Chapter 23

Renal Artery Stenosis—Current Management Perspectives

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INTRODUCTION

Renal artery stenosis (RAS) is often overlooked and frequently under diagnosed as a cause for refractory hypertension, renal insufficiency and increased cardiovascular mortality. Since Goldblatt's seminal experiment in 1934, RAS has become increasingly recognized as an important cause of hypertension and chronic renal failure, the latter by virtue of renal ischemia. The three most important causes for RAS are Atherosclerotic Renal Artery Stenosis (ARAS), Fibro Muscular Dysplasia (FMD) and Takayasu Arteritis.

ARAS is commonly present in patients with clinically manifest atherosclerosis in other vascular beds and is independently associated with increased cardiovascular morbidity. It is usually present in the ostium of renal arteries. The presence of ARAS in patients with coronary disease independently doubles a patient's risk of mortality even when coronary revascularization is performed[1]. The increase in mortality is directly related to the severity of ARAS: The more severe the stenosis, the higher is the mortality risk. Bilateral ARAS has 47% 4-year survival as compared to 59% (*P*<0.001) in unilateral ARAS.

Fibromuscular dysplasia is the 2nd most important cause of renal artery stenosis is more common in females less than 40 years of age (although it has been reported from infancy to old age). The diagnosis should be considered in any young person presenting with severe hypertension with negative family history of hypertension. Generally FMD affects the mid- or distal (rather than proximal) renal artery and may be associated with branch stenosis.

Takayasu Arteritis typically occurs in young individuals, usually females and is associated with stenosis of other medium sized arteries like the aortic arch vessels, coronary or mesenteric vessels. It may be associated with history of tuberculosis, fever or raised ESR.

INCIDENCE OF RAS

1. RAS is present in 63% patients of Peripheral Vascular Disease (PVD) and Hypertension
2. RAS is present in 33% patients of Coronary Artery Disease (CAD) and its incidence increases linearly with severity of CAD
3. Incidence of Bilateral RAS is 30%.

For this reason it has now become a routine practice to screen renal arteries during cardiac catheterization for evaluation of CAD. Atherosclerotic RAS is one of the common causes for End Stage Renal Disease (ESRD) and ARAS accounts for as many as 12-14% of all new patients entering the dialysis program.

ETIOLOGY OF RENAL ARTERY STENOSIS

In the Cooperative Study on Renovascular Hypertension (1972), the incidence and distribution of different etiologies for RAS were as follows:

- Atherosclerotic renovascular disease   62%
- Fibromuscular dysplasia   32%
- Miscellaneous etiology
  (Post renal transplant, iatrogenic)   5%

SUSPICION OF SIGNIFICANT RENAL ARTERY STENOSIS

1. Onset of hypertension at <30 years of age or severe hypertension at >55 years of age

2. Accelerated, resistant, or malignant hypertension

3. Unexplained atrophic kidney or size discrepancy >1.5 cm between kidneys

4. Flash pulmonary edema (unexplained, usually associated with Hypertension)

5. Unexplained renal dysfunction, including individuals starting renal replacement therapy

6. Development of new azotemia or worsening renal function after administration of an ACE-inhibitor or ARB agent

7. Multivessel coronary artery disease or peripheral arterial disease

8. Unexplained congestive heart failure or refractory angina

9. Unexplained Refractory Angina.

INVASIVE TESTING FOR ASSESSMENT OF RENAL ARTERY STENOSIS (FIG. 1 AND FIG. 2)

At present, no sufficiently accurate, noninvasive, radiologic, or serologic screening test is available that, if negative, completely excludes the presence of RAS. Therefore, clinical index of suspicion remains the primary determinant for the degree of evaluation. When the history is highly suggestive and no risk for radio-contrast-mediated renal injury is present, an intraarterial DSA or conventional angiogram is the appropriate initial test. In patients at risk of contrast nephropathy, a carbon dioxide angiogram or Gadolinium contrast DSA can determine the presence of a stenosis.
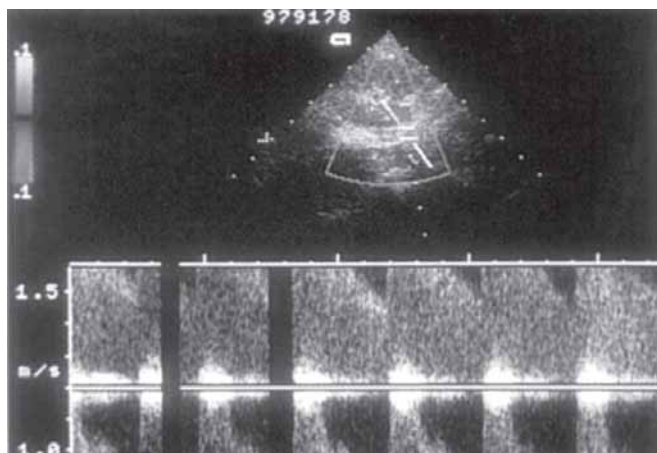

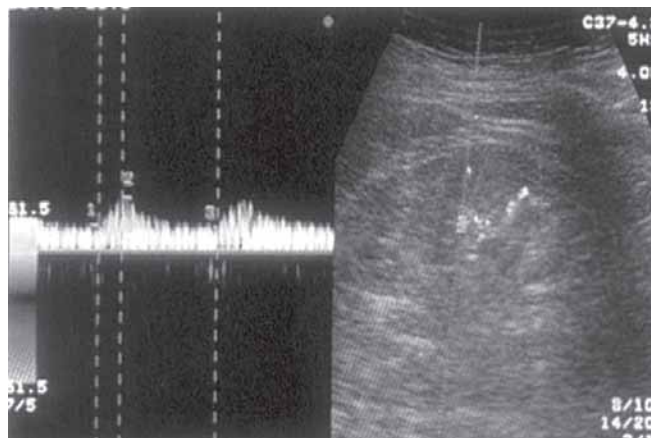**Fig. 1:** Increased velocities in renal artery stenosis

Fig. 2: Damped flow in distal intra-renal artery
(Courtesy: Dr KK Kapur)

TREATMENT

Treatment essentially is aimed at controlling blood pressure, preserving renal function or preventing congestive heart failure. It essentially involves medical therapy and surgical or interventional strategy for removing renal artery stenosis.

1. Medical Therapy

Optimal blood pressure control plays an essential role in the therapeutic management of Renovascular Hypertension (RVHT). However, aggressive control of other risk factors for atherosclerosis also is mandatory. Cessation of smoking and antidyslipidemic therapy is also important.

Antihypertensive Therapy

All classes of antihypertensive medications are used to treat RVHT; however, the most effective therapy is with an ACE inhibitor, which minimizes the ischemia-induced rise in angiotensin production. Because hypertension may be dependent on angiotensin II, antihypertensives that inhibit renin or angiotensin II are used widely. An ACE inhibitor markedly decreases blood flow through the stenotic kidney; thus, in patients with a solitary kidney or bilateral renovascular disease, blood pressure may fall rapidly, with an ensuing deterioration in renal function. This usually is reversible upon discontinuation of the medication.

Although less clinical experience exists with newer angiotensin receptor blockers (ARBs), they appear to be as effective as ACE inhibitors in experimental models. In patients without hemodynamically significant renal artery disease, an increase in serum creatinine level of up to 35% above baseline with an ACE or ARB is consi-

dered acceptable and is not a reason to withhold treatment unless hyperkalemia develops. Both beta-blockers and diuretics also are used, the latter often in conjunction with ACE inhibitors. Diuretics enhance sodium and water diuresis, thereby eliminating the volume-mediated component of RVHT. Calcium channel blockers (CCBs) may provide equally good control of hypertension, with presumably less impairment in function of the ischemic kidney than ACE inhibitors.

A selective aldosterone inhibitor, eplerenone is now available for the treatment of hypertension. It selectively blocks aldosterone at the mineralocorticoid receptors in epithelial (e.g. kidney) and nonepithelial (e.g. heart, blood vessels, brain) tissues, thus decreasing blood pressure and sodium reabsorption. The adult dose is 50 mg PO qd and it may be increased after 4 weeks, not to exceed 100 mg/d. Contraindications include documented hypersensitivity, hyperkalemia, coadministration with drugs causing increased potassium, type 2 diabetes with microalbuminuria, and moderate-to-severe renal insufficiency (i.e. CrCl <50 mL/min or serum creatinine >2 mg/dL [males] or >1.8 mg/dL [females]). Coadministration with potassium supplements, salt substitutes, or drugs known to increase serum potassium (e.g. amiloride, spironolactone, triamterene, ACE inhibitors, angiotensin II inhibitors) increases risk of hyperkalemia. Eplerenone may cause hyperkalemia, headache, or dizziness. Caution is advised with hepatic insufficiency.

2. Renal Angioplasty

Indications for Renal Angioplasty

1. Hypertension control
   a. Onset of hypertension before age 30
   b. Recent onset of hypertension after age 60
   c. Stenosis is caused by fibromuscular hyperplasia
   d. Hypertension refractory to medical therapy with at least three medications of different classes including a diuretic
   e. Accelerated hypertension
   f. Malignant hypertension
   g. The patient is intolerant to antihypertensive medical treatment.
2. Renal salvage
   a. Unexplained worsening of renal function.
   b. Loss of renal mass, especially while under surveillance during medical antihypertensive treatment.
   c. Impairment of renal function or acute renal failure secondary to antihypertensive medication, particularly with an angiotensin converting enzyme inhibitor.
   d. Progression of a hemodynamically significant renal artery stenosis while under surveillance.
3. Cardiac disturbance syndrome
   a. Recurrent "flash" pulmonary edema secondary to impaired left ventricular function.
   b. Unstable angina.
4. Other expanding indications
   a. CHF
   b. Recent development of ESRD partly due to RAS (Patient may avoid dialysis)
   c. Angiographic lesions in absence of HTN or renal insufficiency
   d. Patient with high grade RAS undergoing infra-renal abdominal aortic aneurysm repair.

Contraindication for PTRAI

1. Relative contraindications
   a. An inelastic stenosis that cannot be reduced to less than 50% with balloon angioplasty
   b. The presence of sepsis
   c. If the stent would preclude surgical salvage should restenosis occur, i.e. isolation of branch arteries.
   d. For stenosis of an artery normally measuring 4 mm or less in diameter.
2. Absolute contraindications
   a. Advanced renal disease
   b. Creatinine >3 mg/dl
   c. Kidney length <8 cm
   d. Limited life expectancy due to comorbid condition.

OUTCOMES AFTER PTRA AND STENTING

Predictors of Outcome

A discrepancy between the high technical success rate of PTRA and the modest clinical success is observed. The effectiveness of correcting RAS for treating hypertension also has been shown to be limited in the presence of unilateral atherosclerotic lesions. This relatively low success rate for treating hypertension highlights the importance of finding outcome predictors

Fig. 3: Bilateral renal artery stenosis

for selecting patients who will benefit from PTRA. These are:

1. Duration of hypertension for less than 10 years
2. A diastolic pressure greater than 80 mmHg
3. FMD
4. Younger age
5. Mildly elevated serum creatinine between 1.5-2.0 mg%
6. Impaired left ventricular function
7. Female sex
8. Preserved parenchymal thickness.

Although initially used to treat only hemodynamically significant residual stenosis or a flow-limiting dissection after balloon angioplasty, stents have become the standard of care for ostial renal artery stenosis (Figs 3 and 4). A meta-analysis by Rees reported 99% technical

Fig. 4: Final result after renal stenting

success after stent placement in 1,128 arteries compared with 55% of ostial and 70% of nonostial stenoses in 1,417 arteries treated with balloon angioplasty. There was 77% patency at a mean 7.9 months follow-up angiography in 563 arteries in which stents were placed. **"Stents dilated to less than 6 mm, female sex, age older than 65 years, and smoking are statistically significant risk factors for restenosis**. The lowest risk group was men with renal arteries 6 mm or greater, who had a restenosis rate of 10.5% in the **U.S. Multicenter Renal Artery Stent Trial**.

Increased technical success and patency would be expected if the reference vessel was 6 mm or greater in diameter. The use of stents in ostial and nonostial locations is relatively contraindicated if they traverse renal artery branches or if restenosis would be likely to make surgical revascularization difficult or impossible. Renal artery stents have no established role in the primary treatment of fibromuscular dysplasia. Renal artery stents are the preferred treatment for ostial stenosis in arteries whose reference diameter is 6 mm or greater. Their use in vessels less than 5 mm in diameter should be limited to technically failed balloon angioplasty. Their primary use in lesions where the normal diameter is 5 mm is left to the discretion of the interventionalist.

Impact on Ischemic Nephropathy

A review of atherosclerotic disease in 7,200 end-stage renal disease patients indicated that occlusive disease of the renal arteries may contribute to progressive renal failure in 1.24% of the United States dialysis population or in 14% of the Caucasian patients with hypertensive nephrosclerosis.

The seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure suggests that surgical or endovascular revascularization may be necessary to preserve renal function even though many patients with high-grade renal artery stenosis remain stable for prolonged periods if blood pressure is well controlled.

IMPACT ON BLOOD PRESSURE

Cure of Hypertension in Patients with Atherosclerotic Renal Artery Stenosis (ARAS)

The review of literature shows disappointing results as far as effect of PTRA on control of BP goes, 19% were cured, 51% improved and 30% had no change in BP. Moreover, introduction of stents has not improved outcome of PTRA regarding BP.

These results can be explained by the fact that these patients have coexisting diabetes, essential hypertension, atheroembolic (spontaneous or procedure related) and medication related insults on renal parenchyma which prevents BP from retaining to normal levels even after dilatation of renal artery.

This discrepancy between anatomical correction and clinical outcome stresses the need for careful candidate selection for intervention and it still remains a challenge. Three major studies compared effects of PTRA and medical treatment and meta-analysis revealed that the level of BP control was similar, the only advantage that PTRA had was diminution of drug regimen and their attendant untoward effects. In a meta-analysis by Leertouwer et al, 54 of 544 patients (10%) with athero-sclerotic renal artery stenosis treated with balloon angioplasty alone were reported as "cured." Duration of hypertension of less than 10 years, pre-intervention systolic blood pressure of more than 180 mm Hg, and male sex were collective variables that predicted cure with a sensitivity of 92%, specificity of 77%, positive predictive value of 52%, and negative predictive value of 97%.

The problem of establishing normal blood pressure on no antihypertensive medication after renal revas-cularization is confounded by the coexistence of under-lying essential hypertension in the majority of cases.

All of the studies reported that a decrease of blood pressure on lower doses of medication results from renal revascularization. Because of the low incidence of cure of renovascular hypertension and the ability to adequately control blood pressure with medicine in a large percentage of patients, many prominent hyperten-sion specialists feel that patients with normal renal function have little to gain from renal revascularization and recommend it only for those patients who fail medical therapy. Hypertension should be considered resistant if "the blood pressure cannot be reduced to below 140/90 mm Hg in patients who are adhering to an adequate and appropriate triple-drug regimen that includes a diuretic, with all three drugs prescribed in near maximal doses. Medical control of hypertension is not without risk. Whether controlling blood pressure with less medication outweighs the risks of the revas-cularization procedure must be considered on an individual case basis, the clinician chooses to treat hypertension without knowing the status of renal artery patency, he must be alert to signs of decreased renal function and loss of renal mass.

EFFECT ON RENAL FUNCTIONS

Theoretically, PTRA should be used to preserve renal function rather than controlling Blood Pressure, because renal function preservation is better when renal functions are still normal. Overall cardiovascular risk is increased by 5 times when creative level is >1.5% in patients undergoing PTRA.

Results of Treatment in Ischemic Renal Disease

Harden et al found statistically significant benefit indicated by a reduction in the rate of renal functional loss from -4.3 at baseline to -0.55×10^{-6} L $\mu mol^{-1}/d^{-1}$ at last follow-up in 32 patients treated with renal artery stent placement despite a decrease in serum creatinine of less than 20% in only 34% of patients and an increase in serum creatinine of more than 20% in 28% of patients.

Endovascular revascularization can result in improvement of the glomerular filtration rate in selected patients with ischemic nephropathy. Signs that a patient with ischemic nephropathy is likely to benefit from revascularization include:

1. Normal appearance of the arterioles distal to the renal artery stenosis
2. Bilaterality of reconstructible disease
3. A near normal volume of renal mass available for revascularization
4. A test demonstrating function of the involved kidney
5. Renal biopsy demonstrating well preserved glome-ruli and tubules with minimal arteriolar sclerosis
6. Severe and difficult to control hypertension
7. Abrupt onset of renal insufficiency.

A Doppler ultrasound resistance index of 80 or greater (1-[end-diastolic velocity/maximal systolic velocity] $\times$ 100) and the absence of hypertension are strong negative predictors of renal salvage after revascularization of any type.

CARDIAC DISTURBANCE SYNDROME

Renal artery stenosis may worsen angina or congestive heart failure in patients with coronary artery disease, left ventricular dysfunction, or cardiomyopathy due to alterations in the renin–angiotensin–aldosterone axis resulting in a state of volume overload and peripheral vascular constriction. Renal revascularization may result in relief of these cardiac syndromes due to normalization of excess renin production, which reduces sodium and water retention and vasoconstriction caused

by aldosterone and angiotensin and causes natriuresis because of improved glomerular filtration. Restoring unobstructed renal blood flow has the additional benefit of allowing safe usage of angiotensin-converting enzyme inhibitors without the risk of worsening renal failure and reducing coronary perfusion. Bilateral renal artery stenosis or stenosis of a solitary functioning kidney is frequently present in a patient with a cardiac disturbance syndrome who is likely to receive benefit from percutaneous renal revascularization. In a study by Mann, et al, more than 70% of 73 patients with cardiac disturbance syndromes with this vascular profile who were treated with percutaneous angioplasty and stent placement were free of congestive heart failure and unstable angina at 12-month mean follow-up. Additional benefits in this patient group also frequently include improvement of hypertension control and renal function.

Complication of Endovascular Revascularization

With use of the present technology and depending on patient selection, the mean incidence of complications after endovascular renal revascularization is 14%. Most of these are not life threatening and do not result in renal functional loss. The combined incidence of 30-day mortality, occlusion of the main renal artery, loss of a kidney, renal artery perforation, and the need for surgical salvage is expected to be less than 4%. Renal artery branch occlusions occur in less than 2% of cases. Cholesterol embolization resulting in decreased renal function, visceral symptoms, or peripheral symptoms is expected to be less than 3%. Although loss of life during percutaneous renal revascularization is rare, there is significant risk of a serious complication that may result in loss of renal function or require treatment that is likely to increase the duration and cost of patient care. The anticipated benefit from renal revascularization must outweigh the risks involved. Each case must be evaluated individually.

CONCLUSION

The prognosis of patients with RAS is difficult to ascertain and varies with the extent of the occlusive phenomena, the sensitivity of the individual to antihypertensive therapy, and the efficacy of surgical repair and/or angioplasty.

RAS in the setting of chronic renal ischemia and consequent renal dysfunction has been linked to worse outcomes. However, controversy still revolves regarding appropriate threshold for intervention. Most interventionists and clinicians argue that when the entire renal mass is involved such as in bilateral renal artery stenosis or unilateral RAS is single functioning kidney, i.e. **global renal ischemia**, the response is dramatic and PTRA uniformly improves or at least stabilizes renal function and preserves kidney size. The position of PTRA with respect to medical or surgical treatment would be better delineated through randomized clinical studies and adoption of uniform reporting standards.

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