$\mathcal{R}$eview $\mathcal{A}$rticle

Interventional Treatment of Secondary and Essential Hypertension

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Abstract

The cornerstone of treatment in hypertension is lifestyle management and pharmacotherapy. A remedial cause of hypertension called as secondary is present in small number of patients. Percutaneous or surgical treatment can be curative or highly effective in controlling the blood pressure in these cases. Balloon angioplasty and stent implantation provide excellent blood pressure control in coarctation of aorta and nonspecific aortoarteritis. There is considerable debate regarding stent deployment in atherosclerotic renal artery stenosis and its use should be restricted to select group. The results of percutaneous interventions are remarkable in fibromuscular dysplasia and post renal transplant graft restenosis .Surgery has a definite role in endocrine disorders like pheochromocytoma ,adrenal adenoma and cushing's disease. Renal denervation is an attractive therapy for patients with essential hypertension who are refractory to pharmacotherapy. Ongoing studies will provide real world indications for this technique.

Key words: Aortic stenting, hypertension, renal denervation, renal stenting, transcatheter interventions

Introduction

Systemic hypertension (HTN) is a major public health problem. India had 41.5 million people with HTN in 2000 and the burden is projected to increase by another 5 million by 2025.[1] HTN is divided in to primary and secondary and vast majority (≥90%) of cases belong to former group.[2] The management consists of lifestyle alterations along with judicious use of pharmacotherapy. A remedial cause of HTN, termed secondary can be identified in approximately 10% of cases. The treatment of specific cause can achieve normalization or better control of blood pressure (BP) with improved outcomes. Table 1 shows causes of secondary HTN amenable to surgical or percutaneous interventions. Various device-based therapies have emerged principally targeted at the treatment of resistant HTN. The therapeutic interventions used in secondary and essential HTN will be discussed in following subheads:
1. Endovascular renal interventions
2. Aortic interventions
3. Role of surgery
4. Renal denervation (RND).

Endovascular Renal Interventions

Atherosclerosis remains the dominant etiology though several important conditions also cause renal artery stenosis (RAS) [Table 2]. Renovascular HTN results from stimulation of renin angiotensin aldosterone system following impairment of renal blood flow by RAS.

Atherosclerotic RAS (ARAS)

ARAS is the leading cause of secondary HTN and frequently coexists with coronary and peripheral atherosclerosis. The prevalence ranges from 10.5% among patients undergoing coronary angiography to 54% among those with congestive heart failure.[3] ARAS may lead to refractory HTN, progressive decline in renal function and cardiac destabilization syndromes.

The diagnosis of significant RAS is crucial to optimal treatment. A physical examination may rarely reveal systolic/diastolic abdominal bruit radiating to flank. Table 3 provides clues to the diagnosis and a detailed evaluation should be restricted to those who are potential candidates for revascularization. Doppler ultrasound is noninvasive, cost

effective, and excellent diagnostic tool but the yield depends on the operator expertise. A peak systolic velocity (PSV) of >200 cm/s is associated with 95% sensitivity and 90% specificity of >50%.[4] Computed tomographic angiography or magnetic resonance angiography is highly sensitive and specific but are expensive with issues of contrast and radiation. Invasive renal angiography is appropriate for patients who are likely to need intervention and in those undergoing angiography for other indications. Adequate hydration and minimal use of contrast are recommended. On angiography, the stenosis can be categorized as mild (≤50%), moderate (50–70%), and severe (≥70%). The lesion is considered hemodynamically significant when resting or hyperemic translesional systolic pressure gradient of ≥ of 20 mmHg, or a mean gradient of ≥

Table 1: Causes of secondary HTN

Disorder	Major findings
Renovascular HTN	See Table 3
COA	Inequal pulses, young patients <30 years
NSA	Inequal pulses, young female HTN (<30 years)
PCC	Paroxysmal HTN, established HTN with spells, headache, sweating
Conn's syndrome	HTN, Hypokalemia, incidental detection of adrenal mass
Acromegaly	Skeletal features, DM
CD	Typical obesity, DM

HTN: Hypertension, PCC: Pheochromocytoma, CD: Cushing's disease, NSA: Non-specific aortoarteritis, COA: Coarctation of aorta, DM: Diabetes mellitus

Table 2: Common causes of RAS

Atherosclerosis
Nonspecific aortoarteritis
FMD
Transplant related
Atheroembolic renal disease
Aortorenal dissection
Trauma

RAS: Renal artery stenosis, FMD: Fibromuscular dysplasia

Table 3: Indications for diagnostic testing in RAS

Increase in serum creatinine at least 50% within a week of starting ACEI or ARB therapy
Onset of severe HTN (e.g., >180 mm systolic, >120 mm diastolic) in young patients or those above 55 years
Renal bruit, severe HTN in patients with unilateral small kidney
Severe HTN in patients with known atherosclerosis
Severe HTN in patients with recurrent flash pulmonary edema

RAS: Renal artery stenosis, ACEI: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker, HTN: Hypertension

of 10 mmHg, or renal fractional flow reserve ≤0.8.[4,5] These measurements help to identify patients with refractory HTN who are likely to have favorable BP reduction with stenting.[6,7] Estimation of gradients is also useful in patients with moderate stenosis on angiography.

Treatment options include pharmacotherapy with or without renal revascularization. Percutaneous trans-luminal renal angioplasty (PTRA) with stent placement (PTRAS) is an option for control of HTN and preservation of renal function. A review of seven randomized controlled trials comparing PTRAS plus continued medical treatment (MT) versus MT alone failed to support a beneficial effect of PTRAS on clinical outcomes.[3] Three major trials, STAR,[8] ASTRAL,[9] and CORAL[10] failed to document a definite subset of patients who may benefit from percutaneous treatment. The impact of these studies was considerable reduction in use of PTRAS from its peak in 2006 to selective use.[11] These trials have been strongly criticized for several flaws in selection criteria, inconsistent definitions of improvement, endpoints, and procedural techniques.[4,5] Given the controversies, it is a challenge to select a suitable patient who will respond favorably to the intervention. According to Society for Cardiovascular Angiography and Interventions (SCAI) expert consensus document[5] and review of American College of Cardiology (ACC) and American Heart Association guidelines,[4] PTRAS is recommended for symptomatic patients with significant RAS who have refractory HTN despite guideline directed MT. PTRAS is also effective for prevention of progressive ischemic nephropathy, heart failure, or sudden pulmonary edema (cardiac destabilizing syndrome). Figure 1 shows marked reduction in trans-stenotic gradient with angiographic improvement in renal narrowing in a patient with refractory HTN secondary to ARAS.
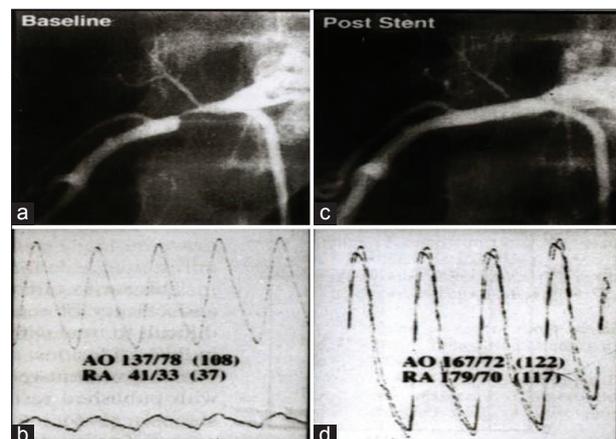

Figure 1: Selective right renal angiography depicts over 90% narrowing (a) with marked trans-stenotic gradient (b) in a patient with severe ARAS in basal state. Remarkable angiographic (c) and hemodynamic (d) improvement after renal stenting. AO: Ascending aorta, RA: Radial artery, ARAS: Atherosclerotic renal artery stenosis

Fibromuscular Dysplasia (FMD)

FMD is a non-inflammatory, non-atherosclerotic arterial disease that predominantly affects carotid, renal, and femoral arteries. Renal artery FMD is often found incidentally in asymptomatic individuals but has a 2–6% prevalence with a female preponderance and can lead to HTN.[12] Medial hyperplasia accounts for 70% of cases and is mostly bilateral. "String of pearls" appearance on angiography is characteristic of FMD. The stenosis can be subtle and only detectable on pressure gradient measurement or by intravascular ultrasound imaging. PTRA without stent implantation is very effective and is recommended for patients who have uncontrolled BP or deteriorating renal function. The procedure is very effective in curing or controlling HTN.[13]

Non-specific Aortoarteritis (NSA)

NSA is common in our country and obstructive lesions of renal artery result in renovascular HTN which is often resistant to pharmacotherapy. There is localized or diffuse involvement of the proximal segment or ostia of renal arteries. PTRA was found to be safe and effective but the high rates of restenosis limited its utility. Cutting or high pressure balloon has been utilized in tough ostial lesions. Stent implantation provides better angiographic results, effective control of BP and is recommended for *de novo* lesions, dissection and in patients with suboptimal results to PTRA.[14]

Transplant RAS (TRAS)

TRAS is a unique subset of RAS and is the most common vascular complication following renal transplantation. There are important differences in the pathology of ARAS and TRAS. Early stenosis with in 1st year of transplantation is related to vascular injury whereas late TRAS resembles severe bilateral ARAS.

Refractory HTN, unexplained rise of serum creatinine or flash pulmonary edema are presenting manifestations. Doppler ultrasound finding of PSV of >2 mm raises strong suspicion. TRAS is a potentially treatable/curable cause of HTN with excellent therapeutic outcomes following percutaneous trans-luminal angioplasty with or without stent.[15,16]

Aortic Interventions

Balloon angioplasty (BA) with or without stent implantation has been used to treat aortic obstruction in coarctation of aorta (COA) and NSA.

COA accounts for 5% of congenital heart disease. Neonates and infants usually present with heart failure and surgical correction is the best option. COA can cause HTN in children but presentation is usually delayed until adulthood. Adult patients with COA are either asymptomatic or present with HTN and its complications. Classic signs include delayed or absent femoral
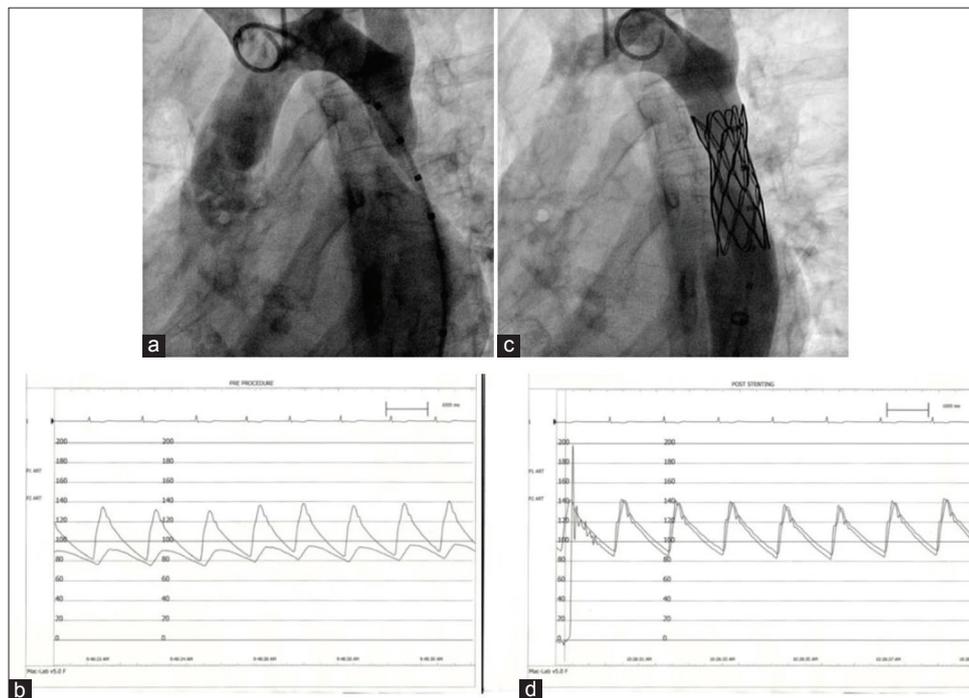

Figure 2: Ascending aortography in left anterior oblique view demonstrates severe aortic narrowing (a) and gradient across descending and ascending aorta (c) in an adult with coarctation of aorta. Stent deployment results in excellent angiographic (b) and hemodynamic (d) improvement

pulses, upper extremity HTN, low or unrecordable BP in the lower extremity and a murmur. Therapeutic options for COA have evolved from surgical correction through BA[17] to stent implantation.[18] The initial application of BA was to successfully dilate post-surgical COA. The dense scar tissue surrounding the recurrent COA makes the re-operation difficult and provides support against aortic rupture during balloon dilatation. BA is the preferred approach for the management of post-operative COA. In older children and adolescents, BA has been widely used as the primary form of therapy. There are variable rates of recurrence and aneurysm formation. In general, the results of balloon dilatation are better and long lasting in discrete COA. In adults, stent is offered as the first choice of treatment. Figure 2 demonstrates angiographic aortic narrowing in an adult with HTN and remarkable angiographic and hemodynamic benefits after stent deployment. Stenting results in effective and predictable relief of the obstruction with effective control of BP in short- and long-term. Accumulated experience including the COAST trial[18] support the use of bare metal stents for most patients with COA, with covered stents usually reserved for those deemed to be high risk or with aneurysm formation.

NSA is a chronic inflammatory arteritis of unknown etiology affecting aorta and its main branches with resultant HTN. Revascularization should be attempted only after suppressing the disease activity. BA, stent, or stent graft placement has been used as percutaneous treatment options. The procedure outcome depends on the site, length, lesion characteristics, and stage of arterial stenosis. BA produced excellent results for short segment lesions.[19] The rigid, noncompliant lesions may yield only to a high pressure dilatation or result in significant residual stenosis .Stents are an important adjuvant to BA when there is vessel recoil or dissection but have been extensively used electively with high procedural success and restenosis rate of 20%. Stent grafts are better than uncovered metal stents or BA with low restenosis and sustained patency.

Role of Surgery

Surgery remains a feasible and effective option in selected patients with COA, NSA, and RAS with complex anatomy or failed percutaneous intervention. Operative options in COA include resection with end to end anastomosis, patch aortoplasty, or bypass graft. Vascular surgery has been the traditional modality in NSA and several procedures including aortorenal bypass are in vogue.[20] The role of surgery in rare endocrine disorders will be discussed briefly.

Pheochromocytoma (PCC)

PCC and paragangliomas are catecholamine producing endocrine tumors arising from chromaffin cells in the adrenal glands and the ganglia. Clinical manifestations such as HTN, headache, palpitations, and pallor are due to catecholamines release. Rarely, patients can present with life threatening hypertensive crisis. Approximately 95% of patients have HTN which can be paroxysmal or sustained. In some patients, hypertensive paroxysms will occur in a background of sustained HTN. Demonstration of elevated levels of catecholamines and/or its metabolites in urine or plasma is essential for the diagnosis. Imaging by computed tomography (CT), magnetic resonance imaging (MRI), or metaiodobenzylguanidine scan is needed to confirm the diagnosis. Laparoscopic techniques are currently in vogue for adrenal removal surgery. Pre-operative alpha and beta blockade and intraoperative hemodynamic monitoring are crucial for a favorable outcome.[21]

Primary Hyperaldosteronism (Conn's syndrome)

Hyper-aldosteronism can result from adrenal adenoma, unilateral or bilateral adrenal hyperplasia, and rarely carcinoma. Adenoma (Conn's syndrome) is Characterized by increased aldosterone secretion from the adrenals, suppressed plasma renin, hypokalemia, and HTN. Hypokalemia in a patient with HTN is the usual clue to consider hyper-aldosteronism, but potassium can remain normal in one-third of patients. These patients have uncontrolled BP, increased vascular risk, and early death. High aldosterone: Renin ratio suggests primary hyper-aldosteronism to be confirmed by CT, MRI, or selective adrenal venous sampling. Laparoscopic surgical adrenalectomy results in significant improvement in 95% and complete cure in one-third.[22]

Cushing's Disease (CD)

CD is caused by a pituitary adenoma that secrets adenocorticotropin (ACTH) autonomously, leading to excess cortisol secretion from the adrenal glands. Adenoma accounts for 70% of patients with endogenous Cushing Syndrome, the remaining 30% are secondary to ectopic ACTH syndrome, adrenal tumors, or hyperplasia. These patients show a cluster of systemic manifestations including abdominal obesity, HTN, and cardiovascular abnormalities. High BP is present in 70–80% of patients and attributed to stimulation of mineralocorticoid and glucocorticoid receptors, insulin resistance, and over expression of renal angiotensin system. CD is associated with increased mortality and morbidity primarily as a consequence of increased risk of CVD. Diagnosis of adenoma is confirmed by MRI. Trans-sphenoidal pituitary surgery is the first line of treatment and carries a favorable prognosis.[23]

Acromegaly

Acromegaly is usually caused by a growth hormone secreting pituitary adenoma which causes a disorder with disproportionate skeletal tissue and organ growth. HTN is among the most frequent cardiovascular complication. Resection of adenoma using highly sophisticated endonasal trans-sphenoidal approach improves outcomes.[24]

RND Therapy

HTN contributes to a significant mortality and morbidity attributable to cardiac, cerebrovascular, and renal complications. Drug therapies are effective but adverse effects; intolerance and non-adherence pose major challenge in effective control of BP. To overcome these limitations, a number of interventional technologies are being evaluated

Chronic elevation of sympathetic nervous system activity has been identified as an important pathological mechanism in the initiation and maintenance of hypertensive state. Historically, surgical splanchniectomy has been used to interrupt sympathetic nerves in the lower thoracic and lumbar regions for treating severe HTN.[25] Sympathomedullary approaches such as RND, baroreflex activation therapy, and endovascular baroreflex modulation have been used to lower BP. Percutaneous RND became possible through the development of a catheter based radio-frequency ablation resulting in selective renal sympathectomy. The procedure effectively modulates the effects of elevated sympathetic activity both by reducing the efferent renal sympathetic control of kidney function (renin release, sodium excretion, and renal flow) and by removing the renal afferent sympathetic contribution to BP control. The initial studies showed effective reduction of office BP. However, the first randomized sham-controlled trial, SYMPLICITY HTN-3[26] did not show significantly lower office or 24 h ambulatory systolic BP compared with sham treatment. The results dampened the enthusiasm and raised questions about the efficacy and the procedural protocols.

The second generation of placebo-controlled trials of renal sympathetic denervation has moved from including the patients with resistant HTN receiving intensive pharmacological treatment to including patients with mild-to-moderate HTN in the presence or absence of antihypertensive medications. Refined radio frequency based and ultrasound based RND systems were used. Three recent sham controlled trials: SPRYAL HTN OFF MED, SPRYAL HTN ON MED, and RADIANCE-HTN provide data supporting the use of RND as a treatment of HTN.[27-29] Ambulatory BP was used as the end point in all these trials. SPRYAL HTN-OFF MED pivotal trial data in 331 patients released in virtual ACC 2020 showed superiority of catheter based RND compared with a sham procedure to safely lower BP in patients off medication.[30] These trials have provided the proof of principle for the BP lowering efficacy of radio frequency based and ultrasound based RND in patients with or without concomitant pharmacotherapy. Clinically relevant and consistent reduction in ambulatory BP and office BP in the short term (2–3 months) and mid-term (6 months) was documented. Future studies will answer the remaining questions regarding the precise mechanism, the most eligible group, procedure protocols, and the duration of efficacy.

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