Percutaneous & Device Treatment of Resistant Hypertension.

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Hypertension remains a major public health problem and is the leading cause of mortality worldwide.

The prevalence among adults was estimated to be 26% in 2000 and is projected to reach 29% by 2025, representing more than 1.56 billion patients globally.

Hypertension is the most common treatable risk factor for cardiovascular and renal morbidity and mortality.

However, overall hypertension control rate is still unsatisfactory and is approximately only 53% in the US.

In 2007, hypertension was the highest ranked cause of death in the US, being responsible for 17.4% of total mortality.
**RESISTANT HYPERTENSION** (RHTN) has been defined as high blood pressure requiring more than 3 medications for treatment, ideally, one of which is a diuretic.

- RHTN continues to significantly contribute to the overall population’s cardiovascular morbidity and mortality.
- The prevalence of RHTN is reported to range between 8 and 18%.
- There are many aetiologies to RHTN, and the role of non-adherence to medications should be considered.

**REFRACTORY HYPERTENSION**

*Definition:* failure to controlled blood pressure with five or more antihypertensive agents, including specifically, use of a long-acting thiazide diuretic such as chlorthalidone and a mineralocorticoid receptor antagonist (MRA), such as spironolactone.
As the percentage of medical treatment failure of hypertension continue to increase so searching for new non pharmacological therapies start to take place.

1-Renal Denervation

Mechanism of Action

- Renal denervation (RDN) has accumulated the largest body of evidence thus far.
- Current endovascular catheter systems typically access the renal arteries via the femoral artery and deliver radiofrequency or ultrasound energy resulting in focal frictional heating of the arterial wall.
- Other devices use neurotoxic agents such as alcohol or guanethidine. This causes the destruction of the peri-arterial adventitial afferent and efferent renal nerves.
The loss of sympathetic efferent nerve signaling may lead to decreased renin secretion by the juxtaglomerular apparatus, renal vasodilatation and sodium excretion.

Furthermore, removal of renal afferent nerve activity could also reduce sympathetic outflow from the central nervous system.
Sympathetic Renal Nerve Anatomy
Anatomic Target for Renal Denervation

- Renal nerves follow the renal artery to the kidney; only location that renal efferent and afferent nerves travel together
- Catheter-based delivery of low-power RF energy administered at multiple sites, facilitates denervation
- Bilateral denervation is the current standard of care

Radiofrequency Catheter Positioning in the Renal Artery
Current Evidence

- The first proof-of-concept open-label study, SYMPLICITY HTN-1, demonstrated that unipolar RF RDN was associated with a mean reduction in office BP of 22/10 mmHg.
- Subsequently, SYMPLICITY HTN-2 was a randomized open-labelled study, with the control group maintained on previous medical therapy for the first 6 months before being offered delayed RDN.
- There was a marked difference between the two groups at 6 months, with better office BP control by 33/11 mmHg in favor of RDN. However, the fall in ambulatory BP levels was less impressive (11/7 mmHg) with the caveat that these measurements were available in only half the patients.

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In early 2014, the first randomized sham controlled trial of RDN, SYMPLICITY HTN-3, reported results that were less promising than the open-labelled trials.

At 6 months, those who received RDN showed a reduction in office BP of 14/7 mmHg, which was comparable to the 12/5 mmHg drop in the sham (renal angiography only) group. There was also a lack of difference between the groups for ambulatory BP recordings.

Clinical indications for percutaneous trans-luminal angioplasty with stenting for renal artery stenosis are controversial.

Recent clinical findings from large prospective randomized controlled trials revealed little or no benefit for BP control, preservation of kidney function, or prevention of cardiovascular or renal events, calling into question broad use of renal artery stenting in hypertensive patients with renal artery stenosis.
Hemodynamically significant renal artery stenosis accompanied by one or more of the following features:

- Uncontrolled hypertension
- Ischemic nephropathy
- Cardiac disturbance syndrome (e.g. 'flash' pulmonary edema, uncontrolled heart failure, or uncontrolled angina pectoris)

3-Baroreflex Activation Therapy

**Mechanism of Action**

- Baroreflex activation therapy (BAT) is predicated upon the role of arterial baroreceptors in detecting carotid sinus and aortic arch distension in response to rises in arterial BP during systole, which then reflexively sends afferent nerve impulses into the nucleus tractus solitarius in the central nervous system.

- This in turn decreases the efferent sympathetic nervous system discharge to the heart, peripheral vasculature and kidneys, resulting in negative inotropy, vasodilatation and reduced renin secretion, respectively.

- This also results in increased parasympathetic outflow with associated reduction in heart rate.
Figure IX-6 The bifurcation of the common carotid artery demonstrating baroreceptors in the wall of the carotid sinus and chemoreceptors within the carotid body.

Baroreflex activation therapy

Baroreflex: Activation Leads

Implantable Pulse Generator
Current Evidence

- The first-generation Rheos™ device (requiring bilateral electrode placement) was initially evaluated in a feasibility study.

- In the non-randomised DEBuT-HT open-label trial with no comparator arm, implantation of the device in 45 patients with RHTN resulted in an average BP reduction of 21/12 mmHg at 3 months and 33/22 mmHg at 2 years.

4-Carotid Body Ablation

- **Mechanism of Action**

- Carotid bodies are peripheral chemoreceptors that regulate sympathetic tone and respiratory minute ventilation in response to stimuli such as hypoxia, hypercapnia, hypoglycaemia, and acidosis.

- The ablation of carotid body (CB) function has been proposed as a target for circulatory regulation as increased efferent signaling from CBs is associated with hypertension that is reversible when the signaling is down-regulated.
Figure IX-6 The bifurcation of the common carotid artery demonstrating baroreceptors in the wall of the carotid sinus and chemoreceptors within the carotid body.

NERVE CENTRE THAT CAN GO WRONG

CAROTID BODY is a sensor that detects changes to oxygen and carbon dioxide levels in the blood that flows through it. But sometimes it can become overactive and send the wrong signals to the brain.

Blood flow to brain

Information sent to brain

Actual size

It is one of the body’s smallest organs, but has the highest blood flow of them all.
Current Evidence

- In COPD patients undergoing bilateral CB resection, systolic BP was reduced by 40 mmHg at 6 months post-operatively in a hypertensive sub-group, despite no long-term improvement in ventilatory parameters.
- A recent proof of concept study of unilateral CB ablation as therapy for RHTN has demonstrated sustained office BP reduction of 23/12 mmHg at 6 months post-operatively in 8 out of 15 patients who had evidence of increased baseline CB activity.
- There were no serious adverse events reported, and hypoxic ventilatory drive was maintained.
5-Central Iliac Arterio-Venous Anastomosis

- **Mechanism of Action**

- In contrast to the above devices that aim to be sympatho-modulatory, a central iliac arterio-venous (AV) anastomosis intends to reduce effective arterial volume, systemic vascular resistance (SVR) and cardiac afterload, thus lowering BP. This is achieved by creating a 4-mm fixed calibre conduit between the proximal arterial and low resistance venous circulation, typically the external iliac artery and vein, using a nitinol stent-like device (ROXAVcoupler) placed under fluoroscopic guidance. This diverts a calibrated amount of arterial blood (0.8 to 1.0 L/min) into the proximal large capacitance venous circuit, which may be of particular benefit in patients with greatly reduced vascular compliance due to arterial stiffening. The opening of the anastomosis results in an immediate and significant reduction of SVR and BP.

- **The immediacy of the BP improvement suggests a negligible contribution from placebo effects.**
1. The stent is inserted via the upper thigh and creates a channel between artery and vein.

2. Stent keeps channel open to allow some blood to exit via the vein, thus reducing hypertension.
6-Deep Brain Stimulation

- **Mechanism of Action**
- The role of specific sub-structures within the brain in modulating autonomic activity for cardiovascular reflexes has previously been indicated in animal studies. The stimulation of the periaqueductal gray region of cats and rats has been shown to be linked to changes in blood pressure, heart rate and vasodilatation.
An initial description of benefit in refractory hypertension was based on targeted stimulation of the venterolateral periaqueductal grey/periventricular grey for analgesia in stroke associated hemibody central pain syndrome. The observed reduction in blood pressure of up to 33/13 mmHg appears to be independent of any analgesic effects, as it persisted even when pain levels returned to pre-surgical levels after several months.

The suggested mechanism may be via vasodilatation and reducing total peripheral resistance.

In a larger cohort of patients, utilizing DBS for chronic neuropathic pain or Parkinson’s disease resulted in improved vasomotor baroreflex sensitivity, decreased muscle sympathetic nerve activity and reduction in BP.

In common with other device therapies for hypertension, there also appears to be a range of BP responses to the therapy, where some could even be regarded as non-responders.
7-Vagal Nerve Stimulation

**Mechanism of Action**

- The parasympathetic nervous system has been largely neglected. The vagus nerve, together with the thoracic ganglia, is the principle source of parasympathetic innervation of the heart with resultant negative inotropic and chronotropic effects.
- Vagal nerve stimulation (VNS) in salt-sensitive rats attenuated salt-induced hypertension and arrhythmias as compared to rats that had sham surgery.
- VNS was able to reduce BP without inducing apnoea or bradycardia, which may be anticipated as a side effect of vagal stimulation.
Central Illustration: 2017 Updated Classification and Management of High Blood Pressure in Adults

Normal BP
Systolic BP (SBP) <120 mm Hg and
Diastolic BP (DBP) <80 mm Hg

Prehypertension
SBP 120-139 mm Hg or
DBP 80-89 mm Hg

Hypertension Stage 1
SBP 140-159 mm Hg or
DBP 90-99 mm Hg

Hypertension Stage 2
SBP ≥160 mm Hg or
DBP ≥100 mm Hg

Promote optimal lifestyle habits
Nonpharmacologic therapy

Management

Presence of ASCVD or 10-year CVD risk ≥10%?

BP-lowering drug therapy not needed
Add BP-lowering drug therapy

For all patients: Appropriate follow-up and ongoing care
Perform appropriate follow-up based on blood pressure classification and treatment strategy
Follow medication and lifestyle adherence strategies where necessary