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Review Article

Renovascular Hypertension

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Abstract

Renovascular Hypertension (RVH) is the most common cause of secondary hypertension. High index of suspicion is needed to diagnose this condition. Two major causes for RVH are renal artery stenosis (RAS) secondary to atherosclerosis (~90%) and fibromuscular dysplasia (~10%). Certain clinical clues for RVH are unprovoked hypokalemia, abdominal bruit, age of the onset of hypertension (<30 years or >55 years), the absence of the family history of hypertension, recent onset of hypertension (duration <1 year), difference of kidney size >1 cm, unexplained azotemia, recurrent flash pulmonary oedema, new onset azotemia with initiation of ACEI, and resistant or refractory hypertension. Revascularization by Percutaneous transluminal renal angioplasty (PTRA)/surgery as indicated should be instituted whenever there is medical failure or worsening of azotemia with maximal medical therapy for RVH.

Key words: Renovascular Hypertension, renal artery stenosis, percutaneous transluminal renal angioplasty

Introduction

Among the secondary causes of hypertension, the renovascular hypertension (RVH) tops the list. It accounts for 3% of hypertensive patients. Renal artery stenosis (RAS) progression has direct correlation with age and the grade of stenosis and has no correlation with BP control.

Etiology

Two major causes for RVH are RAS secondary to atherosclerosis (~90%) and fibromuscular dysplasia (~10%). The other causes are renal artery aneurysm, systemic vasculitis (polyarteritis nodosa and Takayasu arteritis), arteriovenous fistula (congenital or traumatic), acute arterial thrombosis or embolism, acute aortic/renal artery dissection, hypercoagulable state (antiphospholipid antibody syndrome), congenital bands, and radiation-induced fibrosis.

Atherosclerotic RAS (ARAS) occurs usually in elderly individuals and is associated with diffuse atherosclerosis in other vascular territories. It is commonly seen in aged males, diabetics, smokers, and patients with dyslipidemia. It involves the origin of the renal arteries and extends to proximal segment.

Fibromuscular dysplasia (FMD) occurs in young females, often with a history of smoking. It involves mid to distal portion of renal arteries and appears as string of beads appearance in angiography. Usually, renal function is not affected.

Prevalence

The prevalence of RAS increases with the age and in patients with known cardiovascular risk factors such as diabetes, hypertension, and dyslipidemia. The prevalence of RAS of >70% was 7.3% in patient who has undergone cardiac catheterization with resistant hypertension, renal impairment, flash pulmonary edema, or atherosclerosis in other vascular territories.[1] In our study,[2] the incidence of RAS was 7.7% by the routine drive-by angiogram, during coronary angiography for suspected CAD. In the general population, 2–5% of secondary hypertension is due to ARAS. In autopsy series, 27% had RAS of >50% in the group aged >50 years.

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Clinical Clues for RVH

Even though RVH is not easily distinguishable from essential hypertension, there are certain clinical clues such as unprovoked hypokalemia, abdominal bruit, age of the onset of hypertension (<30 years or >55 years), the absence of the family history of hypertension, recent onset of hypertension (duration <1 year), difference of kidney size >1 cm, unexplained azotemia, recurrent flash pulmonary edema, new onset azotemia with initiation of ACEI, and resistant or refractory hypertension.

Diagnosis of RAS

Non-invasive Test [Table 1]

1. Plasma renin activity
2. Renal vein renin ratio
3. Captopril renography
4. Renal artery Doppler
5. MR angiography of RA
6. CT angiography of RA.

Renal Doppler by Duplex Scan

It is the most commonly used non-invasive test to diagnose RAS. It is inexpensive, readily available. It is operator dependent and has limitation in patients with excess gaseous abdomen and obesity. Significant RAS with >60% stenosis can be diagnosed when peak systolic velocity is >200–320 cm/s, resistive index (RI) is <0.8%, RI difference >0.05, RAR (renal to aortic pressure ratio) >3.5–3.8, and missing early systolic peaking and prolonged acceleration time [Figure 1]. The resistance index by renal Doppler test is the only parameter that predicts the blood pressure (BP) control and improvement in kidney function following percutaneous transluminal renal angioplasty (PTRA) with stenting and value >0.8 indicates non-responders.

RENAL DOPPLER
↓
PSV >200-320 Cm/s or RAR >3.5-3.8 plus RI difference >0.05 or ESP missing
↓
conventional angiography and PTRA(S) if pressure gradient significant

Figure 1: Assessment of renal artery stenosis by Renal doppler. PSV - Peak systolic velocity, RAR - Renal aortic ratio, RI - resistance index, ESP - Early systolic peak, PTRA(S) - Percutaneous transluminal renal angioplasty (with stenting)

CT Angiogram

Computerized tomography angiogram will provide accurate renal artery anatomy including accessory renal arteries and better visualization of soft tissue except with dense renal arterial calcification. Contrast-related allergy, nephrotoxicity, and radiation are the issue with this modality and hemodynamic significance of the stenosis cannot be assessed.

Magnetic Resonance Imaging (MRI) Angiogram

MRI provides high-quality imaging of renal arteries. Contrast-enhanced MRI using gadolinium improves image quality. Hemodynamic significance of the stenosis cannot be assessed in routine MRI angiogram. Gadolinium use has been shown to cause nephrogenic systemic fibrosis with incidence of 1–6% for dialysis patients.

Blood-oxygen-level-dependent MRI assesses the level of deoxyhemoglobin in the kidney and following furosemide challenge; there is a reduction in the level of deoxyhemoglobin in normal kidney and no response in atrophic kidney, which helps in planning decision regarding revascularization.

Invasive Test

Catheter angiography with digital subtraction angiography confirms the diagnosis of RAS and helps in assisting the hemodynamic significance of RAS by measuring the pressure gradients. Significant RAS diagnosis is defined as >50% diameter stenosis by eyeball technique, peak translesional gradient of >20 mmHg or >10% of peak systolic aortic BP or >10 mmHg mean translesional pressure gradient. The issues with the invasive angiography are contrast-induced nephropathy, allergy, radiation, and the cost.

Table 1: Accuracy of tests for renal artery stenosis

Test	Sensitivity (%)	Specificity (%)	Pretest probability for renal artery stenosis			
			20%		50%	
			Positive predictive value (%)	Negative predictive value (%)	Positive predictive value (%)	Negative predictive value (%)
Captopril renography	74	59	31	90	64	69
Duplex sonography*	76	75	43	93	75	76
Magnetic resonance angiography**	78	88	64	94	87	80
Computed tomographic angiography**	77	88	76	94	93	80

*Values chosen are intermediate between captopril renal scanning and average of values obtained for magnetic resonance angiography and computed tomography and based on the summary receiver-operator curves from Vasbinder *et al.* **Values reported for atherosclerotic renal artery stenosis

Translesional gradient can be measured using 4 French catheter or with 0.014-inch pressure wire. Gradient (Pd/Pa) across the lesion of <0.8 after intra-arterial papaverine (30 mg) or dopamine (50 mcg/kg) bolus indicates significant stenosis.

Drive by Renal Angiogram with Contrast Flush

It is useful in detecting ostial lesion and can avoid dissection of the origin of renal artery, spasm, atheroembolism, and missing out multiple renal arteries.

Treatment

Medical Therapy

Medical therapy with antihypertensive drugs can be continued indefinitely if BP control is good with stable renal function. Among the antihypertensive drugs, angiotensin convertase inhibitors are the most effective drugs in RVH except in patients with bilateral RAS or ipsilateral RAS with only solitary functioning kidney. Calcium channel blockers are the next choice followed by other groups of drugs. Patients with ARAS with hypertension should be kept on antiplatelet, statin in addition to antihypertensive drugs and smoking should be stopped.

Worsening of azotemia on initiating ACEI indirectly points to significant RAS in these patients. It occurs especially when there is severe congestive heart failure, use of high-dose diuretics, volume depletion, and baseline renal dysfunction. A significant >30% fall in GFR or >0.5 mg/dl rise in creatinine or >30% rise from baseline creatinine may be an indication to consider renal vascularization. Whenever patient does not tolerate ACEI due to hyperkalemia or cough, angiotensin receptor blockers can be substituted.

Revascularization by Angioplasty with Stenting

Revascularization by PTRA is aimed to retard the progression of azotemia, better control of BP, and relief of chronic angina, heart failure, and flash pulmonary edema (cardiac disturbance syndrome) in patients with hemodynamically significant RAS.

Following revascularization by PTRA in patients with RVH, there are four types of responses noted, namely cure, good responders, poor responders, and non-responders. Usually, BP response is seen within 48 h after PTRA. Predictors of the control of BP following revascularization are unilateral versus bilateral RAS, duration of hypertension, angiographic success, and size of kidney by USG, resistance index difference, baseline serum creatinine level, and extent of atherosclerosis, advanced age, and presence of diabetes.

RVH secondary to FMD responds better than ARAS (60% vs. 30%). Cure is relatively rare (11%) in ARAS on follow-up over 2½ years. In our study,[3] cure was noted in 3.75% over 1-year follow-up [Table 2]. PTRA is considered treatment of choice in patients with RVH secondary to FMD with success rate of 82–100%. There is a risk of 10–11% restenosis after PTRA.

In patients with ARAS, PTRA should be followed by stenting, as there is more elastic recoil at the ostium of renal artery, dissection, and residual stenosis with plain PTRA, with a success rate of 94–100%. The rate of restenosis at the end of 1 year is 11–23%.

PTRA Benefit in Aras

1. >70% RAS by angiography in unilateral RAS/bilateral RAS/solitary kidney with rapidly declining renal function
2. Unilateral ARAS with hypertension with renal insufficiency.

Responders

A hyperemic translesional systolic gradient of >20 mmHg following intrarenal papaverine or intravenous dopamine considered as a strong predictor of a positive response to PTRA in patients with unilateral RAS.[4] Those who have higher renal frame count and renal blush have good clinical response following vascularization.[5] The response to PTRA is good, whenever the ipsilateral kidney size is > than 7 cm.

PTRA does not help in patients with unilateral RAS with normal renal function or stable renal function, whose BP could be controlled easily. Subgroup of patients who are least likely to respond to PTRA is those with small kidney size, longer duration of azotemia, baseline creatinine of >3 mg/dl and a high baseline resistance index of >0.8, significant proteinuria, and high risk of atheroembolism. Patients with RAS with Pd/Pa of >0.9 with no rise in baseline renal vein renin level are unlikely to improve following PTRA.[6] A small percentage of patients will deteriorate in renal function after PTRA, possibly due to contrast nephrotoxicity, atheroembolism, and reperfusion injury and it is difficult to predict before the procedure.

A baseline creatinine concentration >130 μmol/L is the strongest independent predictor of death within 4 years after PTRA with stenting. Once azotemia starts worsening in RAS,

Table 2: BP response to PTRA-comparative trials

Author and year	Number of patients	Follow-up in months	Cure%	Improved%	Unchanged/worse%
Iannone *et al*. (1996)	63	11.3	3.7	35.2	61.1
Baumgartner (1997)	35	12	8.6	45.7	45.7
Rees CR (1999)	845	24	6	56	38
Vande Ven (1999)	41	6	4.8	43.9	51.3
Alberto Morganti (2000)	66	6	3	38	59
Stefanio Pinto (2002)	58	6	35	36	29
Sathyamurthy (2010)	80	12	4	55	41

for every 88 μmol/L increment from baseline creatinine, there is 2–3-fold risk of death.

Trial

Drastic trial showed no significant difference between the angioplasty and medical treatment at 1 year.

Astral trial

Angioplasty and stenting for renal artery lesion study[7] did not show any significant clinical benefit following PTRA in ARAS and there was substantial risk.

Flaws

1. RAS severity was possibly overestimated
2. 40% of patients in both the groups had RAS <70%
3. The success rate was 78.6%, which was far below the expected success rate of 96–98%.
4. The primary and secondary end points are poor outcome measures.

Star Trial

Stent placement in patients with ARAS and impaired renal function - a randomized trial[8] did not show any benefit on progression of impaired renal function following PTRA but led to a small number of significant procedure-related complications.

Coral Trial

Cardiovascular outcomes in renal atherosclerotic lesions study[9] did not show a significant benefit in preventing clinical events in patient with ARAS with hypertension or CKD when PTRA added to optimal medical therapy.

Two meta-analyses of these trials, independently reported that PTRA is more effective in controlling BP than medical therapy.

Great Trial

Only prospective study[10] comparing bare metal and sirolimus-coated low profile stent in RAS, showing a relative risk reduction of angiographic binary in-stent restenosis by 50%, which was statistically insignificant. The use of drug-eluting stent is not recommended, as there are no outcome data.

Resist Trial

It is a randomized trial,[11] wherein stenting in moderate RAS in patients with resistant hypertension found to reduce mean baseline transluminal gradient and a gradient of >20 mmHg is highly predictive of BP improvement after PTRA. However, there was no overall improvement in GFR with the use of distal protection device.

SPYRAL HTN-OFF MED[12] was a randomized, sham-controlled, single-blinded trial, found clinically meaningful BP reduction compared to sham control at 3 months in uncontrolled hypertensive patients in the absence of antihypertensive medication with no major safety events.

SPYRAL HTN-ON MED[13] was a randomized, single-blinded, sham-controlled trial in patients with uncontrolled hypertension, aged 20–80 years, wherein 50% of maximum recommended dosage of antihypertensive medications were instituted and followed up for 6 months. Office and 24 h ambulatory BP decreased significantly from baseline at 6 months, which was statistically significant and there were no major safety events.

Sympathetic Nervous System for Kidney and RVH

There is direct relationship between sympathetic nervous system and BP, which was proved beyond doubt that beta-blockers are effective only when native kidneys have not been removed in renal transplant patients. Both efferent and afferent neuronal signals between the kidney and central nervous system create a loop of hemodynamic abnormalities that increase BP. This renal contribution to central sympathetic drive can be blended by deefferentiation of the renal nerve. This can be achieved by radiofrequency ablation, ultrasonic neuronal ablation, chemical neural ablation, cryoablation, and ionizing radiation neural ablation.

Symplicity HTN 3[14] was a randomized, sham-controlled, multicenter, blinded prospective trial. It was a negative trial, wherein denervation was not found superior to sham procedure and medical therapy in reducing office and ambulatory BP at 6 months in patients with severe resistant hypertension but found to be safe of 6 months with no excess increase in RAS.

DENERHTN[15] was a multicenter, open-label randomized, controlled trial in patients with resistant hypertension, wherein denervation found more effective at reducing ambulatory, but not office BP, compared with standardized antihypertensive treatment alone.

RADIANCE-HTN SOLO[16] was a randomized, sham-controlled trial in mild-moderate hypertension used endovascular ultrasound for renal denervation. There was significant reduction in daytime ambulatory BP in renal denervation group at 2 months with no safety issues.

However, ESC 2018 guidelines have given Class III B for device-based therapy for hypertension treatment, as still this modality is mostly investigational only.

Surgery

Surgical correction of RAS by aortorenal, mesenteric/celiac renal bypass is indicated only when patients are not candidates for PTRA or non-responders to PTRA and in whom maximum medical therapy has failed to control RVH. In the current practice, role of surgical treatment in RAS is very limited to a subset of patients where endovascular procedure has failed.

Conclusion

RVH is the most common cause of secondary hypertension. High index of suspicion is needed to diagnose this condition. Revascularization by PTRA/surgery as indicated should be

instituted whenever there is medical failure or worsening of azotemia with maximal medical therapy.

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