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Hypertension: Biochemical Basis and Current Management Strategies

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ABSTRACT

Hypertension **(HTN)** or naturally uncontrolled high blood pressure is a worldwide chronic epidemic that contributes to 12% of all the deaths or about 13 million deaths annually. According to the American Heart Association, about a third of adult Americans (nearly 78 million) have HTN. According to the WHO, globally in 2008, there were a billion people with HTN. Blood pressure elevation is a major risk factor for heart attack, stroke, kidney disease and vascular dementia. Treating systolic blood pressure and diastolic blood pressure until they are less than 140/90 mmHg is associated with a reduction in cardiovascular and all other complications. Recent guidelines go to a preferable goal of less than 120/80. In most cases the underlying biochemical cause remains enigmatic due to the lack of conclusive diagnostic data on the likely causes. In this chapter we discuss the different potential causes of HTN, explore some of the mechanisms, and review some of the treatments that can be used to control HTN.

Keywords: HTN; Hypertension; Malignant HTN; Mechanisms; Managements; Treatment of HTN.

INTRODUCTION

Hypertension, also termed the "silent killer," is among the most common diseases in the United States and the leading risk factor for experiencing a myocardial infarction. Approximately 7.6 million deaths and 92 million disability adjusted life years worldwide were caused by hypertension in 2001 [1]. With this type of global killer on the loose and its occasional asymptomatic presentation it's important to identify the possible risk factors and maintain control over this disease.

WHAT IS HTN?

Hypertension is defined as a BP ≥ 140/90 at two or more recordings at two different outpatient office visits [1], a hypertensive crisis can present as either hypertensive urgency BP≥ 180/90 without organ damage as seen in Figure 1 of a case followed over months while being treated aggressively, or hypertensive emergency when a BP >180/120 with parallel end organ damage, for example, Stroke, MI, Kidney damage, loss of consciousness etc. [2].

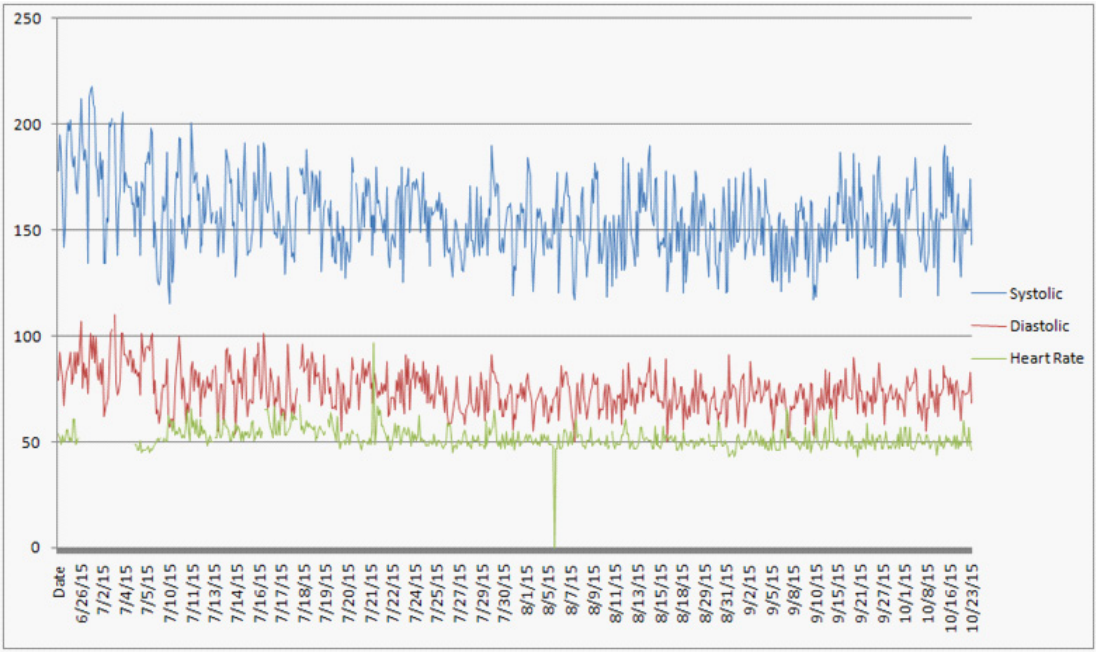

Figure 1:

Hypertension is divided into two groups, primary (or essential) hypertension which has no clear etiology and accounts for 95% of cases. The second group is called secondary (or known) causes of hypertension which accounts for the remaining 5% of cases.

RISK FACTORS

Hypertension has many risk factors, which include increasing age, obesity, poor diet, a lack of exercise, and gender. Women are about as likely as men to develop hypertension during their

lifetimes. However, in patients less than 45 years old hypertension is more common in men than women and then from age 65 years or older hypertension affects more women than men [3]. African Americans experience HTN at an earlier onset, generally more severe, with higher rates of morbidity and mortality compared to Caucasians [1]. Hypertension prevalence is 33.5% in Non-Hispanic African Americans, 28.9% in Non-Hispanic Caucasians, and 20.7% in Mexican Americans. In a study performed on prevalence of hypertension in the U.S., only one third of Mexican Americans with hypertension were being treated (35%), and only 14% achieved control in contrast to 25% and 24% of the non-Hispanic black and non-Hispanic white populations with hypertension, respectively [4].

Other risk factors associated with hypertension are family history and increased sodium intake. The recommended dietary guidelines limit sodium to less than 2,300 mg a day or 1,500 mg if you're age 51 or older, or African American, or if you have hypertension, diabetes or chronic kidney disease, so it is an avoidable cause with proper diet [5]. Smoking is another risk factor--it causes a sympathetic over-activity, which increases myocardial oxygen consumption through a rise in blood pressure, heart rate, and myocardial contractility [6]. Consuming excess alcohol, metabolic syndrome, and obesity (BMI >30 kg/m^2) are other risk factors, and there is especially a positive correlation between central abdominal obesity and increased blood pressure [1]. The different causes of HTN are summarized in Table 1.

Table 1: Causes of HTN.

Idiopathic (95%)	Renal Cell Carcinoma **(RCC)**
Increased Age	Wilms Tumor
Increased Sodium Intake	Pheochromocytoma
Family History	Cushings Syndrome
Smoking Status	Metabolic Syndrome
Alcohol Use	Obesity
Hyperaldosteronism	Renin Secreting Tumors
Renal Artery Stenosis **(RAS)**	Hemangiopericytomas
Chronic Kidney Disease **(CKD)**	Acromegaly
Glomerulonephritis	Hypothyroidism
Polycystic Kidney Disease **(PKD)**	Hyperparathyroidism
Obstructive Sleep Apnea **(OSA)**	Preeclampsia/Eclampsia
Coarctation of the Aorta **(CoA)**	Medications

KIDNEY CAUSES

Renal Artery Stenosis **(RAS)** is the most common and possibly curable cause of secondary hypertension [1]. In RAS there is a narrowing of the renal artery, the main blood supply to the kidney, which activates the Renin Angiotensin Aldosterone System **(RAAS)**, which causes sodium to be reabsorbed causing hypertension. It can be caused by two scenarios, the first is

the patient has atherosclerosis in the renal artery which blocks the blood flow, and the second is fibromuscular dysplasia, especially in young white women, which blocks the blood flow and puts the patient at risk [1].

Chronic kidney disease is when the kidney function progressively gets worse over time leading to the kidneys no longer being able to remove enough wastes and extra fluid from the body leading to hypertension [7]. It has many forms. Glomerulonephritis is a group of diseases that injure the part of the kidney that filters blood (called glomeruli). It is also called nephritis or nephrotic syndrome. Focal segmental glomerulosclerosis is scar tissue formation in the filtering unit of the kidney (glomerulus) resulting in decreased renal blood flow leading to hyper filtration, hypertrophy, and renal damage [1]. Polycystic kidney disease is an inherited autosomal dominant disease that consists of large cystic kidneys that lead to renal failure with hypertension [1]. Renin secreting tumors, benign hemangiopericytomas, renal carcinoma, and Wilms tumor are all additional renal causes of hypertension [1].

ADRENAL TUMORS

Hyperaldosteronism is also a potentially curable cause of hypertension independent of the RAAS system [1]. Aldosterone is made and secreted by the adrenal glands, which causes sodium reabsorption leading to hypertension without being stimulated by renin. 60-70% of patients have an aldosterone secreting adenoma usually unilateral and remainder of patients have bilateral adrenal hyperplasia [1]. Surgical removal of the adrenal gland is usually responsive to curing hypertension in patients with adenomas. There was a study conducted looking at laparoscopic adrenalectomy for aldosterone producing adenomas and results showed normalization or more readily manageable blood pressure in 90% of patients within the first six months [8]. In patients with bilateral adrenal hyperplasia, however, surgery is not as effective and these patients are usually treated medically [1].

Pheochromocytoma is an adrenal medulla tumor that secretes catecholamines resulting in episodic hypertension and flushing, 20% are autosomal dominant and associated with familial inherited disorders MEN 2A and 2B [1]. Cushing's syndrome is caused by excess cortisol due to either too much ACTH secretion (from pituitary sources or an ectopic tumor) or ACTH independent adrenal production of cortisol. It's thought that hypertension which occurs in 75-80% of these patients is due to the activation of mineralocorticoid receptors by cortisol which increases adrenal steroid release [1].

OBSTRUCTIVE SLEEP APNEA

Obstructive Sleep Apnea **(OSA)** also is a major risk factor for hypertension. Sleep apnea episodes cause a surge in systolic and diastolic pressures which keeps the mean blood pressure levels elevated at night [9]. Half of the patients with OSA have hypertension and the more severe the sleep apnea is, the more severe the hypertension is [1]. When using the CPAP (continuous positive airway pressure) machine it prevents the surge of arterial pressure [9].

COARCTATION OF THE AORTA

Coarctation of Aorta **(CoA)** is the most common congenital cardiovascular condition causing hypertension. It is caused by a narrowing of the major artery (the aorta) that carries blood to the body [10].The high blood pressure is seen in the upper extremities, with concurrent weak blood pressure in the lower extremities, the condition is commonly associated with Turners syndrome [1]. Even if the coarctation anatomy is corrected about 30 % of patients still develop hypertension [1].

PREECLAMPSIA/ECLAMPSIA

Hypertension can also be seen in association with pregnancy. If a pregnant patient has hypertension after 20 weeks of pregnancy as well as edema and proteinuria, it's considered preeclampsia. Preeclampsia can progress to eclampsia which involves seizures, and is very dangerous to the mother and unborn baby.

THYROID DISEASES

Hypothyroidism has been linked with diastolic hypertension due to increased peripheral vascular resistance and low cardiac output as the possible etiology. The hypothyroid population is characterized by significant volume changes, initiating a volume dependent, low plasma renin activity mechanism of blood pressure elevation [11].

ACROMEGALY

Acromegaly which is caused by prolonged secretion of growth hormone has the effect of making body tissues larger, especially the face, hands, and feet. Along with other body tissues, the heart becomes enlarged as well which impairs its function and can lead to hypertension [12]. These patients have an increased incidence of heart disease.

HYPERPARATHYROIDISM

A study conducted in 2011, suggest that parathyroid hypertension is mediated or maintained, at least in part, by functional alterations of vascular smooth muscle cells and can be cured by parathyroidectomy in those patients who do not have primary hypertension [13].

MEDICATIONS

Medications can be the culprit when there is no underlying medical cause. The most common medications include: OCPs/estrogen, therapeutic corticosteroids, decongestants, appetite suppressants, TCAs, NSAIDs, Cocaine or other stimulants.

HYPERTENSION STUDY

A recent study published by the New England Journal of Medicine shows that nondiabetic adults at high risk for cardiovascular events may benefit from lower systolic blood pressure targets

(<120 mm Hg vs. <140 mm Hg), according to the primary results of the Systolic Blood Pressure Intervention Trial **(SPRINT)**[14]. What we used to think was that just maintaining a BP of <140 systolic in hypertensive patients was enough to decrease morbidity and mortality, however the SPRINT research had a group of patients that was maintained at an average BP of 136.2 mmHg using the standard treatment and then a group of patients with an average BP of 121.4 mmHg using intensive treatment [15]. They interrupted the study early after a median follow up of 3.26 years because there was a significantly lower rate of fatal and nonfatal cardiovascular events and death in the intensive treatment group. There were incidences of myocardial infarction, acute coronary syndromes, stroke, and heart failure of 1.65% per year in the group with intense treatment ($P<0.001$). The intense treatment group also showed significantly lower mortality rate ($P=0.003$) compared to the standard treatment group, which had a 2.19% per year incidence of aforementioned cardiovascular events [15].

TARGETED PATHWAYS IN HTN

As discussed in the above sections, there are many factors which cause hypertension; therefore there are a number of different factors and pathways which can be targeted to control high blood pressure. The treatments summarized in Table 2 include lifestyle modification, mono- and multi- medication therapy and procedural interventions. There are essentially 2 reasons for hypertension; there is too much fluids in the pipes or the pipes are too narrow. Each treatment option will target one or both of these mechanisms. The following are the different type of modification and how they impact blood pressure.

Table 2: HTN Treatment.

Weight Reduction			**Calcium Channel Blocker**		
Dietary Approaches to Stop HTN (DASH)				Dihydropyridine	
Sodium Reduction					Amlodipine
Diuretics					Felodipine
	Thiazide				Isradipine
		Chlorthalidone			Lacidipine
		HCTZ			Lercanidipine
	Loop Diuretics				Nicardipine
		Furosemide			Nifedipine
		Bumetanide			Nisoldipine
		Torsemide		Non-Dihydropyridine	
		Ethacrynic Acid			Verapamil
	Potassium-Sparing Diuretics				Diltiazem
		Amiloride	**Alpha Blocker**		
		Triameterene		Doxazosin	
		Spironolactone		Prazosin	
		Eplerenone	**Vasodilators**		
	Acetazolamide			Hydralazine	
	Osmotically Active Agents			Clonidine	
		Mannitol	**Beta Blocker**		
RAAS Inhibitors				Atenolol	
	ACE-Inhibitors			Labatolol	
		Lisinopril		Esmolol	
		Enalapril		Acebutolol	
		Captopril		Bisoprolol	
		Fosinopril		Metoprolol	
	ARB			Nadolol	
		Candesartan		Propranolol	
		Eprosartan	**Procedural Treatment**		
		Irbesartan		Renal Artery Denervation	
		Losartan			
		Olmesartan			
		Telmisartan			
		Valsartan			

LIFESTYLE MODIFICATIONS

Diet

Weight reduction

There is a strong correlation between obesity and hypertension. Hypertension is nearly twice as prevalent in obese patients as opposed to non-obese [16]. One theory is because obese individuals have an increased amount of fatty tissue surrounding the vascular structures. This fatty tissue pushes against the vessels increasing the vascular resistance. This also increases the work of the heart to pump blood throughout the body. By decreasing the amount of fatty tissue it is decreasing the resistance of the vessels.

The best way to counteract this problem is by weight reduction. Several studies have examined the effects of weight loss versus pharmacological intervention and found that both methods provide improvement. In 25 randomized, controlled trials published between 1966 and 2002 with 4874 participants it was found that a decrease in weight of 5.1 kg resulted in a decrease in systolic blood pressure by 4.44 mmHg and decrease in diastolic pressure by 3.57 mmHg [17].

DASH (Dietary Approaches to Stop Hypertension)

Another relatively effective method of decreasing hypertension is a change in diet. The most effective diet is the Dietary Approaches to Stop Hypertension **(DASH)** [16]. This diet consists of eating foods that are low in saturated fats, total fats, dairy, and cholesterol, and high in fruits and vegetables. The diet emphasizes eating whole grains, poultry, fish, and nuts and avoids fats, red meats, sweets and sugary beverages. The diet is also rich in potassium, calcium, magnesium, protein and fiber.

Dietary sodium reduction

Sodium is an essential nutrient in our diet which serves a number of functions. It is necessary for the maintenance of plasma volume, acid base balance, transmission of nerve impulses and normal cell function [18]. The average intake necessary to maintain physiological function is 200-500mg per day, but the average sodium intake in developed countries is much greater than 2g per day. The excess sodium intake contributes to a number of medical conditions.

Among the many factors contributing to hypertension, one is salt sensitivity. African Americans, older age, and female gender are all factors that influence the degree of salt sensitivity. Being salt sensitive means that there is impaired renal capacity to excrete sodium [19]. The high sodium diet is disruptive to the natural balance in the body. It can cause fluid retention increasing pressure within the vessels, which can ultimately cause morbidity and mortality [20].

There are 2 mechanisms for the impaired renal excretion of sodium [19]. The first is over-activation of the mineralocorticoid receptor. This happens when a person has a mutation which allows Rac1 to be activated by an excess of sodium. Rac1 then activates the MR. When MR is

activated it facilitates the distal sodium reabsorption through epithelial sodium channel activation. The over activation leads to hypertension; this is referred to as salt sensitivity hypertension. The second type is due to a reno-specific sympathoactivation which is activated under conditions of excess sodium. If the beta 2 adrenoceptor cells in the kidney are activated, they are supposed to decrease the transcription of the gene WNK4, which causes a down regulation of sodium reabsorption in the distal convoluting tubules. A dysfunction in this system would allow sodium to continue to be reabsorbed, leading to increased blood pressure. These two pathways could be potentially targeted.

One strategy for targeting the salt sensitive population is to limit the sodium intake. The recommended dietary guidelines suggest limiting sodium to less than 2300mg per day or less than 1500mg with age greater than 50, African Americans or with contributory comorbidities [5]. In meta-analyses of randomized trials of sodium restriction of subjects with hypertension predicted BP decreased of 3-6 mmHg systolic and 1-3mmHg diastolic for a decrease of 100 mmol (2.30 gm) in sodium intake, but this decrease in consumption is difficult to achieve [22]. Another landmark study is the Inter Salt study which is a meta-analysis focusing on salt and blood pressure in 28 randomized trials [20]. The study was able to find a strong positive relationship between salt intake, blood pressure and age. The results of the study showed that an increase in 6g of salt per day over 30 years would lead to an increase in systolic blood pressure by 9 mmHg. It also showed that there was a dose response relationship between a reduction of salt intake and a decrease in blood pressure. Reduction of salt by 6 g per day lowered blood pressure by 7 mmHg systolic and 4 mmHg diastolic in individuals with documented hypertension and 4 mmHg systolic and 2 mmHg diastolic in normotensive individuals.

MEDICATION INTERVENTIONS

Diuretics

Diuretics work by increasing the excretion of excess fluids. They are often referred to as "water pills" because their action is on the kidney causing increased urine production [21]. The general reduction of blood volume leads to a reduction in overall blood pressure.

Thiazide: chlorthalidone, HCTZ

Thiazide type diuretics take action on the distal tubule to the early cortical collecting tubule. These areas are responsible for a small portion of the reabsorption of sodium and water. The most effective of these is chlorthalidone, but HCTZ is the most commonly prescribed and used in combination pills. They act by primarily inhibiting the sodium transport in the distal tubule [23]. This class of medication has a small natriuretic effect which inhibits the reabsorption of 3-5% of the filtered sodium, which can cause a moderate decrease in blood pressure.

Loop Diuretics: furosemide, bumetanide, torsemide, and ethacrynic acid

Loop diuretics are a powerful class of diuretic medications. They are on the medullary and cortical aspects of the thick ascending limp of the loop of Henle [23]. In this part of the nephron, the sodium entry is mediated by the Na-K-2Cl carriers in the luminal membrane. Loop diuretics activate this site by competing for the chloride site leading to diminished net sodium reabsorption. The use of loop diuretics causes an excretion of up to 25% of all filtered sodium [23].

Potassium-sparing diuretics: amiloride, triamterene, spironolactone, and eplerenone

Potassium sparing diuretics mechanism of action is on the cortical collecting tubules through aldosterone sensitive sodium channels [23]. They have a relatively weak natriuretic activity with excretion of 1-2% filtered sodium. While diuretics are a highly effective way of controlling hypertension, they can lead to loss of essential minerals, such as potassium. This happens because sodium reabsorption of cations leaves a negative electrical gradient within the lumen. This causes secretion of potassium and hydrogen ions. Inhibition of the sodium reabsorption can cause a hyperkalemia and metabolic acidosis due to the reduction of potassium and hydrogen excretion so ion levels should be closely monitored. If hypokalemia is an issue, the potassium sparing diuretics can be a good choice.

Acetazolamide

This drug is a diuresis promoting agent. It inhibits the activity of carbonic anhydrase which causes a net loss of sodium chloride and NaHCO3 [23]. Due to the net loss of bicarbonate through the urine, the metabolic acidosis leads to a progressively attenuated effect of the drug, therefore it is not recommended for chronic use.

Osmotically Active Agents: mannitol

Osmotically active agents act by inhibiting the reabsorption of water in the proximate tubule in order to promote diuresis. Mannitol is a non-reabsorbable sugar alcohol that acts as an osmotic agent to hold water within the lumen of the nephron and prevent reabsorption within the proximal tubule and the loop of Henle. This leads to a relative water diuresis because water is lost in excess to that of sodium or potassium [23].

RAAS Inhibitors

The Renin-angiotensin-aldosterone-system, or RAAS, is a physiologic hormonal system which has much control and regulation of the fluctuations in blood pressure [24]. Renin is released by the juxtaglomerular apparatus which causes the production of angiotensin. The angiotensin then stimulates the adrenal gland to produce aldosterone. Aldosterone stimulates the reabsorption of water and conservation of sodium leading to an elevation in blood pressure. RAAS is activated by a decrease in blood pressure which disrupts the salt-water balance, but sometimes there are disruptions in this system which can result in a persistent hypertensive state.

ACE-Inhibitors: Lisinopril, enalapril, captopril, fosinopril, perindopril, ramipril and quinapril

In the RAAS system there are many enzymes involved. In order for angiotensin to act on the adrenal gland it must be converted from angiotensin I to angiotensin II by the angiotensin converting enzyme, or ACE [21]. Angiotensin II also acts on the blood vessels to cause vasoconstriction. By inhibiting ACE, the RAAS is inhibited as well. The ACE-Inhibitor class of drugs is a competitive inhibitor of ACE which prevents the formation of angiotensin II in the kidneys, blood vessels, heart, brain and adrenal gland [24]. This leads to an increase in sodium and urine excretion which decreases the volume within the vessels as well as decreasing the resistance in the vessels.

ARB: candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan

Another method of blocking the RAAS is by use of an angiotensin receptor blocker, or ARB. ARBs are a complete angiotensin II inhibitor which interacts selectively with the receptor sites [25]. It is a competitive antagonism. This works because ARBs displace the angiotensin II from the angiotensin I receptor. They diminish the angiotensin 1 activity without changing the angiotensin 2 receptor-mediated effects [26]. The ARB shields the blood vessel from the angiotensin II which results in a general vasodilation [21]. It also blocks the release of aldosterone and catecholamine's and decreases water reabsorption. The blood pressure lowering mechanism of action of ARBs is secondary to vasodilation [27]

Ca Channel Blocker

Calcium channel blockers, or CCBs, are a class of drugs which prevent calcium from entering the muscle cells of the heart and blood vessels. Without the calcium entry, the blood vessels will relax causing the blood pressure to decrease [21]. The CCBs also act by decreasing the heart rate, decreasing the myocardial force and decreasing the conduction velocity within the heart, particularly at the AV node [28]. The advantage of using CCBs over other drugs which lower vascular resistance is that CCBs do not cause any clinically relevant sympathetic reflex activation [29]. There are 2 main classes of CCBs.

Dihydropyridine: amlodipine, felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nisoldipine

Dihydropyridines have pronounced peripheral vasodilator properties [30]. They work primarily by reducing systemic vascular resistance and reducing arterial pressure.

Nondihydropyridine: verapamil, diltiazem

There are two nondihydropyridine drugs, verapamil and diltiazem. Each has a unique mechanism of action. Verapamil belongs to the phenylalkylamine class of calcium channel blockers, and is a systemic vasodilator which is selective for the myocardium [28]. Diltiazem is

in the benzothiazepine class and is an intermediate between verapamil and dihydropyridines. It is selective for the vascular calcium channels and acts as a cardiac depressant and a vasodilator.

Alpha Blocker- Doxazosin, Prazosin

Alpha blockers are a drug class which work by reducing the nerve impulses to the blood vessels. This allows the vessels to dilate and blood to pass more easily [21].

Vasodilators- Hydralazine, Clonidine

Vasodilators act on the smooth muscle to induce relaxation. The action is primarily in the arteries and arterioles. Mechanism of action is unknown, but it is only active *in vivo* when the endothelium is able to provide nitric oxide [29]. Hydralazine is not a first line treatment except in pregnancy.

Clonidine is another vasodilator. It is a combined alpha 2 adrenergic agonist and imidazoline receptor agonist. The drug stimulated the alpha 2 receptors in the brain which leads to a decrease in peripheral vascular resistance and decreasing blood pressure. The other proposed method of decreasing blood pressure with clonidine is through the I1 receptor. This mediated the sympatho-inhibitory actions of imidazolines to lower blood pressure [29].

Beta Blocker- Atenolol, Labetalol, Esmolol, Acebutolol, Atenolol, Bisoprolol, Metoprolol, Nadolol, Propranolol

Beta Blockers have different effects on the different target organs. In the heart, the BBs work by reducing the nerve impulses to the heart and blood vessels [21]. It causes a decrease in the heart rate as well as decreases the force in which the heart contracts. This combination causes a drop in blood pressure and decreases the work load of the heart muscles. In the kidney, the BBs cause a block of the beta 1 receptors decreasing the release of renin from the juxtaglomerular cells and decreasing the action of RAAS [31]. Classically it is thought that the effects of BB in reducing hypertension was due to the cardiac action, but long term use appears greater in individuals with high renin suggestion that the renal action plays a greater role.

PROCEDURES

Renal Artery Denervation

In some instances, hypertension can be resistant and not respond to multi drug treatment regiments. When this happens, one procedure that can be used is the renal artery denervation. In the kidney there are 2 networks [32]. The efferent network supplies the kidney with noradrenergic sympathetic fibers. The efferent vessels raise blood pressure by promoting salt and water retention. The second system is the afferent network which returns signals from the central nervous system. Nerve fibers from both systems are located within the adventitia of the renal arteries. This location makes them potential targets for modification.

The renal artery denervation is done by therapeutic catheterization and ablation. A catheter is thread through the femoral artery into the renal artery and a circumferential radiofrequency ablation is performed [32].

The simplicity HTN2 study is a multicenter randomized trial which compared a treatment group of individuals undergoing renal artery denervation vs a control group with medication only [33]. The trial looked at the 6 month post procedure results. At 6 months it was found that the renal artery denervation group had a significant decrease in systolic blood pressure. The average systolic BP before was 190.0±19.6 mmHg and average systolic blood pressure after the procedure was 166.3±24.7 mmHg. At 12 months after the procedure the patients' blood pressures were still significantly reduced and under good control. The conclusion of the study was that renal artery denervation procedure provided a safe and sustainable way to treat resistant hypertension.

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