium-labeled pentetic acid (DTPA) without captopril challenge can be used to estimate fractional flow to each kidney [42]. Selective ^{133}Xenon washout technique can also be used to measure renal blood flow directly but the technique is invasive and requires blood sampling from aorta and both renal veins [43]. Patients with severe unilateral renal artery stenosis beyond autoregulatory range may have lower resting renal blood flow in the affected side than the contralateral side while patients without renal artery stenosis were presumed to have similar blood flow to each kidney. However, more recent studies indicated that essential hypertensive patients with no evidence of renovascular diseases also have asymmetric renal blood flow [44]. Difference between renal blood flow to the left and the right kidneys of more than 25% were found in 51% of patients with patent renal arteries [44].

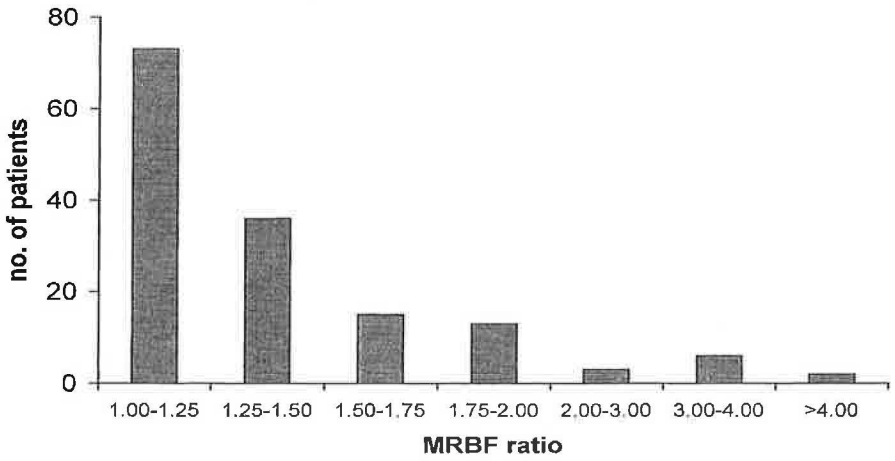


Figure 3. Frequency distribution of mean highest-to-lowest renal blood flow (MRBF) ratio in 148 patients with essential hypertension with no evidence of renal artery stenosis confirmed by conventional angiography.

Mechanism underlying this observation is not completely understood but patients with marked difference in renal blood flow are also more likely to have false positive captopril renal scintigraphy.

4.3 Duplex Doppler Ultrasonography

Detection of renal blood flow velocity by Doppler sonography is another technique often employed to detect renal artery stenosis. The abdominal aorta is usually imaged first, and the peak systolic velocities (PSV) are measured from the origin, proximal, middle, and distal segments of each renal artery. Acceleration of velocity normally occurs at the stenotic site and the Doppler signal distal to high-grade stenosis appears dampened with low velocity, so called "tardus and parvus". The presence of renal artery PSV of ≥ 180 cm/sec and the ratio of PSV of renal artery to suprarenal abdominal aorta of ≥ 3.5 indicates severe stenosis of ≥ 60% [45]. The procedure is time-consuming and highly dependent on the skill of the sonographer. Bowel gas and abdominal obesity are the major limiting factors for a successful study. It also has limited usefulness in diagnosis of the accessory vessel or branch vessel disease [12].

Overall sensitivity is between 70-85% and specificity of the test is approximately 80-90%.

Duplex Doppler sonography may have both prognostic as well as diagnostic value. Recent study indicates that high renal resistance index (1- end diastolic velocity/peak systolic velocity)×100 of ≥ 80, is a reliable predictor of unsuccessful outcome after revascularization (figure 4) [46]. A resistance index of ≥ 80 is indicative of irreversible renal parenchymal disease [47]. The resistance index of the contralateral kidney is often even higher than that of the kidney with renal artery stenosis [13] and may also be predictive of the clinical response to revascularization.

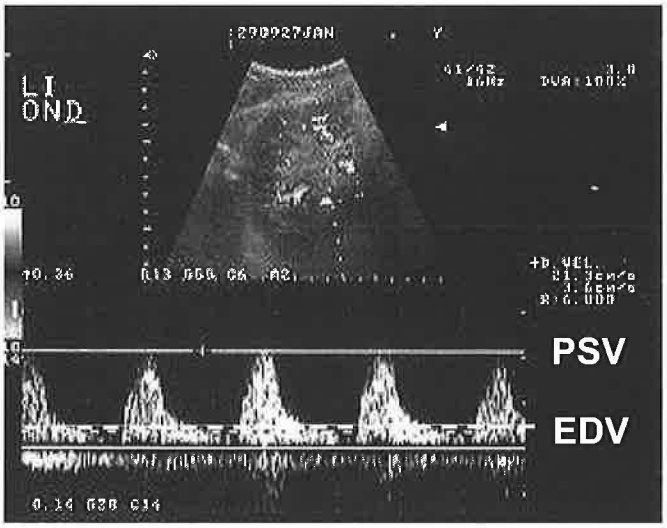


Figure 4: Duplex ultrasonography in a 70-year-old hypertensive patient with less than 50% luminal narrowing of the left renal artery stenosis. The resistance index (RI) is increased in both the upper and lower pole arteries, indicative of renal parenchymal disease, likely to be from long standing hypertension.

RI =(1– 3.6/21.3)=0.83

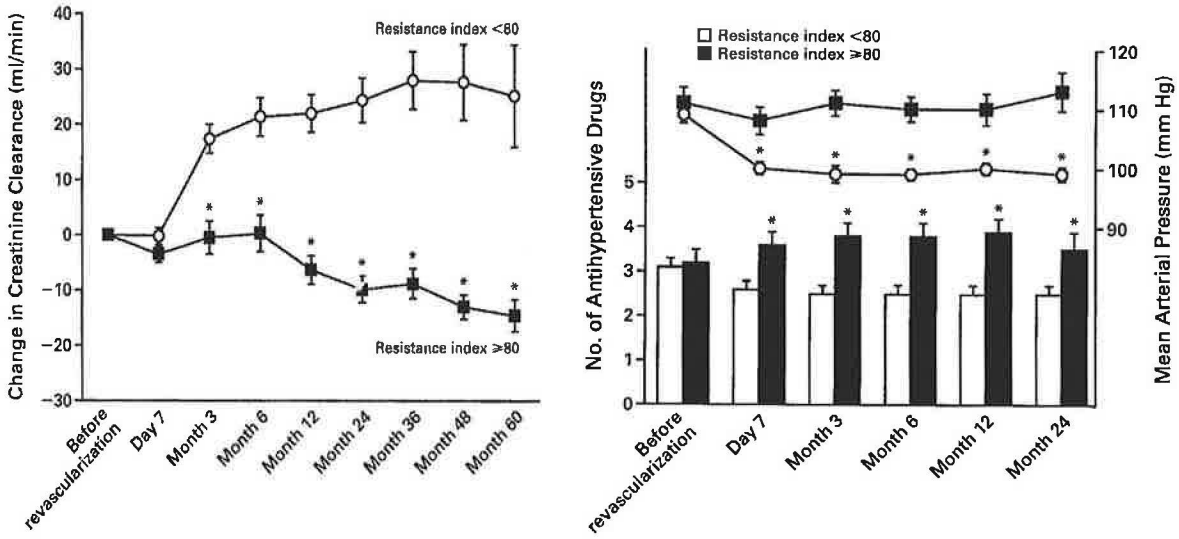


Figure 5: Change in creatinine clearance (left) and numbers of antihypertensive medications and mean arterial pressure (right) before and 60 months after renal revascularization in patients with high resistance index (≥ 80) and low index (<80) at baseline.

4.4 Renal Vein Renin

This test is based on the premise that ischemic kidneys produce excessive amount of renin while renin production from contralateral kidney is suppressed. The test is considered to be positive when the renal vein renin ratio from ischemic to nonischemic kidney is more than 1.5:1 or 2:1. However, the test is almost never used any more for the following reasons. It is invasive and cumbersome with low sensitivity (60-80%) and specificity (55-65%). Furthermore, there can be lateralization in patients with primary hypertension [48].

4.5 Magnetic Resonance Angiography (MRA)

This noninvasive procedure allows visualization of renal arteries without exposure to iodinated contrast. Because the contrast agent gadolinium used during MRA is not nephrotoxic, the test can be performed safely in patients with renal insufficiency or those with contrast dye allergy. Patients are required to hold their breath during the acquisition, which typically lasts about 15–20 seconds depending on the resolution and other technical factors of the system performance. Motion artifacts may occur when patients are unable to sustain the breath-hold because the acquisition time is too long. Spatial resolution in current reports is typically in the order of 1.5X1.5X2.0 mm3 (craniocaudal/frequency direction X left-right direction X anteroposterior/slice direction) or better [49]. MRA is suitable for detection of stenosis in the ostium and proximal portion of renal arteries, which are found in majority of patients with atherosclerotic renal artery stenosis. It has limitation in detecting stenosis in the distal main renal arteries or intrarenal branches, which limits the usefulness in patients with fibromuscular dysplasia [50]. The sensitivity and specificity of the gadolinium-enhanced three-dimensional MRA in diagnosis of RAS is discussed in the next section.

4.6 Spiral CT Angiography (CTA)

Over the past decade spiral CT angiography has become an important imaging tool used in diagnosis and management of peripheral arterial disease, pulmonary embolism, and even coronary artery disease. Multidetector-row (MDCT) scanners, which are equipped with a belt of 4, 8, 16, 32, or even 64 adjacent rings of detectors encircling the patients, have now replaced older generation scanners, which operate with only one ring of detector. Spatial resolution of MD-CTA is now superior to that of MRA. The resolution of MDCT is reported to be 0.75 mm for 16-row scanners and even lower (0.4 mm) for 64-row scanners with smaller-sized detectors [51]. Consequently, spiral CTA has been shown to superior to MRA in identifying smaller renal accessory artery, which is present in 20% of normal individuals [52-54]. However, administration of nephrotoxic contrast agents during the test limits its safety in patients with chronic renal insufficiency. A large prospective multicenter study comparing accuracy of spiral CTA to MRA in diagnosis of atherosclerotic renal artery stenosis reported that sensitivity of spiral CT angiography is comparable to that of gadolinium-enhanced MRA between 70-80% but specificity of CT angiography is superior to MRA (94 vs 88% respectively) [55]. This is likely to be due to the speed of MDCT in acquiring the image, which significantly reduces respiratory motion artifact and false positive results. In the same study, both CTA and MRA were found to have poor sensitivity in diagnosis of FMD (28% and 22% respectively), probably due to the location of disease in smaller distal vessels. However,

almost all CT scanners used in this study, with exception in one center, were only single-row. The accuracy of CTA is likely to be much greater with current 16-row or 64-row scanners, which have much faster speed and scanning time from 17-21 seconds with single row and 4-row MDCT to 6-9 seconds with 16- and 64-row MDCT [56].

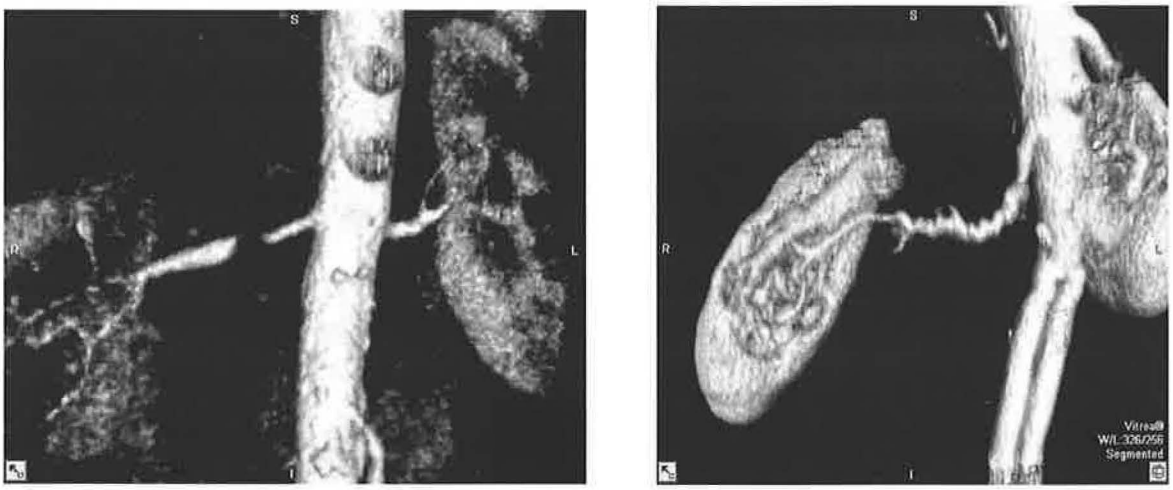


Figure 6: CT angiography images from 16-row scanners showing severe atherosclerotic renal artery stenosis (left panel) and fibromuscular dysplasia of the right renal artery (right panel). Image courtesy of Dr. Bart Dolmatch, Department of Radiology, UTSW.

Nevertheless, both CTA and MRA were found to be superior to captopril renal scintigraphy and Duplex Doppler ultrasonography in diagnosing renal artery stenosis [34] (figure 7).

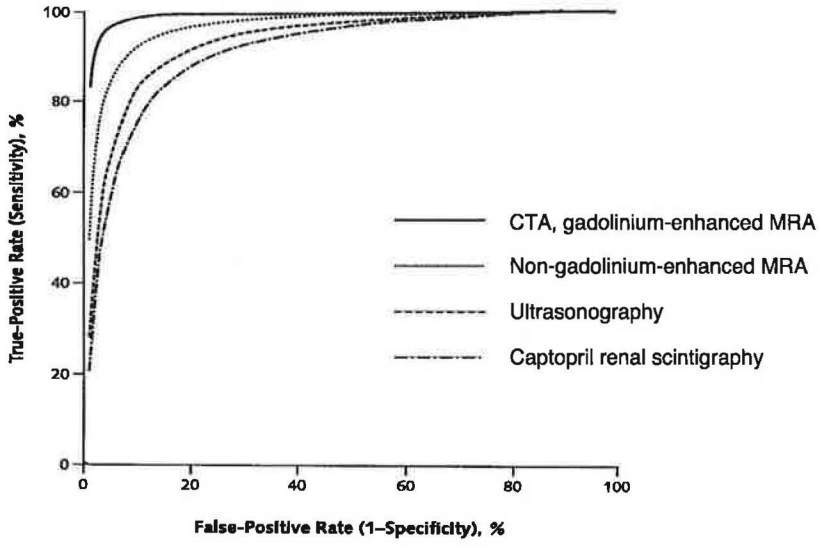


Figure 7: Data from a meta-analysis [34] showing receiver-operating characteristic (ROC) curves comparing captopril renal scintigraphy, ultrasonography, non-gadolinium-enhanced MRA, and computed tomography angiography (CTA) and gadolinium-enhanced MRA in the diagnosis of renal artery stenosis.

5. Management

5.1 Medical Therapy

Role of Angiotensin converting enzyme (ACE) inhibitor and angiotensin receptor blocker (ARB)

Unilateral RVH: In experimented animals with high renin Goldblatt hypertension, treatment with ACE inhibitors or ARBs consistently reduces systemic arterial pressure and intraglomerular pressure while increasing GFR, urine flow, and sodium excretion in the unclipped kidney [57,58]. Thus, antagonism of effects of angiotensin II by these medications can attenuate glomerular sclerosis and tubulointerstitial injury in the unclipped kidney and prevent the rise in serum creatinine in the chronic phase of hypertension [26]. The effect of ACE inhibitors or ARBs on the clipped kidney, however, is much more variable depending on the dose and magnitude of BP reduction. At low doses, GFR of the clipped kidney is well maintained [59,60] but at the high doses, excessive reduction in BP is accompanied by a deleterious reduction in GFR and urine flow [58].

While these experimental findings initially raise concern about the safety of long-term ACE inhibitor use in patients with renal artery stenosis, ACE inhibitors did not increase incidence of renal atrophy in a prospective study by Caps and colleagues [18]. In addition, one retrospective study by Chabova et al demonstrated the safety of ACEI use in elderly hypertensive patients with atherosclerotic renal artery stenosis who were managed without revascularization [19]. After an average follow-up of 39 months, renal function is stable in 85% of patients and worsens in 15% with no change in BP. However, the need for antihypertensive medications increased from 1.6 to 1.9 drugs.

ACE inhibitors not only exert beneficial effects on renal structure and function, but also cause regression of left ventricular and aortic hypertrophy [61,62] and improved survival better than other antihypertensive drugs in the rat model, compared with diuretics or hydralazine. Improved survival of patient with renovascular disease treated with ACE inhibitors has also recently been reported in a prospective study with long-term follow-up by Losito and colleagues [63].

Overall, studies in patients with renovascular hypertension indicated that ACE inhibitors were effective in controlling BP in 70-80% of patients with documented RVH [64]. Discontinuation of treatment due to progressive renal failure occurred in only 5% of patients, generally in association with bilateral disease or a solitary kidney [64].

Bilateral RVH: Medical therapy has a limited role in this clinical condition and most patients require revascularization. Reduction of BP even into normal but not below normal range causes a significant reduction in renal plasma flow [65]. Nearly all patients with bilateral disease or unilateral disease involving solitary functioning kidney developed significant increase in serum creatinine with ACE inhibitor [40] and between 6-30% of these patients developed acute renal failure [66-68].

Role of Lipid Lowering Therapy

Patients with atherosclerotic renal artery stenosis should be treated with lipid-lowering drug based on current guidelines to keep LDL levels at the minimal goal of below 100 mg/dL and optional goal of less than 70 mg/dL [69]. Although there is currently no clinical trial that has examined efficacy of lipid lowering therapy alone in preventing renal artery

stenosis progression, several case reports have demonstrated regression of renovascular disease with a statin drug [70] or combination of fibrate and cholestyramine [71]. Statin drugs have also been shown to reduce progressive deterioration in renal function in patients with nondiabetic chronic kidney diseases [72] and even in patients with coronary artery disease with normal baseline renal function [73]. Whether such treatment will prevent progressive renal dysfunction in patients with atherosclerotic renal artery stenosis remains unknown.

5.2 Percutaneous Intervention

Percutaneous intervention is the revascularization procedure developed to improve BP control while preserving renal function with less morbidity and mortality than surgical revascularization. In most nonrandomized studies, the procedural success of percutaneous transluminal renal angioplasty (PTRA) is more favorable in young patients with fibromuscular dysplasia (FMD) than in older patients with atherosclerotic renal artery stenosis (90-100% vs 60-70%, respectively) [74]. The hypertension cure rates are also much higher in patients with FMD than those with atherosclerotic renal artery stenosis (30-60% vs 0-29%) [75]. In addition, a significant proportion of the latter patients experienced no improvement or even deterioration of global renal function assessed by creatinine clearance or individual kidney function assessed by nuclear imaging study, despite successful revascularization [76,77]. This is probably related to frequent atheroembolism and associated hypertensive nephrosclerosis in elderly patients with atherosclerosis. Therefore, while PTRA is the treatment of choice in patients with FMD, the role of percutaneous intervention in those with atherosclerotic renovascular hypertension is still evolving. Most of the published studies of PTRA are retrospective with incomplete follow-up and inadequate control group. Outcomes of studies are less well defined and rely on single measurement of office BP or serum creatinine, and thus, are subjected to observational bias and regression to the mean [78].

Randomized studies of PTRA vs. Medical Therapy

Three recent randomized prospective studies have compared effects of PTRA vs. medical therapy in hypertensive patients with atherosclerotic renal artery stenosis. The results of these studies are summarized in table 1.

The Scottish and Newcastle Renal Artery Stenosis Collaborative Group (SNRASCG) [79] randomized 55 hypertensive patients with renal artery stenosis (in whom BP cannot be controlled despite 2 antihypertensive medications) to PTRA vs. continued medical therapy. Patients over the age of 75 and those with serum creatinine > 5 mg/dL were excluded from the study. There was no crossover between the two groups. A benefit of angioplasty on BP control was seen mainly in the group with bilateral renal artery stenosis. There was no benefit on BP control in the unilateral artery stenosis patients treated with PTRA compared with medical therapy. There was no difference in renal function in either unilateral or bilateral renal artery stenosis patients treated with PTRA compared with those treated medically.

The Essai Multicentrique Medicaments vs Angioplastie (EMMA) Study Group randomized 49 patients with unilateral renal artery stenosis with mild to moderate

hypertension and positive captopril renography or elevated renal vein renin ratio to PTRA vs. medical therapy [80]. All patients had a creatinine clearance > 50 ml/min. During the study, 28% of patients treated with medical therapy were crossed over to the PTRA due to refractory hypertension. Periprocedural complications occurred in 26% of patient undergoing PTRA, mainly related to groin hematoma. At 6-month follow-up, there was no difference in 24-hour ambulatory BP or renal function between the 2 treatment groups but the patients treated with medical therapy alone required more antihypertensive medications than those treated with angioplasty.

The Dutch Renal Artery Stenosis Interventional Cooperative (DRASTIC) study [81] is the most recent randomized study of 106 difficult-to-treat hypertensive patients with atherosclerotic renal artery stenosis and positive renal captopril renography. The study excluded patients age > 75, serum creatinine > 2.3 mg/dL, and those with kidney size < 8 cm. During the study, 44% of patients randomized to medical therapy were crossed over to PTRA due to uncontrolled hypertension or progressive azotemia. Restenosis occurred in 48% of the patients randomized to PTRA. Based on intention-to-treat analysis, there was no difference in office BP or creatinine clearance between the two groups at 12-month follow-up but the angioplasty group required less antihypertensive medication than the drug-therapy group.

Taken together, the data from these three trials indicate that PTRA improves BP control but rarely cures hypertension. Recent meta-analysis of these 3 trials indicates a modest benefit in BP pressure control with 7/3 mmHg BP difference in favor of angioplasty without benefit in preserving renal function [82].

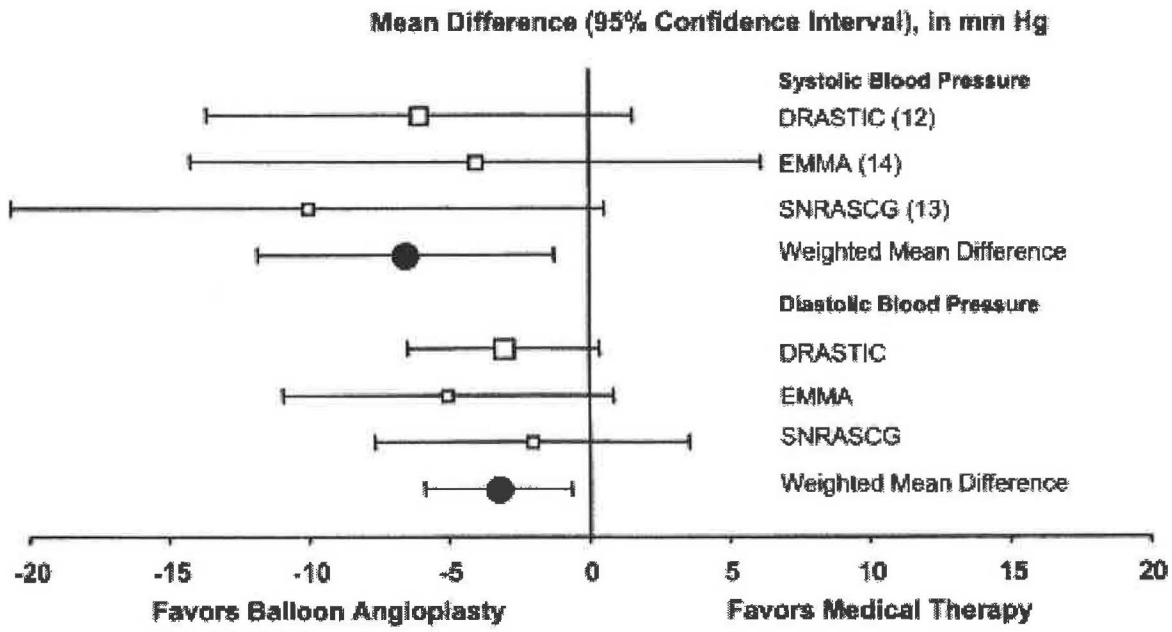


Figure 8. Data from a meta-analysis [82] of 3 randomized studies showing differences in systolic and diastolic BP between angioplasty vs. medical therapy during follow-up. DRASTIC trial. DRASTIC = Dutch Renal Artery Stenosis Intervention Cooperative trial; EMMA = Essai Multicentrique Medicaments vs Angioplastie trial; SNRASCG = Scottish and Newcastle Renal Artery Stenosis Collaborative Group trial.

The main criticism of these angioplasty trials is the high restenosis rate, which may be responsible for the modest results and, thus, should be avoidable by stent placement.

Studies of renal artery stenting

Stenting now has replaced angioplasty for percutaneous revascularization of atherosclerotic renal artery stenosis because of its ability to prevent elastic recoil seen commonly in the ostial or proximal location of the artery. Meta-analysis of 14 renal arterial stent studies indicated that renal stenting can cure hypertension in 20% of the patients and improve BP control in 49% [83]. However, 4 of 14 studies defined "cure" as BP < 150-160 mmHg. Renal function is improved in 30% of patients, unchanged in 38%, and worsens in 32% [83]. When stenting was directly compared with PTRA in a randomized prospective study [84], stenting was associated with higher technical success (88% vs. 57%) and less restenosis (14% vs. 48%). No difference in BP control or renal outcome was demonstrated at follow-up.

Table 1. Effects of renal angioplasty vs. stenting on renal function and BP in atherosclerotic renal artery stenosis [84] (PTA = angioplasty, PTAS = stenting)

	PTA (n=41)	PTAS (n=40)	Difference (%)
Patency rates			
Primary patency	12 (29%)	30 (75%)	46 (24–68)†
Secondary patency	21 (51%)	32 (80%)	29 (8–50)†
Renal function (all patients)			
Improved	4	5	2
Unchanged	29	26	−6
Deteriorated	8	9	4
Renal function (patients with impaired function at baseline)*			
Improved	4	5	1
Unchanged	12	16	0
Deteriorated	6	8	1
Hypertension (all patients)			
Cured	2	6	10
Improved	18	17	−2
Failing	21	17	−8

*n=22 (PTA), 29 (PTAS). †95% CI.

Failure to demonstrate improvement in renal function despite the higher patency rates in the stent group may be related to contrast nephropathy, hypertensive nephrosclerosis, or distal embolization during procedure. Indeed, ex vivo angioplasty study in the renal arteries removed from patients with renovascular diseases demonstrated that significant embolization of atherosclerotic debris occurred during insertion of guide wire and balloon inflation with or without stent implantation [85].

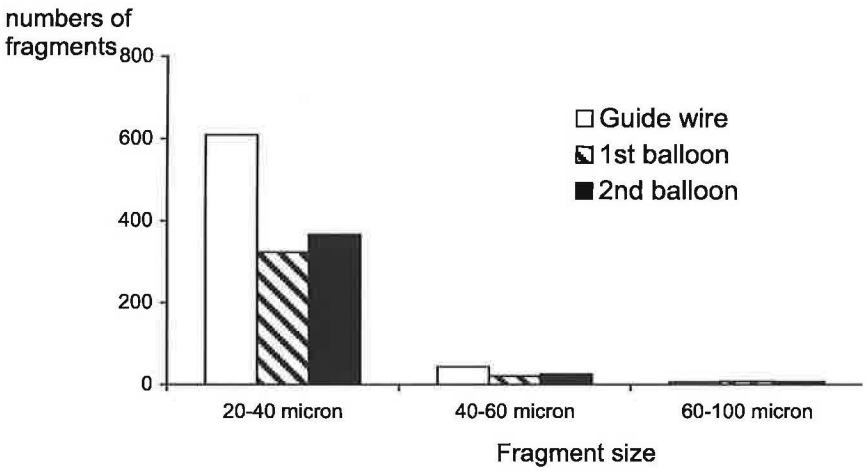


Figure9. Graph showing sizes and numbers of embolic fragments recovered during ex vivo angioplasty. More than 1,000 fragments with the size between 20-40 micron, which is similar to the size of afferent arterioles, were released from each renal artery during the entire procedure [85].

Despite failure in improving renal function in most clinical trials of percutaneous renal intervention, the presence of rapid decline in renal function before stenting [86,87] or angioplasty [88] is associated with reduction in renal failure progression after procedure in prospective observation studies. This is possibly related to the amount of viable nephron mass at risk, which may be salvaged by percutaneous intervention.

5.3 Surgical Revascularization

Surgical revascularization of renal arteries can be achieved using three techniques: the endarterectomy, aortorenal bypass, or extra-anatomic bypass. Endarterectomy is suitable for patient with focal disease or those who also require aortic replacement [89]. Aortorenal bypass can be performed with autologous or prosthetic conduits and is shown to have excellent long-term results. Extra-anatomic bypass such hepatorenal or splenorenal bypass grafting avoids aortic clamping and direct operation on diseased aorta. Long-term results of all these surgical techniques are comparable, with 5-year patency of 80-90% [89-91]. However, operative mortality is 20% in patients over the age of 65 [89,91,92]. Surgical revascularization offers comparable clinical results to percutaneous revascularization in terms of BP responses [93 89], but the cost of surgery is much higher [94]. Renal function is improved in 30-60% of patients, unchanged in 30-50%, and worsened in 10-30% [92,95,96]. The presence of atheroembolism [97] or elevated renal resistance index by Duplex Doppler ultrasonography [98] predicts poor long-term outcome after surgery. In one study, patients with a rapid decline in renal function (GFR decreased > 5ml/min/week) derived more benefit from surgical revascularization in terms of preventing further decline in GFR than those with slower decline in renal function [95]. For these reasons, surgery should be considered in elderly patients only when the renal function deteriorates on medical therapy and in whom the lesions are not suitable for percutaneous intervention.

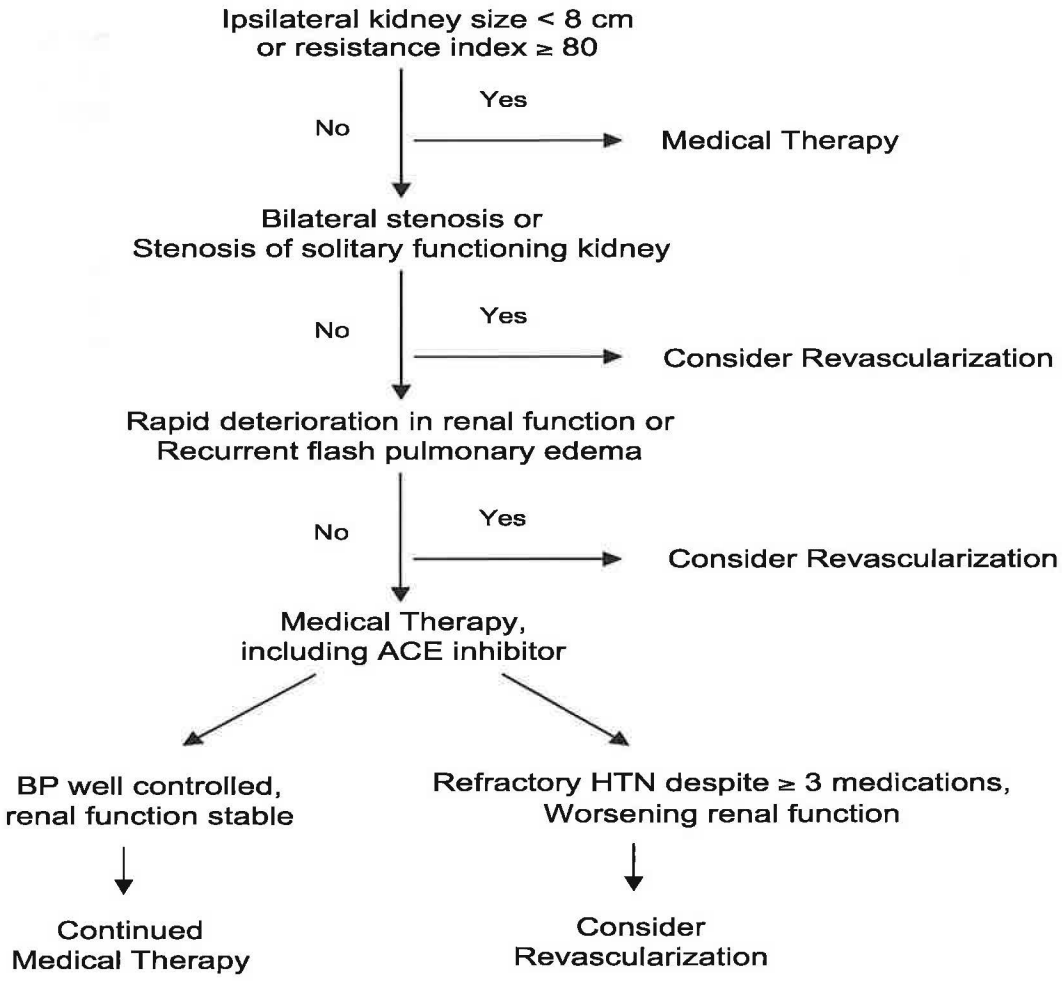
6. Recommendations

Treatment of patients with renovascular hypertension needs to be highly individualized, with a careful assessment of comorbid diseases and benefit vs. risk from revascularization. Approach to the patients with suspected renovascular hypertension

begins with an accurate assessment of kidney size (by KUB, ultrasonography, MRI, or CT angiography). A unilateral atrophic kidney (< 8 cm) suggests irreversible renal parenchymal disease that is not amendable to revascularization. In the absence of atrophic kidneys, a Doppler study showing a resistance index of ≥ 80 units also is indicative of irreversible renal disease. Such patients should be treated medically. In contrast, revascularization should be considered for patients with a) bilateral stenoses or stenoses of solitary functioning kidney b) rapid deterioration in renal function, or c) recurrent flash pulmonary edema. In the absence of these clinical features, medical therapy of hypertension should be initiated with an ACE inhibitor and additional classes of antihyperetensives as needed. Revascularization should be considered if hypertension cannot be adequately controlled with three or more medications of different classes including ACE inhibitors and diuretics.

The algorithm, based on our current knowledge, is shown in the figure below.

Hypertension + Atherosclerotic Renovascular Disease



7. Future Directions

There are many areas of uncertainty in the management of hypertension in patients with RAS largely because of our limited ability to predict BP response to revascularization and, to a lesser extent, our ability to protect the kidneys against contrast nephropathy and distal embolization during percutaneous intervention.

In the future, our ability to determine functional significance of a given renal artery stenosis may be improved with measurement of renal vasodilator flow reserve (fig 16). The concept was pioneered in the coronary vascular bed showing that hemodynamically significant stenosis in an epicardial vessel can lead to attenuated increase in blood flow in response to vasodilator challenge, even if the resting blood flow is well maintained by autoregulatory mechanism [99]. Recent clinical trial in patients with coronary artery diseases indicated that deferring percutaneous coronary intervention in patients with normal flow reserve is safe and associated with low adverse cardiovascular events, confirming the usefulness of this measurement in clinical practice [100]. To date, renal vasodilator flow reserve has not been shown to correlate with percent diameter stenosis but it has been shown to significantly correlate with transtenotic pressure gradient, implicating a functional rather than morphological predictor [101]. Renal flow reserve was found to be reduced in the kidney with stenotic artery compared with contralateral kidney. This impaired renal flow reserve was shown to be abolished by renal angioplasty [102].

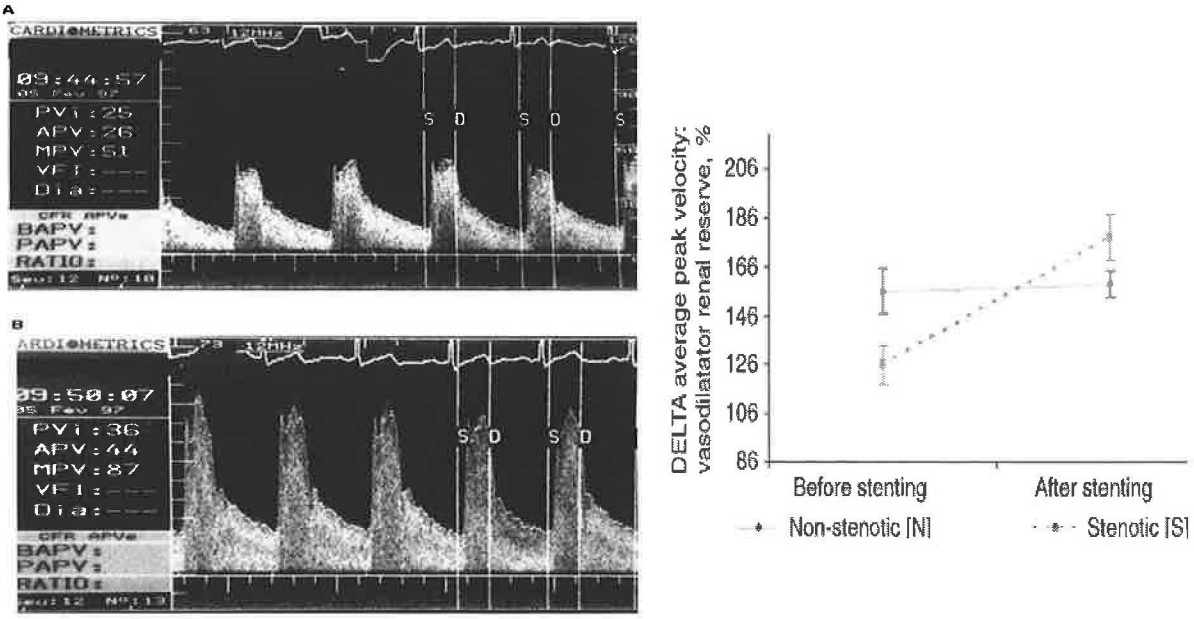


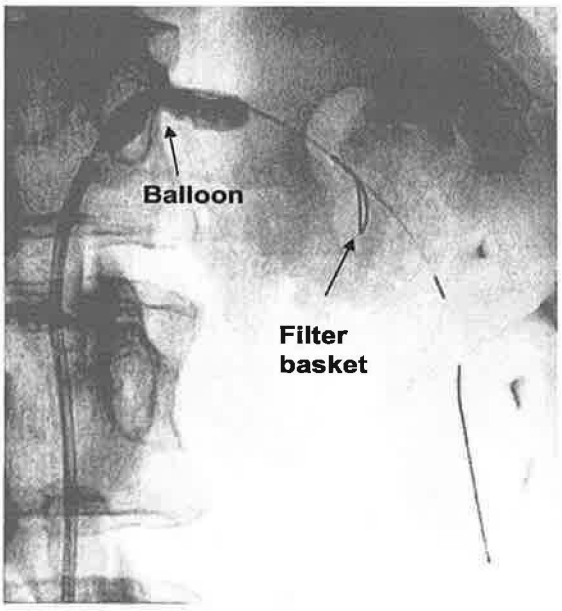
Figure 11: (Right) A typical example of a Doppler recording in the right artery at baseline (top) and after injection of papaverine (bottom). The average peak velocity (APV) is almost doubled after papaverine injection. (Left) Renal vasodilator reserve and Doppler average peak velocity (d APV) was lower in the stenotic [S] than normal renal arteries [N] group before stenting. After stenting, however, the flow reserve was similar in both groups of patients.

Whether renal flow reserve will be useful in predicting functional significance of a borderline lesion and improvement in BP and/or renal function after revascularization remains to be seen.

Renal cortical thickness is another potential marker for hemodynamically significant renal artery stenosis [103]. A recent cross-sectional study indicated that cortical thinning of less than 8 mm measured by spiral CT angiography occurred in patients with atherosclerotic RAS before development of small atrophic kidneys [103]. However, renal cortical thinning is not specific for the kidney with RAS as it is also found in the contralateral kidneys of the same subjects, although at a lesser extent. Whether renal cortical thinning will improve accuracy in predicting outcomes after revascularization is not known.

In addition to vasodilator flow reserve and renal cortical thickness, recent study indicates potential usefulness of a neurohormone, brain natriuretic peptide (BNP), as a predictor for BP response to stenting in patients with RAS [104]. Although BNP is synthesized mainly by the ventricular myocardium, it main actions occurs in the kidneys to promote diuresis, natriuresis, and vasodilation. Animal experimental studies indicated upregulation of BNP gene expression within 6 hours after clipping of the renal artery [105], possibly by direct action of angiotensin II. Baseline BNP levels of > 80 pg/ml predicted clinical improvement in 77% of patients after successful stent implantation [104]. Because BNP is also elevated in variety of diseases such as congestive heart failure and chronic renal insufficiency, the applicability of this test is likely to be limited to a subset of patients without comorbid conditions that may influence BNP levels.

To minimize the risk of revascularization, cardiologists and interventional radiologists are now beginning to use distal protection devices developed for coronary and peripheral interventions to reduce the risk of atheroembolism during renal stent placement [106,107].



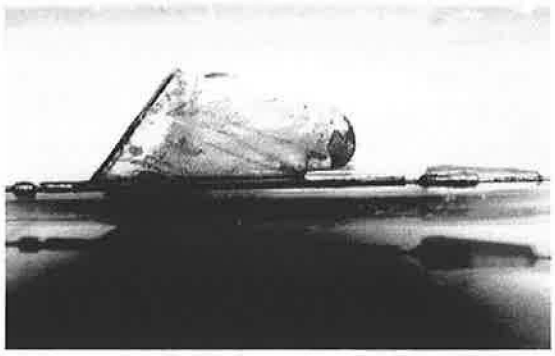


Figure 12: (left) Angioplasty of the ostial left renal artery while the filter basket was deployed in the distal end of the filter wire (right) Photograph of distal protection basket with atherosclerotic debris retrieved.

Preliminary experience in a few centers indicates that these devices are safe and debris can be retrieved during the renal intervention. However, currently available filter baskets equipped in the protection device have the pore size of approximately 100 micron, which may not be adequate to prevent embolism of smaller athersclerotic debris shown previously in figure 9. Furthermore, significant embolization already occurred during the guide wire insertion, which is the preliminary step before any distal protection system can be deployed. Whether the device will reduce the renal dysfunction and improve BP control after renal stenting is the subject of further investigation.

Several ongoing clinical trials, such as the large **C**ardiovascular **O**utcomes in **R**enal **A**therosclerotic **L**esions (CORAL) and the **ST**ent placement and blood pressure and lipid-lowering for the prevention of progressive renal dysfunction caused by **A**therosclerotic ostial stenosis of the **R**enal artery (STAR) will compare effects of renal stenting plus optimal medical therapy vs. optimal medical therapy alone on both cardiovascular and renal endpoints in hypertensive patients with atherosclerotic renal artery stenosis. Optimal medical therapy will include statin drugs, antihypertensive medications, and antiplatelet therapy. Distal protection device will be used in the CORAL study. These important clinical trials will likely provide important information regarding the cardiovascular benefit as well as the cost-effectiveness of revascularization in patients with atherosclerotic renal artery stenosis and hypertension.

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