Chapter 21
Interventions in Hypertension

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INTRODUCTION
Blood pressure (BP) is the force exerted by the blood against any unit area of the vessel wall. It is chiefly determined by cardiac output and the peripheral vascular resistance. Hypertension results from the interplay of several pathophysiological mechanisms regulating plasma volume, peripheral vascular resistance and cardiac output.

- Secondary hypertension: Secondary hypertension by definition is a result of identifiable causes.
- Identifiable causes of secondary hypertension amenable for catheter based intervention: Renovascular hypertension, coarctation of aorta, fibromuscular dysplasia (FMD) and aortoarteritis.
- Newer catheter based modalities in the armamentarium of interventional cardiologist: Renal sympathetic denervation and baroreceptor activation therapy.

THEORIES OF RENOVASCULAR HYPERTENSION
According to the Goldblatt model the pathophysiology of RAS can be explained by two-kidney one-clip and one-kidney one-clip model simulating unilateral and bilateral RAS, respectively.

As demonstrated by Goldblatt’s classical experiment, renal artery occlusion triggers the release of renin which in turn promotes production of angiotensin II and aldosterone resulting in severe vasoconstriction. In the setting of two kidneys, aldosterone-mediated sodium and water retention is handled properly by the nonstenotic kidney thus preventing volume overload as a mechanism of hypertension. By contrast a solitary ischemic kidney has little or no capacity of pressure natriuresis proving the fact that volume plays an important role in hypertension.

What is the role of angiotensin-converting enzyme (ACE) I in unilateral versus bilateral renal artery stenosis?
For patients with unilateral RAS and two functional kidneys, ACE inhibitors and angiotensin II receptor antagonists are preferred drugs for control of hypertension and their use is not contraindicated as long as renal function remains stable. On the other hand, ACE inhibitors and angiotensin II receptor antagonists are contraindicated in patients with significant bilateral RAS or RAS of a solitary kidney and every effort should be exercised to revascularize this subset of patients as they would not tolerate this therapy without significant renal deterioration.

When do you suspect renovascular hypertension?
- Hypertension detected for the first time before age 30 or after 55
- Acute elevation of plasma creatinine or azotemia after initiation of ACE inhibitor or angiotensin receptor blocker
- Patients with hypertension and asymmetrical kidney size
- Flash pulmonary edema in a patient with accelerated hypertension
- Malignant hypertension
- Resistant hypertension
- Renal bruit.

When do you intervene in renal artery stenosis?
Identification of patient who will benefit from renal artery revascularization is of critical importance. Associated underlying essential hypertension, renal parenchymal disease and RAS itself may contribute variably to hyper-tension. Identifying patient with pure or predominant RAS contributing to hypertension is aided by diagnostic tools like Doppler resistive index (RI), B-type natriuretic peptide (BNP) levels and fractional flow reserve (FFR) across the stenotic segment.

- Doppler resistive index: An elevated RI is considered to be an indicator of nephrosclerosis and intrinsic kidney disease.

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**RENSAL SYMPATHETIC DENERVATION AND ITS ROLE IN RESISTANT HYPERTENSION**

Resistant hypertension: “Resistant hypertension is the failure to reach goal BP in patients who are adhering to full doses of an appropriate three-drug regimen that includes a diuretic.”

The kidneys play an essential role in the regulation of BP through sodium and water regulation, renin modulation and renal sympathetic neuronal activation. Renal sympathetic nerves contribute to the development and maintenance of hypertension. Renal sympathetic outflow is increased in patients with essential hypertension. Efferent sympathetic outflow stimulates renin release, increases tubular sodium reabsorption and reduces renal blood flow. Additionally, afferent signals from the kidney modulate central sympathetic outflow and directly contribute to neurogenic hypertension.

Surgical renal sympathetic denervation was utilized as treatment modality in 1950s, but was abandoned because of procedure-related complications and increased availability of drug therapy. Renal sympathetic denervation addresses uncontrolled hypertension by reducing the drive of the sympathetic nervous system. It is a minimally invasive procedure that modulates the output of the sympathetic nerves located outside the renal artery walls and represents a breakthrough approach and first-of-its-kind device-based treatment for resistant hypertension. Specifically, renal denervation (RDN) involves selectively disabling renal nerves within the sympathetic nervous system with radiofrequency energy delivered to the renal artery lumen, ablating the renal nerves located in the adventitia of the renal arteries with the help of Simplicity catheter (Ardian Inc., Mountain View, CA). This exciting new therapeutic innovation affirms the crucial relevance of renal nerves in the pathogenesis of resistant hypertension.

We currently do not have a method to visualize or map the nerves during treatment. Remember that nerves arborize around the artery. Ablations are applied both circumferentially and longitudinally to target as many nerves as possible. Simplicity catheter emits a small fraction of the energy (5–8 W). The generator continuously monitors temperature and impedance and automatically shuts off after 2 minutes or when either impedance or temperature exceeds program limits. Renal imaging has shown no restenosis at the site of denervation (Figure 3).

Two randomized controlled trials—Simplicity HTN I and Simplicity HTN II trials—demonstrated efficacy and safety of catheter-based RDN in patients with resistant hypertension. A mean BP reduction of 32/12 mm Hg was noted in the treatment arm. A third trial Simplicity HTN III is currently underway and its results would throw some light on the future of this therapy.

**COARCTATION OF AORTA**

In 1760, the Prussian anatomist, Johann Friedrich Meckel, characterized coarctation of the aorta as an "extraordinary dilatation of the heart which came from the fact that the aortic conduit was too narrow." Coarctation of the aorta is typically located near the aortic attachment of the ligamentum arteriosum or patent ductus arteriosus.

**FIBROMUSCULAR DYSPLASIA**

Fibromuscular dysplasia is an angiopathy affecting medium-sized arteries in young woman, of which renal artery is most commonly involved vessel. It is recognized by its beaded appearance on angiography (Figure 2).

In general, balloon angioplasty is recommended for uncontrollable hypertension, intolerance to medications or declining renal function as evidenced by a rise in serum creatinine. Unlike in atherosclerotic RAS metallic stent is rarely used here, but may be used in case of dissection of artery during balloon inflation or restenosis. Reconstructive surgery may be recommended for patients with complex FMD of the renal arteries. Surgery depends upon the location and the extent of disease, but generally involves removing or bypassing the affected portion of the artery to restore normal blood flow.
arteriosus. An obtuse indentation in the posterolateral wall of the aorta corresponds to the location of an internal ridge or shelf that eccentrically narrows the aortic lumen, hence the term *coarctatus* (Latin, contracted or tightened). The coarctation ridge is thought to represent the original wall of the distal left sixth aortic arch (Figure 4). The neural crest is thought to play a role in the pathogenesis of some types of coarctation.\(^{21}\)

There are three types of hypertension in coarctation of aorta:

1. **Pre-repair hypertension**: There are three main theories to explain the cause of this pre-repair hypertension namely: (a) the mechanical, (b) neural and (c) Goldblatt phenomenon.
   a. *Mechanical theory*: It states the hypertension proximal to the coarcted segment is a function of the high resistance to left ventricle output imposed by the narrowing itself.
   b. *Neural theory*: It states that hypertension as a readjustment of baroreceptors in the aortic arch such that the increased proximal pressure is necessary to ensure an adequate blood supply to the organs distal to the obstruction.
   c. *Goldblatt phenomenon*: It states that due to the obstruction there is renal hypoperfusion and this leads to activation of RAS and subsequently hypertension.

2. **Post-repair hypertension**: It occurs in the first week after surgical repair of the coarctation segment. This may be due to activation of sympathetic system and RAS. However, this is not a consideration after balloon angioplasty.

3. **Late post-repair hypertension**: This type of systolic hypertension occurs as a result of abnormal compliance and responsiveness of the vessels in the vascular bed proximal to the coarctation segment. Patients may present with:
   - Heart failure in early infancy (after ductal closure) especially in the presence of a patent foramen ovale (PFO)\(^{22}\)
   - Upper limb hypertension
   - Lower limb claudication and effort intolerance in early adolescence and later in life
   - May remain silent to again present with heart failure later in life.\(^{23,24}\)

Treatment in neonatal life includes surgical repair of the coarctation segment.\(^{25}\) Emergent balloon angioplasty may be considered for refractory heart failure wherein the condition precludes surgery.\(^{26}\)

As 50% of the adult diameter is achieved by 8 years of life, balloon angioplasty with stenting should be performed preferably after 10 years.
years of life which can be re-expanded, if needed as the child grows. Balloon angioplasty and stenting has been the mainstay of treatment in adult coarctation patients. The patient has to be at least 30 kg for safe use of stents as it involves using large French (10–14 Fr) sheaths in the femoral artery. Cheatham platinum (CP) or Genesis stent is used which is mounted on an appropriate sized high pressure balloon (Z-Med or Atlas).

Patients who develop complications of earlier surgical repair like restenosis, aneurysm formation at the site of repair are effectively treated with covered stent deployment. In largest reported case series of coarctation stenting, successful outcomes were achieved in 98% of cases immediately after the procedure.

Complications of the procedure include aortic dissection, aortic rupture, stent migration, subclavian artery jailing (in case of a covered stent) and vascular complications related to sheath size. Other transient side effects include paradoxical hypertension and intestinal ischemia.

TAKAYASU’S AORTOARTERITIS (NONSPECIFIC AORTOARTERITIS)

Takayasu’s arteritis (TA) is an inflammatory vascular disease of the young females involving the large elastic arteries resulting in occlusive or ectatic changes mainly in the aorta and its major branches, pulmonary arteries and rarely coronaries. In Southeast Asia and Africa, descending thoracic and abdominal aorta involvement with renovascular lesions, the so-called “middle aortic syndrome” is found more commonly. Hypertension is seen in 72% of patients which is an important determinant of heart failure and mortality in aortoarteritis.

Most common etiology for hypertension is RAS (~80%). Other causes are atypical coarctation, reduced aortic capacitance as well as diminished baroreceptor reactivity.

Treatment of RAS includes balloon dilatation of stenotic artery and stenting of the vessel in selective circumstances (ostial lesion, dissection, recol of lesion, restenosis). Monitoring at 6 monthly intervals for clues of appearance of new lesions and restenosis is essential. In a study by Panja et al. stenting was used in 50% patients, with restenosis was seen in 28% lesions, which were successfully stented subsequently. Thus, renal artery intervention is treatment of choice for patients with RAS, with effective reduction in BP and ultimate outcome.

Abdominal aortic involvement is another important cause of hypertension (Type III aortoarteritis). Mechanism of hypertension in these patients is secondary to renal hypoperfusion and/or aortic stiffness. Balloon angioplasty has been effectively used to treat hypertension and maintain perfusion distally. Panja et al. performed balloon angioplasty in thoracic and abdominal aorta (52 patients), with stenting in 12 patients. On follow-up of 1–5 years, restenosis was noted in three thoracic aortic lesions and six abdominal aortic lesions. Restenosis was noted in one stented case. Balloon angioplasty should not be attempted in patients with calcific aorta.

BAROREFLEX ACTIVATION THERAPY

The role of the carotid baroreceptors (nerve endings located in the aortic arch and carotid sinuses) in the regulation of long-term BP control is well documented. Activation of the baroreceptors by pressure/stretching leads to buffer-like compensatory adjustments in the parasympathetic and sympathetic nervous system. Electrical
baroreceptor stimulation has been shown to decrease BP by attenuation of sympathetic activity and increase in parasympathetic activity.\textsuperscript{44,45} The Rheos Baroreflex Activation Therapy System (CVRx) consists of a programmable pacemaker-like pulse generator implanted in the right infraclavicular space and connected to bilateral electrode leads that encompass the perivascular space of the carotid sinuses (Figure 6).

The Rheos system was initially tested in a small series of 10 patients in a multicenter phase 2 Rheos feasibility trial which included patients with resistant hypertension. Results showed that the implantation of the device was safe and produced a significant decrease in BP.\textsuperscript{46} A favorable safety profile was reported.

More recently, the results of the US Rheos pivotal trial\textsuperscript{47} were reported. This was a double-blind randomized clinical trial evaluating baroreflex activation therapy and safety and device efficacy. This responder group experienced an average systolic BP (SBP) decrease of 44 mm Hg, with 63% of these subjects reaching 140 mm Hg. The US Rheos pivotal trial did show some promise for baroreflex activation therapy in achieving sustained BP reductions.

In addition to BP reduction in patients with resistant hypertension, the Rheos system has been shown to have potentially desirable effects on cardiac structure and function, including reduction of left ventricular mass index, left atrial dimensions and mitral A-wave velocity. Normalization of these key cardiac parameters suggests improvement of diastolic filling pressures, thus potentially improving diastolic dysfunction that is often seen in patients with chronic uncontrolled hypertension. The Rheos system has therefore stimulated further research into the applicability of baroreflex activation therapy for resistant hypertension.

REFERENCES
Section 3


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