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AIMS & SCOPE

Hypertension Journal is a peer-reviewed journal which highlights epidemiology, health implications and cardiovascular risk from hypertension in India/South-Asia. Hypertension is much more common than diabetes. It is vastly under diagnosed and poorly treated in India/South-Asia. There are excellent therapeutic options to treat hypertension, but the available resources are not fully utilized by doctors therefore neglecting this disorder. The journal will hereby promote the significance of hypertension and the urgent need to bring it under control. The medical community should be educated on hypertension evaluation, diagnosis, workup and management simultaneously bringing up the literature, research, guidelines and scientific advances related to hypertension and its disorders. We are hereby starting a high-quality journal dedicated solely to hypertension and thus promoting the awareness, evaluation and effective management in India/South-Asia. Dr C Venkata S Ram is a world authority on hypertension with lifelong work (research, clinical and publications).
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Special issue on Hypertension

Introduction

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Hypertension (HTN) is the most common risk factor for cardiovascular, cerebrovascular, and chronic kidney disease (CKD) affecting nearly two-thirds of adults aged 60 years or older. It is estimated that uncontrolled HTN is responsible for 7.5 million deaths/year worldwide and accounts for over 47 billion dollars spent for health care in the United States. Despite various advances in the field, it is projected that 1.56 billion people will suffer from HTN by 2025. Various randomized controlled trials have demonstrated that even 10 mmHg blood pressure reduction lowers the risk of death due to cardiovascular disease by 25% and of stroke by 40%. Hence, the pressing need for better understanding and for novel therapies in the treatment of HTN.

A clearer understanding of the pathogenesis of HTN will probably lead to more highly targeted therapies and to a greater reduction in HTN-related cardiovascular morbidity. >90% of cases of the HTN do not have a clear cause. HTN clusters in families and results from a complex interaction between genetic and environmental factors. The HTN-related genes have been identified that regulate renal salt and water handling. Major pathophysiologic mechanisms of HTN identified include activation of the sympathetic nervous system, maladaptive renin–angiotensin–aldosterone system, endothelial dysfunction, increased vascular reactivity, and vascular remodeling.

HTN in women, particularly in the reproductive age group and during pregnancy, is one of the leading causes of maternal morbidity and mortality worldwide. Preeclampsia is a pregnancy complication characterized by the onset of high blood pressure and significant proteinuria. Due to multiple factors and complex pathophysiology, a definitive treatment for preeclampsia remains elusive. A close relationship also exists between preeclampsia and chronic HTN.

Over the past several decades, childhood HTN has undergone a considerable conceptual change, as HTN is a predictor of future development of cardiovascular disease in adults. Childhood HTN has distinctive features that distinguish it from HTN in adults. Pediatric HTN is often secondary. It is widely believed that therapeutic intervention at an early age favorably modifies the long-term outcome of HTN. Despite its significance as a cause for morbidity, childhood HTN is often underdiagnosed and less studied with many basic issues still remaining contentious.

Arterial HTN is age dependent, and increased life expectancy affects more and more elderly people. Approximately 80% of the elderly have HTN mainly isolated systolic HTN. During the past few years, the general medical opinion was to have higher blood pressure targets in elderly to avoid possible ischemic events. This strong belief raised the question of whether or not aged people should receive pharmacological treatment similarly to other younger patients. This journal edition aims to answer these questions, particularly focusing the discussion on whether the paradigm "the lower, the better" maintains a prognostic role in elderly and very old hypertensives.

HTN is commonly associated with cardiac arrhythmias in patients with and without concomitant cardiovascular disease. Experimental and epidemiological studies have demonstrated potential links between HTN and atrial and ventricular arrhythmias. Nonetheless, the importance of HTN as a cause of atrial and ventricular arrhythmias is not well recognized. Prospective clinical trials reveal that antihypertensive therapy may delay or prevent the occurrence of cardiac arrhythmias and sudden cardiac death.

HTN is a major risk factor for the development of ischemic white matter lesions in the brain which are associated cognitive dysfunction. Numerous studies have demonstrated that HTN increases the risk for cognitive impairment, vascular dementia, and Alzheimer's disease. Compared to non-hypertensives, white matter lesions were 2.3 times higher in patients with HTN and 3.4 times higher in patients with uncontrolled HTN.

The prevalence of HTN is higher among patients with CKD, progressively increasing with the severity of CKD. It is estimated that HTN occurs in 23.3% of individuals without CKD but is seen in 35.8% of Stage 1, 48.1% of Stage 2, 59.9% of Stage 3, and 84.1% of Stage 4–5 CKD patients. HTN is

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also extremely common among patients on hemodialysis or peritoneal dialysis. Unlike in patients on peritoneal dialysis, removal fluid in patients on intermittent hemodialysis is episodic, leading to large differences between pre-, post- and inter-dialytic blood pressure. This variation in blood pressure impedes a clear definition of HTN and targets blood pressure in hemodialysis patients. Nearly 85% of hemodialysis patients have HTN, of which only 30% had adequate control. Similar prevalence of HTN was reported in peritoneal dialysis patients. Intense controversy surrounds the benefit of blood pressure control in dialysis patients. Analyses of registry data show a U-shaped relationship between blood pressure and mortality. While the exact pathophysiologic basis for this discrepancy is unclear, it has been suggested that high mortality in dialysis patients with lower blood pressure is due to coexisting severe cardiac disease. Over 70% of renal transplant recipients have HTN. Observational studies suggest that post-transplant HTN is an independent risk factor for graft failure and death, and adequate blood pressure control reduces this risk.

The prevalence of resistant HTN varies from 8% to 18%. Increased sympathetic nervous system activity has been identified as one potential cause for resistant HTN. Catheter-based renal denervation (RDN) has been studied for the treatment of resistant HTN. Clinical data for the usefulness of RDN until date show mixed results, and overall, indications for procedure are unclear. Various observational studies and randomized controlled trials support both safety and efficacy of procedure, while some trials failed to show the superiority of RDN compared to medical therapy. The present review aims to give an overview of RDN therapy in the treatment of HTN and current status of this procedure.

This special issue of the journal aims to address all the above-mentioned challenges pertaining to HTN, namely diagnosis, pathophysiology, age- and gender-specific issues, cardiovascular and cerebrovascular, renal morbidity and mortality, treatment guidelines, and clinical outcomes. A better understanding would go a long way in achieving better blood pressure control, thereby leading to better clinical outcomes.

Review Article

New Guidelines for the Treatment of Hypertension: Re-emergence of Chlorthalidone in the Treatment of Hypertension

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Abstract

Hypertension is the most common modifiable risk factor for cardiovascular diseases, stroke, and renal dysfunction. Its treatment is the main focus of primary and secondary disease prevention strategies. The guidelines for the treatment of hypertension continues to evolve over the past few decades for early detection, risk stratification, and better control to improve clinical outcomes. This article highlights the newer guidelines for the treatment of hypertension and the role of diuretics.

Key words: Cardiovascular diseases, hypertension, renal dysfunction, stroke

Introduction

Hypertension is the major risk factor for cardiovascular deaths and stroke. It accounts for an estimated 57% of all strokes and 24% of all ischemic heart disease events in India.[1] Hypertension prevalence in India accounts for 33% of urban and 25% of rural population.[2] In spite of this awareness, treatment and adequate control of hypertension is far from complete. The first comprehensive guideline for detection, evaluation, and management of high blood pressure (BP) was published in 1977, under the sponsorship of the National Heart, Lung, and Blood Institute.[3] In subsequent years, a series of Joint National Committee (JNC) BP guidelines were published to assist the clinicians to improve prevention, awareness, treatment, and control of high BP.[4] To address the existing controversies and to account for the evidence from the new randomized controlled trials on hypertension, the American College of Cardiology (ACC)/American Heart Association (AHA) and the European Society of Cardiology/European Society of Hypertension (ESC/ESH) have come up with new guidelines for hypertension.[5,6] The newer guidelines emphasized on the accuracy as well as out-of-office BP measurement, classification of BP, new approach to decision-making for treatment that incorporates underlying cardiovascular risk, lower targets for BP, and strategies to improve BP control during treatment with an emphasis on lifestyle approaches.

Classification

In a meta-analysis of 61 prospective studies, the risk of cardiovascular diseases (CVD) increased in a log-linear fashion from systolic blood pressure (SBP) levels <115 mmHg to >180 mmHg and from diastolic blood pressure (DBP) levels <75 mmHg to >105 mmHg.[7] In that analysis, 20 mmHg higher SBP and 10 mmHg higher DBP were each associated with a doubling in the risk of death from stroke, heart disease, or other vascular diseases. Although the relative risk of incident CVD associated with higher SBP and DBP is smaller at older ages, the corresponding high BP-related increase in absolute risk is larger in older persons (>65 years) given the higher absolute risk of CVD at an older age.

Although a continuous association exists between higher BP and increased CVD risk, it is useful to classify BP levels for clinical and public health for decision-making. In 2017, the ACC/AHA classified on the basis of average office BP into

four categories - normal, elevated BP, and hypertension Stage 1 and Stage 2. The BP readings used for classification should be an average of two or more readings on two or more different occasions instead of relying on a single value. This classification differs from that previously recommended in the JNC 7 report[4] [Table 1], with Stage 1 hypertension now defined as an SBP of 130–139 or a DBP of 80–89 mmHg, and with Stage 2 hypertension corresponding to Stages 1 and 2 in the JNC 7 report. The ESC/ESH 2018 guidelines have not changed previous classification of optimal, normal, high-normal, and hypertension Grade 1, 2, and 3.

The rationale for the new classification of BP is provided by meta-analysis studies showing hazard ratios for coronary heart disease and stroke were between 1.1 and 1.5 for the comparison of the SBP/DBP of 120–129/80–84 mmHg versus <120/80 mmHg and between 1.5 and 2.0 for the comparison of the SBP/DBP of 130–139/85–89 mmHg versus <120/80 mmHg. This risk gradient was consistent across subgroups defined by sex and race/ethnicity. The relative increase in CVD risk associated with higher BP was attenuated but still present among older adults.[7]

The new classification of BP results in a substantial increase in the prevalence of hypertension, but a small increase in the percentage of adults needing antihypertensive medication. The rationale behind this is only the patients with BP of 130–139/80–89 mmHg with atherosclerotic CVD (ASCVD) risk of >10% would be offered treatment, and the remainder should be given advice on lifestyle modification.

Out-Of-Office BP Measurement

The newer guidelines emphasize on the use of either form of out-of-office BP measurement - home BP monitoring (HBPM) or ambulatory BP monitoring (ABPM) for both diagnosis and management of hypertension. Although ABPM is accepted as a better form of out-of-office measurement, HBPM is a more practical form of measurement. Both the methods help in diagnosing and managing "white coat hypertension" and "masked hypertension." The corresponding SBP/DBP values for clinic, HBPM, daytime, nighttime, and 24-h ABPM measurements are shown in Figure 1.

Table 1: Classification of BP by JNC7 and 2017 ACC/AHA hypertension guidelines

SBP and DBP (mmHg)	JNC7	2017 ACC/AHA
<120 and <80	Normal BP	Normal BP
120–129 and <80	Prehypertension	Elevated BP
130–139 or 80–89	Prehypertension	Stage 1 hypertension
140–159 or 90–99	Stage 1 hypertension	Stage 2 hypertension
>160 or >100	Stage 2 hypertension	Stage 2 hypertension

BP: Blood pressure, JNC: Joint National Committee, ACC: American College of Cardiology, AHA: American Heart Association, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Evaluation of Hypertension

The newer guidelines emphasize on the evaluation of hypertensive individuals for the risk factors and the evidence for the end-organ damage. The risk factors to be considered are smoking, diabetes, dyslipidemia, sedentary lifestyle, abnormal diet, alcohol intake, obesity, sleep apnea, and stress. Although secondary hypertension accounts for around 10% of hypertensive individuals, multiple clinical scenarios given in Table 2 should alert the physician to search for them. Screening includes testing for common causes such as renal diseases, renovascular disease, primary aldosteronism, obstructive sleep apnea, and drug- and alcohol-induced hypertension. Testing for less common causes such as pheochromocytoma, Cushing's syndrome, congenital adrenal hyperplasia, hypothyroidism, hyperthyroidism, and aortic coarctation to be considered based on clinical indications.

When to Initiate Treatment

The treatment of high BP involves non-pharmacological, pharmacological, and recently device therapies. The non-pharmacological therapy is indicated in all categories of hypertension. The newer guidelines recommend the use of estimating 10-year ASCVD risk of >10% for decision-making in initiation of pharmacotherapy. The limitation of ACC/AHA CVD risk assessment equation is that it is not applicable for very elderly (>79 years) and it overestimates risk in Asians. The Joint British Society 3 risk score or the World Health Organization-International Society of Hypertension modified risk scores for Southeast Asian region are suited better for Indian population and may be used instead for our patients.[8]

The use of pharmacological therapy is recommended for:
- Stage 1 hypertension (SBP ≥130 mmHg or DBP ≥80 mmHg) and an estimated 10-year ASCVD risk of 10% or higher
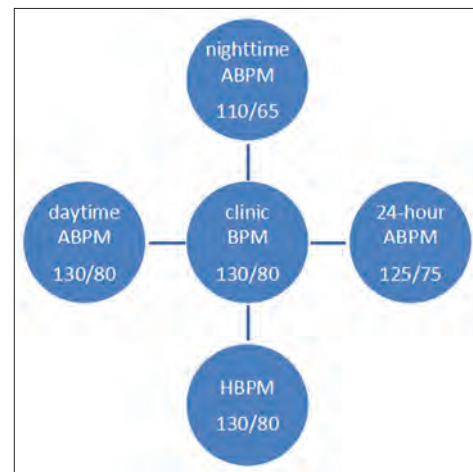

Figure 1: Corresponding systolic blood pressure (BP)/diastolic BP values for clinic, home BP monitoring, daytime, nighttime, and 24-h ambulatory BP monitoring measurements

Table 2: Indicators for secondary hypertension

Resistant hypertension

Sudden onset of hypertension

Hypertension onset <30 years of age

Onset of diastolic hypertension >65 years

Target organ damage disproportionate to severity of hypertension

Unprovoked or excessive hypokalemia

Accelerated/malignant hypertension

- Stage 1 hypertension (SBP ≥130 mmHg or DBP ≥80 mmHg) and clinical CVD
- Stage 2 hypertension (SBP ≥140 mmHg or DBP ≥90 mmHg).

Make 130 the New 140 Target Goal

Meta-analyses and systematic reviews of multiple trials comparing an aggressive versus standard BP goals have shown a consistent reduction in stroke, coronary events, and major adverse cardiovascular events.[9] The SPRINT trial showed significant reduction in composite cardiovascular deaths and mortality in the more intense BP control group compared to standard BP group.[10]

The guidelines recommend a BP goal of 130/80 mmHg in persons who are on treatment for hypertension. Treatment of hypertension with an SBP treatment goal of 130–139 mmHg is recommended for non-institutionalized ambulatory community-dwelling older adults (>65 years of age) if they tolerate well. For older adults (≥65 years of age) with hypertension and a high burden of comorbidity and limited life expectancy, the clinical judgment, patient preference, and a team-based approach to assess risk/benefit are reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs.

Non-Pharmacological Therapy

The non-pharmacological therapies have very important role in controlling BP and recommended in all stages of hypertension. These interventions help in 2–10 mmHg reduction of BP. The maximum benefit of BP reduction of 11 mmHg is seen with Dietary Approaches to Stop Hypertension (DASH) diet which includes diet rich in fruits, vegetables, whole grains, and low-fat dairy products with reduced content of saturated and total fat. The other interventions include tobacco cessation, weight reduction, low sodium intake of <1.5 g/day, increased potassium intake of 3.5–5 g/day, physical activity, and moderation of alcohol intake.

Pharmacological Therapies

The pharmacological therapies in addition to lifestyle modifications form the primary basis for achieving the target BP goal. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), calcium channel blockers (CCB), and diuretics are recommended as the first-line antihypertensive agents as they reduce CVD and strokes. Beta-blockers and alpha-blockers may not be the first-choice drugs as they were the only drug classes that were not significantly superior to any other drug, for any outcomes.[11]

The choice of agents depends on the comorbid factors in an individual. In adults with chronic kidney disease, ACE inhibitors/ARBs are preferred. In diabetes mellitus with hypertension, ACE inhibitors or ARBs are considered in the presence of albuminuria. Beta-blockers and/or CCBs might be considered to control hypertension in patients with coronary artery disease. The addition of spironolactone for the treatment of resistant hypertension is considered, unless contraindicated.

The combination of two renin–angiotensin system (RAS) blockers is not recommended due to increased risk of hyperkalemia, cardiovascular events, and reduction in renal function.[12] Similarly, the beta-blockers and thiazide diuretic combinations are not recommended due to metabolic adverse effects.

Reemergence of Chlorthalidone

Thiazide and thiazide-like diuretics have been the mainstay of therapy for primary hypertension since 1960. The BP reduction with diuretics occurs due to initial reduction in plasma volume and cardiac output. The fall in BP later is blunted by hypovolemia-induced RAS activation. Long-term maintenance of the decrease in BP is associated with partial reversal of the initial hemodynamic changes: The plasma volume and cardiac output partially rise toward the baseline level, while the systemic vascular resistance falls.

The initial use of high dose of thiazides to reduce BP resulted in metabolic complications such as hypokalemia, hyponatremia, dyslipidemia, and hyperuricemia, leading to increased incidence of sudden cardiac deaths.[13] Later, the thiazides and thiazide-like diuretics are typically used at low doses of 12.5–25 mg/day of chlorthalidone and hydrochlorothiazide or 1.25 mg/day of indapamide to minimize metabolic complications while maintaining the antihypertensive response. The low-dose chlorthalidone and indapamide are long acting and have shown significant reduction in BP as compared to hydrochlorothiazides with lesser metabolic disturbances. The reductions in cardiovascular events have been noted with chlorthalidone in ALLHAT trial.[14]

Due to the longer duration of action with significant reduction in BP and cardiovascular events with lesser metabolic disturbances, the chlorthalidone has emerged as low-dose diuretic of choice in the treatment of hypertension.

Strategies to Improve Hypertension Treatment and Control

Various strategies are planned to achieve sustained BP control below the target BP to reduce CVD and strokes. Initiation with a single antihypertensive drug is reasonable in adults with Stage
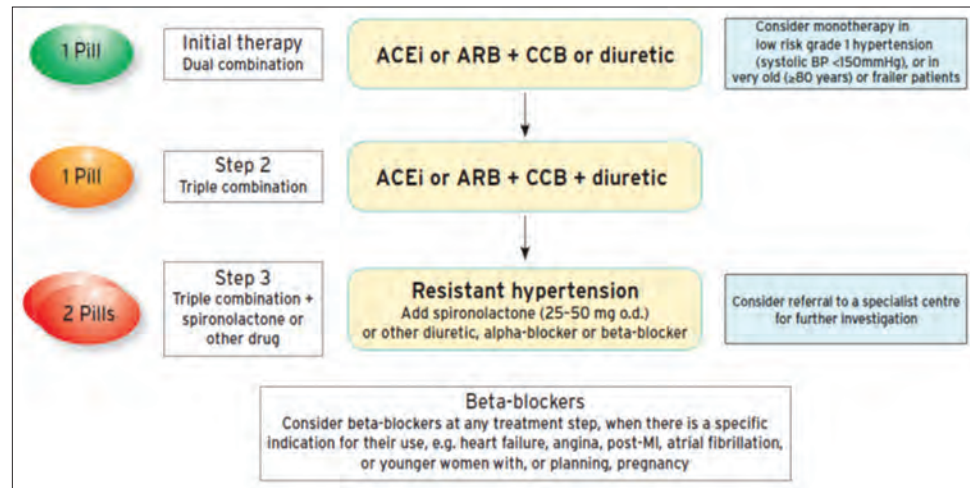
Figure 2: Treatment strategy for hypertension[6]

1 hypertension (130–139) and in frail very elderly persons in whom sequential addition of other agents is done to achieve the BP target. Initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a single pill combination (SPC), is recommended in adults with hypertension >140/90 mmHg and an average BP >20/10 mmHg above their BP target. The use of SPCs leads to reduction in pill burden, improve compliance, and better control of BP.[15] The preferred combinations are ACEI or ARBs with CCB or diuretics as shown in Figure 2.[6] HBPM, ABPM, team-based care, and telehealth strategies all should be used based on availability for better monitoring of BP control and patient compliance.

Device-Based Hypertension Treatment

Various device-based therapies for the treatment of resistant hypertension are under trial to understand the efficacy and safety. Carotid baroreceptor stimulation (pacemaker and stent), renal denervation, and creation of central iliac arteriovenous fistula are tried but are not recommended as there efficacy and safety need to be proved.

Conclusions

Hypertension is the major non-communicable risk factor for increased cardiovascular events. It needs to be detected early and treated adequately to reduce the cardiovascular morbidity and mortality. In this regard, the newer guidelines emphasize on accurate measurement of BP with liberal use of out-of-office BP monitoring methods. The target BP has been reduced to 130/80 mmHg in all hypertension individuals including in those with age >65 years if they tolerate well. The incorporation of CV risk assessment helps in better decision making in the treatment of hypertension. Lifestyle modification is emphasized in all stages of hypertension. The ACE inhibitors, ARBS, CCB, and diuretics are

considered as the first-line antihypertensives with chlorthalidone as the diuretic of choice. The use of SPCs is promoted for better control of BP and to improve the compliance. Overall, the newer guidelines emphasized on accuracy of BP measurement, lower BP targets, incorporation of cardiovascular risk assessment in deciding treatment, and strategies to improve BP control which help the clinicians for better management of hypertension.

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*R*eview *A*rticle

Endothelial Dysfunction and Hypertension

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Abstract

The endothelium the largest organ in the human body is no longer considered a dormant organ but is actively involved in the pathogenesis of hypertension. Its dysfunction brought about by various factors causes alteration in the vascular tone primarily and changes in the synthesis of various vasoactive substances which in turn contribute to the development of hypertension. Certain non pharmacological and pharmacological interventions aid in the improvement of the endothelial dysfunction.

Key words: Endothelial dysfunction, micro and macrovascular effects, vasoactive substances, hypertension

Introduction

Endothelium for long considered to be just an inert inner lining of the vessel wall and a mechanical barrier has now its role well established in vascular health and homeostasis. It is one of the largest organs of the body comprising of one trillion cells, weighing over 1 kg and three square meters in a 70 kg male.[1] It is intricately involved in the pathophysiology of hypertension.

This review focuses on the complex interplay between hypertension and endothelial dysfunction and their impact on outcomes in cardiovascular disease. Endothelial dysfunction has been defined as the alteration of the properties of the endothelium leading to impaired vasodilatation of blood vessels, creation of a proinflammatory and prothrombotic milieu, and in the long term, to the development of atherosclerosis.

Pathogenesis

The vascular endothelium that forms the inner lining of blood vessels consists of a single layer of flat cells having a central nucleus with overlapping edges that maintain the integrity of the vessel. The endothelium and its function are impaired in conditions that constitute the risk factors for atherosclerosis including smoking, hypertension, diabetes, dyslipidemia, and chronic kidney disease.[2] Adhesion molecules are expressed by the dysfunctional endothelium. The endothelium regulates vascular tone, its interactions with leukocytes and platelets, and cell growth. It synthesizes and secretes in paracrine manner growth factors and thromboregulatory and vasoregulatory molecules and responds to both physical and chemical signals.

The term "endothelial dysfunction" not only is generally used to denote the deterioration of endothelium-dependent vasodilatation but also implies abnormal regulation of interactions between the endothelium and leukocytes, thrombocytes, other regulatory molecules, and inflammation.[3]

The endothelium secretes both endothelium-derived relaxing factors (EDRFs) and endothelium-derived constricting factors (EDCFs) and, with their action on vascular smooth muscle cells, regulates vascular tone. One major EDRF is nitric oxide (NO), but others such as endothelium-derived hyperpolarizing factor and prostaglandins also contribute to endothelium-derived vasodilation. EDCFs include angiotensin II and endothelins. NO acts as a vasodilator, inhibits inflammation, and has an antiaggregatory effect on platelets. In cardiovascular disease states, increased levels of superoxide anion and reactive oxygen species reduce the bioavailability of NO, resulting in vasoconstriction and platelet aggregation.

The endothelium, thus, plays a critical role in the pathogenesis of cardiovascular diseases such as atherosclerosis, systemic and pulmonary hypertension, cardiomyopathies, and vasculitides.[4] It is often referred to as a "barometer of cardiovascular health."

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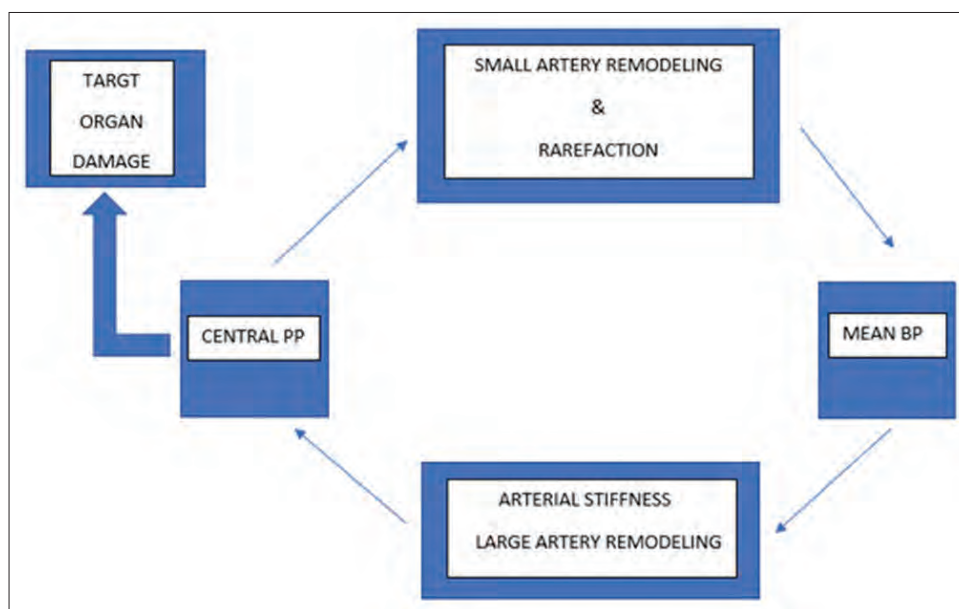
Figure 1: Cycle of microvascular damage in hypertension (modified from Bleakley *et al.*)[10] BP: Blood pressure, PP: Pulse pressure

Hypertension, NO, Microvascular Dysfunction, and Macrovascular Events

Whether microvascular dysfunction is a culprit or a victim in hypertension remains a contentious issue. Atherosclerotic cardiovascular disease risk factors such as aging, smoking, lack of physical exercise, hypertension, diabetes, and atherogenic dyslipidemia are known to reduce NO bioactivity, leading to endothelial dysfunction. In hypertension, the exposure of the microvasculature to sustained high pressures results in unfavorable changes in the endothelium with increased production of reactive oxygen species leading to reduced bioavailability of NO. This endothelial dysfunction results in microvascular dysfunction, which, in turn, appears to be predictive of macrovascular events.

Endothelial dysfunction may be preceded the development of hypertension as it has been noted in subjects with normal blood pressure (BP) with a strong family history of hypertension.[5] This allows one to speculate whether endothelial dysfunction is an early stage of hypertension and whether it is possible to intervene at this stage.

Hypertension induces two types of changes in the microvasculature - vascular remodeling and vascular rarefaction.[6-8] In vascular remodeling, there is a rearrangement of vessel wall components leading to luminal narrowing and an increase in vascular resistance. This remodeling effect is hypertension dependent as well as pressure independent, where angiotensin II has been implicated. Vascular rarefaction is a reduction in the number of small vessels in a given volume of tissue and could be either structural or functional. Available evidence indicates that the microvascular alterations occur as a result of sustained elevations in BP in hypertension. However, it is possible that microvascular dysfunction in some individuals may predispose them to the

development of worsening in hypertension. Some even suggest that there may exist a cyclical process of microvascular damage and hypertension[9,10] [Figure 1]. One condition where endothelial dysfunction plays a pathogenic role is preeclampsia, a hypertensive condition affecting about 15% of pregnant women.[11]

Interventions for Endothelial Dysfunction

Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and newer beta-blockers appear to improve endothelial dysfunction along with their BP reducing effect, whereas first-generation beta blockers and diuretics have no effect.[7,12,13] Statins have actions beyond cholesterol lowering, one of them being an improvement of endothelial dysfunction.[14] Lifestyle interventions including a diet rich in fruit and vegetables and regular physical activity also improve endothelial dysfunction.[1,15,16]

Conclusion

Endothelial dysfunction pathophysiologically has intricate interactions with hypertension. There is a large body of evidence to suggest that hypertension results in endothelial dysfunction, which in turn leads to microvascular dysfunction. This microvascular dysfunction is highly predictive of future cardiovascular events and is a potential target for intervention. In some instances, however, endothelial dysfunction is clearly involved in the pathogenesis of hypertension.

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Review Article

Hypertension and Cardiac Arrhythmias

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Abstract

Hypertension is a major modifiable risk factor for atherosclerotic cardiovascular disease. Cardiac arrhythmias and conduction defects associated with hypertension could be the cause for serious morbidity and mortality. Hypertension leading to myocardial changes and drug induced dyselectrolemia are some of the factors in t he genesis of cardiac arrhythmias. Effective blood pressure control reduces the risk of arrhythmias.

Key words: Hypertension, Cardiac arryhtmia, Antihypertensive drugs

Introduction

Hypertensive heart disease can manifest with various cardiac arrhythmias with atrial fibrillation (AF) being the most common. The left ventricular hypertrophy (LVH) is associated with several other supraventricular and ventricular arrhythmias also. Thiazide or thiazide-like diuretics alone or in combination with other antihypertensive agents can precipitate arrhythmias due to associated electrolyte abnormalities such as hypokalemia and/or hypomagnesemia. Effective control of blood pressure (BP) will reduce arrhythmia burden, particularly in subset of patients with congestive heart failure (CHF), cerebrovascular accident (CVA), and chronic kidney disease (CKD) resulting in improved clinical outcomes.

Pathophysiology

Hemodynamic changes, neuroendocrine factors, and remodeling of atria and ventricles are the factors that lead to a proarrhythmic substrate through a complex pathophysiology.[1] AF is the most common arrhythmia accounting for comorbidities in hypertension. "Non-dipper" (<10% fall in nocturnal BP) response seen on ambulatory BP monitoring in some hypertensives increases the risk of AF.[2] Activation of renin–angiotensin–aldosterone system (RAAS) is also strongly connected to arrhythmias in hypertension secondary to LVH. LVH is often associated with relative myocardial ischemia and myocardial fibrosis which by triggering electrical instability may result in cardiac arrhythmias.[3,4] Sympathetic activation may also trigger ventricular arrhythmias.[5]

Supraventricular Arrhythmias

Atrial ectopics are associated with nocturnal hypertension. Subsets with higher atrial ectopics during recovery phase of exercise in hypertension with LVH are more likely to develop supraventricular tachycardia (SVT) including AF.[6] The presence of LVH has been strongly correlated with the development of SVT.[7]

Hypertension has been recognized as an independent risk factor for incidence and progression of AF as well as AF-related CVA and mortality.[8,9] AF may be viewed as a target organ damage of hypertension. Higher resting heart rate in patients with hypertension is positively associated with poor cardiovascular outcomes including coronary artery disease (CAD) and CHF.

Ventricular Arrhythmias

LVH of any etiology has been associated with ventricular arrhythmias.[10] Hypertension-associated LVH increases the risk of sustained ventricular arrhythmias like ventricular tachycardia.[11] Sudden cardiac death (SCD) due to ventricular tachycardia or fibrillation in hypertension is linked to LV mass.[12] Increased QT dispersion with increased LV mass in hypertensive patients is associated with risk of dangerous ventricular arrhythmias.[13]

Regression of LV mass on antihypertensive medications is positively correlated to the reduction of SCD independent of the level of BP reduction.[14] Thiazide diuretic use is also linked to increase SCD in a dose-dependent manner with probable hypokalemia and worsening QT dispersion.[15] Blocking the RAAS pathway has been shown to reduce ventricular arrhythmias as well as SCD.[16]

Sick Sinus Syndrome and Bradyarrhythmias

Association of LVH was found in patients more often with atrioventricular conduction disturbances (particularly infra-Hisian block) rather than sick sinus syndrome in a large population with hypertension.[17] Both AV conduction defects and sick sinus syndrome are observed in LVH patients with sleep disorder breathing.[18] The use of continuous positive airway pressure effectively in this subset of patients could reverse bradyarrhythmias, suggesting that obstructive sleep apnea most likely induces bradyarrhythmias. Other drug-related bradyarrhythmias including atrioventricular blocks due to the use of beta-blockers and non-dihydropyridine group of calcium channel blockers are well described.[19] Caution should be exercised with the use of beta-blockers in CKD patients due to their cumulative bradyarrhythmic side effects.[20] Temporarily withdrawing such medications or reducing the dosage will address the problem.

Evaluation and Management

This includes proper evaluation and treatment. A 12-lead electrocardiography (ECG) and 2D echocardiogram, as well as 24 h Holter monitoring, will help in understanding the existing pathophysiology and burden of cardiac arrhythmias. If underlying CAD is suspected, exercise testing should be done for the evaluation of myocardial ischemia as a causative factor for arrhythmias. Ambulatory BP monitoring would identify patients with inadequate BP control and non-dippers. In selected cases, a sleep study should be carried out to diagnose obstructive sleep apnea. A blood biochemistry profile including electrolytes, renal function, thyroid levels, as well as blood glucose level should be assessed. Agents that lengthen QT interval should be avoided, especially if LVH is evident on ECG and/or ECHO.[21] Excessive intake of caffeine, alcohol, and other recreational drugs should be investigated and corrected. Coronary angiogram should be done and revascularization should be planned if deemed appropriate. [22] In addition, cardiac magnetic resonance imaging is useful to assess myocardial fibrosis and scar in the setting of dangerous reentrant ventricular reentrant arrhythmias and SCD.[23]

An optimal control of BP reduces the risk and burden of arrhythmias. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have evidence toward the reduction of SCD in the setting of hypertension and should be used.[24] Beta-blockers should be concomitantly used in the presence of CAD.[24] Preventing marked hypokalemia or

avoiding drugs that prolong QT interval are important in the management. Advice on therapeutic lifestyle changes is an integral part of the management of hypertension. It is extremely important to have optimal BP control in hypertensive patients with AF to reduce the risk of bleeding with anticoagulation.

Antiarrhythmic drugs are generally not recommended in asymptomatic patients with benign arrhythmias when there is no LVH with structurally normal heart. The use of catheter ablation or implantation of AICD should be followed as per the available guidelines as for as ventricular arrhythmias are concerned. Rate control or rhythm control strategy and the use of oral anticoagulation based on CHADS and HASBLED scores should be applied to AF patients with hypertension as per the guideline recommendations. Catheter ablation is recommended in paroxysmal AF patients with structurally normal heart.

Conventional SVT should be managed by medical therapy or ablation as per the set guidelines as in any other patient population.

Finally, achieving adequate BP control and prompting LVH regression are the crux of the management and any appropriate combination of drug classes should be considered as needed to achieve this goal.

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Review Article

Hypertension in Aging Population

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Abstract

Hypertension is a major problem among the geriatric population and is usually associated with multiple comorbidities and organ system damage. Isolated systolic hypertension is commonly found in older (60–79 years of age) and elderly (≥80 years of age) people. It is now clear that isolated systolic hypertension and elevated pulse pressure also play an important role in the development of cerebrovascular disease, congestive heart failure, and coronary heart disease, which are the major causes of cardiovascular (CV) morbidity and mortality in the population aged older than 65 years. The elderly population represents several medical challenges, particularly in the management of hypertension. These individuals have more organ damage or clinical CV disease, and they may respond differently to treatment goals of normal aged populations. Each patient responds differently to treatment; thus, there is a need to individualize hypertension management in the elderly population.

Key words: Aging population, hypertension, systolic hypertension

Introduction

Hypertension is one of the most common morbidities in the older age groups significantly impacting their health conditions.[1] Older is defined as 65 years or more and the very old as 80 years or more.

Hypertension remains a growing problem in our aging population. The overall prevalence of hypertension in adults is around 30–45%,[1] with a global age-standardized prevalence of 24 and 20% in men and women, respectively, in 2015.[2]

This high prevalence of hypertension is consistent across the world, irrespective of income status, that is, in lower, middle, and higher income countries.[1] Hypertension becomes progressively more common with advancing age, with a prevalence of >60% in people aged >60 years.[2] It is estimated that the number of people with hypertension will increase by 15–20% by 2025, reaching close to 1.5 billion.

Hypertension is the main risk factor for most of the morbidities in older age including cardiovascular (CV) and cerebrovascular diseases and poor quality of life.[3] Numerous studies have demonstrated risk for stroke, left ventricular hypertrophy, congestive heart failure, coronary and peripheral artery diseases, vision impairment, end-stage renal disease, cognitive impairment, and dementia among hypertensives.[4] In addition, hypertension has adverse effects on most organ systems including cerebrovascular, CV, renal, ocular, and vascular.[5,6]

Although both systolic blood pressure (SBP) and diastolic blood pressure (DBP) are established risk factors, with advancing age, SBP becomes a better predictor than DBP, of CV disease and other comorbidities.[7,8] Hypertension in the elderly is a complicated disease and warrants control and adherence to prescribed medication to reduce the risks of CV, cerebrovascular, and renal disease.

Pathophysiology of Hypertension in the Elderly Population

Age-related BP elevations derive from changes in the arterial structure and function accompanying aging. The elasticity of the large vessels decreases due to the alteration of the various collagen components in the vessel wall.[9]

These changes cause increases in the pulse wave velocity, leading to late systolic BP augmentation and increasing myocardial oxygen demand. Reduction of forward flow also occurs, limiting organ perfusion. The arterial stiffness is

manifested clinically by the widening of pulse pressure, which is seen commonly in the elderly patients.[10,11] Data from the Framingham heart study suggest that after age 50, systolic BP continues to increase, whereas diastolic BP decreases, resulting in the widened pulse pressure.[12]

Elderly patients are relatively more salt sensitive due to their reduced ability to excrete a sodium load. This is partly due to the decline in kidney function with age and secondarily due to the reduced generation of the natriuretic substances such as prostaglandin E2 and dopamine. Progressive renal dysfunction due to glomerulosclerosis and interstitial fibrosis with a reduction of glomerular filtration rate and other renal homeostatic mechanisms, leading to increased intracellular sodium, reduced Na-Ca exchange, and volume expansion may also contribute to the pathophysiology of hypertension in the elderly population.[13-15]

Secondary causes of hypertension should also be considered in this age group, such as renal artery stenosis,[16] sleep apnea, primary hyperaldosteronism, and thyroid disorders. Excess in lifestyle such as overeating or high alcohol consumption as well as medications such as nonsteroidal anti-inflammatory medications can also contribute to the elevation of BP in the elderly patients.

The prevalence of glucose intolerance and diabetes mellitus also increases with age, which further accelerates vascular injury and adversely affects kidney function. In addition, CV reflexes in older people become less responsive to maneuvers that activate the sinoaortic reflex and to upright tilt, and this change may contribute to the greater variability of ambulatory SBP associated with aging.[17,18]

Despite advances in diagnosis and treatment over the past 30 years, the disability-adjusted life years attributable to hypertension have increased by 40% since1990.[19]

SBP appears to be a better predictor of events than DBP after the age of 50 years. Both office BP and out-of-office BP have an independent and continuous relationship with the incidence of several CV events such as hemorrhagic stroke, ischemic stroke, myocardial infarction, sudden death, heart failure, and peripheral artery disease, as well as end-stage renal disease.[20]

Hypertension increases the risk of developing atrial fibrillation,[21] and evidence is emerging that links early elevations of BP to increased risk of cognitive decline and dementia.[22] In middle-aged and older people, increased pulse pressure has additional adverse prognostic significance.[23]

Diagnosis and Treatment

Diagnosis of hypertension is established by demonstrating a SBP of ≥140 mmHg and/or diastolic BP of ≥90 mmHg on at least three different BP measurements taken on two or more than two separate office visits to account for natural variability.

Alternatively, checking BP at home can be done with a clinic-calibrated arm cuff, though errors in measurement and reproducibility can confound the clinical picture. When BP is high at home but not in the office, the so-called "masked hypertensive," the diagnosis of hypertension can be more challenging.

Masked and situational hypertension (previously known as "white coat hypertension") must always be considered, and in addition to home and office BP measurements, 24-h ambulatory BP monitoring may be helpful in selected patients. Isolated office hypertension is more common at older ages and in females[24] and is often mistaken for uncontrolled hypertension, which may lead to overtreatment.[25]

Ambulatory BP monitoring provides important information on the pattern of nocturnal BP (nocturnal hypertension, nocturnal hypotension, dipping status, and autonomic dysfunction).[26]

Several studies have shown that nocturnal hypertension and non-dipping of BP during sleep are important harbingers of poor CV prognosis and that nighttime pressures more accurately predict the occurrence of death and CV events than daytime pressures, independent of other confounders.[27,28] The prevalence of non-dippers among hypertensive men and women increases progressively with age, reaching more than 40% in subjects aged 70 years or older.[29]

Pseudohypertension is more common in older adults and should be considered early. Pseudohypertension is the result of age-related calcific arteriosclerosis that causes incompressible peripheral arteries. Essentially, the BP cuff is unable to measure the true intraluminal BP. A standing BP can be helpful in distinguishing pseudohypertension from true hypertension. For example, if a "resistant" patient is on several drugs and reporting symptoms of orthostasis, an elevated resting and standing BP would suggest pseudohypertension. Being aware of this entity in the elderly is important since unnecessary therapy escalation can lead to falls or functional impairment, causing significant disability in this population.

Risks

Elderly patients, in comparison to younger cohorts, have a higher baseline cardiac risk profile and benefit from even modest reductions in BP.[30] In patients over the age of 60, isolated systolic hypertension is more common, and SBP is a better predictor of CV risk when compared to DBP.[31] Data from The Second National Health and Nutrition Examination Survey-II and the SHEP trial revealed that in patients over the age of 65 years of age, there is a linear relationship between CV risk, particularly stroke, and increasing SBP (the absolute stroke risk in the placebo group of the SHEP trial was 8.2% over 5 years, compared to 5% in the treatment arm).[32] Paradoxically, when DBP dropped >65 mmHg, there was an enhanced risk of mortality, possibly the result of decreased tissue perfusion and increased CV risk ("J-curve" phenomenon).[33]

Subclinical organ damage is considered to be an important component in determining total CV risk. Simple, well-standardized, and inexpensive tests to detect subclinical organ damage such as electrocardiogram, echocardiogram, serum creatinine, urinalysis, and microalbuminuria are widely recommended for all hypertensive patients. Recently, the role of several emerging risk factors such as the blood levels of high-

sensitivity C-reactive protein and homocysteine, and the urine albumin-to-creatinine ratio to predict risk have been evaluated, and none was shown to substantially improve on the ability of conventional risk factors to classify risk.[33]

Treatment

Accurate measurement of BP is important before initiating treatment for hypertension.

Effective non-pharmacologic options for reducing BP include lifestyle modifications as weight loss, dietary changes such as the dietary approaches to stop hypertension diet, and an increase in physical activity.

A 6-month study of aerobic and resistance training in 51 hypertensives compared to 53 controls lowered DBP but not SBP in older adults. The absence of improvement in aortic stiffness in exercisers suggests that older persons may be resistant to exercise-induced reductions in SBP. Body compositional improvements due to exercise probably improve CV health in older men and women.[34]

Non-pharmacologic options are typically associated with fewer side effects than pharmacologic therapies and have other positive effects; ideally, they are included as the first therapy or used concurrently with drug for most patients with hypertension therapy.

Before initiating medical therapy, consideration should be given to the following variables: (1) The frailty of the patient, (2) their ability to follow instructions, (3) the complexity of their current medication regimen, and (4) supporting care. The anticipated benefits versus potential harm of BP treatment in older patients will be influenced by the patient's ability to tolerate treatment and their health and functional status.

Careful review, the patient's medication list is necessary to stop or reduce nonsteroidal anti-inflammatory drugs and decongestants. Reviewing the patient's electrolytes and renal function before initiation of therapy is prudent, particularly if considering use of RAAS blockers or suspecting aldosteronism.

In the HYVET trial, treating to an SBP target of <150 mmHg (achieving a mean SBP of 144 mmHg) in the very old patients (>80 years) demonstrated significant reductions in mortality, fatal stroke, and heart failure, with the caveat that the "very old" patients in this study were active and independent.[35]

However, more recent evidence supports a lower SBP target for older patients (older than 65 years). The SPRINT trial included a high proportion of patients over the age of 75 years (n = 2636) and demonstrated that more intensive BP-lowering treatment (mean achieved BP = 124/62 mmHg) significantly reduced the risk of major CV events, heart failure, and all-cause death by >30%, compared with standard treatment (mean achieved BP = 135/67 mmHg).[36]

It has been noted that the BP measurement technique used in SPRINT generated lower values than those provided by the conventional office BP measurement.[37] Consequently, the SBP of 124 mmHg achieved in the intensively treated older patients in the SPRINT trial most probably reflects a conventional office

SBP range of 130–139 mmHg.

Although HYVET and most other RCTs in older patients have recruited relatively fit and independent patients, the SPRINT study also suggested that there are benefits of more intensive treatment being extended to older patients who were frailer meeting the inclusion criteria, with reduced gait speed.[37]

Several trials have shown that in old and very old patients, antihypertensive treatment substantially reduces CV morbidity and CV and all-cause mortality. Treatment has been found to be generally well tolerated. However, older patients are more likely to have comorbidities such as renal impairment, atherosclerotic vascular disease, and postural hypotension, which may be worsened by BP-lowering drugs.

Furthermore, a recent study of a cohort of older patients from the general population (thus including those with frailty) has shown that better adherence to antihypertensive treatment was associated with a reduced risk of CV events and mortality, even when age was >85 years (mean 90 years).[36]

Antihypertensive doses should start low, and BP should be lowered gradually. In very old patients, it may be appropriate to initiate treatment with monotherapy. In all older patients, when combination therapy is used, it is recommended that this is initiated at the lowest available doses. In all older patients, and especially very old or frail patients, the possible occurrence of postural BP should be closely monitored and symptoms of possible hypotensive. Renal function should be frequently assessed to detect possible increases in serum creatinine and reductions in eGFR as a result of BP-related reductions in renal perfusion.

The risk of orthostatic hypotension increases with aging, diabetes, and certain antihypertensive drugs.[21] Angiotensin-converting enzyme inhibition (ACEI) is reasonable, especially if there is concurrent coronary artery disease, diabetes, proteinuria chronic kidney disease, or heart failure.

While the JNC 8 guidelines[38] have no preference among ACEIs, calcium channel blockers, or diuretics as the initial medication, the ESH/ESC guideline recommends a calcium antagonist or diuretic in elderly patients with isolated systolic hypertension.

Robust randomized evidence, specifically the antihypertensive and lipid-lowering treatment to prevent heart attack trial data, would suggest that low-dose daily chlorthalidone is the most effective agent in this population.[39] However, consideration of the patients free water intake and comorbid alcohol intake is important due to a real risk of hyponatremia with this medication. Hypokalemia is also relatively common with thiazide diuretics, and there are small, adverse effects on lipids, and glucose levels.

In a primarily elderly Scandinavian population, the Anglo-Scandinavian cardiac outcomes trial - BP-lowering arm study showed significant overall mortality benefit in subjects aged >60 years when using a combination regimen of calcium channel blocker and ACEI when compared to a beta-blocker and thiazide regimen.[40]

In some of these old patients, it may not be possible to

Table 1: Office blood pressure treatment target range in older and very old patients[41]

Age group	Office SBP treatment target ranges (mmHg)					Office DBP treatment target range (mm Kg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke[a]/TIA	
65–79 years	Target to 130–15 if tolerated	Target to 130–139 if tolerated	Target to 130–139 if tolerated	Target to 130–139 if tolerated	Target to 130–139 if tolerated	70–79
>80 years[b]	Target to 130–139 if tolerated	Target to 130–139 if tolerated	Target to 110–139 if tolerated	Target to 130–139 if tolerated	Target to 130–139 if tolerated	70–79
Office DBF treatment target range (mmHg)	70–79	70–79	70–79	70–79	70–79	

CAD: Coronary artery disease; CKO: Chronic kidney disease (includes diabetic and non-diabetic CKD); DBP: Diastolic blood pressure; SBP: Systolic blood pressure; TIA: Transient ischemic attack. [a]Refers to patient with previous stroke and does not refer to blood pressure targets immediately after acute stroke. [b]Treatment decisions and blood pressure targets may need to be modified in older patients who are frail and independent

achieve the recommended targets of BP, but it needs to be appreciated that any amount of BP lowering is likely to reduce the risk of major CV events (especially stroke and heart failure) and mortality.

The recommendations by ESC/ESH in their 2018 guidelines[41] are shown in Table 1.

Conclusion

Aging is an inevitable event and hypertension in the old is a complex issue to manage. However, studies have shown that it is safe to treat hypertension in this population with individualization of therapy and careful monitoring and that does reduce mortality and morbidity.

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Review Article

Hypertension in Pregnancy

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Abstract

Hypertension disorders of pregnancy are the second most frequent cause of pregnancy associated maternal mortality. Accurate measurement of blood pressure is most essential and integral part of diagnosing Hypertensive Disorders of Pregnancy. Several risk factors for Pre-Eclampsia have been identified. Biomarkers are available for early detection of Pre-Eclampsia. There is growing awareness about Pre-Eclampsia as a risk factor for mother and fetus for future development of cardiovascular disease. This review covers most of the issues related to hypertension in pregnancy.

Key words: HDP-Hypertensive disorders of pregnancy, PHTN-Pregnancy related hypertension, CHTN-Chronic hypertension, PE-Pre eclampsia, SUA-Spiral uterine arteries

Introduction

Hypertension (HTN) is a common disorder during pregnancy and affects 7–10% of pregnancies. Hypertensive disorders of pregnancy (HDP) are the second most frequent cause of pregnancy-associated maternal mortality. Hypertensive disease of pregnancy also carries significant fetal and neonatal morbidity and mortality. Maternal risks are placental abruption, stroke, multiple organ failure, and disseminated intravascular coagulation. The fetal risks are intrauterine growth retardation, prematurity, and intrauterine death.[1] There is, now, a clear evidence that preeclampsia (PE) increases the risk of cardiovascular events in later life.

Normal Blood Pressure (BP) Changes in Pregnancy

During normal pregnancy, various circulatory changes take place due to the action of sex hormones and the effect of placenta on blood flow. Early in pregnancy, there is a reduction in peripheral vascular resistance. Other hemodynamic changes occurring late in pregnancy include an increase in circulatory plasma volume, increase in cardiac output, and increase in renal blood flow and in turn increase in glomerular filtration rate. Overall BP in the first trimester tends to be similar to preconception. In the second trimester, there tends to be a reduction in BP of a few mm of Hg. In the third trimester, BP rises again. This is the trimester in which there is a greater risk of development of high BP or even PE. Note that the BP changes described above also occur in women who are hypertensive before conception such that BP will again be lowest in the second trimester. Hence, there is a need for adjusting antihypertensive therapy to account for normal physiological changes.

The 2013 guidelines on HTN in pregnancy[2] distinguish between pregnancy-related HTN (PHTN) and chronic HTN. This distinction is essential because of both mechanistic and prognostic considerations that heavily impact patient management; however, it can be challenging during clinical evaluation. Importantly, PHTN can have negative long-term impacts on mother and child.

Diagnosis

The diagnosis of PHTN is made by extrapolating thresholds for normal BP in the general population. However, adequacy of such criteria is debatable. Although BP physiologically declines 10–15 mm of Hg by the end of the first trimester and recovers to near normal levels in the third trimester, no large-scale clinical trial has evaluated the optimal level of BP in pregnancy. Tight (diastolic BP [DBP] target <85 mmHg vs. less tight [DB target <100 mmHg]) BP control in the Control of HTN in Pregnancy[2]

study found no significant fetal adverse effects. However, women in the less tight BP control more frequently presented with severe HTN (>160/110 mmHg).

Measurement

Accurate BP measurement is essential to appropriately recognize and treat HDP. In brief, women should have their BP measured using a standardized protocol after a period of rest in a quiet environment in sitting position with their arm at the level of the heart using appropriately sized cuff (i.e., length 1.5 times the circumference of the arm). The arm with higher BP values should be used for HTN diagnosis and BP monitoring. On finding a severe elevated BP, it should be remeasured at the same visit, with at least a gap of 15 min from the first measurement. Over 50% of women with a first BP reading of ≥140/90 mmHg have white coat effect.[3]

HTN in pregnancy is defined as a systolic BP (SBP) of ≥140 mm Hg and/or a DBP ≥90 mmHg (average of at least two measurements taken at least 15 min apart). The severity of HTN in pregnancy is considered based on both the presence of target organ involvement (i.e., maternal or the fetus itself) and the actual BP level.[4]

Classification of HTN in Pregnancy[5]

Chronic–Pre-existing HTN

Systolic blood pressure >140mmofHg and or diastolic blood pressure of> 90mm of Hg before the 20th week of pregnancy. This CHTN May be associated with proteinuria and usually persists post-partum.Protenuria not necessarily mean PE.

Pregnancy-induced (gestational) HTN

Systolic blood pressure>140 m /or diastolic blood pressure >90mmHg and developing after 20th weeks of pregnancy or >

30/15 mmHg rise in blood pressure over and above the first-trimester or pre-conception blood pressure values, in the absence of pre-eclampsia. This PIH returns to normal post-partum.

PE–eclampsia

New onset hypertension, i.e. A >15 mmHg rises in diastolic blood pressure or > 25mmHg rise in systolic blood pressure from early pregnancy or a single diastolic blood pressure reading of 110mmHg or two readings 4 hours apart of >90mmHg DBP after 20weeks's gestation in a previously normotensive woman plus evidence of end organ damage I.e. proteinuria, thrombocytopenia, hepatic or renal dysfunction, pulmonary edema or central nervous or visual disturbances.

PE superimposed on Chronic HTN

There is new proteinuria, sudden increase in BP or proteinuria, thrombocytopenia, or hepatocellular enzymes in pregnancy in patients with chronic HTN.

The US Preventive Services Task Force[6] recommends screening of all pregnant women by measuring BP at every prenatal visit. PE diagnosis requires two measurements at least 4 h apart. Proteinuria has been eliminated as a compulsory criterion for PE, which can be diagnosed when new onset HTN is accompanied by signs of end-organ damage not explained by other pathologies [Table 1].

Finally, PE is a disease of placenta and does not require the presence of a fetus; thus, it can complicate pregnancies in hydatidiform mole. Furthermore, PE can develop exclusively in the post-partum period, and women should be cautioned to contact their physician in case of severe headaches or epigastric pain.[8]

Maternal Risk Factors for PE and Early Diagnosis[8]

A multisystemic disorder stems from malimplantation of the developing placenta. The severity of PE for mother and

Table 1: PE diagnosis criterion

Hypertension	SBP ≥ 140 mmHg or DBP ≥90 mmHg: Severe ≥160 mmHg or DBP ≥110 mmHg
Signs of end-organ dysfunction	
	≥300 mg proteins/24-h urinary volume or a ratio of protein to creatinine in a single voided urine ≥3.0
Thrombocytopenia	Platelet <100,000/μL
Hepatic dysfunction	Liver transaminases 2×greater than normal levels or severe upper quadrant or epigastric pain.
Renal insufficiency	Serum creatinine >1.1 mg/dl or a 2-fold increase above previous values, in the absence of other causes of renal impairment.
Pulmonary edema	
Acute neurological dysfunction (including vision impairment)	
The HELLP syndrome	Stands for hemolysis, elevated liver enzymes, and low platelets.
Eclampsia	Grand mal seizures: Premonitory signs: Severe headaches, blurred vision, hyperreflexia, or altered mental status.

DBP: Diastolic blood pressure, SBP: Systolic blood pressure, PE: Preeclampsia

Table 2: Risk factors for PE[7]

Increased risk of placental malimplantation	Primiparity
	Previous PE pregnancy
	Family history of PE
	Short stature
	Multifetal pregnancy
	In vitro fertilization
	Advanced maternal age (>40 years)
	Migraine
Maternal comorbidities associated with endothelial dysfunction	Chronic hypertension/renal disease
	Type I/II diabetes mellitus
	Obesity
	Systemic lupus erythematosus
	Hydatidiform mole

PE: Preeclampsia

fetus depends on symptom onset; 34 weeks' gestation defines early versus late PE. Early PE exposes the fetus to high risk of mortality and early delivery. However, prompt aspirin therapy can improve placentation and decrease PE risk. Thus, there is an urgent need to accurately diagnose pregnancies at high risk of early PE [Table 2].

Mechanism of PE[9]

Normal placental development requires the spiral uterine arteries (SUAs) to be enlarged and transformed into capacitance vessels. Remodeling of the SUAs takes place in an early, trophoblast-independent phase, followed by a later trophoblast-dependent phase.[10] In normal pregnancies, remodeling is completed by the beginning of the second trimester. In contrast, in PE, the insufficient remodeling of SUAs generates a sustained pathologic ischemic milieu[11] with the dysfunctional placenta releasing pathogenic mediators into the maternal blood that induces generalized endothelial dysfunction (ED), perturbed coagulation, HTN, and organ dysfunction.

SUA (from placental samples during CS) have larger diameters and a media with scarce VSMCs and fibrinoid deposition. Further studies showed that these changes took place in the presence of trophoblast cells in the vicinity. At present, extravillous trophoblast (EVT) invasion of SUAs is considered to be at the cornerstone of PE pathophysiology.[10] The etiology of EVT malfunction in PE is unclear; however, incomplete immune tolerance for semi-allogeneic fetal antigens has been proposed as a major cause.

Pathogenesis of HTN

Regardless of underlying etiology, insufficient SUA remodeling by EVTs leads to a persistently hypoxic dysfunctional placenta that releases pathogenic molecules into the maternal circulation. Exposing endothelial cells to serum from PE women leads to ED.[11,12] The hypoxic placenta releases antiangiogenic molecules such as sFlt-1 and soluble endoglin (sEng), the soluble receptor for transforming growth factor

beta, and endothelium derived vasoconstrictor (ET-1). sFlt-1 is elevated toward delivery in normal pregnancy but is constantly elevated in PW. It inhibits both vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) by sequestering circulating molecules and by blocking their common cellular receptor. Increasing sFlt-1 in pregnant rats leads to glomerular endotheliosis and proteinuria, whereas pregnant mice and its Flt-1 level are predictive of PE severity. The rennin-angiotensin (AT)-aldosterone (RAA) axis has also been involved in PE pathogenesis through AA-AT1-activating auto antibody against AT 1 receptor.[13] Finally, hypoxia inducible factor 1alfa has also been implicated as it is the main regulator of sFlt-1.

Molecular Mechanism of ED in PE

The wide array of pathological molecules released by insufficient placenta disturbs the maternal endothelium, altering the balance between endothelial-derived relaxing and constricting factors (endothelium-derived relaxing factor [EDRF] and endothelium-derived contracting factor [EDCF], respectively). The main EDRFs are prostacyclin (PGI_2) and nitric oxide (NO), whereas the main EDCFs are TXA_2, ET-1, and AT. In normal pregnancies, the balance is tipped in favor of the vasodilatory PGI_2. In pregnancies complicated by PE, lipid peroxidation activates COX but inhibits PGI_2 synthase, which tips the TXA_2/PGI_2 balance in favor of TXA_2, with a rapid decrease in PGI_2. These changes occur starting at 13 weeks of gestation. Aspirin treatment inactivates COX.[13]

Treatment Strategies in Hypertensive Women

Investigation of HTN in Pregnancy[14]

Basic laboratory tests such as CBC, serum creatinine, urine analysis, serum uric acid, liver enzymes, and hyperuricemia in hypertensive pregnancies identify women at an increased risk of adverse maternal and fetal outcomes.

All pregnant women should be assessed for proteinuria in early pregnancy to detect pre-existing renal disease and, in the second half of pregnancy, to screen for pre-eclampsia. A dip stick test of ≥1+ should prompt evaluation of ACR in a single spot urine sample and a value of <30 mg/mmol can reliably rule out proteinuria in pregnancy.[14]

In addition to basic laboratory test, the following investigations may be considered.[14]

If there is clinical suspicion of CHTN/Secondary cause for HTN -Ultrasound investigation of the kidneys and adrenals.

Doppler ultrasound of uterine arteries (performed after 20 weeks of gestation) to detect those at higher risk of gestational hypertension eclampsia, and intrauterine growth retardation.

A soluble fms-like tyrosine kinase1 (sFlt-1): PIGF ratio of <38 can be used to exclude the development of PE in the next week when suspected clinically.

Prevention of HTN and PE[14]

Women at high or moderate risk of PE should be advised to take 100–150 mg of aspirin daily from weeks 12 to 16.[15]

High risk of PE includes any of the following:

- Hypertensive disease during a previous pregnancy
- CKD
- Autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome.
- Type 1 or type 2 diabetes
- Chronic HTN

Moderate risk of PE includes one or more of the following factors:

- Age >40 years
- Pregnancy interval of >10 years
- BMI of ≥35 kg/m² at first visit
- Family history –PE
- Multiple pregnancy.

Clinical Management of HTN of Pregnancy (BP 140–159/90–109)

The goal of drug treatment of HTN in pregnancy is to reduce maternal risk; however, the agents selected must be safe for the fetus. The tighter control of BP may reduce the risk of developing more severe HTN and PE.

Most women with pre-existing HTN and normal renal function will not have severe HTN and will have a low risk for developing complications during pregnancy. Indeed, some of these women may be able to withdraw their medication in the first half of pregnancy because of the physiological fall in BP.

European Guidelines[16] have recommended Initiating Drug Treatment

1. In all women with pre-elevation of BP ≥150/95 mmHg
2. In all women with gestational HTN (with or without proteinuria). Preexisting HTN, or HTN with superimposition of gestational HTN, or HTN with subclinical HMOD when BP is ≥140/90.

Women with pre-existing HTN may continue their current antihypertensive medications, but AT-converting enzyme inhibitors, AT receptor blockers, and direct renin inhibitors contraindicated due to adverse fetal and neonatal outcomes. Methyldopa, labetalol, and calcium channel blockers are the drug of choice. Beta-blockers may induce fetal bradycardia; consequently; if used, their type and dose should be carefully selected, with atenolol best avoided. Diuretic therapy is generally avoided abuse. Plasma volume is reduced in women who develop PE. A BP target of <140/90 is suggested for pregnant women receiving antihypertensive therapy [Table 3].

BP Postpartum[14]

Postpartum HTN is common in the 1st week. Any drug combination can be given as per the guidelines with the caveats: (') Methyldopa should be avoided because of the risk of postpartum depression and (ii) consideration should be given to drug choice in breastfeeding women.

HTN and Breastfeeding

All antihypertensive medications taken by nursing mother are excreted into breast milk. Most are present at very low concentrations except propranolol and nifedipine, with breast milk concentrations similar to maternal plasma concentration.

Table 3: Management of hypertension in pregnancy[14]

Recommendations	Class	Level
In women with gestational hypertension-existing hypertension superimposed by gestational hypertension or with hypertension and subclinical organ damage or symptoms, initiation of drug treatment is recommended when SBP ≥140 mmHg or DBP ≥90 mmHg	I	C
In all other cases, initiation of drug treatment is recommended when SBP is ≥150 mmHg or DBP is ≥95 mmHg	I	C
Methyldopa, labetalol, and CCBs are recommended as the drugs of choice for the treatment of hypertension in pregnancy.	I	B (methyldopa)
	I	C (Labetalol or CCBs)
ACE inhibitors, ARBs, or direct renin inhibitors are not recommended during pregnancy	III	C
SBP ≥170 mmHg or DBP ≥110 mmHg in a pregnant woman is an emergency, and admission to hospital is recommended	I	C
In severe hypertension, drug treatment with i.v labetalol, oral methyldopa, or nifedipine is recommended	I	C
The recommended treatment for hypertensive crises is i.v labetalol or nicardipine and magnesium	I	C
	I	C
In women with gestational hypertense, mild preeclampsia delivery is recommended at 37 weeks	I	C
It is recommended to expedite delivery in preeclampsia with adverse conditions, such as visual disturbances or hemostatic disorders	I	C

DBP: Diastolic blood pressure, SBP: Systolic blood pressure, CCB: Calcium channel blockers

Risk of Recurrence of Hypertensive Disorders in Subsequent Pregnancy

Women experiencing HTN in their first pregnancy are at increased risk in a subsequent pregnancy. The earlier the onset of HTN in first pregnancy, higher the risk of recurrence in a subsequent pregnancy.

Long-term Cardiovascular Consequences of Gestational HTN

Women who develop gestational HTN or PE are at increased risk of HTN, stroke, and ischemic heart disease in later adult life. A history of PE increases the mother's CV risk to a magnitude similar to that of diabetes which has included PE as one of the risk factors for CV disease in women. They should be followed by a cardiologist. Moreover, delivering a FUGR child, regardless of the underlying pathology, is also associated with increased maternal risk of developing ischemic heart disease, cerebrovascular disease, or CV insufficiency in later life.[9]

Finally, a recent study - Women's ischemia Syndrome Evaluation-Coronary Vascular Dysfunction (WISE-CVD) found that there is a correlation between PHTN and lower coronary flow reserves, which is an indirect measurement of coronary microvascular dysfunction,[16,17] Recent 2018 AHA/ACC guidelines on the management of Blood Cholesterol have included Pre-eclampsia as a risk enhancer for stratifying Atherosclerotic cardiovascular Disease in women.[28]

Long-term Risk for Child

In PE, main determinant of fetal risk is FUGR. There are data showing long-term CV risk. FUGR may also induce *in utero* cardiac remodeling that was persistent at 6 months after birth. Furthermore, adult women, rather than men, with low birth weight (under 2.5 kg) have a higher incidence of glucose intolerance, metabolic syndrome, and diabetes. Chances that these women have premature delivery and the prematurity in itself is associated with higher risk for HTN and insulin resistance in infancy.[18]

There are currently few preventive strategies and no cure other than delivery of the placenta. There have been wide-ranging investigations into possible biomarkers for the early detection of pre-term PE. The release of factors from the placenta into the maternal bloodstream or maternal generation of factors may precede clinical symptoms. Therefore, there remains substantial interest in the use of these factors as potential biomarkers for subsequent disease. Table 1 summarizes the biomarkers. These biomarkers, alone or in combination with biophysical and sonographic findings, may allow development of a reliable and valid screening or diagnostic test for PE to enable risk stratification and timely use of pharmacological interventions such as aspirin (or other novel therapies) to reduce the risk of PE.[19,20]

Angiogenic Factors

The placental hypoxia resulting from the impaired trophoblast invasion that occurs in PE results in an imbalance between pro- and anti-angiogenic factors, in particular, anti-angiogenic soluble fms-like tyrosine kinase-1 (sFlt-1) and the pro angiogenic (VEGF) and a (PIGF).[21-24] The diagnostic accuracy of low PIGF concentration of <5th percentile in women suspected of PE between 20 and 35 weeks' gestation had a sensitivity of 96%, a negative predictive value of 98%, and a specificity of (55%).[25]

For short-term prediction of PE, a sFlt-1:PIGF ratio cutoff of 38 has been shown to have a negative predictive value for the development of PE in the subsequent week of 99.3% (95%CI, 97.9–99.9) with 80% sensitivity and 78.4% specificity. Other studies have shown mixed results. Further recent study has shown that women with eclampsia had higher of sFlt-1 from 28 weeks onward ($P = 00.003$) lower PIGF from 18 weeks ($P = 0.004$). In a recent systematic review which included a total of 103 studies and 432,621 participants with pre-eclampsia, the best predictor of PE was PIGF with a positive likelihood ratio 4.01 (3.74,4.28) and negative likelihood ratio of 0.67 (0.64,0.69).[26,27]

FUTURE THERAPEUTIC PROSPECTIVE IN PE

The antiangiogenic and pathogenic sFlt-1 molecule may be an adequate target for future PE preventive strategies.

Conclusion

Hypertension in pregnancy is a cause for concern, there is evidence based strategy is available for early detection and effective management available for women who are planning pregnancy, and who are at risk of HDP,or who already have HDP in current pregnancy, or HDP post-partum. The objective is to improve short and long term maternal and fetal outcomes.

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Review Article

Renal Sympathetic Denervation Therapy in Hypertension

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Abstract

Sympathetic nervous system plays an important role in the pathogenesis of hypertension. In r esistant hypertension, when pharmacotherpy fails, there may be a place for renal sympathetic denervation. Though initial studies showed promising results, sham controlled studies proved negative. However, learning lessons from the previous trials, recent studies probably with better design and methodology seem to be resurrecting renal sympathetic denervation therapy for resistant hypertension

Key words: Resistant hypertension, Sympathetic nervous system, Renal sympathetic denervation

Introduction

Hypertension (HTN) is among the most prevalent chronic illness around the world and a powerful risk factor for cardiovascular events and chronic kidney disease.[1] Globally, HTN affects approximately one in four adults[2] and results in over 10 million deaths annually.[3] Among patients with HTN, around 50% do not meet treatment targets and about 10–20% of these uncontrolled hypertensives have what is called as resistant HTN. The prevalence of resistant HTN ranges approximately from 5% in general medical practice to 50% in nephrology clinics.[4] Resistant HTN is defined as blood pressure that remains above goal despite concurrent use of three antihypertensive agents of different classes, one of which should be a diuretic, in their optimal or maximal tolerated doses.[5] Patients whose blood pressure is controlled with four or more medications are also considered to have resistant HTN.

Such individuals are more likely to suffer from cardiovascular events and have a poor outcome compared to people whose BP is under control. Therefore, despite the availability of various classes of antihypertensive drugs, the need to control HTN further led to the discovery of various interventional measures including renal denervation therapy (RDN).

What is Renal Sympathetic Denervation?

It is a minimally invasive procedure during which an intra-arterial catheter is placed in the renal artery lumen and radiofrequency or ultrasonographic energy or a chemical agent is used to ablate the renal sympathetic nerves present in the vascular adventitia, thereby reducing the renal sympathetic efferent and sensory afferent signaling to and from the kidneys. However, before doing the procedure, it is important to establish anatomical suitability, with renal artery length >20 mm and diameter >4 mm considered ideal. The presence of renal artery stenosis, calcification, and plaques is relative contraindications for this procedure. As the nociceptive C fibers are colocated with the sympathetic nerves, it is important to ensure adequate analgesia and sedation throughout the procedure. Aspirin 75–100 mg per day is recommended for up to 4 weeks post-procedure.

Pathophysiology

Numerous studies have shown that sympathetic nervous system plays a key role in the development and progression of HTN and various other cardiovascular diseases. The afferent nerves from the kidney connect with the hypothalamus in the brain, which hosts various centers involved in regulating the autonomic nervous system. The efferent sympathetic activity, in turn, leads to renin release, systemic vasoconstriction, and sodium and water retention contributing to HTN [Figures 1 and 2].

Patient selection

Before recommending the procedure, it is important to carefully select the patient who is likely to benefit from it. Initial studies
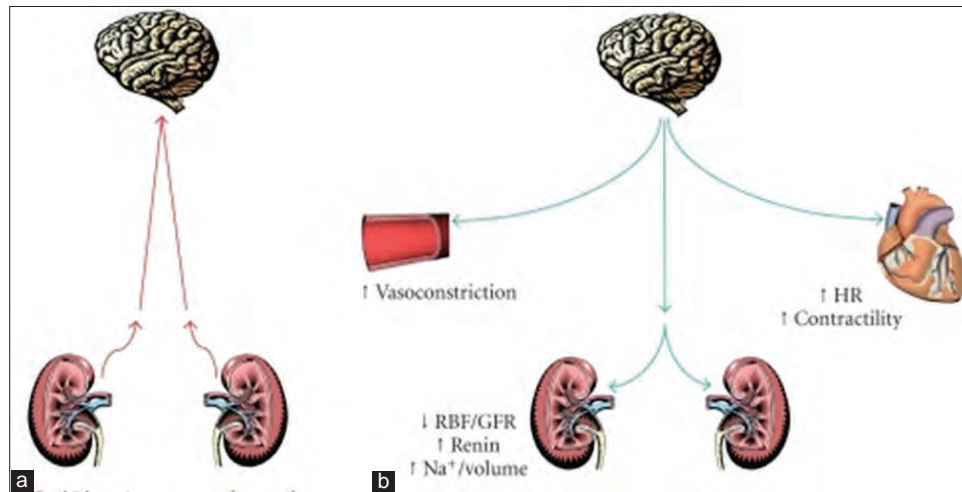
Figure 1: Integration of sympathetic afferent and efferent activity in regulation of blood pressure. (a) Afferent renal sympathetics, (b) efferent sympathetic activation
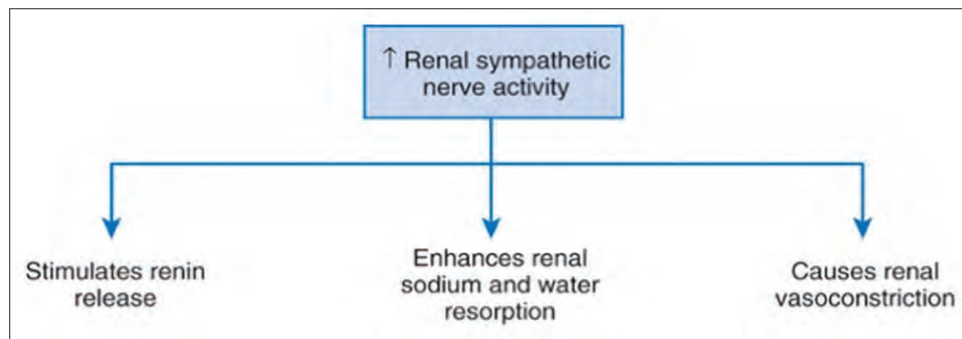

Figure 2: Actions of renal sympathetic activation

were in patients with resistant HTN.[6-10] Now, there are studies in patients with no background antihypertensive therapy and also along with antihypertensive therapy.[11-13] There is also a recent study which reported the comparison in efficacy between different modalities of denervation.[14]

The following criteria have been suggested when RDN was tried in patients with resistant HTN:

- Office BP >160 mmHg or >150 in type 2 diabetic patients
- ≥3 antihypertensive drugs in adequate dose including a diuretic
- Confirm adherence to medications
- Exclude secondary HTN and pseudo-resistant HTN
- Glomerular filtration rate >45 ml/min
- Suitable renal artery anatomy.

Clinical Data

Many trials have been conducted to study the effect of RDN in controlling HTN.

Positive studies

In a multicenter safety and proof-of-principle cohort study titled "Catheter-based renal sympathetic denervation for resistant

HTN,"[6] 45 patients of resistant HTN were studied and were followed up to 1 year. The study concluded that RDN caused significant and sustained blood pressure reduction, with no adverse events, in patients with resistant HTN. It also showed mean reduction of 47% in renal noradrenaline spillover.

Following this study of 45 patients and adding some more patients in a nonrandomized fashion, an open-label study looked at the durability of blood pressure reduction out to 24 months in 153 patients.[7] The procedure was without complication in 97% of patients and RDN resulted in a significant reduction in BP and the effect was sustained up to ≥2 years of follow-up, and there were no significant adverse events.

Subsequent to this open-label study, 11 patients of 153 were followed up to 36 months.[8] At 36 months, there was significant reduction in SBP and DBP. A reduction of 10 mmHg or more was seen in 93% at 36 months. There was one new renal artery stenosis requiring stenting and there were three deaths unrelated to RDN occurred during follow-up.

SIMPLICITY HTN-2 was a multicenter, prospective RCT, and a larger study.[9] It included 106 patients randomized in 1:1 fashion to RDN with standard medical treatment versus standard medical treatment alone. Primary end point was 6 months office

BP. Between-group differences in blood pressure at 6 months were 33/11 mmHg ($P < 0.0001$). Thus, this study showed significant reduction in BP compared to controls and 84% patients in the RDN group had >10 mmHg reduction in systolic BP. No serious adverse events were reported.

These trials so far were quite encouraging.

Sobering studies

However, then came SIMPLICITY-HTN 3, a sham study[10] which dampened the enthusiasm of those who reveled in RDN. It was an RCT, blinded, and parallel study that enrolled 535 patients with a mean age of 57 years, who were randomized in 2:1 manner to RDN or a sham procedure. Primary end point was changed in office systolic BP at 6 months and secondary end point was changed in 24 h ambulatory BP monitoring (ABPM). This study failed to show efficacy of RDN over sham procedure. It concluded that RDN was not superior to sham procedure and medical treatment in reducing office and ambulatory BP at 6 months in patients with resistant HTN.

A Cochrane review[15] looked at 1149 patients from 12 studies. The authors concluded, "in patients with resistant HTN, there is low-quality evidence that RDN does not change major cardiovascular events and renal function. There was moderate quality evidence that it does not change blood pressure and low-quality evidence that it caused an increase of bradycardia episodes." They suggested that future trials should have a larger sample size, standardized procedural methods, longer follow-up, and hard clinical endpoints.

A meta-analysis by Fadl *et al.*[16] which included 5652 patients from seven major trials of RDN sounded a similar note. 985 patients were randomized to control (n 397) or RDN with SYMPLICITY™ catheters (n 588). Follow-up was for 6 months. The study concluded that, in selected patients of resistant HTN on antihypertensive drugs, RDN with the SYMPLICITY systems did not significantly decrease BP, but the procedure was safe. The authors suggested that future trials should make an effort to identify responders among hypertensive patients with evidence of sympathetic nervous overactivity.

Discrepancy between the study results

Prior studies[6-8] were non-randomized and compared the treatment results with baseline observations rather than with the results in a control group. Without a control group, the observed beneficial effect may have been a result of a close follow-up the patients received (i.e., the Hawthorne effect). SIMPLICITY-HTN 2 trial[9] lacked blinding and that is likely to introduce bias. The other limitations of the SIMPLICITY-HTN 2 trial[9] were probably unrecognized cases of white coat HTN and secondary HTN. The SIMPLICITY-HTN 3 trial[10] was a sham-controlled study and underscores the importance of conducting blinded trials with sham controls of a strategy before their clinical adoption. The SIMPLICITY-HTN 3 trial[10] clearly established an important placebo effect on results.

New studies: New era and ray of hope for RDN

After learning lessons from the previous trials in aspects of methodology, devices, and techniques, more studies on RDN were carried out, rolling out positive results, and resurrecting RDN in a way.

A randomized control trial, the RDN for HTN trial,[17] where 106 patients of resistant HTN were randomized, showed the superiority of RDN in combination with optimized pharmacotherapy compared with pharmacotherapy alone.

The PRAGUE-15 study[18] a randomized, open-label trial in 106 patients documented similar effects between RDN and optimized pharmacotherapy (mainly by adding spironolactone) with respect to BP-lowering efficacy; however, the pharmacotherapy was associated with more side effects and high discontinuation rates.

RCT-SPYRAL-HTN-OFF MED:[11] In this study, 353 patients were screened. 80 patients were randomly assigned to RDN ($n = 38$) or sham control ($n = 42$) and followed up for 3 months. The efficacy of RDN was studied in the absence of antihypertensive medications, and it showed that office BP and 24 h ABPM reduced significantly from baseline to 3 months in the RDN group compared to control group and gave a biological proof of principle for the blood pressure-lowering efficacy of RDN. There were no major adverse events.

RCT-SPYRAL-HTN-ON MED[12] an international, randomized, single-blind, sham control, and proof-of-concept trial studied patients with uncontrolled HTN (aged 20–80 years) on antihypertensive medications and they included drug adherence testing also.

467 patients were screened and enrolled and the analysis of the first 80 patients randomly assigned to RDN ($n = 38$) and sham control ($n = 42$) was reported.

The reduction in blood pressure was significantly greater at 6 months in the RDN group than the sham control group for office systolic blood pressure, 24 h systolic blood pressure, office diastolic blood pressure, and 24 h diastolic blood pressure.

The study concluded that RDN in the main renal arteries and branches significantly reduced blood pressure compared with sham control with no major safety events. However, it was noted that incomplete medication adherence was common.

RADIANCE-HTN SOLO[13] study examined the treatment effect of the paradise RDN system (ReCor Medical) using ultrasound energy in hypertensive patients not on antihypertensive medication (daytime ambulatory blood pressure >135/85–<170/105). In this trial, RDN was by performing a circumferential ablation of the renal artery using ultrasound energy. Approximately two–three ablations lasting 7 s were delivered to each main renal artery. Here, too, the sham control strategy was followed.

The advantage of ultrasound energy is that it is able to be targeted to a specific depth.

At 2 months, treatment with RDN reduced daytime ambulatory systolic blood pressure to a greater extent than was observed in the sham arm. Overall, 20% of those who underwent RDN had

a daytime ambulatory blood pressure of <135/85 mmHg in the absence of antihypertensive medication. In addition, 24% had a 24-h ambulatory blood pressure <130/80 mmHg without medication. Comparatively, just 3% of patients in the sham arm achieved either of these treatment targets.

Three-arm randomized trial of different RDN devices and techniques in patients with resistant HTN,[14] this trial compared the effectiveness of three different strategies for RDN among patients with resistant HTN. 120 patients were randomized to RDN of the main renal arteries (RFM-RDN) (n = 39) versus radiofrequency RDN of the main renal arteries, side branches, and accessories (RFB-RDN) (n = 39) versus endovascular ultrasound-based RDN of the main renal artery (USM-RDN) (n = 42). Duration of follow-up was 3 months, mean patient age was 63.5 years, and 31% were females. It showed that among patients with resistant HTN, RDN using the paradise endovascular ultrasound RDN system resulted in a greater reduction in ambulatory SBP at 3 months compared with radiofrequency ablation of the main renal artery alone, but not over radiofrequency ablation of the side branches in addition to the main artery.

What do the Guidelines Say?

ACC/AHA guidelines[19] state that "several studies have investigated devices that interrupt sympathetic nerve activity (carotid baroreceptor pacing and catheter ablation of renal sympathetic nerves); however, these studies have not provided sufficient evidence to recommend the use of this device in managing resistant HTN. In particular, two RCTs of renal sympathetic nerve ablation have been negative.

ESC/ESH guidelines[20] state that "use of device-based therapies is not recommended for the routine treatment of HTN, unless in the context of clinical studies and RCTs, until further evidence regarding their safety and efficacy becomes available."

These guidelines were published before the present series of positive studies in favor of RDN. It appears that RDN has staged a comeback and is likely to find a place it deserves in the future guidelines.

Role of RDN

Role of RDN could be traced back to the years 1935–1960 when surgical sympathectomy was the treatment for malignant HTN and was found to be beneficial.[21] Although it improved survival and reversed target organ damage, it had to be discontinued due to disabling side effects such as hypotension and syncope.

RDN has a sound physiologic, pathophysiologic, and anatomic basis to be a therapeutic procedure for HTN. There are some questions to be answered in this interesting field of RDN.[22]

1. Are there predictors for responders?
2. Are there any intraprocedural feedbacks to inform the effectiveness of the sympathetic denervation?
3. Although researchers feel that BP reduction is an excellent surrogate marker, clinicians would like to have its effect on hard cardiovascular endpoints.

Conclusion

RDN as a form of treatment for HTN has gone through ups and downs. The present studies seem to be resurrecting RDN strategy in a select group of hypertensive patients. It is a minimally invasive percutaneous procedure and has established its safety, efficacy, and durability. It is likely to find a place in our therapeutic armamentarium and in guidelines in near future.

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Review Article

Hypertension and Cognitive Function

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Abstract

Persistent hypertension is a modifiable risk factor for stroke, cognitive impairment, and dementia. Cognitive impairment and dementia may be due to acute or recurrent strokes secondary to hypertension or due to chronic structural changes in the brain induced by chronic hypertension.

Key words: Hypertension, cognitive, dementia.

Introduction

Hypertension is known to damage many organs in the body, including the brain. Persistent hypertension is a modifiable risk factor for stroke, cognitive impairment, and dementia. Hypertension is linked to the development of both vascular dementia and Alzheimer's disease (AD), which are the two most common forms of dementia. Cognitive impairment and dementia may be due to acute or recurrent strokes secondary to hypertension or due to chronic structural changes in the brain induced by chronic hypertension.

Observational Studies

Several long-term observational studies have provided strong evidence for a relationship between hypertension and cognitive dysfunction.[1-8] A study of 1301 persons aged 75 years or more without dementia who were followed up for 3 years showed that the incidence of dementia reduced by 30% in persons with hypertension who were treated with antihypertensive drugs.[1] In a French study of persons aged 59–71 years, the risk of cognitive impairment was increased 2.8 times at 4-year assessment in persons with hypertension.[2] A community-based study of persons with a mean age of 72 years showed poorer cognitive function associated with increased blood pressure (BP) variability.[4] In the Rotterdam study, 7046 elderly persons who were free of dementia at baseline were followed for about 2 years. The incidence of dementia decreased by 24% in persons on

antihypertensive drug therapy, vascular dementia risk decreased by 30%, and AD decreased by 13%.[8]

A few studies showed a strong association between midlife hypertension and cognitive impairment and dementia.[9-11] Executive function and processing speed were the cognitive domains more affected, whereas memory was less affected. As far as late-life BP was concerned, the risk of dementia increased only with extremes of BP.[12] A couple of recent studies yielded further evidence for an association between midlife systolic hypertension and cognitive impairment two decades later.[13,14]

Supportive Evidence

Neuroimaging and autopsy studies which have looked at the relationship between BP and cognitive dysfunction provide further evidence. Magnetic resonance imaging showing cerebrovascular disease and atrophy, quantitative analysis of Aβ deposition on positron-emission tomography, and autopsy studies of pathological correlates of dementia constitute this evidence.

Hypertension is the main risk factor for chronic ischemic white matter lesions in the brain, which are associated with cognitive dysfunction.[15] Radiological studies using magnetic resonance imaging have shown 2.3–3.4 times higher incidence of ischemic white matter lesions in persons with hypertension.[16]

A meta-analysis showed that higher BP levels are associated with smaller total, cortical, and hippocampal brain volumes,

regardless of treatment with antihypertensives.[17,18] There is also evidence linking BP and AD pathology. The deposition of vascular Aβ leading to cerebral amyloid angiopathy is a risk factor for AD, microhemorrhages, macrohemorrhages, microinfarction, and vascular cognitive dysfunction.[19] Positron-emission tomography studies have shown that the extent of Aβ deposition in the brain positively correlates with higher pulse pressure and higher systolic and diastolic BP. Autopsy studies have shown evidence of neurofibrillary tangles and neuritic Aβ plaques, typical of AD pathology, in the brains of hypertensive older adults.

Randomized Controlled Trials

Many randomized controlled trials have provided evidence that treatment of hypertension reduces the incidence of stroke.[20] However, randomized controlled trials that studied the role of antihypertensive treatment in preventing dementia have yielded mixed results.[5] While some studies showed a benefit of antihypertensive therapy in reducing incidence of dementia, others failed to do so. The Systolic Hypertension in Europe trial,[21] Perindopril Protection Against Recurrent Stroke Study,[22] and Heart Outcomes Prevention Evaluation study[23] all showed decrease in the incidence of dementia, whereas the Systolic Hypertension in the Elderly Program[24] and the Hypertension in the Very Elderly Ttrial[25] showed insignificant improvement in cognitive dysfunction.

Possible explanations for the negative results could include methodological issues. Many of these studies did not have prevention of cognitive dysfunction as a primary endpoint and looked at cognitive dysfunction among secondary end points. Consequently, appropriate parameters were not considered when assessing cognitive functions. Most studies have not considered the duration of hypertension, which is thought to be a more important risk factor than age itself. A recent study demonstrated that midlife hypertension modifies the relationship between late-life hypertension and brain function. In persons without midlife hypertension, higher systolic and diastolic BPs in late life were associated with cerebral small vessel disease, whereas in persons with midlife hypertension, lower late-life diastolic BP was associated with more atrophy and cognitive dysfunction.[26] Another reason could be the non-inclusion of dementia biomarkers. It is known in AD that tau and Aβ biomarkers precede the onset of clinical features of dementia by several years. The effect of individual antihypertensives also needs to be considered. The beneficial effects on cognition were found to be highest for the angiotensin receptor blockers, followed by calcium channel blockers, beta-blockers, diuretics, and angiotensin-converting enzyme inhibitors (ACEIs).[27]

The Systolic BP Intervention Trial (SPRINT) focused on the effect of intensive (systolic BP <120 mmHg)[28] versus standard (systolic BP <140 mmHg) BP control on cardiovascular outcome. The trial was stopped early because of the cardiovascular benefit, but collection of data on cognitive functions in persons aged 75 years or more was continued as the SPRINT MIND[28] study which was presented at the Alzheimer's Association International Conference.[29] Lowering systolic BP to a target of 120 mmHg or less in people with cardiovascular risk factors reduced the risk of primary end point, probably all-cause dementia by 17% which was not statistically significant. However, it reduced the risk of secondary end points of mild cognitive impairment (MCI) by a statistically significant 19% and combined secondary endpoint of MCI and probable dementia by a significant 15%.

The imaging part of the study of 454 subjects had brain MRI at baseline and 4 years later. Although there was no change in total brain volume, those receiving intensive BP lowering had 18% lower white matter lesion load than those in the standard care group, statistically a significant reduction.

Animal studies have shown that angiotensin II type 1 receptor blockers (ARBs) and ACEIs reduce the amount of AD-like pathology and improve cognitive performance in most mouse models of AD. This beneficial effect seen in animal studies is supported in secondary outcomes of clinical trials of various ARBs and ACEIs, as well as in epidemiological studies where the prevalence of AD was reduced.[21-22,30-32]

Conclusion

The available evidence suggests that hypertension is strongly associated with cognitive impairment and dementia. Midlife hypertension and duration of hypertension correlate better with cognitive dysfunction in later life. While there is enough evidence to show that hypertension is associated with vascular dysfunction, cerebrovascular disease, and Aβ deposition, there is a lack of consistent data from randomized controlled clinical studies evaluating the effect of lowering BP on dementia.

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Review Article

Renin-angiotensin-aldosterone System Blockers, Hypertension and Clinical Outcomes

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Abstract

The renin-angiotensin-aldosterone system (RAAS) plays a key role in the physiology of blood pressure control and the pathophysiology of hypertension (HTN). Fortunately, RAAS blocking agents have been available to treat HTN since the 1970s and newer medications are being developed. In this review, we will refresh our current understanding of the RAAS pathway, examine anti-hypertensive medications affecting the RAAS, evaluate recent studies that help provide a better understanding of RAAS blockade on clinical outcomes and review newer RAAS blocking agents and RAAS modulation in clinical practice.

Key words: Advances, hypertension, outcomes, RAAS system, RAAS blockers

Introduction

The renin-angiotensin (Ang)-aldosterone system (RAAS) consists of a group of enzymes and peptides whose main function is to control blood pressure (BP) by regulating vasoconstriction, sodium reabsorption and body fluid homeostasis.

Historical Perspective

Our knowledge of the RAAS started in 1898 when Tigerstedt and Bergman showed that renal extract from rabbits increased BP when infused and named it as renin.[1] In 1934, Goldblatt demonstrated that renal artery constriction caused renal ischemia and induced hypertension (HTN) in dogs. Later, in 1939–1940, Braun-Menende in Argentina and Page and Helmer in the USA simultaneously discovered a pressor substance capable of causing renal HTN. This was originally named hypertensin in Argentina and angiotonin in the USA and later renamed as angiotensin to give credit to both groups.[1] The discovery of captopril, an orally active Ang-converting enzyme inhibitor (ACE-I) in 1980 and Ang receptor blockers (ARBs) in 1998, went on to revolutionize medical care.[3]

Current Understanding of the RAAS Pathway

The modern view of the RAAS began with the concept that this was a lifesaving system, which raised BP in case of an acute hemorrhage. RAAS raises BP beginning with the release of renin into the bloodstream.[4] This circulating renin cleaves hepatic angiotensinogen and generates Ang I, which is converted to Ang II by pulmonary ACE. Ang II causes smooth muscle cell vasoconstriction, stimulates the sympathetic nervous system, and promotes renal retention of salt and water. Moreover, in the adrenal glands, Ang II stimulates the release of aldosterone, which enhances tubular sodium reabsorption in the kidney and increases the effective circulating plasma volume [Figure 1].[4]

In the heart, kidney, and brain, AII is also produced by non-ACE pathways namely chymases, cathepsin G, kallikrein-like enzymes and endopeptidases.[2] AII acts by binding to the G protein-coupled receptors type 1 (ATR1) and type 2 (ATR2). The ATR1 receptor mediates the more deleterious effects of AII - that is, vasoconstriction and cardiac and vascular hypertrophy. The ATR2 receptor regulates opposing effects. In addition to the conversion of AI to AII, ACE inactivates two vasodilator peptides, bradykinin and kallidin.[4]

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ACE2 and (Pro)Renin Discovery

Recently, ACE2 discovery represents a paradigm shift in RAAS understanding [Figure 3]. ACE2 is a carboxypeptidase whose main function is to degrade Ang II to generate Ang 1–7.[4] Although ACE2 can also degrade Ang I to generate Ang 1–9, its catalytic efficiency is 400-fold higher with Ang II.[4] Therefore, its main effect is the degradation of Ang II to Ang 1–7. Ang 1–7 exerts opposite peripheral actions to those of Ang II by binding predominantly to the Mas1 receptor (Mas1R).[4] The most prominent effect of A(1-7) is the inhibition of the AII-induced vasoconstriction apart from its antiarrhythmogenic, antithrombotic, and growth inhibitory effects [Figure 2].

The identification of ACE2 provided evidence that the RAAS had two pathways with opposite effects: The classic ACE/Ang II/AT1R and the new ACE2/Ang 1–7/Mas1R (and AT2R) pathway [Figure 3].[4] Accordingly, the current scientific opinion is that what is critical in CVD development is an imbalance between ACE-Ang II and ACE2-Ang 1–7. ACE2 is regarded as the central regulator of the RAAS.[4] Changes in ACE2 level/activity can enhance Ang II detrimental actions and negate Ang 1–7 protective effects [Figure 3].

The final entry in our understanding of the RAAS is the (pro) renin receptor [(P)RR], which is a specific receptor for both renin and its inactive precursor prorenin.[4] When (pro)rennin binds to (P)RR, it results in the degradation of angiotensinogen to Ang I and also activates mitogen-activated protein kinases.[4] These mechanisms, independent of Ang II generation, have adverse consequences in terms of organ damage and progression of

cardiovascular disease. RAAS is targeted at different places by the existing antihypertensive therapies. ACEIs and ARBs block the feedback loop and increase plasma renin activity (PRA) [Figure 4].[5] This increase in PRA may limit the organ protection offered by these drugs. The whole RAAS is therefore upregulated although Ang II is blocked. Direct renin inhibitors (DRI) target the RAAS at its point of activation, resulting in the reduction of PRA.[5] Hence, the production of Ang I decreases resulting in less substrate available for conversion to Ang II. In doing so, DRI produces effective overall RAAS suppression.
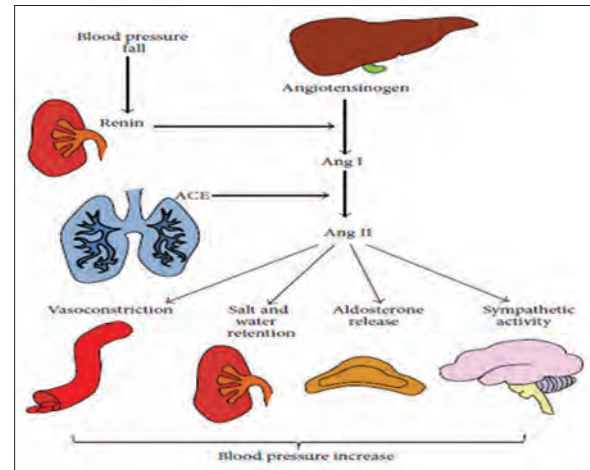

Figure 1: The activation of systemic renin-angiotensin-aldosterone system cascade for blood pressure control.[4] Journal of Diabetes Research Volume 2016, Article ID 8917578
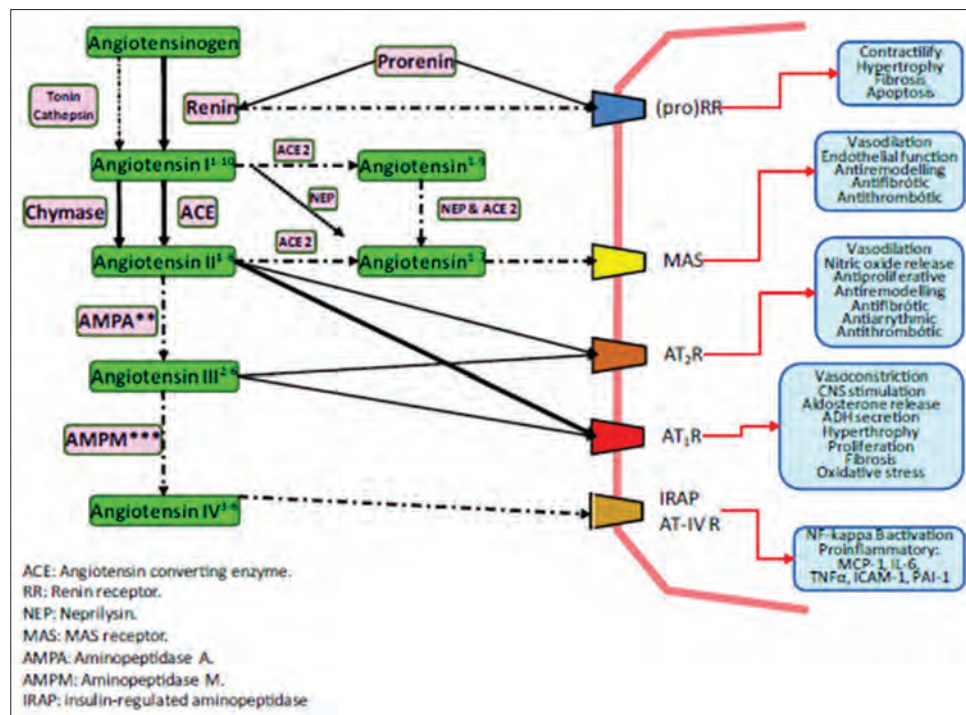

Figure 2: Renin-angiotensin-aldosterone system. J Diabetes Metab 3:171

Circulating and Tissue Renin-Ang-Aldosterone System

The observation that many tissues were capable of synthesizing the RAAS led to another paradigm shift in RAAS understanding[4]: That RAAS is not anymore only a circulating hormonal system but also a tissue system widespread in cardiovascular organs.[4] ACE and Ang II receptors were identified in all the relevant target tissues including the heart, kidney, blood vessels and adrenal glands, where they have not only endocrine but also paracrine and autocrine effects [Table 1].[4]

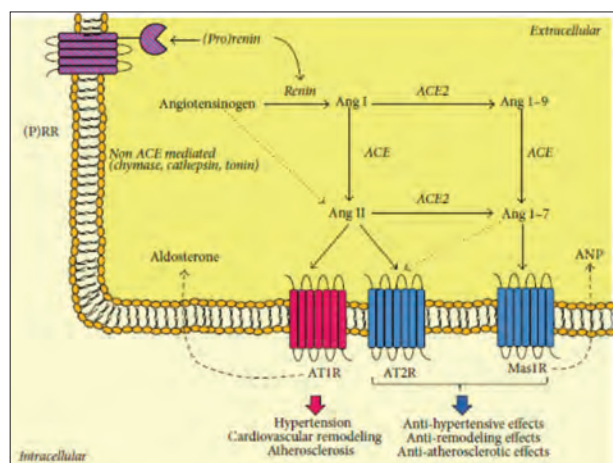## Agents that Block the RAAS: Their Effects on CVD and Renal Disease

Figure 3: The new angiotensin (Ang)-converting enzyme 2/Ang 1–7/Mas1R (and AT2R) pathway.[4] Journal of Diabetes Research Volume 2016, Article ID 8917578

The pharmacological inhibition of the RAAS can be obtained through three different basic mechanisms: (1) Inhibition of AII generation from AI, achieved through inhibition of ACE; (2) inhibition of the action of AII at the level of its receptor(s), and (3) inhibition of AI generation from angiotensinogen obtained by direct inhibition of renin.[2] Thus, drugs acting on the RAAS include the DRIs, the ACEIs, the ARBs, the aldosterone receptor antagonists and a new class of combined ACE and neutral endopeptidase inhibitors called the vasopeptidase inhibitors [Figure 5].[2]

ACE Inhibitors

Oral ACE inhibitors, the oldest category of RAAS inhibitors, were commercially released over 30 years ago in the early 1980s.[2] The introduction of ACE inhibitors heralded major changes in the way HTN and cardiovascular disease was treated. They are categorized into three subgroups according to their mode of metabolism: Active compounds that are metabolized to form inactive metabolites (e.g., captopril); prodrugs that require hepatic metabolism (e.g., enalapril maleate, fosinopril, perindopril, quinapril, ramipril, and trandolapril); and active compounds that are excreted unchanged (e.g., lisinopril).[2] However, ACEIs also differ within these groups in their bioavailability, protein binding, lipid solubility, affinity to the ACE binding site, duration of onset, half-life and potency. ACEIs have proved to be highly successful in the treatment of HTN-related target organ damage, including left ventricular hypertrophy, heart failure, postmyocardial infarction left ventricular remodeling, renal insufficiency and diabetes with proteinuria. The most common reported adverse reactions ascribed to ACEIs include hypotension, renal impairment, hyperkalemia, cough and angioedema.[2]

Table 1: Cellular and tissue effects of Ang II, Ang 1–7, aldosterone, and (pro) renin in normal conditions[4]

Tissue	ATII through AT1R	Ang1-7 through MAS1R	Aldosterone through MR	Pro (rennin) through (P) RR
Cardiomyocytes	Hypertrophy	Hypertrophy inhibition	Hypertrophy Apoptosis Oxidative stress	Hypertrophy Hyperplasia
Cardiac fibroblasts	Proliferation Extracellular matrix production	Antiproliferative effects Inhibition of collagen production	Proliferation and migration Extracellular matrix production	
Endothelial cells	Oxidative stress Inflammation	No production Anti-inflammatory effects	Oxidative stress Inflammation	Hyperplasia survival
Smooth muscle cells	Oxidative stress Hypertrophy Proliferation Migration Extracellular matrix production	Antiproliferative effects	Proliferation Migration Extracellular matrix production	Hyperplasia Survival Oxidative stress
Macrophages	Inflammation	Anti-inflammatory effects	Inflammation Oxidative stress	Inflammation
Heart	Hypertrophy Fibrosis apoptosis	Antiarrhythmic Antifibrotic Antiremodeling effects	Hypertrophy Fibrosis Proarrhythmogenic Inflammation	Cardiac function deterioration Fibrosis Angiogenesis
Vessels	Impaired vascular relaxation Atherosclerosis	Vasodilatation Antiatherosclerotic	Impaired vascular relaxation Atherosclerosis	Angiogenesis

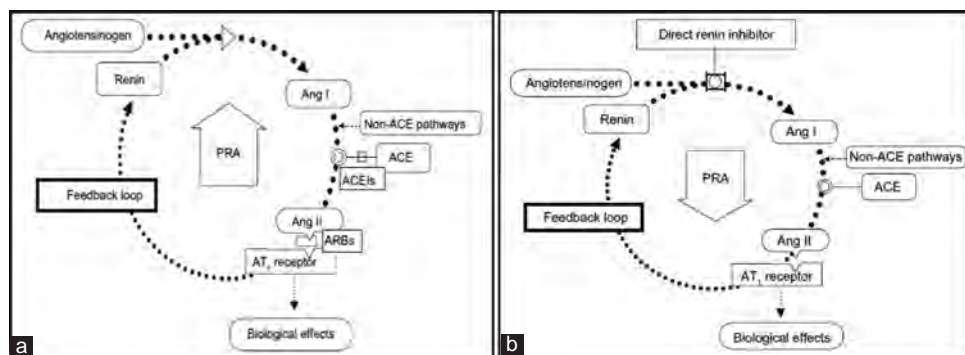Journal of Diabetes Research Volume 2016, Article ID 8917578

Figure 4: (a) Angiotensin (Ang)-converting enzyme inhibitor and Ang receptor blockers cause compensatory increases in plasma renin activity (PRA). (b) Direct renin inhibition acts at the point of activation of the renin system and neutralizes the PRA increase. Vascular Health and Risk Management 2010:6 549–559[5]
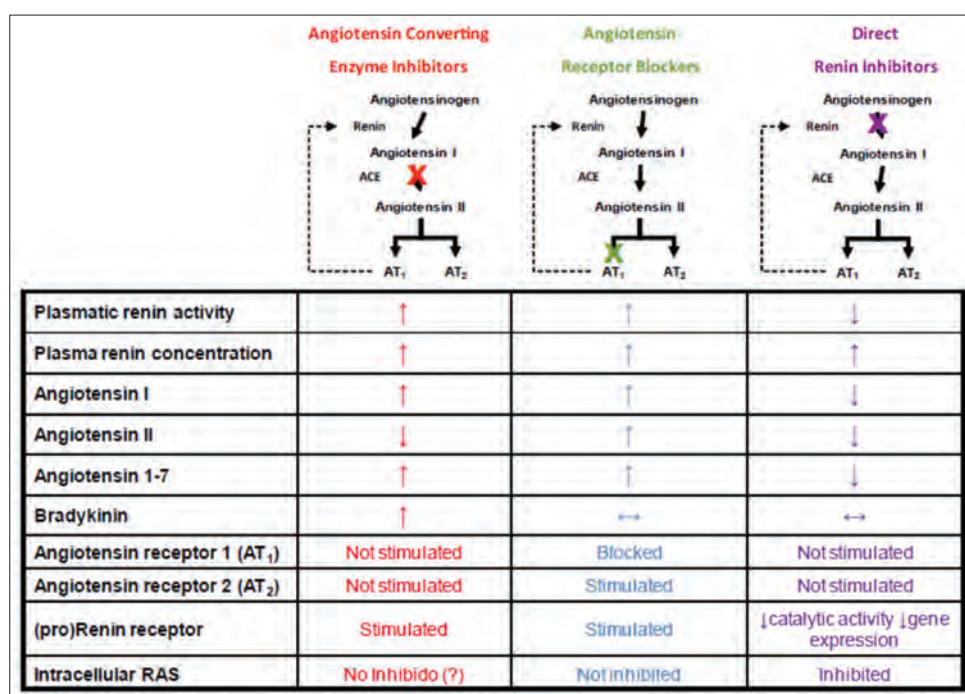

Figure 5: Inhibition of renin-angiotensin system.[2] J Diabetes Metab 3:171

Ang II-Aldosterone Escape

The advantages of Ang II reduction by ACE inhibition are substantial but may be compromised in the long term due to "Ang II and aldosterone escape." [6] Disrupted negative feedback mechanisms cause renin and Ang I concentrations to rise, eventually leading to Ang II escape when non-ACE enzymes such as chymase convert Ang I to Ang II.[6] Similarly, aldosterone escape occurs after long-term ACE inhibitor therapy. Given this scenario, one might expect ACE inhibitors to lose all their efficacy in the long term, but this is not the case. ACE inhibitors also increase concentrations of the vasodilatory peptide bradykinin. Bradykinin causes the release of the vasodilator nitric oxide and other relaxing factors. Physiologically, bradykinin is regarded to have opposite effects of Ang II, namely it reduces BP, protects the heart and improves arterial function. These bradykinin-mediated effects help counter the "escape" effects and maintain the efficacy of ACE inhibition in the long term.[6]

Ang 1 Receptor Blockers

ARBs prevent the binding of Ang II to AT1 receptors.[2] Vasoconstriction, sympathetic stimulation, oxidative stress, release of inflammatory factors and aldosterone release are all reduced by AT1 receptor blockade. Compared with ACE inhibition, selective AT1 receptor blockade has certain distinct advantages, like the absence of Ang II escape by blockade of all Ang II, independent of the site of production.[2] Pure AT1 receptor blockade may, however be a mixed blessing. Ang II increases in response to AT1R blockade allows Ang II to bind to Ang receptors (AT2, AT3, and AT4). AT2 receptor activation causes positive effects
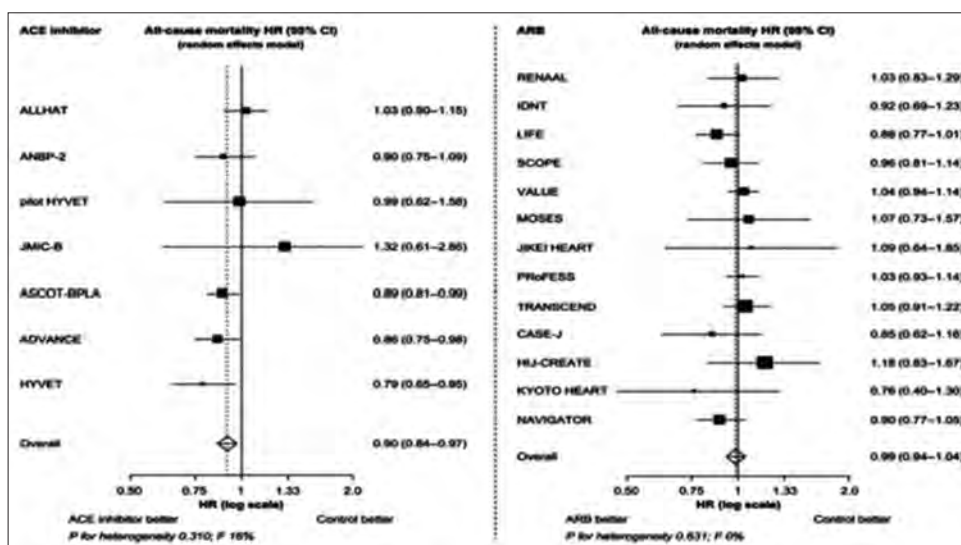
Figure 6: The effect of treatment on all-cause mortality in angiotensin (Ang)-converting enzyme (ACE) inhibitor and Ang receptor blockers (ARB) hypertension trials. The effect of treatment on all-cause mortality was significant with ACE inhibitors ($P = 0.004$), but not with ARBs ($P = 0.683$). Eur Heart J. 2012;33:2088–2097
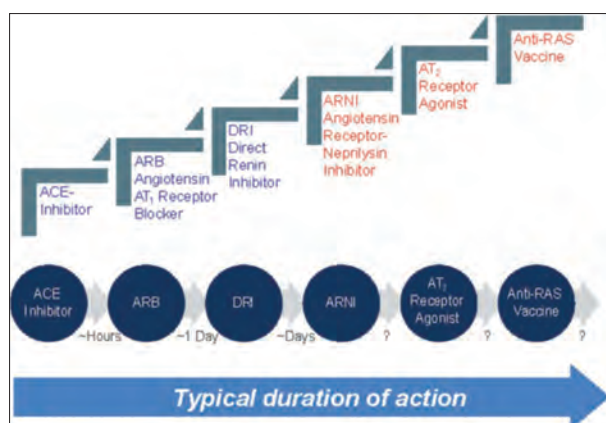

Figure 7: Evolution of renin-angiotensin system (RAS) inhibition strategies.[3] Ther Adv Cardiovasc Dis 2016, Vol. 10(3) 118–125

such as vasodilation and diminished proliferation.[2] The AT2 receptor is also responsible for regulating aldosterone escape in ARBs. Not much is known about the effect of AT3 receptor stimulation, while AT4 receptor stimulation is thought to promote thrombosis.[2]

ACEIs and ARBs have been the cornerstone of RAAS inhibition for years and are key therapeutic options in patients with HTN, reducing cardiovascular morbidity and mortality and improving renal outcomes.[1] In the HOPE (Heart Outcomes Prevention Evaluation), MICRO-HOPE (The Microalbuminuria, Cardiovascular, and Renal Outcomes in HOPE), EUROPA (European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease), SOLVD (Studies of Left Ventricular Dysfunction)and Captopril Prevention Project studies. ACEIs were beneficial in

reducing rates of death, myocardial infarction, stroke, coronary revascularization, cardiac arrest and complications related to diabetes and heart failure.[1,7] Both the RENAAL[15] and IDNT trials demonstrated a renoprotective effect of RAAS inhibition in diabetic nephropathy (DN).[1,7] ACEIs and ARBs are considered to be equally beneficial on the basis of studies such as ONTARGET, which compared telmisartan and ramipril and DETAIL,[12] which compared telmisartan with enalapril and found no difference in progression of diabetic nephropathy[1,7]

In patients with HTN and left ventricular hypertrophy, ARB-based therapy, compared with beta-blocker (atenolol)-based therapy with identical BP control, has shown to significantly reduce the composite risk of cardiovascular death, stroke and MI and to decrease the rate of new-onset diabetes (LIFE study).[1,7]

In patients with chronic heart failure, addition of an ARB to conventional treatment compared with placebo, has been shown to significantly reduce the risk of cardiovascular mortality and hospitalization (CHARM and Val-HeFT studies).[1,7] In high-risk post-MI patients, ARB therapy has been shown to reduce the risks of all-cause mortality, recurrent MI, sudden cardiac death, revascularization, coronary artery bypass grafting, or all-cause hospital admission to a degree similar to that of ACEI therapy (OPTIMAAL study).[1,7]

Mortality Reduction with RAAS Inhibitors In Contemporary Trials of HTN: Are ACE-I and ARB equivalent?[6,9,10]

The most recent meta-analysis of mortality reduction with RAAS inhibition in HTN, published in the European Heart Journal, confirmed a difference between ACE inhibitors and ARBs in terms of mortality reduction in HTN. Overall, there were
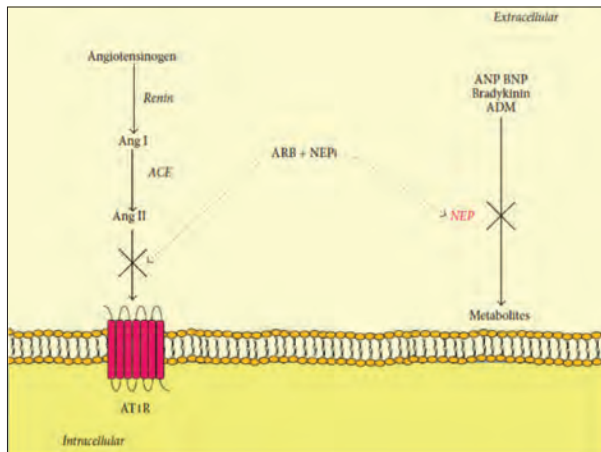
Figure 8: Mechanisms of action of angiotensin receptor/neprilysin inhibitors. Journal of Diabetes Research Volume 2016, Article ID 8917578

76,615 patients from ACE inhibitor trials and 82,383 patients from ARB trials in the meta-analysis. Approximately half of the 158,998 patients were randomized to active treatment (n = 71,401) and half to control (n = 87,597).[6,9] The relative risk of all-cause mortality fell significantly by 5% (P = 0.032) with RAAS inhibitors. ACE inhibitors were responsible for much of this mortality reduction; 10% (P = 0.004).[6,9] In contrast, there was no significant relative risk reduction in all-cause mortality with ARBs (P = 0.683). There was a significant difference in treatment effect between ACE inhibitors and ARBs (P = 0.036) [Figure 6].[6,9]

With regard to cardiovascular mortality, RAAS inhibition was shown to significantly reduce the relative risk of cardiovascular mortality by 7% (P = 0.018).[6] Analysis of nine ARB trials that reported cardiovascular mortality data showed that ARBs were not responsible for this reduction (P = 0.143). Mortality reduction was dominated by the effect of ACE inhibitors, with a relative risk reduction of 12% (P = 0.051) from seven ACE inhibitor trials [Figure 6].[6,9]

Dual RAAS Blockade

The dual blockade strategy comes from the concept called "Ang 2-Aldo escape". Incomplete blockade of the RAAS with ACEI causes Ang II escape by non-ACE pathways. ARB monotherapy causes lack of negative feedback producing high PRA and consequent increases in AI and AII and AT2R-mediated Aldo escape. Dual blockade would, therefore, provide a more complete blockade of the RAAS. This "maximization approach," however, may induce more adverse effects such as hyperkalemia, symptomatic hypotension or hemodynamically mediated deterioration of renal function. However, the role of dual RAAS blockade in clinical practice is unclear based on large clinical trials both for congestive heart failure (CHF) and chronic kidney disease (CKD).

Dual RAAS Blockade on Cardiovascular Outcomes

The valsartan in acute myocardial infarction (VALIANT)[5] study of 14,703 elderly patients with the left ventricular systolic dysfunction, CHF, or both after MI reported similar rates of all-cause mortality, death from cardiovascular events, recurrent MI and hospitalization for heart failure in all three treatment groups (ACEI, ARB, and ACEI/ARB), accompanied by significantly (P = 0.05) more adverse events in the combination therapy group.

Two meta-analyses of patients with CHF or left ventricular dystrophy (CHARM-Added, Val-HeFT, and VALIANT)[5] showed that ACEI/ARB combination therapy significantly increases the risk for adverse events (e.g., HTN, worsening renal function, and hyperkalemia), inducing treatment discontinuation.[5]

The valsartan heart failure trial[5] determined whether valsartan could further reduce morbidity and mortality in patients with heart failure, who were already receiving optimal therapy (including ACEIs in 93% of patients and β-blockers in 35% of patients). The primary end point of mortality was similar for the valsartan and placebo groups, whereas the combined primary end point of morbidity and mortality was significantly reduced (P = 0.009) in patients receiving valsartan plus optimal therapy compared with the placebo group.[5]

Based on this data, dual RAAS blockade could be indicated for the treatment of CHF although hard end point benefits are lacking.

Dual RAAS Blockade on Renal Outcomes

In patients with CKD, dual blockade with ACEI/ARB has been shown to reduce BP and proteinuria more effectively than either monotherapy. However, evidence for the benefit of ACEI/ARB combination on hard endpoints in CKD is lacking. In the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial[5,10,11] (ONTARGET), combination therapy with telmisartan plus ramipril produced no greater reduction in the primary end point of death from cardiovascular events, MI, stroke, or hospitalization for heart failure than monotherapy in high-risk patients with cardiovascular disease or diabetes but without heart failure.[5] The decline of estimated glomerular filtration rate (eGFR) and dialysis requirement was higher with dual RAAS blockade than that of monotherapy group.[5] Combination therapy was associated with an increased risk of hypotension (P = 0.001), syncope (P = 0.03), hyperkalemia (P = 0.001), and acute renal impairment (P = 0.001).[5,10] However, followup reported that the risks of development and progression of microalbuminuria and macroalbuminuria were lower for those receiving combination therapy (hazard ratio [HR] = 0.88, P = 0.003 and HR = 0.76, P = 0.019, respectively), compared to the ramipril alone. Other metaanalyses have also shown that as compared with ACEI or ARB alone, combination therapy results in 20–30% additional reduction in proteinuria.

The goal of the Veterans Affairs Nephropathy in Diabetes trial[7,14] (VA NEPHRON-D) was to evaluate whether

combination treatment with ACEI (lisinopril) and ARB (losartan) compared with ARB alone in patients with DN slows the progression of CKD. Patients with diabetes, eGFR of 30.0–89.9 mL/min per 1.73 m² and a UACR of >300 mg/g were included in the study. After 2.2 years, the primary outcome of decrease in eGFR, end-stage renal disease or death occurred in 18.2% in the combination of ACEI/ARB group versus 21.0% in the ARB group (P = 0.30).[7,14] There was increased risk for adverse events in the combination group versus ARB alone, including acute kidney injury (18.0% vs. 11.0%; P < 0.001) and hyperkalemia (9.9% vs. 4.4%; P < 0.001).[7,14] The increased risk for adverse events led to early termination of the trial.

The results of ONTARGET, VA NEPHRON-D confirms that dual RAAS blockade has not shown to be superior to monotherapy in any trial of validated hard renal end points, namely doubling of creatinine, time to dialysis or death. It shows promise in nephrotic syndromes, advanced proteinuric nephropathy for additional proteinuria reduction. Whether this additional proteinuria reduction translates into meaningful outcomes of CKD is unknown, as proteinuria change is not a validated surrogate end point. Until we know the answer to this question, only those with very high levels of proteinuria should receive combination RAAS blocking therapy with carefully monitoring.

DRI

Renin secretion is the first step of the RAAS cascade.[3,8] Inhibition of renin provides an attractive option to inhibit the RAAS from its origin.[8] The development of DRI started >30 years ago, but there were issues with potency, bioavailability and cost. At present, aliskiren is the only approved DRI for use in HTN and a significant BP reduction has been demonstrated in patients with essential HTN.[3,8] Aliskiren is well tolerated and has a similar dose-dependent BP reduction in hypertensive patients as ARBs.[8]

However, several recent studies have shown either no benefit or even harmful effects of aliskiren in certain populations. The Aliskiren in Type 2 Diabetes Using Cardio-Renal Endpoints trial (ALTITUDE) randomly assigned patients with type 2 diabetes and CKD or with cardiovascular disease already on ACEI or ARB to aliskiren or placebo.[7,13] Although there was a lower BP in the aliskiren arm, there was no reduction in the primary composite outcome, which included cardiovascular and renal events and mortality.[7,13]

In the Aliskiren Trial to Minimize Outcomes in Patients with Heart failure (ATMOSPHERE trial), the addition of aliskiren to enalapril in patients with chronic heart failure was not associated with reduction in adverse outcomes.[7] Similarly, no improvement in coronary atherosclerosis in prehypertensive patients (AQUARIUS) or improvement in cardiovascular outcomes in patients hospitalized with heart failure (ASTRONAUT) was seen with aliskiren compared with placebo.[7] Given the lack of demonstrated benefit and increased rates of adverse events such as hyperkalemia, hypotension, and renal impairment as seen in ASTRONAUT when combined with ACEIs or ARBs, the current use of aliskiren in combination is limited.[7]

Mineralocorticoid Receptor Antagonists (MRA)

MRAs competitively inhibit mineralocorticoid receptors and decrease the number of epithelial sodium channels in the distal renal tubule.[7] Spironolactone has long been used for the treatment of HTN; however, it is non-specific for mineralocorticoid receptors and has anti-androgenic and progestational effects. Spironolactone was found to be the most effective add-on antihypertensive drug in treating resistant HTN in the PATHWAY-2 trial.[7]

This trial supports the important role of sodium retention in resistant HTN. Eplerenone, an MRA with lower affinity to progesterone and androgen receptors than spironolactone, has been shown to be efficacious and safe in the management of HTN. The third- and fourth-generation MRAs are being developed having the potency of spironolactone and the selectivity of eplerenone.[7] Finerenone, a novel nonsteroidal MRA, has a greater affinity to the mineralocorticoid receptor than eplerenone and greater selectivity than spironolactone.[7]

The Mineralocorticoid Receptor Antagonist Tolerability Study (ARTS) finerenone (2.5–10 mg per day), decreased albuminuria with lower rates of hyperkalemia compared with spironolactone in patients with CKD and albuminuria.[7] The recent Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy(ARTS-DN) study demonstrated greater reduction in albuminuria with the addition of finerenone to ACEI or ARB in patients with DN compared with placebo.[7]

Ang Receptor-Neprilysin Inhibition (ARNi)[4]

ACE inhibition, AT1R antagonism and MR blockade are some of the most classic therapeutic strategies against CVD. Another classic therapeutic strategy against heart failure is to increase natriuretic peptide levels as they are natriuretic, diuretic and vasodilating and able to inhibit pathologic growth in heart failure.[4] These approaches included short-term intravenous infusions of natriuretic peptides or inhibition of neprilysin, which is the enzyme that degrades natriuretic peptides along with bradykinin, adrenomedullin and Ang II. The disappointing effect of neprilysin inhibitor was that neprilysin also degraded Ang II. Therefore, inhibiting neprilysin would increase both natriuretic peptides and Ang II and with it the detrimental effects of AT II. Hence, the combination of an ACEI and a neprilysin inhibitor was tried. Unfortunately, in clinical trials, this combination was associated with bradykinin-mediated angioedema. To overcome this issue, ARNis were developed, such as LCZ696, which is an association of the ARB valsartan with the neprilysin inhibitor sacubitril.[4] In the PARADIGM and the PARAMOUNT trial, this valsartan/sacubitril combination was found superior to enalapril in reducing the risk of death and hospitalization in patients with heart failure.[4] This is consistent with experimental models where it showed significantly reduced cardiac hypertrophy and fibrosis with improved ejection fraction.[4]

Aldosterone Synthase Inhibitors

Another way of blocking the effects of mineralocorticoid receptor activation is to inhibit aldosterone formation.[4] LCI699 is a potent first-in-class aldosterone synthase inhibitor. In patients with primary hyperaldosteronism, LCI699 (up to 1.0 mg twice a day) caused modest reduction in 24-h systolic BP (SBP) and office SBP compared with placebo.[4] LCI699 significantly lowered office and ambulatory BP in patients with primary HTN, but 20% of the patients on LCI699 developed blunted cortisol release.[4] Due to this non-specificity, the development of LCI699 has been stopped in favor of developing more specific inhibitors.

New Agents for New Targets [Figure 7]

ACE2 Replenishing Strategies

A promising therapeutic strategy in cardiovascular medicine is represented by RAAS modulation. As compared to RAAS antagonism, RAAS modulation combines ACE/AngII/AT1R blockade with the stimulation of ACE2/Ang 1-7/Mas1R and AT2R.[4] The latter can be achieved by a series of new therapies that include ACE2 replenishing strategies, Ang 1–7 administration and AT2R agonists.[4] The current therapeutic tools that modulate ACE2 levels/activity include adenoviral ACE2 gene transfer, recombinant human ACE2 (rhACE2), ACE2 activators, oral ACE2 and Ang 1–7 bioencapsulated in plant cells.[4] Both ACE2 gene transfer and the administration of an ACE2 activator have ameliorated diabetic cardiomyopathy. rhACE2 administered intravenously to healthy human subjects was well tolerated and has resulted in sustained reduction in plasma Ang II levels and elevation in Ang 1–7 levels.[4]

Ang 1–7 Administration

Several experimental studies have tested the hypothesis that Ang 1–7 infusion could ameliorate diabetic cardiomyopathy. Ang 1–7 improved all the structural hallmarks of diabetic cardiomyopathy.[4] Ang 1–7 improved cardiac recovery from ischemia/reperfusion and restored the normal vascular reactivity. These effects were completely blocked by the Mas1R antagonist, suggesting that Mas1R was the main receptor mediating Ang 1–7 effects on endothelial cells.[4]

AT2R Agonists

AT2R activation has been currently achieved by compound 21 (C21), which is a non-peptide that acts as a highly selective AT2R agonist and stimulates AT2 receptors.[4] Several studies have shown its efficacy in reducing cardiac tissue fibrosis. C21 was also able to significantly reduce renal fibrosis in experimental models. C21 was able to significantly reduce the expression of several inflammatory mediators.[4]

RAAS Blockade: Renoprotection Versus Renoprevention

While it has been shown that RAAS blockade is cardioprotective, renoprotective and hence being extensively used in clinical practice, its continued use in certain clinical settings could have deleterious effects on the kidneys. For example, continuation of RAAS blockers during episodes of volume depletion - diarrhea, during use of nonsteroidal anti-inflammatory drug, perioperatively during episodes of hemorrhage, and severe infections can precipitate acute kidney injury. Patients not only need to be educated regarding the renal benefits of RAAS blockage in the long term but also to be educated regarding stopping RAAS blockade in the short term during episodes of volume depletion - thereby gaining renoprotection.

Conclusion

The RAAS has been studied for more than a century. The current picture of the RAAS is that of an extremely complex pathway, which has not yet been fully characterized and might hold in store new aspects that have still to be discovered. Certainly, what we do know is that blocking Ang II reduces cardiovascular and renal complications. This is particularly true in diabetes, where Ang II/AT1R pathway is activated, whereas the Ang 1–7/Mas1R is not. Therefore, the aim of new therapies is not only to block ACE/AngII/AT1R-mediated harmful effects but also to augment the activity of potentially beneficial pathways, with the stimulation of ACE2/Ang 1-7/Mas1R and AT2R. Here is another paradigm shift: To move from RAAS inhibition to RAAS modulation.

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Review Article

Pathophysiology of Hypertension in Chronic Kidney Disease

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Abstract

There are a multitude of mechanism of pathogenesis of hypertension in CKD. The most important is the rennin angiotensin axis and the renal autoregulation. However the role of other mechanism like the sympathetic nervous system overactivity, drugs, endothelial dysfunction, genetics and oxidative stress cannot be ignored. In this article, we present a detailed description of the various mechanism involved in the pathogenesis of hypertension in CKD.

Key words: CKD, pathophysiology, hypertension, Renin angiotensin axis.

Introduction

Chronic kidney disease (CKD) is the most common cause of secondary hypertension.[1] CKD contributes to around 50% of secondary hypertension and 5% of all-cause hypertension. The higher prevalence of hypertension in this population increases the cardiovascular morbidity and mortality.[1] The complex interplay of factors leads to the development and persistence of hypertension in CKD.[2] The major players are extracellular volume (ECV) overload, increased renin-angiotensin-aldosterone axis (RAAS) activation, enhanced endothelin-1 release, and sympathetic nervous system (SNS) activation.[2] The dietary and lifestyle factors also have some contributory roles. The prevalence of hypertension is higher among patients with CKD when compared to the general population (64.5% vs. 41%).[3] Based on a national survey of representative sample of non-institutionalized adults in the USA, it is estimated that hypertension occurs in 23.3% of individuals without CKD, and 35.8% of Stage 1, 48.1% of Stage 2, 59.9% of Stage 3, and 84.1% of Stage 4–5 CKD patients.[4] Almost 85–90% of the incident dialysis patients will have hypertension. The prevalence of hypertension also varies with the etiology of CKD. A strong association with hypertension was found in patients with renal artery stenosis (93%), diabetic nephropathy (87%), and polycystic kidney disease (74%).[5]

Pathophysiological Mechanisms

Hypertension in CKD can be broadly classified into two categories: Volume-mediated hypertension and renin-mediated hypertension. Hypertension in CKD is primarily an imbalance in the renal autoregulatory mechanisms due to the impaired renal functions [Figures 1 and 2].

Impaired renal sodium handling and volume overload

The kidneys play such a vital role in long-term blood pressure regulation that Guyton *et al.* argued that sustained hypertension could not occur in the absence of the impairment of renal handling of sodium.[7]

Guyton *et al.* proposed that sodium balance after salt intake is regulated by the pressure-natriuresis mechanism. Sodium loading is associated with a transient increase in blood pressure which returns to primary values after pressure-natriuresis and regulation of ECV. Some individuals have impairments of sodium elimination mechanisms, and for the same sodium natriuresis effect, they need to have higher blood pressure. Thus, sodium retention causes expansion of ECV, causing higher cardiac output with tissue perfusion that exceeds metabolic needs. Peripheral tissue vasculature responds by activating autoregulatory vasoconstriction, causing further increases in peripheral resistance. All these facts, as well as studies performed on transplanted kidney patients, place the kidney in a central position in the regulation of blood pressure.

Hence, impaired renal functions in CKD patients cause more abnormal sodium handling, increased total body sodium, and hence, impaired water excretion leading to a volume overloaded status. The abnormal renal sodium handling happens much before the drop in glomerular filtration rate. The renal autoregulation could be responsible for the secondary increase of the peripheral
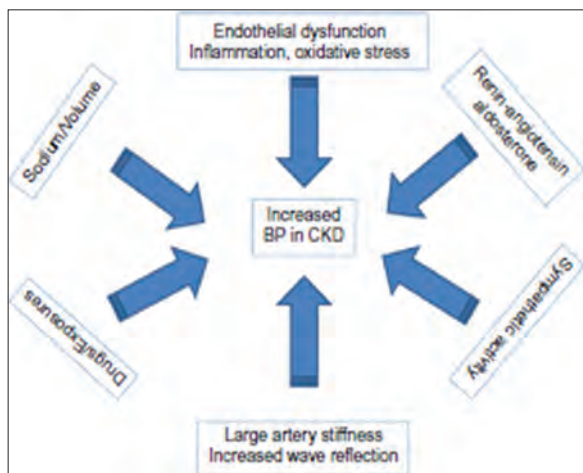

Figure 1: Pathogenesis of hypertension in chronic kidney disease

Figure 2: Factors and mechanisms of hypertension in chronic kidney disease[6]

resistance in the presence of blood volume expansion, as it occurs in CKD.[6]

It was demonstrated in Sprague-Dawley rats[8] that hypertension can be induced by a prolonged high-salt diet and that it is associated with increased renal injury and significant changes in renal cytokine gene expression profiles that are closely related to the pro-inflammatory response, pro-matrix formation and endothelial dysfunction, and attenuated cell survival and differentiation. They found that a high-salt diet decreases renal expression of vascular endothelial growth factor, whereas a subsequent study revealed that inhibition of the vascular endothelial growth factor receptor enhances dietary salt-induced hypertension. The salt sensitivity (effects on BP in relation to the sodium intake) is augmented in renal disease.[9] Hence, the need for diuretics and volume control even in dialysis patients is self-explanatory.

The Dietary Approach to Stop Hypertension (DASH) diet for the control of hypertension further stresses the role of salt in the pathogenesis of hypertension. It includes a diet low on salt, high fruits, vegetable and whole grain intake, less animal and dairy fat, less saturated fats, and plenty of fluids. It was proven in the DASH trial that the participants who followed the DASH diet had a significantly lower systolic blood pressures and also there were no episodes of accelerated hypertension.[10]

RAAS

The intrarenal and circulating RAAS which are interdependent systems control the systemic blood pressure. The intrarenal RAAS is also involved in renal autoregulation. Activation of the RAAS axis is well documented in CKD and dialysis patients. In addition to its direct vasoconstrictor effects, it also activates the SNS which contributes to the hypertension. In patients with CKD, vascular disease or areas of local ischemia and renal injury may activate the local RAAS which, in turn, increases the hypertension in CKD.[11] The role of RAAS blockade in CKD in the treatment of hypertension in CKD is quite beneficial. [Figure 3].

SNS

The SNS activity is enhanced in CKD. In health, SNS is also one of the arms of the renal autoregulation. The kidney has both baroreceptors
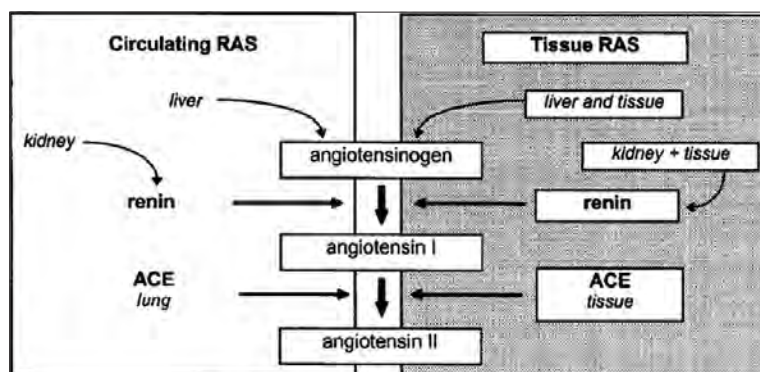

Figure 3: Circulating and tissue renin-angiotensin system

and chemoreceptors, and the signals of which are conveyed to the vasomotor centre of the brain. Increased SNS activity leads to an increased renal tubular sodium reabsorption, hence contributing to the volume overload. In addition, it also increases the peripheral vascular resistance by its vasoconstrictor effects.[12]

Oxidative Stress and Nitric Oxide Antagonism in CKD

Oxidative stress occurs due an overplay of the oxidants as compared to the antioxidants in CKD. The oxidant excess of molecules such as superoxide and hydrogen peroxide in CKD causes an antagonism of endothelial nitric oxide,[13] vasoconstriction and increased peripheral vascular resistance. And hence the causal association of oxidative stress with hypertension in CKD is proven through a lot of experiments on animal models.

Exogenous Drugs

The above-mentioned drugs also form an important part of the pathogenesis of hypertension as many of these drugs such as cyclosporine and tacrolimus in transplant patients and erythropoietins form an inseparable part of the medication list in CKD patients [Figure 4].

Smoking and Alcohol

It is recognized that cigarette smoking is accompanied by an acute increase in blood pressure and heart rate. One of the first studies conducted on this regard, evaluating the effects of heavy smoking (one cigarette every 15 min for 1 h) on blood pressure and heart rate in a group of normotensive smokers, documented that, in resting conditions, the first cigarette caused an immediate and marked increase in blood pressure and heart rate, with the values achieved similar for the remaining three cigarettes. The hemodynamic effects were so prolonged that, throughout the smoking hour, blood pressure and heart rate were persistently higher than during the non-smoking hour, indicating that heavy smoking is associated with a rise in blood pressure, persisting for more than 15 min after smoking one cigarette and with also an increase in blood pressure variability. Through a mechanism which involves the stimulation of the sympathetic nervous system mainly at nerve endings, smoking is responsible for a marked and prolonged increase in plasma catecholamines parallel to the blood pressure increase [Figure 5].[15]

Recent epidemiological and clinical studies have demonstrated that chronic ethanol consumption (more than three drinks per day, 30 g ethanol) is associated with an increased incidence of hypertension and an increased risk of cardiovascular disease. The magnitude of the increase in blood pressure in heavy drinkers averages about 5–10 mmHg, with systolic increases nearly always greater than diastolic increases. Similar changes in blood pressure were also reported in preclinical studies. In the Framingham cohort, there was an increase of 7 mmHg in mean arterial pressure when heavy alcohol users were compared with all others. In some epidemiological studies, a linear dose-response relationship
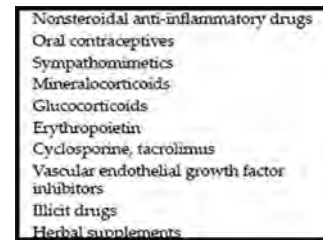
Figure 4: Drugs causing hypertension[14]
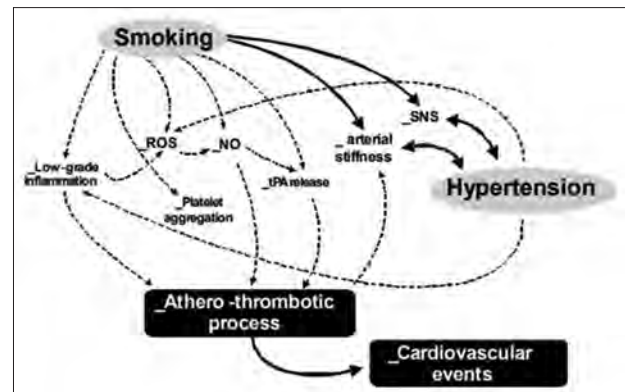
Figure 5: Mechanisms of smoking and hypertension
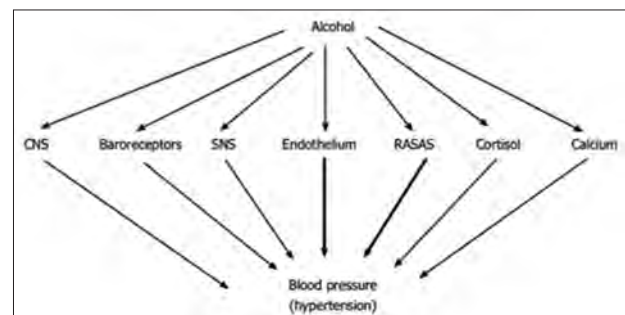
Figure 6: Mechanisms of alcohol and hypertension

has been established, sometimes starting with a consumption threshold of three drinks per day (30 g of ethanol) [Figure 6].[16]

Others

Role of a potent vasoconstrictor endothelin-1 cannot be overemphasized. In CKD, endothelin levels are increased. It binds to endothelin A receptor and causes vasoconstriction. Antagonism of endothelin A causes a reduction in blood pressure.[17]

The role of parathormone is still controversial.

Other factors such as vascular stiffness in CKD, renal artery stenosis, genetic factors such as family history, age, and ethnicity, vascular endothelial dysfunction in CKD due to ADMA, high levels of endogenous digitalis-like factors in CKD,[18] high arginine vasopressin levels, and reduced vasodilatory prostaglandins may also contribute to the hypertension in CKD.

Genetics

Heritability studies and genome-wide association studies have established that hypertension, a prevalent cardiovascular disease, has a genetic component that may be modulated by the environment (such as lifestyle factors). In BP, family and twin studies have yielded heritability estimates in the ranges of 48–60% (systolic BP) and 34–67% (diastolic BP). It has a polygenic inheritance pattern.[19]

With specific reference to CKD, an association of APO L1 gene and kidney disease and in turn hypertension was found in African populations.

Conclusion

There is a multitude of mechanisms of hypertension in CKD including the abnormal renal sodium handling to the numerous vasoconstrictor mechanisms. A better understanding of these concepts has helped us to develop a targeted therapeutic approach to the management of hypertension in CKD. The ACE inhibitors and ARBs (RAAS blockade), beta-blockers (SNS blockade), and diuretics form the mainstay of management. The dietary modifications in terms of salt reduction also play a major role due to the salt-sensitive hypertension in CKD. Lifestyle modifications in the form of regular physical exercise may improve the control of blood pressure and endothelial function and decrease inflammation and insulin resistance.[20] Moreover, physical exercise has no untoward effect on the progression of CKD. In short, the 6's of metabolic syndrome such as sugars, spirits, smoking, salt, stress, and sedentary lifestyle should be handled accordingly for a healthy living.

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*R*eview *A*rticle

Hypertension in Post-renal Transplant Patients

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Abstract

Hypertension in renal transplant recipients is known to be a major risk factor for cardiovascular morbidity and mortality, as also reduced allograft survival. Importantly, hypertension in renal transplant patients is common and ranges from 50% to 80% in adult recipients and from 47% to 82% in pediatric recipients. Many patients experience a remarkable improvement in blood pressure (BP) control, requiring lesser medications within months of transplantation. However, the benefits of improved glomerular filtration rate (GFR) and fluid status may be negated by various donor and recipient factors, acute and chronic allograft injury, and immunosuppressive medications, thereby explaining some of the pathophysiologies of post-transplant hypertension. Other contributory factors for hypertension after transplant, beyond a progressive decrease in GFR, include transplant renal artery stenosis and adrenal causes of hypertension, as noted in some patient cohorts. Notably, targets for hypertension management in renal transplant recipients remain an enigma, since there are not sufficient data from randomized controlled trials to support a benefit from targeting lower BP levels on graft and patient survival. Although no specific antihypertensive medications have been shown to be more effective than others at improving survival in this cohort, calcium channel blockers may be the most useful medication for mitigating calcineurin inhibitor-induced vasoconstriction, and their use may improve GFR. Use of inhibitors of the renin-angiotensin system remains an attractive strategy, but the potential for drug-drug interactions and altered pharmacokinetics and pharmacodynamics of the different antihypertensive medications need to be carefully considered. In conclusion, hypertension control affects both patient and long-term transplant survival, thereby necessitating the identification of the underlying pathophysiology and subsequent individualization of treatment goals.

Key words: Hypertension, Renal transplant, Renin angiotensin system

Introduction

Atherosclerotic cardiovascular (CV) disease is a significant cause of morbidity and mortality after renal transplant.[1] Hypertension is one of the most common clinical problems seen in renal transplant recipients and is a major "traditional" determinant of shortened allograft survival and increased CV events.[2] The major goals of antihypertensive therapy after transplant are the preservation of kidney function and reduction of CV disease risk. Recently published evidence-based guidelines recommend a goal blood pressure (BP) of 140/90 mmHg be adopted for the general population, regardless of risk factors.[3] Whether the same can be applied to renal transplant recipients is unclear. The BP frequently often rises early after kidney

transplantation after saline loading interacts with initial high-dose immunosuppression.[4] Long-term BP is often easier to control after transplantation, as long as the individual achieves a good glomerular filtration rate (GFR).

Definition and Diagnosis

The relationship between BP and CV/renal events is continuous, making the distinction between normo- and hypertension based on BP cutoff values arbitrary to an extent. However, hypertension is defined as the level of BP at which the treatment benefits undoubtedly outweigh treatment risks, as demonstrated in clinical trials. Hypertension is defined by an office BP recording of >140/90 mmHg. BP is classified as optimal, normal, high

normal, or Grades 1–3 hypertension in young, middle-aged, and the elderly. BP centiles are used in children and teenagers.[5] The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP (JNC 7) recommends that treatment is provided to achieve BP <130/80 mm Hg in patients with diabetes or chronic kidney disease (CKD).[6] The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative[7] has similar treatment target recommendations that have been endorsed recently by the Kidney Disease Improving Global Outcomes working group.[8] In patients with significant proteinuria (defined as spot urine protein-creatinine ratio >500 mg/g), a European Best Practice Guideline suggests that the BP goal can be decreased to <125/75 mmHg.[9] There are no targeted BP goals for the treatment of hypertension in post renal transplant patients.

Recent studies have assessed the correlation between ambulatory BP monitoring (ABPM), home BP monitoring (HBPM), and office clinic BP monitoring (CBP) in the post-transplant setting. The use of standardized techniques, as used in clinical trials of hypertension with >1 measurement of BP, can provide improved concordance rates between CBP and ABPM as seen in a study by Haydar et al.[10] Other researchers have demonstrated that HBPM determinations had a significantly better agreement with ABPM than CBP (72% vs. 54%) even though both the CBP and the HBPM correlated with ABPM.[11] The use of ABPM is being recommended more broadly in the general population to better assess the clinical importance of nocturnal hypertension, masked hypertension, and white coat hypertension on the risk of vascular events.[12] The diagnostic utility of ABPM should be considered in the kidney transplant recipient because it may prove helpful in guiding management decisions.

Epidemiology and Outcomes

Close to half of all renal transplant recipients had hypertension before the introduction of calcineurin inhibitors (CNIs). At present, the overall prevalence of hypertension is reported to be as high as 85%;[13] however, it varies depending on the population studied and definition used. Even though it is generally accepted that hypertension negatively influences renal transplant outcomes, the precise effect of post-transplant hypertension on renal allograft outcomes is difficult to gauge because hypertension accelerates renal failure and declining allograft function worsens BP control. In a single-center observational study of deceased-donor transplant recipients, the odds ratio of allograft failure per 10 mmHg increase in BP measured at 1 year after transplantation (after adjustment for renal function) was 1.15 (95% confidence interval [CI], 1.02–1.30) for systolic pressure, 1.27 (95% CI, 1.01–1.60) for diastolic pressure, and 1.30 (95% CI, 1.05–1.61) for mean arterial pressure.[14] The collaborative transplant study, a large cohort study of nearly 30,000 renal transplant recipients, demonstrated a graded association between systolic BP (SBP), diastolic BP (DBP), and allograft failure.[15] In addition to decreased allograft survival, post-transplantation hypertension is associated with decreased patient

survival as well. Each 10 mmHg increment of SBP >140 has been shown to be associated with a hazard ratio of death of 1.18 (95% CI, 1.12–1.23), and this risk persists after adjusting for allograft function.[16] The association between hypertension and death in kidney transplant recipients is mediated by the increased risk of CV disease because uncontrolled hypertension post-transplant is associated with an increased risk of *de novo* congestive heart failure and ischemic heart disease.[2] However, as with allograft failure, it has not been demonstrated in prospective studies that tight BP control mitigates the risks of CV disease and death in these patients. Nonetheless, strong observational data showing a relationship between higher BPs and worse outcomes warrant the treatment of post-transplant hypertension and the pursuit of prospective clinical trials to establish optimal BP targets.

Pathophysiology

In contrast to the general and CKD populations, risk factors for hypertension post-transplant include determinants of both donor and recipient origin and also factors that relate to the transplant process and immunosuppression. The interplay of such factors was demonstrated in a prospective observational study of 85 transplant recipients with stable renal function (without cyclosporine therapy), followed up for 8 years, by Guidi et al. Recipients without a family history of hypertension and who received a kidney from a hypertensive family developed hypertension more frequently compared to those with a kidney transplant from a normotensive family or recipients with familial hypertension (in whom the origin of the kidney did not influence the prevalence of post-transplant hypertension). During follow-up of these patients, it was noted that recipients of kidneys derived from hypertensive families developed higher DBPs and greater degrees of acute kidney injury during acute rejection than the other recipients.[17]

Donor Factors

Donor factors independently associated with post-transplant hypertension include pre-existing hypertension, older age, and poor allograft quality. Recently, several genetic variants, including polymorphisms within genes that encode for ABCC2, ABC1, CYP 3A5, and APOL-1, have been shown to be associated with early graft dysfunction and subsequent post-transplant hypertension.[2] The size of the donor kidney relative to the recipient also plays a role in the development of post-transplant hypertension. A disparity between donor and recipient size can lead to a relative underdosing of nephrons and subsequent maladaptive hyperfiltration, glomerular hypertrophy, and intraglomerular hypertension.[18]

Acute Rejection and Chronic Allograft Injury

Hypertension and GFR are intimately interrelated after renal transplant. Karthikeyan et al.[19] demonstrated increasing

requirements of antihypertensive medications from 0.7 in kidney transplant recipients with CKD Stage 1–2.3 in those with Stage 5 function. Kasiske *et al.* examined the impact of hypertension on transplant survival. After adjusting for the effects of rejection, kidney function, and other variables, each 10 mmHg rise of SBP was associated with an increased RR of transplant failure and death.[16]

Any injury to a transplanted kidney can result in the initiation or worsening of post-transplant hypertension. The most common causes are acute rejection (cellular and antibody mediated), chronic allograft injury (including chronic antibody-mediated rejection and interstitial fibrosis/tubular atrophy), thrombotic microangiopathy, and recurrent glomerular disease.[2] A renal transplant recipient with new-onset hypertension must be evaluated for an acute rejection, since this may be associated with RAAS stimulation and responds well to treatment of rejection. A recent report of patients with antibody-mediated rejection by non-DSA antibodies that bind to angiotensin II type I receptors suggests that AT1 receptor blockers might prevent this type of hypertension.[20] Commonly, AT1 receptor-related vascular rejection occurs during the 1st week after surgery. Notably, hypertension related to chronic allograft injury is similar to that associated with CKD and occurs at least 3 months post-transplant in the absence of active acute rejection and CNIs. Recurrent disease commonly focal glomerulosclerosis that results in injury to the allograft also leads to hypertension. Rarely, a transplant renal artery kink confirmed by parvus tardus waveform on ultrasound Doppler and a page kidney caused by external renal compression due to hematoma, lymphocele, or urinoma can lead to early graft dysfunction and severe hypertension.[21]

Immunosuppressive Agents

These medications are known to be associated with post-transplant hypertension. Corticosteroids mediate hypertension through mineralocorticoid-induced sodium retention, increased responsiveness to vasoconstrictors, and decreased vasodilator production. The incidence of steroid-related hypertension is approximately 15%, especially in recipients with pre-existing hypertension.[22] Transplant centers have tended to either lower the steroid dose or withdraw steroids to decrease the risk of post-transplant hypertension. Question arises whether such protocols result in tangible improvements in primary outcomes. In a 12-month open-label multicenter study, renal transplant recipients were randomly assigned to receive no steroids, steroids to day 7 post-transplant (steroid withdrawal), or standard steroid therapy, all in combination with cyclosporine, enteric-coated mycophenolate, and basiliximab. The study found no differences in terms of SBP or DBP between groups. However, there was a significantly higher incidence of rejection in the steroid avoidance or withdrawal groups. Most importantly, there were no differences in patient or transplant survival at the end of the study.[23] Most likely, we are now seeing a practice of steroid-treated patients receiving much lower cumulative immunotherapy than their predecessors, and therefore, consequent impact of steroids on BP is negligible.

CNIs, particularly cyclosporine, are well-established causes of post-transplant hypertension. They have been shown to worsen BP control in HLA-identical renal transplants.[24] The pathophysiology of cyclosporine-induced hypertension is related to direct vascular effects, through activation of the sympathetic nervous system, endothelin upregulation, and inhibition of nitric oxide, leading to potent vasoconstriction.[25] The renal sodium retention stimulated by cyclosporine is also related to afferent glomerular arteriole vasoconstriction. Tacrolimus activates the renal sodium chloride cotransporter and causes a sodium sensitive forum of hypertension. Evidence suggests lower rates of post-transplant hypertension with tacrolimus as against cyclosporine.[26] Decreasing the dose of cyclosporine by 50% at 1 year or longer post-transplant has been shown to decrease the risk of hypertension in patients treated with steroids and mycophenolate mofetil without increasing rejection risk.[27] Given the importance of adequate immunosuppression to avoid rejection, decisions about adjusting immunosuppressive medications to facilitate BP control need to be carefully considered. It may be easier and safer to use lifestyle modifications or antihypertensive medication rather than modify immunosuppression.

Recipient Factors

Recipients with prior longstanding hypertension have a loss of vascular compliance due to stiffening of vessels. These vascular changes can contribute to the hypertensive process, especially in the presence of volume excess. The genetic profile, age, body mass index, presence of obstructive sleep apnea syndrome (OSAS), and secondary causes of hypertension (either pre-existing or incident) are all important contributory factors to post-transplant hypertension.[2] Transplant renal artery stenosis (TRAS), causing a form of renovascular hypertension, is the most common form of secondary hypertension. TRAS most commonly presents 3–24 months post-transplant, while risk factors include CMV infection, delayed transplant function, organ procurement complications, and surgical techniques. Incidence is also suggested to be higher in recipients of live donors and pediatric donors when compared to deceased donors.[28]

TRAS has been reported in 1–23% of renal transplant recipients, mainly due to stenosis at the renal artery anastomosis, but it may also occur at more proximal sites, such as the recipient iliac artery.[29] Presentation includes worsened hypertension, hypokalemia caused by secondary aldosteronism, a decline in allograft function, or worsening function with reduction in perfusion pressure, particularly with angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blocker (ARB) therapy. Less commonly, flash pulmonary edema may occur in the setting of a single functioning transplant kidney with TRAS.[2] Clinically evident bruit, non-invasive imaging with renal artery Doppler is the initial diagnostic step. If inconclusive or suboptimal, then CT imaging with a small amount of contrast should be considered or even CO_2 angiography. Magnetic

resonance angiography (MRA) with gadolinium may not be an option in the setting of reduced GFR; however, non-contract MRA is being used more frequently.[4]

Intravascular intervention for TRAS is indicated for either increased serum creatinine or worsened hypertension. Percutaneous intervention by angioplasty, with or without stenting, is considered as the treatment of choice if medical therapy is inadequate. Success rates are as high as 82–94%. Restenosis occurs in about 10% and transplant loss in up to 30% of recipients.[29] Surgical revascularization is reserved for lesions that are not amenable to percutaneous intervention or for recurrence after angioplasty. Whether platelet inhibitors should be used is unclear and, as with the native renal artery, stents are generally available for this site only as bare metal stents related to size requirements.[4]

Renin-dependent hypertension is likely to persist despite successful transplantation in rare cases. A high native kidney to transplant renal vein renin ratio can confirm the diagnosis. Bilateral native kidney nephrectomy[30] or ablation by embolization[31] has been found to be effective.

Secondary hypertension may be pre-existent and remain unrecognized, or it may present post-transplant. Primary hyperaldosteronism is a common cause of secondary hypertension in hypertensives, estimated to affect 20% of those with resistant hypertension. With this degree of penetrance and the common association of hypertension with CKD, prevalence rates are likely to be at least as high in the renal transplant population. Therefore, the presence of hypokalemia to any degree in association with severe hypertension should raise diagnostic suspicion, although registry data have suggested lower rates of post-transplant hypertension due to primary hyperaldosteronism.[2]

The association of primary hyperaldosteronism and OSA reported in patients with resistant hypertension should also be considered after renal transplantation, as it contributes to the development of pulmonary hypertension if not diagnosed and treated. The diagnosis depends on an elevated aldosterone-to-renin ratio, confirmed by the evidence of autonomous aldosterone production. Treatment is by suppressing the effect of aldosterone because of its potential vascular toxicity. A trial of spironolactone or eplerenone is reasonable and may even be helpful for facilitating BP control in patients on higher doses of corticosteroids.[2]

Management of Post-renal Transplant Hypertension

There is a lack of randomized controlled trials to examine optimal levels of BP in renal transplant recipients to prolong graft survival or limit the risk of CV events. There are also no data to define optimal treatment strategies. The target BP control for renal transplant recipients must be individualized based on all CV and renal risk factors. Lower BP goals (<140/90 mmHg) may be beneficial, given the epidemiologic data linking it to prolonged graft survival.[3,5]

The timing of the development of hypertension post-renal transplantation is an important consideration for effective management. In the initial few weeks to months post-transplantation, hypertension may be influenced by volume overload, higher doses of corticosteroids, and CNI levels and poor or delayed allograft function. Hence, their management requires achievement of ideal volume status and the employment of lower doses of both corticosteroids and CNIs while avoiding acute rejection episodes. Thiazide or loop diuretics should be considered. Beta blockers and calcium channel blockers (CCBs) can also be used if indicated. It is recommended to avoid ACEi and ARBs early post-transplantation due to their hemodynamic effect on GFR and potassium homeostasis.[32] Non-pharmacologic management with lifestyle modifications, including exercise, weight control, cessation of smoking, and dietary salt modification, must be an integral component of the management strategy as in the general population. The salutary effect of dietary sodium restriction in transplant recipients is supported by studies. In one study comprising relatively small number of kidney transplant recipients, a 3-month trial of an 80–100 mmol/day sodium-restricted diet resulted in a statistically significant drop in SBP and DBP compared with a control group on a non-restricted diet.[33]

Specific Classes of Antihypertensive Agents

A clinician has to choose antihypertensive medications in renal transplant recipients on the basis of efficacy, tolerability, lack of known drug-drug interactions, and medical comorbidity. CCB, diuretics, beta-blockers, alpha1 blockers, ACEi, and ARBs have all been used singly or in combination to reduce BP in the transplant population.

CCBs

CCBs act by inhibiting voltage-gated calcium channels in vascular smooth muscle cells and cardiac myocytes, thereby reducing contractility and inducing vasodilatation. Such drugs fall into two major classes: Dihydropyridine (e.g., amlodipine and nifedipine) and non-dihydropyridine (e.g., diltiazem and verapamil). It is well known that vasoconstriction is the dominant mechanism by which CNIs induce acute nephrotoxicity and hypertension. Therefore, vasodilatory CCBs have been an attractive option at least for the early management of hypertension after transplant, especially when target CNI levels are highest.[34] A large, prospective, randomized, comparative study found the following benefits of nifedipine compared to lisinopril, despite equivalent initial GFRs and attainment of similar BP levels. (1) At 1 year, GFR had significantly increased in those treated with nifedipine (56 vs. 46 mL/min at baseline) but was unchanged with lisinopril (44 and 43 mL/min, respectively); (2) at 2 years, improvement in GFR with nifedipine was maintained (10.3 mL/min; CI, 4.0–16.6); no such benefit was observed with lisinopril.[35] Non-dihydropyridines such as verapamil and diltiazem are potent inhibitors of cytochrome P450 and C3A4 and cause plasma levels of the immunosuppressive drugs to increase sharply soon after initiation. This is a transcriptional event and typically occurs during a 2–5 days' period after initiation. Similarly,

discontinuation of CCB therapy leads to the decrease in the levels of immunotherapy; therefore, clinical acumen dictates that such drugs be used with caution and frequent monitoring. The dihydropyridine CCBs share these properties to a much lesser extent and therefore are easier to use in transplant recipients, although they are more likely to be associated with the development of edema.[4]

ACEi/ARB

The clinical benefits of RAS blockade have been clearly demonstrated in non-transplanted hypertensives with elevated CV risk.[36] However, studies in transplant recipients have been inconclusive. Two systematic meta-analyses have attempted to consolidate the data on the use of ACEi/ARB in renal transplant recipients. Hiremath *et al.*[37] identified 21 randomized trials of ACEi/ARBs in three databases from 1966 to 2007 involving 1549 patients. With a 27-month median follow-up time, the use of ACE inhibition/ARBs was associated with significant reductions in GFR (−5.8 cc/min), hematocrit (−3.5%), and proteinuria (−0.47 g/dl), without a significant effect on serum potassium. Cross *et al.* published a Cochrane Database Systematic Review, which included 10 studies comparing ACEi with placebo with 445 patients and 7 studies comparing ACEi with CCBs with 405 patients. Compared with CCBs, the use of ACEi was found to be associated with a significant reduction in GFR (−11.49 cc/min), proteinuria (−0.28 g/d), and hemoglobin (−1.3 g/dl), with a 2.74-fold elevated relative risk of hyperkalemia.[38] Heinze *et al.*[39] used the Austrian Dialysis and Transplant Registry and Eurotransplant databases and identified 2031 transplant recipients at a single center between 1990 and 2003. Compared with no ACEi/ARB therapy, any documented ACEi/ARB use was associated with improved 10-year patient (74% vs. 53%, *P*, 0.001) and graft (59% vs. 41%, *P* = 0.002) survival. However, another retrospective analysis of 17,209 patients transplanted between 1995 and 2004 from the collaborative transplant study was unable to show a difference in graft or patient survival at 6 years in those either on or off ACEi/ARB therapy.[15]

Therefore, definitive evidence of the benefit of ACEi/ARB therapy in transplant recipients is lacking. Several factors have to be considered when choosing such medications for kidney recipients.

- ACEi or ARB therapy can cause or exacerbate a decrease in GFR, and this effect may mimic or mask early signs of acute transplant rejection. Consequently, these drugs are difficult to use early after transplant when patients are at the highest risk of developing complications.[4]
- Hyperkalemia is a frequent finding after renal transplant that is associated commonly with delayed transplant function and is an adverse effect of CNI (particularly tacrolimus) therapy. ACEi/ARB therapy can exacerbate the frequency and severity of hyperkalemia.[4]
- ACEi can cause or exacerbate anemia in transplant recipients, decreasing hematocrit by as much as 5–10% through a mechanism that may be potentiated by cyclosporine. This

incompletely understood phenomenon is believed to be caused by the inhibition of erythropoiesis and may be useful in the management of post-transplant erythrocytosis, a condition characterized by a progressive increase in hematocrit (>50%) and risk of atherothrombotic events.[4]

Apart from CCBs and ACEi/ARB, there are no or few published data on other classes of antihypertensives in post-renal transplant recipients.

Pharmacologic Principles in Post-transplant Therapeutics

Pharmacokinetic considerations are more significant in renal transplant recipients given the variability of renal function, comorbidities and large drug burden, and their interactions. Drug-drug interactions can be pharmacokinetic or pharmacodynamic in nature. Complete dose-response curves are rarely generated for antihypertensive drugs in renal transplant recipients. Hence, it is better to focus on the additive response with multiple drug combinations and not on uptitration of monotherapies.[2] Tachyphylaxis due to enzyme induction leading to increased drug metabolism does not usually occur in this patient population. Antihypertensive drugs are typically dosed till the desired effect is achieved and dosage reduction is only considered thereafter or if there are drug concentration-dependent adverse effects.

Conclusion

Renal transplant recipients commonly have hypertension post-transplantation. Many transplant recipients have poorly controlled BP despite evidence suggesting improved CV outcomes with good BP control. Much of the challenge arises from the complexity of multidimensional medical care that they require. The BP goals need to be lower than the general population and individualized to each patient. ABPM is a helpful tool to assess the adequacy of treatment and secondary causes of hypertension need to be considered in patients with resistant hypertension. Future clinical trials need to define optimal BP treatment goals and therapies in renal transplant recipients as also clearly demonstrate their influence on graft and patient survival.

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Review Article

Hypertension and Coronary Artery Disease

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Abstract

Hypertension is one of the major modifiable risk factors for atherosclerotic cardiovascular disease, with diastolic blood pressure being the strongest predictor of coronary artery disease. Hypertension is easily detectable and eminently treatable. Existence of J curve is a debatable issue. Effective treatment of blood pressure in hypertensive individuals reduces the risk of atherosclerotic coronary artery disease.

Key words: Hypertension, Coronary artery disease, Risk factor, J curve

Introduction

Hypertension is a major modifiable risk factor for all the various clinical manifestations of coronary artery disease (CAD). Diastolic blood pressure (DBP) is the strongest predictor of CAD in young and middle age population, whereas in age groups >60, pulse pressure (PP) shows the strongest correlation with CAD.

Pathophysiological mechanisms include BP as a physical factor on the formation of atherosclerotic plaque. Pulsatility and stiffness of the coronary arteries and the interplay of the two with respect to coronary perfusion play a role. Treatment of hypertension is proven to prevent coronary events in patients without clinical CAD. In patients with established CAD, the effect of BP lowering has shown a J-curve phenomenon, having an increase in coronary events at lower DBP, one explanation being that coronary perfusion is a predominantly diastolic phenomenon.

Epidemiology

The INTERHEART study demonstrated that about 50% population-attributable risk of myocardial infarction was accounted for by lipids, and hypertension accounting for 25%.[1] The association of BP with various manifestations of CAD was studied in 1.25 million primary care patients in the UK aged 30 years and above.[2] The findings of this study showed that hypertension had a lifetime risk of cardiovascular disease of 63.3% from 30 years of age compared to 46.1% for those with normal BP. The lowest risk for CAD was noted in the lowest BP group (systolic blood pressure [SBP]: 90–114 and DBP: 60–74) among the 30–79 years of age group. The association of SBP was strongest with intracerebral bleed, hazard ratio (HR) 1.44, subarachnoid bleed HR 1.43, and stable angina HR 1.41 and weakest for abdominal aortic aneurysm (AAA) HR 1.08. SBP had a greater effect on angina, MI, and PVD; DBP had a greater impact on AAA. PP association was inverse with AAA and strongest for PVD HR 1.23.

The FRAMINGHAM study showed that DBP was the strongest risk predictor among the <50 years of age group, and 50–59 years was a transition phase where SBP, DBP, and PP were comparable predictors. From 60 years and above, DBP had a negative correlation, with PP being the strongest predictor of CAD in this group. As recommended by the Austrian Society of Hypertension[3] in 24 h BP monitoring, PP is a strong independent predictor of coronary events.[4]

Pathophysiology

The myocardial oxygen demand during exercise is related to the increase in SBP,[5] which is met almost exclusively by the decrease in coronary vascular resistance and increase in perfusion pressure. Oxygen extraction in the myocardium is maximal in basal state

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hence the dependence on coronary perfusion.[6] Roughly 85% of the perfusion in the left ventricle occurs in diastole under resting condition,[5] during heavy exercise, diastolic time shortens, and 40–50% of the total coronary flow occurs in systole,[7] creating a substrate for subendocardial ischemia due to the throttling effect of cardiac contraction on the intramural vessels. The coronary vasculature can dilate five-fold, and thus, the flow reserve is five.[6] This reserve is reduced by half with 80% stenosis of the epicardial coronary artery and near zero with 90% stenosis.

The compliance of the aorta plays a vital role in the interplay of BP and cardiac workload. Each systole creates a pressure wave which travels forward along the length of the aorta roughly at 5 m/s. As the aorta stiffens with age and degradation of elastin fibers in the media, this pulse wave velocity increases. The pressure wave front is reflected back from the branching points of the aorta. This reflected wave in young individuals reaches the ascending aorta in diastole, thus augmenting the DBP and coronary perfusion pressure. As age advances, the reflected wave front reaches earlier in the systole; this increases the wall tension and oxygen consumption and decreases the myocardial perfusion (DBP).[8] The pulse wave velocity has a strong inverse relationship with coronary blood flow and flow reserve.[9] Thus, measures of pulsatile hemodynamics are independent predictors of coronary events with or without established CAD.

Management

A recent meta-analysis of 68 randomized controlled trials (RCTs) studying the effect of antihypertensive medications on the occurrence of cardiovascular events was reported.[10] Trials comparing antihypertensive medications to placebo showed a reduction in the occurrence of CAD by 16% (7 events per 5000 patient-years). In trials comparing less intense versus more intense, BP lowering CAD was reduced in the more intense group by 19%. This risk reduction was unrelated to the baseline BP.[11] Benefit was seen also in Grade I hypertension and in patients with low-to-moderate cardiovascular risk. SBP <130 versus SBP >130 and DBP <80 versus DBP > 80 mm Hg were associated with a significant CAD risk reduction.

Among the drug classes, the risk reductions were achieved with diuretics (−16%), angiotensin-converting enzyme inhibitor (ACE-I) (−13%), BB (−12%), calcium channel blockers (CCBs) (−17%), angiotensin-receptor blocker (ARB) (−6%), and centrally acting drugs (−13%). These trials were not randomized head-to-head comparison, so they do not prove the superiority of each drug class over the other. When head-to-head comparisons were meta-analyzed,[12] ACE-I was superior to all other drug classes. The other drug classes did not differ significantly from each other.

The recently reported SPRINT trial[13] showed that, among non-diabetics with high cardiovascular risk, targeting a SBP <120 mm Hg compared to <140 mm Hg resulted in a significant reduction in cardiovascular events (25%), heart failure (38%), cardiovascular mortality (43%), and all-cause mortality (27%)

and a non-significant reduction in myocardial infarction (17%). In this trial, the target BP was monitored by automated measuring system in a quiet room, and thus, the effect of white coat BP rise or office BP versus home-based BP measurements must be considered when applying the SPRINT trial findings into practice.[14]

The concept of J-curve relationship between BP control and CV outcomes has been critically evaluated. In a recent analysis of 22,672 patients[15] with stable CAD, after a median follow-up of 5 years, SBP ≥ 140 mm Hg and DBP ≥ 80 mm Hg were associated with increased CV risk. This increased risk was also noted with SBP < 120 and DBP < 70 mm Hg at higher CV risk. In a post hoc analysis of data from the International Verapamil-Trandolapril Study (INVEST)[16], it was seen that the risk for all-cause death, and MI, but not stroke, progressively increased with low diastolic blood pressure. Caution should be exercised in reducing diastolic pressure in patients with CAD who are being treated for hypertension [Figure 1a and b]. Other analyses do not support the existence of a J-curve even in hypertensive patients at increased CV risk.[17]

In patients with CAD who were free from congestive heart failure to begin with, in ONTARGET, BP reduction from baseline had no significant risk reduction in myocardial infarction
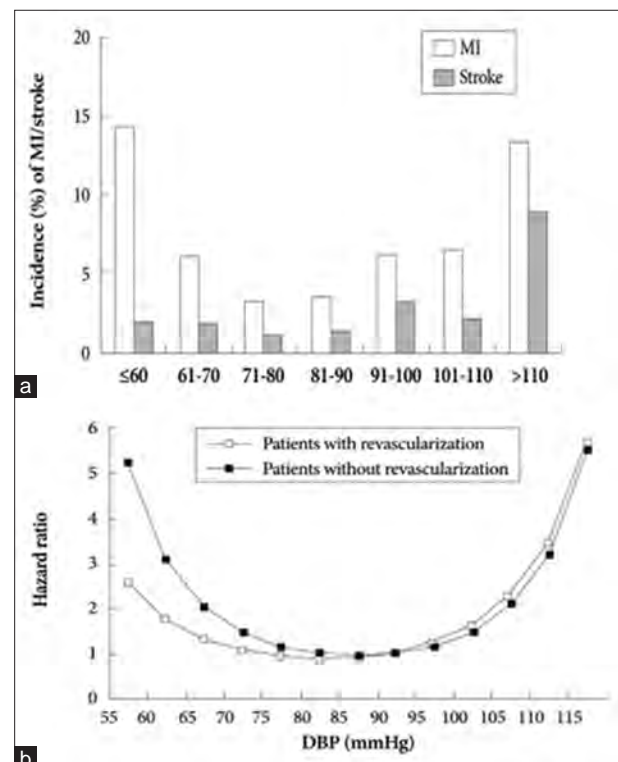

Figure 1: a) J shaped curve seen for MI, but not for stroke, b) Lower risk of MI in coronary revascularised patients as compared to non-revascularised patients with decreasing DBP
Source: Messerli FH, Mancia G, Conti CR, *et al.* Dogma disputed: Can aggressively lowering BP in hypertensive patients with CAD be dangerous? Ann Intern Med 2006;144:884-93

Table 1: Trials of antihypertensive medications in CAD patients (+: positive results and + / -: neutral outcomes).

Trial (aus)	Intervention	Number of patients	CAD %	Previous MI %	BP at entry	BP on treatment	Results
HOPE[20]	Ramipril versus P	9297	79.5	51.9 R/53.4 P	130/79	136/76 (R)/139/77 (P)	+
ACCORD[21]	SBP goal <120 versus <140	4733	na	33.7 CV event	139/76	119/64 (I)/133/70 (S)	+/-
CAMELOT[22]	Amlodipine/P/Enalapril	1991	100	37.4 A/37.7 P/40.3 E	128/78 129/78 129/77	125/75 (A)/130/78 (P)/124/75 (E)	+
INVEST[23]	Calcium antagonist based strategy (CAS) versus non–calcium antagonist based strategy(NCAS)	22576	100	32.1 V/31.8 At	149/86	131/76 (V)/130/76 (At)	+/-
ONTARGET[24]	Ramipril versus telmisartan versus both	25588	74.6	48.3 R/49.3 T/49.3 both	142/82	135/78 (R)/134/77 (T)/132/76 (both	+/-
TRANSCEND[25]	Telmisartan versus P	5926	74.8	46.8 T/45.8 P	141/82	136/(T)/140/(P)	+/-
EUROPA[26]	Perindopril versus P	12218	100	64.9 Pe/64.7 P	137/82	128/78 (Pe)/133/80 (P)	+
PEACE[27]	Trandolapril versus P	8290	100	54 Tr/56 P	134/78 Tr 133/78 P	129/74 (Tr)/132/76 (P)	+/-
ACTION[28]	Nifedipine versus P	3825	100	52 N/50 P	137/80 N 138/80 P	130/76 (N)/136/78 (P)	+/-

P: Placebo, R: Ramipril, I: Intensive therapy, S: Standard therapy, A: Amlodipine, At: Atenolol, E: Enalapril, V: Verapamil, T: Telmisartan, Tr: Trandolapril (Peace study), Pe: Perindopril, N: Nifedipine. CAD: Coronary artery disease, BP: Blood pressure

but showed a lower risk of stroke.[18] A meta-analysis was done by Law *et al*.[19] The study group was divided into three groups, one without CAD, second group with history of CAD, and third with a history of stroke. When BBs were used in patients with CAD, the relative risk reduction was 13% comparable to the 15% risk reduction with all other drug classes, and 11% reduction in patients without CAD. The subgroup with a recent MI had more significant benefit with beta-blocker use.

Table 1 shows various trials where different drugs have been used to control hypertension in patients with CAD.

Therapeutic Strategies Patients with CAD Receiving Antihypertensive Medications in (ESC 2018)

Hypertension is present in about 65–80% of patients presenting with acute coronary syndromes.[29] Observational studies have suggested a poor prognosis with both a very high and very low BP. A high BP on presentation increases the risk of intracerebral bleed.[30] Refractory hypertension (>180/110 mm Hg) is considered a relative contraindication to thrombolysis.[30] Both high and low BPs are risk factors for bleeding in NSTEMI.[31] Furthermore, BP fluctuation is known in early course of an ACS. There is a lack of dedicated RCTs for BP target in ACS. A reasonable BP goal in stable ACS patients is <140/90 mm Hg. A BP target <130/80 mm Hg at discharge may be considered in select patients.[32] The addition of antihypertensive medications such as beta blockers and ACE I/ARBs is more with the intention of mortality benefit and cardiac remodeling post-acute coronary syndrome.

Antihypertensive treatment in patients of heart failure reduces the risk of hospitalization, as it reduces the risk of incident heart failure among patients treated for hypertension.[33-35] This positive effect has been observed with beta blockers, ACE I, and ARBs. CCBs have been found to be less effective in comparative trials.[36] Reducing BP also causes regression of LVH with a consequent decline in CV events, and mortality, ARBs, ACE I, and CCBs cause more effective regression in LVH than beta blockers or diuretics.[37]

In patients with HFrEF, antihypertensive medications are initiated when BP >140/90 mm Hg [Tables 3 and 4]. The target BP in this patient subset has not been clearly defined. As low BP has been shown to predict a poor outcome in heart failure, it is prudent to avoid actively lowering BP <120/70 mm Hg. However, some patients tolerate lower BPs seen while on guideline directed medications and are advisable to continue treatment for them.[38] Sacubitril/valsartan lowers the BPs and improves outcomes in these patients. In patients with HFpEF, the same BP threshold and treatment target are applicable.

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