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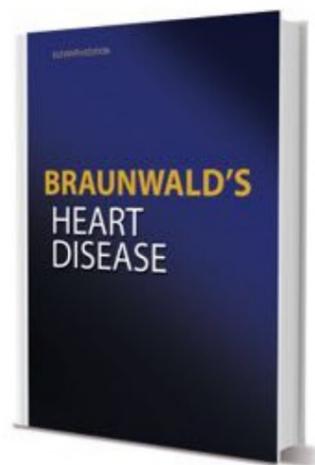
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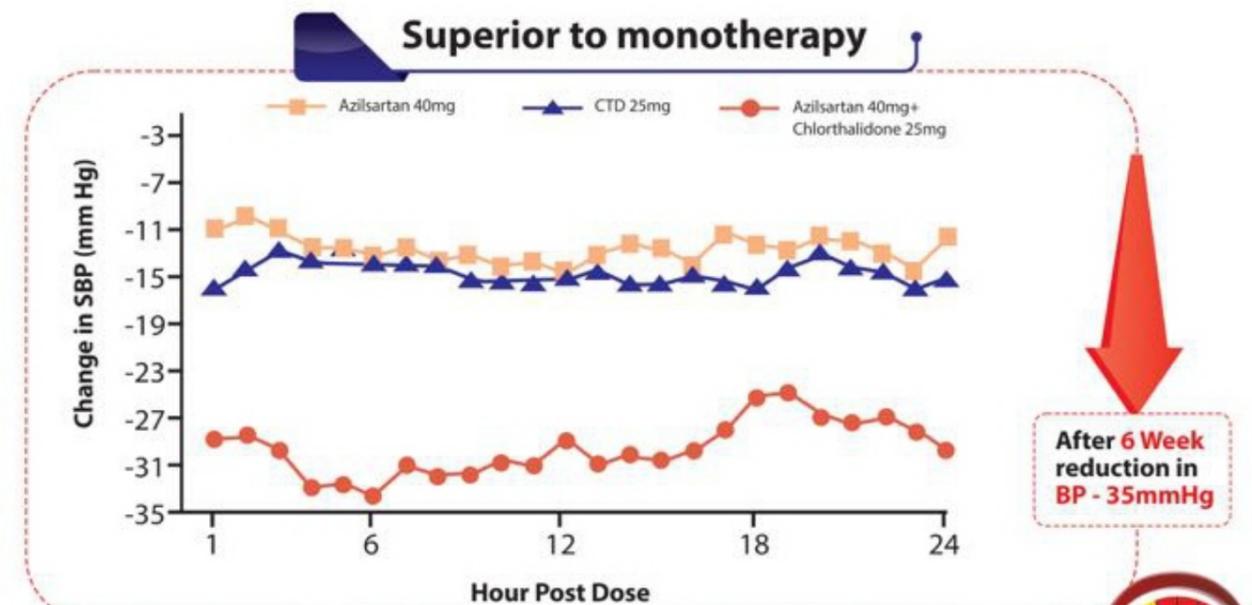
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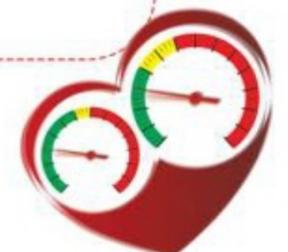
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AIMS & SCOPE

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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Hypertension Journal

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Contents

$\mathcal{F}$rom the Desk of Editor

It gives me great pleasure to be the Guest Editor for this issue of Hypertension Journal. This journal covers many interesting topics which were delivered as guest lectures during BPCON 2018 conducted by the Indian Society of Hypertension on September 7–9, 2018, at Chennai. The authors who contributed articles to this special and exclusive journal are leading experts in their own field with special interest in the field of hypertension. Sharing knowledge and disseminating the same are of at most importance when we are witnessing so much of advances in the field of hypertension.

A number of major scientific advances in hypertension were covered at BPCON 2018. Moreover, the topics discussed in the journal are from renowned specialists who would definitely enrich our knowledge in hypertension and its complications including recent advances in the management.

I am very much grateful to all contributors for their input and I am sure this issue on BPCON 2018 proceedings in hypertension journal will attract the attention of all readers.

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$\mathcal{G}$uest $\mathcal{E}$ditorial

Hypertension and Heart Failure with Preserved Ejection Fraction

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In the past four decades, there is an increase in the incidence and prevalence of heart failure. It is the most common cause of hospital admission after the age of 65-year-old individuals. In heart failure, there is structural and functional impairment of ventricular filling or ejection of blood. More than 75% of heart failure patients have antecedent hypertension. Hypertension accounts for 39% of risk in men and 59% of risk in women. Elevation of blood pressure leads to structural changes in the myocardium which, in turn, results in heart failure. Based on ejection fraction, the heart failure is classified as heart failure with reduced ejection fraction (HFrEF) when the ejection is <40%, and when the ejection fraction is >50%, it is known as heart failure with preserved ejection fraction (HFpEF). Nearly half of all the patients with heart failure have HFpEF. HFpEF continues to increase in prevalence due to common risk factors such as hypertension, old age, female sex, metabolic syndrome, and obesity. Hypertension, in particular, is a strong risk factor, and 80–90% of the people with hypertension have HFpEF. Historically, HFpEF was termed as diastolic heart failure, and this terminology is no more used now because recent investigations suggest a more complex and heterogeneous pathophysiology for HFpEF apart from diastolic dysfunction.

Heart failure	Ejection fraction
HFrEF	<40%
HFpEF	>50%
Heart failure with borderline or midrange EF (HFmrEF)	40–49%
HF-recovered EF	EF improved from HFrEF to >40%

HFpEF is prevalent but incompletely understood syndrome. Alterations in passive ventricular stiffness, ventriculoarterial coupling, and microvascular function occur. HFpEF is a heterogeneous state in nature and it is difficult to prescribe uniform therapies to all patients. Treating hypertension is the cornerstone of HFpEF. Antihypertensive therapies have been linked to LV hypertrophy regression and improvement in diastolic dysfunction.

However, to date, no therapy has definitive mortality benefit in HFpEF. Non-pharmacological management for hypertension, including dietary modification and exercise, may provide some morbidity benefit in the HFpEF population. When compared to patients with HFrEF, patients with HFpEF are older and less likely to have ischemic etiology. The mortality in HFrEF is reduced as a result of a number of evidence-based medical therapies, but in contrast in HFpEF, the mortality outcomes have not improved.

Hypertension remains as one of the major modifiable risk factors in HFpEF development and progression. The model of HFpEF pathophysiology emphasizes the role of hypertension causing LV hypertrophy and LV diastolic dysfunction. In the hypertrophied myocardium, there are limited vasodilation and altered electrical properties that can change the global function of the heart. Diastolic dysfunction is defined as the inability of LV to expand and relax, and it can be determined by echocardiographic studies. HFpEF is a heterogeneous disease entity with multiple contributors to its pathophysiology. A new paradigm for HFpEF was recently proposed where comorbid conditions including hypertension, diabetes, and obesity promote a pro-inflammatory state that leads to the development of HFpEF. It is postulated that systemic pro-inflammatory state leads to the development of coronary microvascular endothelial dysfunction, with subsequent reductions of nitric oxide bioavailability. Correction of protein kinase G activity and increasing nitric oxide bioavailability have been suggested for the treatment of HFpEF.

Prevalence of HFpEF is common in hypertensive individuals and elderly population. Atrial fibrillation is the common arrhythmia seen patients having HFpEF. The incidence of coronary artery disease is lower in patients with HFpEF. The other causes of abnormal diastolic function are hypertrophic and restrictive cardiomyopathies, coronary artery disease, diabetes mellitus, obesity, sleep apnea, chronic kidney disease, and aortic stenosis. LV filling may be impaired by abnormal active relaxation (early filling phase) and passive ventricular stiffness (late filling phase). HFrEF involves progressive expansion of the ventricle (LV dilation) and elongation of myocytes. HFpEF triggers a hypertrophic response with a marked increase in fibrosis leading to

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concentric remodeling without LV dilation. In HFpEF, ventricular hypertrophy, role of neurohormones, inflammatory process, and impaired cardiac relaxation are involved. HFpEF can progress to HFrEF, and diastolic dysfunction can occur in HFrEF.

Diagnosis of HFpEF is based on three factors: (1) Signs and symptoms of heart failure, (2) echocardiographic abnormalities such as increased LV mass and LA size and presence of Doppler parameters of diastolic dysfunction, and (3) elevated levels of brain natriuretic peptides (BNP). BNP levels are increased in HFrEF also.

Parameter	Clinical presentation (%)	
	HFpEF	HFrEF
Dyspnea	60	73
Paroxysmal nocturnal dyspnea	55	50
Pedal edema	35	46
Lung crepitations	72	70
Fatigue	+	+
Loss of appetite	+	+
Elevated JVP	+	+

1. Doppler interrogation of transmitral valve flow with E and A velocity ratio.
2. Pulmonary venous flow pattern.
3. Tissue Doppler assessment of E/E' ratio
4. Color flow M-mode measurements.

All these four assessments are very useful to assess the grading of LV diastolic dysfunction. Echocardiography in HFpEF will show the features of diastolic dysfunction, LA enlargement, LV hypertrophy, LA volume index >34 mL/m^2, and increased LV mass index.

Management of HFpEF is started with lifestyle modification such as reduction of salt intake, control of body weight, and regular physical exercise.

Therapeutic strategies are as follows:
1. Control of hypertension
2. Control of pulmonary congestion and peripheral edema with diuretics
3. Control of heart rate in atrial fibrillation
4. Coronary revascularization in patients with CAD.

The common drugs used in HFpEF are diuretics, verapamil, digoxin, beta-blockers, nitrates, ACE inhibitors/ARBs, aldosterone antagonists, and statins.

The treatment targets and options include,

LV volume and edema - diuretics, salt restriction

Hypertension - diuretics, CCBs, BB, ACEIs, ARBs

Reverse LVH - most antihypertensives

Prevent ischemia - BB, nitrates, CCB

Reduce heart rate in AF - BB, CCB, digoxin

Prognosis of HFpEF is as bad as HFrEF. Studies utilizing a variety of agents such as beta-blockers, calcium channel blockers, and diuretics demonstrated regression of LV hypertrophy, though the renin-angiotensin aldosterone blockers lead to higher rates of LVH regression. In perindopril in elderly people with chronic heart failure trial, there was a trend toward a reduced mortality and heart failure hospitalization with perindopril therapy. Candesartan in heart failure reduction in mortality trial assessed the role of candesartan, and there was a significant reduction in hospitalizations. Irbesartan in patients with heart failure and preserved ejection fraction (I-PRESERVE) trial, there was no significant difference in primary endpoint of all-cause mortality or hospitalizations. The valsartan in diastolic dysfunction trial demonstrated reductions in blood pressure and improvements in diastolic dysfunction. Recently, angiotensin receptor neprilysin inhibitors have generated much interest. To date, Valsartan-Sacubitril therapy outcome is encouraging in reducing the left atrial size and systolic blood pressure.

In the treatment of preserved cardiac function heart failure with aldosterone antagonist trial, the frequency of hospitalizations was less with spironolactone therapy, LA size reduction is noticed, decrease in pulmonary venous flow reversal occurs, and significant improvement is noted in diastolic dysfunction in echocardiographic assessment. A study of the effects of Nebivolol Intervention on outcome and rehabilitation in seniors with heart failure trial compared nebivolol with placebo in elderly patients. There was a reduction in all-cause mortality and hospitalizations. ALLHAT trial demonstrated a reduction in new-onset hospitalization incidence with chlorthalidone. Dig trial with digoxin reduces the ventricular rate in atrial fibrillation.

Conclusion

The overall prognosis of HFpEF is bad as HFrEF. Hypertension frequently contributes to the pathophysiology of HFpEF. HFpEF is recognized as a multifactorial syndrome. Management of hypertension is the cornerstone of HFpEF management, and careful matching of antihypertensive treatment holds a great promise for improving outcomes in patients with HFpEF.

Review Article

Hypertension: New Facets

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Abstract

The guidelines for hypertension provide all information regarding day-to-day management of hypertension. However, there are several issues such as mortality in a controlled hypertensive, fibrosis in cardiovascular system, vascular age, and target heterogeneity in response to decrease blood pressure which also require attention as they are clinically relevant.

Key words: J-Curve, BPV, fibrosis

Introduction

The numbers of blood pressure (BP) are very important and crucial in hypertension. The guidelines cover the number game with great precision and perfection in terms of diagnosis, initiation of treatment, and targets of BP control. However, there is panoply of facets beyond the number game which require refinements and are of interest to a clinician.

Mortality in Controlled Hypertensive

The mortality in a controlled hypertensive is at least 1½–2 times compared to a normal individual. There are two main reasons for it.

Atherosclerosis

This continues unabated even after control of BP and accounts for morbidity and mortality even in a controlled hypertensive. There is no doubt that lipids play a very important role in atherosclerosis, but when we look at the specimen of coarctation of the aorta, there are severe atheroscleroses in the segment above the coarctation and no atherosclerosis below the coarctation segment, indicating that hypertension alone can initiate atherosclerosis. It is important to remember that most of the antihypertensive agents, no doubt, decreases the BP-related complications of hypertension such as cerebral hemorrhage, acute left ventricular failure, and aortic dissection but do not provide atheroprotection as shown the result of the hope-3 trial which showed that, in patients of intermediate risk, if only antihypertensive agents are used (Candesartan 60 mg + hydrochlorothiazide 12.5 mg), there is no decrease in the primary endpoint of cardiovascular death myocardial infarction (MI) and stroke, but when rosuvastatin 10 mg is added, there is a statistically significant decrease in the cardiovascular events by 24% (3.7% vs. 4.8%, hazard ratios 0.76, 95% confidence interval 0.64–0.91, $P = 0.002$).

Fibrosis in the cardiovascular system

This occurs in various parts of the cardiovascular system such as myocardium, left atrium (LA), big arteries, and small arteries. The fibrosis is beautifully delineated by late gadolinium enhancement on cardiac magnetic resonance (CMR).

Fibrosis in myocardium[1]

This predisposes the individual to heart failure[2] with preserved ejection fraction and also predisposes to ventricular arrhythmias[3] which may culminate in sudden cardiac death.

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Fibrosis in the LA[4,5]

This predisposes the individual to atrial fibrillation and thromboembolism. The electrophysiologist always looks at the AL fibrosis by CMR before doing radiofrequency ablation (RFA) for atrial fibrillation because, if there is marked fibrosis, the probability of sustaining sinus rhythm after RFA is remote.

Fibrosis in the large arteries such as the aorta

Normally, the aorta has elastic tissue and is compliant, but when fibrosis occurs in the aorta,[6-8] the compliance decreases. Normally, the pulse wave velocity (PWV) is 8 m/s. When the impulse travels from the aorta to the periphery, it moves slowly, and when it is come back to the aorta, the diastole has already started. This results is increased in aortic diastolic pressure and produces augmentation of coronary blood flow. In aortopathy, there is fibrosis in the walls of the aorta and this results 12 m/sec in a decrease in compliance and an increase in the PWV about 12 m/s. Under such circumstances when the impulse travels rapidly from the aorta to the periphery and when it comes back to the aorta, the systolic is still ongoing [Figure 1].

This produces several adverse effects such as increase in central aortic pressure, increase in left ventricle afterload, increase in pulsatile strain with chances of plaque rupture, and no diastolic augmentation of coronary blood flow. The arterioles also undergo remodeling and capillaries also show changes such as increase in tone, remodeling, and rarefaction which results in increased resistance and decrease in blood supply to the tissues. Interestingly, certain drugs such as angiotensin-converting enzyme inhibitors (ACEI) (perindopril and ramipril), angiotensin receptor blockers (ARBs) (losartan and irbesartan), and calcium channel blockers (CCBs) (amlodipine) improve vascular remodeling while beta-blockers such as atenolol do not affect vascular remodeling. The question arises, is there any solution to minimize fibrosis? ACE inhibitors have shown to decrease myocardial fibrosis.[9] Very interesting data emerged from the long-term follow of ALLHAT[10] trial which showed that there was a significant reduction in conduction system disease with lisinopril compared to chlorthalidone and amlodipine after 5 years' follow-up. The effects were seen despite higher BP in the lisinopril arm, and its seems that antifibrotic properties of renin–angiotensin–aldosterone–system inhibition could play a key role. Azilsartan due to its vasculoprotective and antifibrotic properties may be another possible solution to this difficult problem of preventing/minimizing fibrosis, but we do not have any trials at the moment.

Therefore, we should drift from a merely BP-centric approach to a disease-centric approach. This involves 24 h BP control including control of nocturnal BP, morning surges and BP variability (BPV), and small and large vessel remodeling.

Chronological Age and Vascular Age

Hypertension is a very important cause of premature vascular aging so that vascular age of an individual may be much higher than his chronological age. Early and good control of BP may improve vascular aging.

BPV

The BPV is the missing link in the current treatment of hypertension.[11] In simplistic terms, it implies variation in BP over time. Although BPV is well known for several years, it is often not targeted. It is a threat to target organ damage, increase cardiovascular events, and has comparatively poor prognosis.[12] CCBs such as amlodipine effectively decrease BPV. The various types of BPV[13] are shown in Table 1. The normal values for BPVs are shown in Table 2.

Target Heterogeneity in Hypertension

The target organs of the body such as the heart, brain, and kidney do not respond in a similar way to decrease in BP. In brain lower is better applies both for systolic and diastolic BP. The action to control cardiovascular risk in diabetes BP study[14] [Figure 2] was negative, but still, the stroke was significantly decreased in the arm of 120 versus 140 mmHg. Indicating lower systolic BP is better for the prevention of stroke. The INVEST trial[15] showed that lower diastolic BP is also better for the prevention of stroke and there is no J-curve [Figure 3].
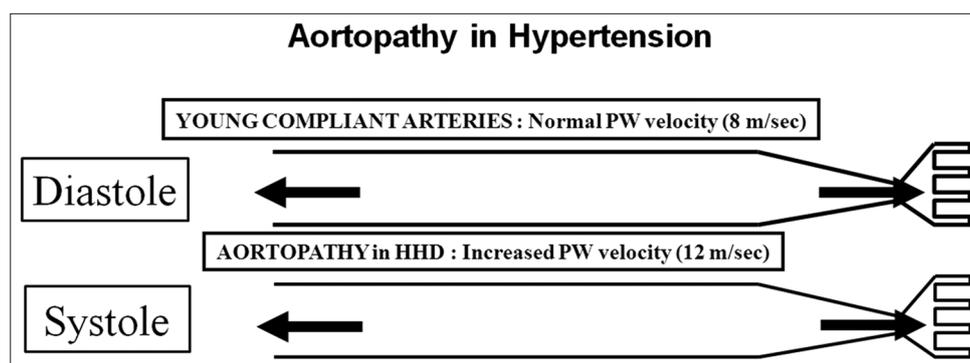
Figure 1: Pulse wave velocity in normal individual and aortopathy

Table 1: Types of BP variability

BPV	Oscillation of BP	Method	Indices of BPV
Very short term	Beat-to-beat variability	Continuous BP recordings in laboratory ABPM	SD, CV, Spectral analysis of 24 h BP fluctuations
Short term	Variation within 24 h	ABPM	SD, 24 h-weighted SD, CV, ARV
Mid term	Day-to-day variability	ABPM >48 h HBPM	SD, CV
Long term	Visit-to-visit variability <5 years	OBP, ABPM, HBPM	SD, CV
Very long term	Visit-to-visit variability >5 years	OBP, ABPM, HBPM	SD, CV

SD: Standard deviation, CV: Coefficient of variation, HBPM: Home blood pressure monitoring, OBP: Office blood pressure, ARV: Average real variability, ABPM: Ambulatory blood pressure monitoring, BP: Blood pressure

Table 2: BPV on the basis of 24 h ABPM in healthy persons

Mean SD SBP mmHg			Mean DBP mmHg		
24 h	Day time	Night time	24 h	Day time	Night time
15.2±3.5	13.6±3.8	11.2±4.1	13.0 ±2.6	12.1±2.8	9.8±3.0

BPV: Blood pressure variability, ABPM: Ambulatory blood pressure monitoring, SBP: Systolic blood pressure
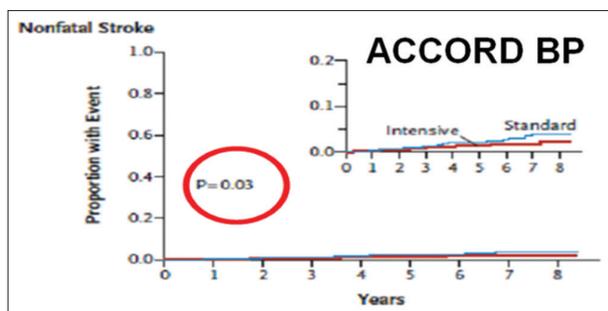
Figure 2: Action to control cardiovascular risk in diabetes blood pressure (BP) study showing decrease in stroke with lower BP
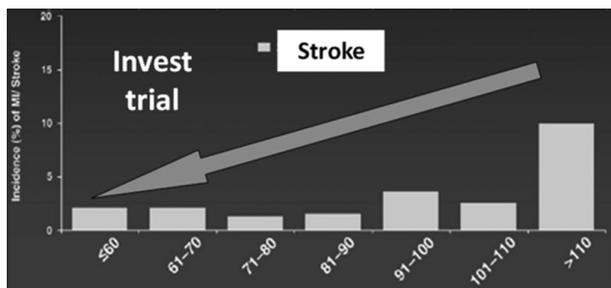
Figure 3: Invest study showing lower diastolic blood pressure is associated with lower incidence of stroke

In the heart, lower diastolic BP is not good because coronary arteries are filled during diastole, and if diastolic BP is decreased, it may increase coronary events. Even the hypertension optimal treatment study, when the data were analyzed on the basis of ischemic versus non-ischemic group, the MI was higher in the ischemic group when BP was lowered to <90/<85/<80, indicating that lower diastolic BP is not good for the heart [Figure 4]. The INVEST study [Figure 5] also showed that, when BP is decreased to <80, there is an increase in MI.

Thus, a J-Curve exists for the heart in hypertension, and in most studies, the J-shaped curve is found to be at the level of DPB below 80–70 mm/Hg. Interestingly, when a DBP of 80–90 was compared with DBP below 60, there was more than doubled the odds of high sensitivity cardiac troponin-T levels equaling or exceeding 14 mg/ml and increased the risk of incident coronary heart disease by about 50%.[16] Moreover, patients of coronary artery disease with coronary revascularization when compared to those without it tolerated lower diastolic BP better.[17] In the kidneys, more important than the arterial BP is the intraglomerular pressure and an increase in it results in increased in proteinuria and rapid progression of coronary kidney disease. ACEI/ARB are the preferred agents in CKD because, by dilating efferent arterioles, they decrease intraglomerular pressure which decreases proteinuria.

Why J-Curve is Present for the Heart and Not for the Brain or Kidneys

Coronary perfusion occurs in diastole, whereas cerebral perfusion and renal perfusion occur mainly in systole. Cerebral perfusion is capable of autoregulation in the range of 40–125 mmHg, so it is resistant to low BP. As a result, the J-curve phenomenon does not hold true for the incidence of stroke.

Quality of Life

It is important to remember that the treatment of hypertension is a long drawn out process for several years, and therefore, special attention must be paid on quality of life. We must never forget life is not merely being alive, but being well. Our hypertensive patient should not only live but also feel well. Hydrochlorothiazide, Chlorhexidine, and atenolol produce erectile dysfunction while indapamide, ACEI/ARB, and CCB do have this side effect.

Although we have a variety of powerful antihypertensive drugs to control BP, prevention should be our goal because the mortality in a controlled hypertensive is at least 1½ and 2 times that of normotensive. This is possible by adopting simple measures life eat less, eat right, eat in time walk more, sleep well, and smile.

Conclusion

We have conquered the number game of BP with non-pharmacological measures and drug treatment. However, several other areas in hypertension require attention for further improving its treatment.
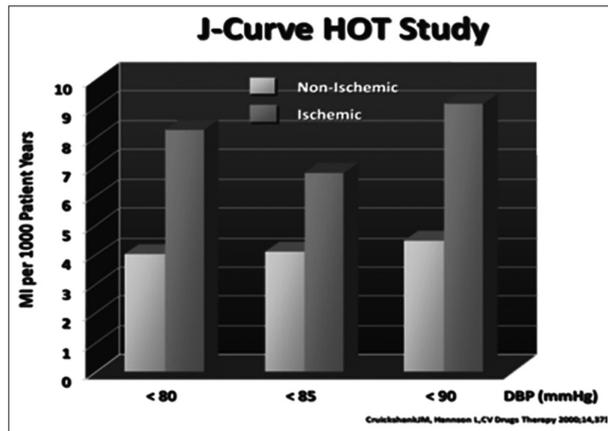
Figure 4: Hypertension optimal treatment study showing increase in myocardial infarction in the ischemic group at all levels of diastolic blood pressure compared to the non ischemic group
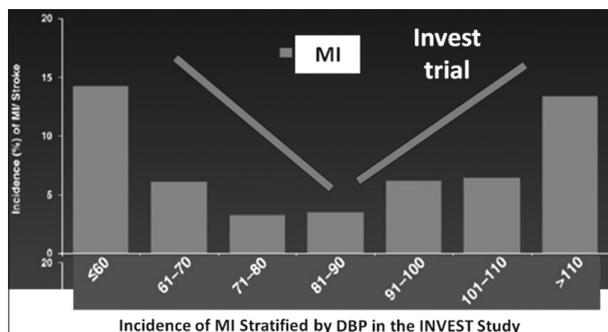
Figure 5: Inverse study showing increase in myocardial infarction when diastolic blood pressure is decreased below 80 mmHg

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Review Article

Assessment of Cardiovascular Risk Profile in Clinical Practice

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Abstract

The burden of cardiovascular disease continues to be high and heavy. There is some encouraging declining trend emerging in the west, but it is on the increase in our country. Prevention, in general, and primordial and primary prevention, in particular, are important in dealing with cardiovascular disease in resource-constrained countries. Risk assessment of atherosclerotic cardiovascular disease is necessary to decide the intensity of preventive measures. There are a number of risk assessment tools available, and one that suits our practice and population should be utilized.

Key words: Cardiovascular risk, Atherosclerotic cardiovascular disease, Risk assesment tools.

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is taking a heavy toll of socioeconomics of our country. ASCVD has been shown to affect our population about a decade earlier, is more serious, and carries a higher mortality as compared to the western population. This has been explained by the fact that ASCVD risk factors are operative much earlier in the lives our population.[1,2]

On a global scene, deaths from non-communicable diseases (NCD) have increased by 8 million between 1990 and 2010, and it means two of every three deaths are due to NCD.

Ischemic heart disease and stroke accounted for 12.9 million deaths in 2010 or one in four deaths worldwide. Years of life lost due to ischemic heart disease and stroke have increased by 17–28%.[3]

Looking at our objective of achieving 25% reduction in cardiovascular mortality by 2025 globally, South Asian countries are lagging far behind, and there is an urgent need to address aggressively the risk factor reduction.[4]

The Indian scenario is quite depressing. From 1990 to 2015, there is a significant increase in mortality rates from CVD (40.7% increase) and ischemic heart disease (IHD) (33.7% increase) while stroke mortality rates have stabilized (around 7.0%), and it is heartening to see that stroke mortality has decreased in women by 2%.[5] The increase in CVD and IHD mortality in

India is in contrast to developed countries showing decline in CVD mortality in the past 50 years.

Access to health care not being optimal and secondary prevention strategies being expensive emphasizes the need to focus on primordial (health behavior) and primary preventive (risk factor reduction) measures.[6]

Risk Assessment

When it comes to secondary prevention of ASCVD, there is not much of a discussion or controversy on aggressive treatment with lipid-modifying drugs along with lifestyle changes and other risk factor modification. However, in primary prevention, the situation is different and risk assessment is necessary so that the intensity of treatment is proportional to the risk. It also helps to avoid unnecessary lifelong medication in low-risk subjects, allowing appropriate resource utilization. Risk assessment at baseline and during follow-up would also motivate the person to adopt health-related behavior.

Assessment of ASCVD risk is usually challenging due to various factors such as contemporary nature of the data, a delay in acquiring data on clinical events, confounders, and validation of the risk assessment tools. There is always a possibility of overestimation and underestimation of the risk, depending on the

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population. Risk assessment is a probabilistic exercise. Risk factors are dynamic and assessment tools need to change with time.

With all the limitations that risk assessment has, it is still logical and appropriate to employ risk-based prevention with proven therapies in people who are likely to benefit.

A very important aspect of risk assessment is that it is the starting point for a discussion with the patient/subject. An exchange of ideas and information will help in taking a decision on preventive drug therapy.

Ideally, risk assessment and advise on health behavior should start early in childhood. It is well known that it is not only the severity of risk factor, but the duration of exposure to the risk factor also matters. Consensus statements from India recommend ASCVD screening at age 30 years[7] and 20 years.[8] Universal screening of all Indians for ASCVD risk factors at 20 years of age or at the time of college entry or at the earliest opportunity is recommended for early detection of high-risk individuals. It should be global risk assessment. All efforts

should be made to rule out secondary causes of hypertension and dyslipidemia and to optimize management of all other modifiable CVD risk factors.[8]

Risk Assessment Tools

There are a number of risk assessment calculators available and most estimate 10-year risk of cardiovascular events for primary prevention. The predictive accuracy of these tools has not been adequately evaluated in Indians. A study showed that the Risk-JBS3 calculator proposed by Joint British Society 3rd Iteration provided the most accurate risk prediction in Indians.[9] Another option may be to recalibrate the estimated 10-year Framingham risk score by multiplying it with a calibration factor. The second Indo-US Health summit[10] task force suggested a calibration factor of two for Indians, whereas the recent UK lipid-lowering guidelines have recommended a multiplication factor of 1.4 for men of South Asian origin. In comparison, the International Atherosclerosis Society
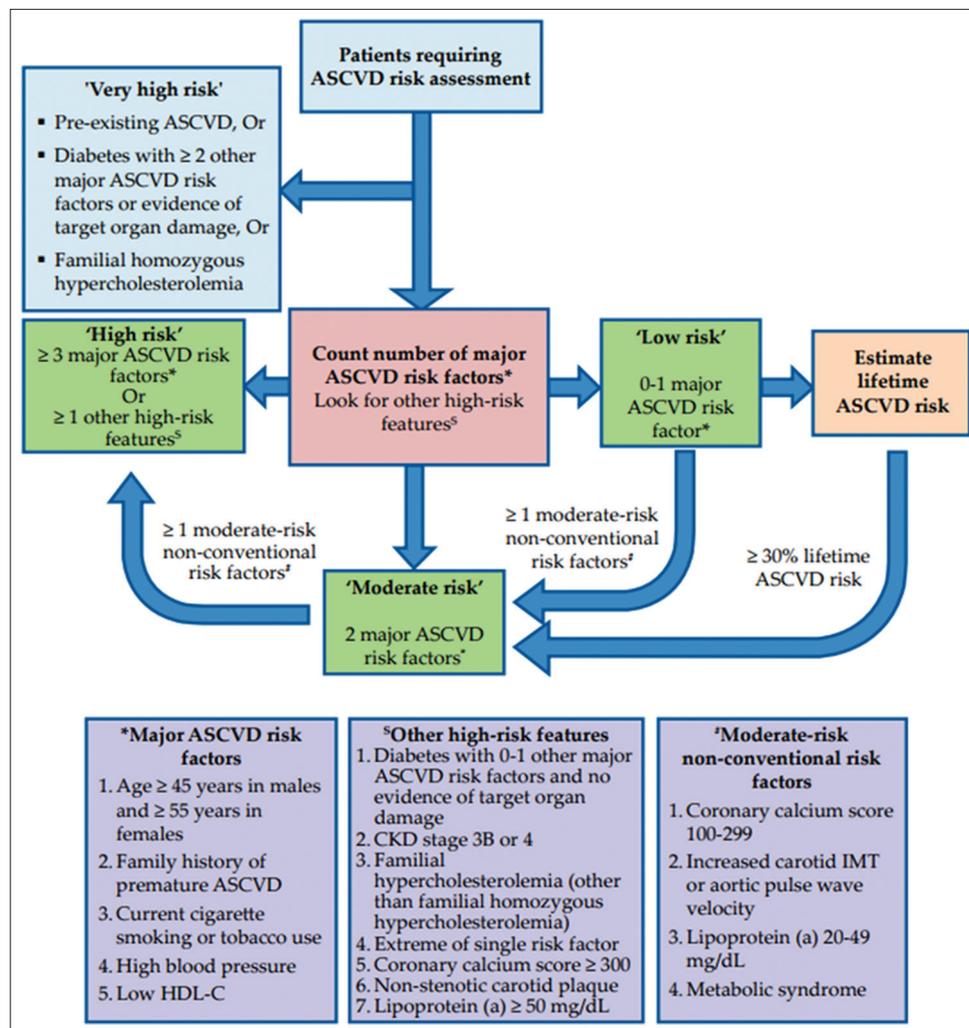
Figure 1: Recommended approach to atherosclerotic cardiovascular disease risk stratification in Indians[8]

has proposed calibration factors of 1.81 and 1.54 for urban men and women and 1.0 and 0.8 for rural men and women, respectively.[11]

In 2014, Cardiological Society of India brought out a consensus document on management of dyslipidemia in Indian subjects.[7] This statement integrated global information with local requirement. The statement recommended the use of the WHO/ISH risk prediction chart or JBS 3 risk score since these two have some Indian element. Screening for ASCVD risk factors was recommended to be carried out at age 30 years. Non-conventional risk factors could be used to refine the risk further in intermediate risk group.

In 2016, lipid association of India published a consensus document.[8] The screening age for risk factors was recommended to be 20 years or at college entry or the earliest opportunity. Risk assessment avoided scoring system and computers and was based on risk factors - conventional and non-conventional [Figure 1]. It also encourages the use of lifetime risk assessment in low-risk individuals. The importance of primordial prevention was emphasized.

Both the statements have incorporated international information with the local data and suitable recommendations have been made. Both highlight the necessity of global risk assessment, primary prevention, appropriate secondary preventive measures, and participation of patients/subjects in decision-making.

Any one risk scoring system could be followed. The clinician should choose the one he is familiar and comfortable with, use the same score during follow-up, and keep in mind the dynamic nature of the scoring systems.

New factors which impart increased cardiovascular risk are emerging. Subjects with erectile dysfunction, women with a history of preeclampsia or eclampsia, gestational hypertension or diabetes, and children born with assisted reproductive technology have to be followed up carefully for cardiovascular risk assessment.[12,13]

Conclusion

Assessment of cardiovascular risk profile is an important step in the primary prevention strategy. The intensity of preventive therapies should match ASCVD risk. The clinician should use ASCVD risk tool that suits our population and should engage the subject in discussion and involve in the management.

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Review Article

Hypertension Outcome Trials: How Relevant are they in the Real World Practice of Medicine?

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Abstract

Hypertension is a major risk factor for cardiovascular (CV) morbidity and mortality. The prevalence of hypertension is increasing in alarming proportion in both urban and rural population in India. Benefits of lowering blood pressure (BP) resulted in the reduction of CV risk, including mortality benefit. Randomized control trials conducted in people with hypertension had shown beneficial effects in the treatment group compared to that of the placebo or other comparator drugs. Trials in hypertensive participants have given us lot of information about efficacy and safety of pharmacological agents. Combination therapy has shown more advantages for reaching the BP goals early and for additional benefits of CV outcome. There are some controversial issues about usage of certain drugs and the goals of BP in people with diabetes and chronic kidney disease. However, meta-analysis of various trials gave answers for some issues. This chapter will focus on major hypertension outcome trials and their relevance in the real world practice of medicine.

Key words: Hypertension, CV risk, anti hypertensive drugs

Introduction

Hypertension is the most common condition seen in primary care and leads to myocardial infarction (MI), stroke, renal failure, and heart failure (HF). Atrial fibrillation, peripheral arterial disease, and aortic dissection are not uncommon complications. Death occurs if not detected early and treated appropriately. Hypertension is a major public health challenge globally and affects nearly 26% of the population in India as per the data projected in 2015.[1]

It is not only a silent killer but also a leading risk factor for mortality. There is a huge body of evidence from randomized control trials (RCTs) on hypertension indicating not only the benefit of lowering blood pressure (BP) but also reflecting appreciable benefit in cardiovascular (CV) morbidity and mortality. This chapter will focus on major hypertension outcome trials and their relevance in the real world practice of medicine.

Lessons Learnt from Hypertension Trials

Hypertension treatment recommendations are based on strict interpretation of data only from RCTs which compared placebo

and comparator drug. There are good number of RCTs which had used different group of drugs either alone or in combination and compared. These RCTs paved the way for health-care providers to manage hypertension at all stages, including complications with target organ damage. These outcome trials have provided useful and relevant information in people with diabetes, the elderly and with chronic kidney disease (CKD) and cardiovascular disease CVD.

Pharmacotherapy: Renin-Angiotensin Inhibitors

Renin-angiotensin-aldosterone system (RAAS) is active not only in the initial stages of hypertension but also in the progression of hypertension, including clinical CVD and nephropathy. Blocking the RAAS by angiotensin-converting enzyme inhibitors (ACEIs) have shown remarkable improvement in BP control and reduction in CV morbidity and mortality. RCTs conducted using various ACEI have shown beneficial affects in reducing proteinuria with marginal benefit in CV outcome. Ramipril in hope study has proved for its safety and efficacy in the prevention of CV complications. Angiotensin II receptor blockers (ARBs)

which block AT1 receptors have demonstrated to match with the benefits that are obtained with ACEI. Number of RCTs with ARBs compared with the placebo or other comparator drugs proved to have beneficial effects. ARBs are good in the prevention of stroke events in the general population and diabetics. Although ARBs were linked with a fear of inducing MI in the past, a recent meta-analysis published in BMJ[2] clearly has shown that there is no correlation between ARBs and increase in MI risk. Now, it is clear that ARBs do not induce MI and are considered safe. ARBs are potent drugs to reduce proteinuria and for reducing renal morbidity. Ongoing telmisartan alone and in combination with ramipril global endpoint trial have clearly shown that telmisartan is noninferior to ramipril in bringing down CV hard end-points. However, the study has proved the bad effects of increasing renal morbidity by combining ramipril with telmisartan. Combination of ACEI and ARB is not an ideal choice in any clinical situation, either with diabetes or hypertension and or CKD. Aliskiren trial in Type 2 diabetes using cardio-renal endpoints showed that the addition of direct renin inhibitor aliskiren to background therapy with an ACEI or ARB increases the incidence of hyperkalemia and hypotension while producing no added CV benefit: These results led to a black box Food and Drug Administration (FDA) warning against this form of dual renin-angiotensin system (RAS) blockade.[3-5] Dual RAS blockade either with ACEI + an ARB or with Aliskiren + an ACEI or ARB is now contraindicated.

As monotherapy, ACEIs are generally less effective in lowering BP in Africans and in older patients with low-renin hypertension, but they are quite effective in these groups when combined with a low-dose diuretic or calcium channel blocker (CCB). In meta-analysis, ACEIs are found to be equivalent to CCBs in protecting against coronary events, slightly less effective in protecting against stroke, but better in protecting against HF.[6]

Diuretics

Systolic hypertension in the elderly program (SHEP) and systolic hypertension in Europe study revealed that diabetics derive more benefit from the same degree of BP lowering than those without diabetes. SHEP – long-term follow-up determined whether the effect of BP lowering during SHEP is associated with long-term (22 years) outcomes such as CV and all-cause mortality and extended life expectancy. People on active therapy with chlorthalidone lived an average 516 days longer and 205 days free of all cause mortality, not necessarily CV mortality.[7]

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[8]

This is the largest hypertension trial which recruited nearly 42,418 patients with comorbid conditions, including diabetes. There were 4 arms in the study. Doxazosin arm was stopped because of increase in HF. Chlorthalidone, a good old diuretic, was compared with CCB – Amlodipine and ACEI, lisinopril in this study and all patients were followed up for a period of 5 years.

Primary end-point: Fatal coronary heart disease (CHD) and non-fatal MI. Chlorthalidone was found to be equal compared to amlodipine and lisinopril in reducing CV risk. Chlorthalidone was found to be superior when compared to amlodipine and lisinopril in HF, and it was better in the prevention of stroke compared to that of lisinopril.

Chlorthalidone versus Hydrochlorothiazide (HCTZ)

Even though HCTZ has enjoyed widespread use in clinical practice, chlorthalidone is the choice in clinical practice with good evidence from RCTs. Greater effectiveness of chlorthalidone than HCTZ is strongly suggested by *post hoc* analysis of the multiple risk factor intervention trial data[9] which showed better outcomes with chlorthalidone. A small single-center ambulatory BP monitoring (ABPM) study showed a much longer duration of action of chlorthalidone. Loop diuretics are less effective BP-lowering agents and should be reserved for treating hypertension in the setting of advanced CKD (stage 3 or higher). Chlorthalidone may also be effective in patients with Stage 3 CKD. Diuretics enhance the potency of all other classes of antihypertensive agents. Thiazide and thiazide-like diuretics combine, particularly well with ACEIs and ARBs. This combination blunts reactive RAS activation and thus increase antihypertensive efficacy. The current trend is to recommend thiazide-like diuretics such as chlorthalidone and indapamide in the place of hydrochlorothiazide. Multiple RCTs have shown that thiazide-type diuretics reduce coronary events, strokes, and HF in elderly patients.

Hypertension in the Very Elderly Trial (HYVET)[10]

This trial has focused on the treatment of hypertension, in elderly patients >80 years. Before the study publication, we were not very sure of treating octogenarians. This study used diuretic indapamide with ACEI perindopril and compared with the placebo. All end-points, including stroke (hazard ratio [HR]:0.70), stroke-deaths (HR:0.61), all-cause mortality (HR:0.79), CV death (HR:0.77), cardiac death (HR:0.71), and hospitalization for HF (HR:0.36) were reduced considerably compared to that of the placebo. This study emphasizes the role of pharmacotherapy and advantages in reducing CV morbidity and mortality in the elderly. The results of this study will help us to adopt the same measures of controlling HYVET.

Importance of Home BP Monitoring (HBPM) and ABPM

The 2011 U.K. guidelines from the National Institute of Clinical Excellence (NICE) and the 2013 European Society of Hypertension/European Society of Cardiology guidelines place far greater emphasis than U.S. guidelines on home and ABPM for clinical decision-making.[11-13] Based on registry data from the 11-country International database on ambulatory BP in relation to CV outcomes ambulatory and HBPM should be routine in hypertension. Masked (out-of-office only) hypertension

is so common in older adults and in people with diabetes. Conventional office BP readings alone will promote either over treatment or under treatment of hypertension.

Role of Beta Blockers

Beta-blockers in the management of hypertension are still debated. Lindholm *et al.* published a meta-analysis which revealed that atenolol-based anti-hypertensive therapy increased the incidence of stroke by 16% and precipitated new-onset diabetes. Beta blocker like atenolol has to be avoided in managing hypertension. However, non-atenolol based betablockers have a role in managing hypertension. This is more relevant in people with diabetes because of adverse metabolic effects and alteration in the lipid profile. NICE guidelines in 2011, pushed beta-blockers as a last resort in the management of hypertension. In view of the adverse effects such as increase in stroke and new-onset diabetes, beta-blockers do not enjoy the first place in the management of hypertension. There is a definite role for usage of vasodilating beta-blockers other than atenolol, particularly for secondary prevention. Hence, the current role of beta-blockers is in situations such as arrhythmias, increased sympathetic activity, coronary artery disease (CAD), and congestive HF complicated by hypertension.[14] Vasodilating beta-blockers are much more potent antihypertensive agents. They do not adversely affect glucose tolerance. There is a lack of data from large RCTs on this issue at this point in time.

Carvedilol

Carvedilol has both alpha- and beta-blocking action. It reduces CVD mortality in HF and microalbuminuria without affecting glucose or lipid profiles. In combination with RAS blockade, more reduction in albuminuria was seen. It slows the progression of nephropathy, improves insulin sensitivity and has useful role in CAD and HF. It is underutilized as an add-on agent in hypertension with diabetes.

Nebivolol

A selective beta-blocker which improves endothelial function by increasing the nitric oxide production and reducing the oxidative stress. Study of effects of nebivolol intervention on outcomes and rehospitalization in seniors trial has shown lower incidence of new-onset diabetes.

Labetalol

Labetalol is effective in hypertensive emergencies. It is a short-acting drug and to be used for managing chronic hypertension. This is the drug of choice for pregnancy hypertension.

Role of CCBs

CCBs are ideal antihypertensive drugs. They are lipid neutral and do not disturb glucose metabolism. CCB amlodipine +/− perindopril was evaluated in comparison with atenolol and hydrochlorothiazide in a landmark study called anglo-Scandinavian cardiac outcomes trial (ASCOT).[15] Summary of all endpoints starting from primary to tertiary, including *post hoc* analysis revealed that amlodipine +/− perindopril combination is far superior compared to atenolol and hydrochlorothiazide Ref Figure 1.

Long-term mortality after BP lowering and lipid-lowering treatment in patients with hypertension in the ASCOT Legacy study: This is a 16-year follow-up results of a randomized factorial trial.
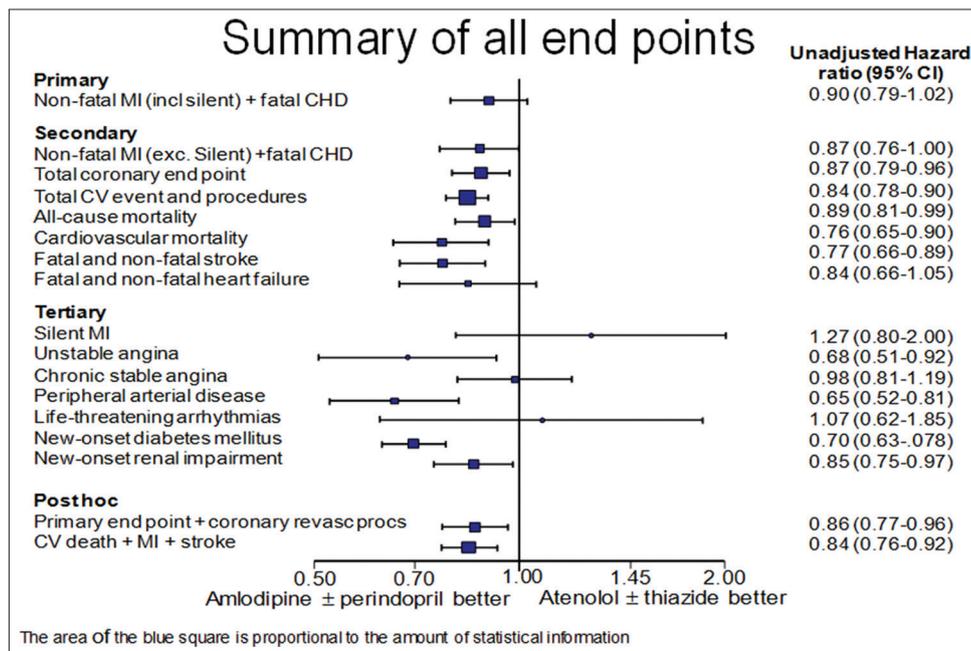
Figure 1: Anglo-scandinavian cardiac outcomes trial results

Findings show the long-term beneficial effects on mortality of antihypertensive treatment with a CCB based treatment regimen and lipid lowering with a statin. Patients on amlodipine-based treatment had fewer stroke deaths and patients on atorvastatin had fewer CV deaths (HR 0.85, 0.72–0.99, $P = 0.0395$) >10 years after trial closure. Overall, the ASCOT legacy study supports the notion that interventions for BP and cholesterol are associated with long-term benefits on CV outcomes.[16]

Avoiding CV Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) study[17]

This study evaluated the efficacy of amlodipine with benazepril compared to a combination of hydrochlorothiazide with benazepril. This study had nearly 60% of participants with diabetes and a follow-up period of nearly 5 years. It was interesting to see the beneficial effects of amlodipine with benazepril to the extent of reducing relative risk of CVD by 19.6% compared to the other group. Hence, a combination of CCB with ACEI is considered superior when compared to ACEI with hydrochlorothiazide. The primary endpoint with the percentage of relative risk reduction is depicted in this [Figure 2].

Hypertension and Left Ventricular Hypertrophy (LVH)[18]

LVH is a major risk factor for CV morbidity and mortality. The study by Klingbeil *et al.* revealed that ARBs are superior for reducing LVH and LV mass compared to that of the other drugs.

The efficacy rating for reducing LVH is ARB > CCB > ACEI > Diuretic > Beta Blocker in that order.

Aldosterone Blockers

Aldosterone is now known to affect insulin resistance and pancreatic beta-cell function. Spironolactone which was evaluated in randomized aldactone evaluation study in people with HF showed beneficial effects in reducing CV morbidity and mortality. Eplerenone which is a newer aldosterone blocker was evaluated in the Eplerenone Post-Acute MI HF Efficacy and Survival study. Eplerenone is considered superior when compared to spironolactone which has other side effects, including gynecomastia. 2000 participants who were diabetics in this study had shown remarkable advantages of this drug with its antihypertensive effect equivalent to ACEIs and CCBs and provided additional effect when added to ACEI and ARB. The drug reduced proteinuria in diabetic patients with nephropathy and proved to improve diastolic function. Surprisingly this drug worked well in blacks and elderly. If aldosterone blockers are added to control hypertension, a major side effect of hyperkalemia has to be monitored. These drugs are really promising for the treatment of resistant hypertension. People with diabetes should be given the benefit of this drug for proper control of BP to the goal.

Low-dose spironolactone (Normal dosage 12.5–100 mg daily) is widely recommended as a highly effective add-on drug for difficult cases of hypertension. This recommendation is based on small single-site series and *post hoc* analysis of ASCOT, which used spironolactone (12.5–25 mg daily) as a fourth-line therapy. Hyperkalemia must be avoided when using these agents in patients
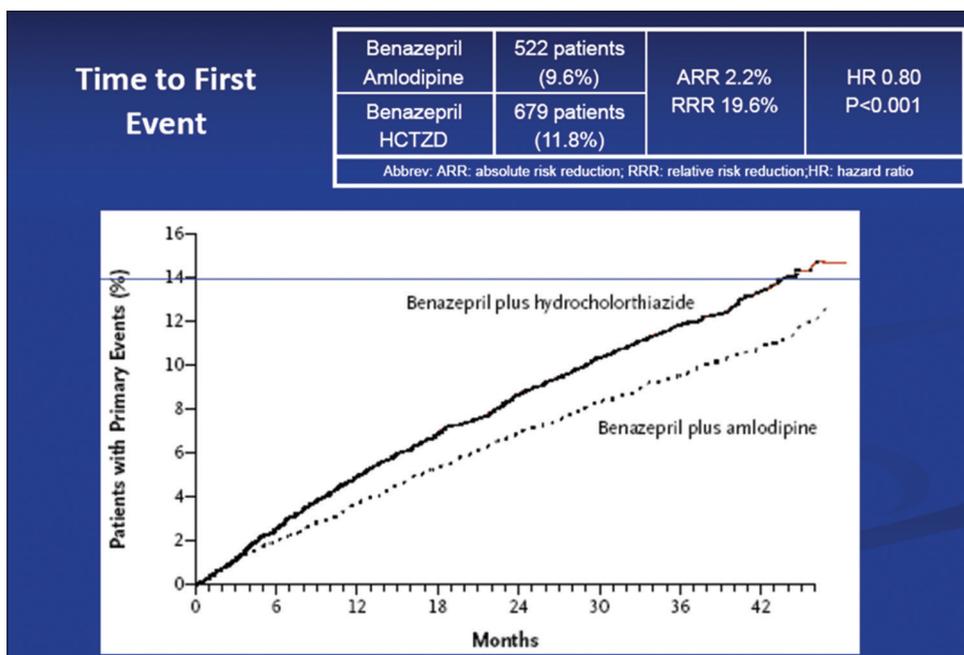
Figure 2: Avoiding cardiovascular events through combination therapy in patients living with systolic hypertension study results: Primary endpoint

with kidney disease. Aldosterone antagonist should find a place as a fourth drug in the management of resistant hypertension.

Need for Combination Therapy

Monotherapy fails in many patients who are not reaching the goal of BP. Majority of patients in general and diabetes, in particular, require combination therapy. Many studies such as HOT, ALLHAT, IDNT, and UKPDS used combination therapy with 3–4 drugs to reach the goals of BP. Combination therapy with different groups of drugs has synergistic action. Most of the patients though started with one or two drugs ultimately require 3–4 drugs for reaching the goal. Combining drugs with half the standard dose either with two or three drugs have shown beneficial effects. Fixed-dose combination in a single pill is useful for the elderly and for patients who are less compliant. American Diabetes Association (ADA), Standards of Medical Care 2019 recommendations are to administer one or more antihypertensive medications at bedtime when multiple drugs are given to control BP and the statement is reemphasized by ADA in 2019.

Priority of Antihypertensive Drug Combinations

1. ACEI plus diuretic
2. ACEI plus CCB
3. ARB plus diuretic
4. ARB plus CCB
5. Diuretic plus CCB.

Why is a CCB Preferred to a Diuretic?

CCBs are very popular antihypertensive drugs. They are generally well-tolerated, do not require monitoring with blood tests, and have proved safe and effective in many large RCTs. CCBs also have anti-anginal and some antiarrhythmic effects and seem to provide more protection against stroke than other antihypertensive agents do. Among CCB, amlodipine is the most cost-effective and metabolically neutral. Amlodipine is the best at reducing BP variability which is an independent predictor of clinical outcomes, especially the stroke. The combination of A + C is superior to A + D in improving the clinical outcomes (A: ACEI/ARB, C: CCB, D: Diuretic).

Combination therapy for Managing Hypertension

Simplifying Combination Therapy and the Optimal Drug Combination are depicted in Figures 3 and 4.

Hypertension in People with Diabetes

Hypertension is seen in 70–80% of patients with Type 2 diabetes mellitus (T2DM) and in >25% in those with Type 1 DM (T1DM). The prevalence increases with age, type of diabetes, obesity, and ethnicity. In T1DM, hypertension is mostly due to
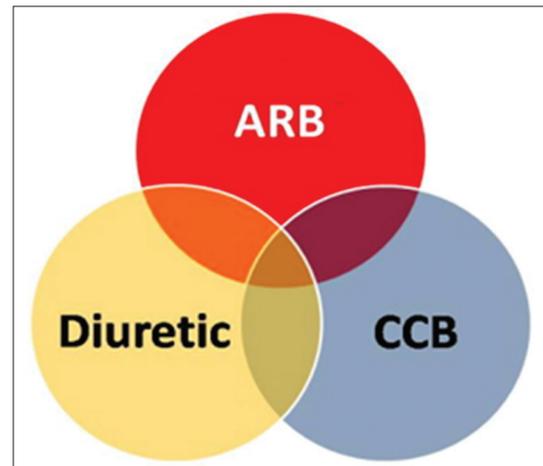
Figure 3: Simplifying combination therapy
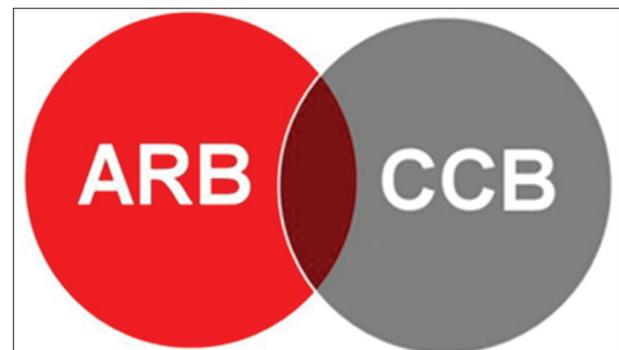
Figure 4: Optimal combination therapy for hypertension

nephropathy and in T2DM, hypertension is often present at the time diabetes is diagnosed. Diabetes and hypertension are typical components of metabolic syndrome. Hypertension increases both micro and macrovascular complications of diabetes. More than 75% of diabetics die due to CVD.

Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) Trial[19]

Trial recruited 11,140 patients with T2DM. They were randomized to perindopril/indapamide combination or placebo and followed for a mean of 4.3 years. Those in the treatment wing had a mean reduction of systolic BP of 5.6 mmHg and diastolic BP of 2.2 mmHg. The HR for vascular events was 0.91 (95% Confidence interval [CI]: 0.83–1.00, $P = 0.004$). Similar reductions were noted for micro and macrovascular events. The relative risk for CV death fell by 18%.

Action to Control CV Risk in Diabetes (ACCORD) Trial[20]

Researchers randomly assigned 4,733 participants with elevated BP to a target systolic BP of either <120 mmHg (the intensive

group) or to <140 mmHg (the standard group). A variety of FDA-approved BP medications were used to reach BP goals. After an average follow-up of about 5 years, researchers found no significant differences between the intensive group and the standard group in rates of a combined endpoint, including nonfatal heart attack, nonfatal stroke, or CV death. Lowering the BP to below the standard level significantly cut the risk of stroke by about 40%. ACCORD study results show that there is no significant difference in outcome parameters for spontaneous bacterial peritonitis (SBP) levels of 119 or 130 mm Hg though there was trend toward benefits in the intensive BP lowering arm for stroke events. Serious adverse events such as syncope and hyperkalemia were more in the intensive control group.

ACCORD study may have lacked the power to establish such a difference because of the very low number of CV events that occurred in the diabetic study patients, most of whom received treatment with statins and other CV risk reduction measures. Moreover, reliance on clinic BP presents particular problems in trials of diabetic patients because of the prevalence of masked hypertension. This issue was not addressed in this trial. Two meta-analyses also concluded that in patients with diabetes protection from stroke but not myocardial infarction increases with the magnitude of reduction in BP.[21,22]

Hypertension in Patients with Diabetic Nephropathy

In RCTs, the addition of an ARB to background antihypertensive therapy was found to slow progression of nephropathy in patients with T2DM, whereas amlodipine did not.[23,24] T2DM with nephropathy is an indication for ARB therapy. There is evidence to recommend an office BP goal of 140/90 mm Hg or lower. The 2013 kidney disease improving global outcomes (KDIGO) guidelines[25] recommend a stretch goal of <130/80 mm Hg in those with significant proteinuria (urine-to-plasma albumin-to-creatinine ratio of ≥30 mg/g, a figure corresponding to ≥30 mg of urinary albumin excretion in 24 h), which is the case in most patients.

Hypertension in Patients with Nondiabetic CKD

The 2013 KDIGO guideline recommends a goal office BP of lower than 140/90 mm Hg for patients with nondiabetic nonproteinuric CKD and a stretch goal of <130/80 mm Hg with an ACEI- or ARB-based regimen for those with proteinuria.

BP Goal

Since mid-1990s most guidelines recommended 140/90 mm Hg as the threshold for diagnosing hypertension and achieving BP below this threshold should be an appropriate target of treatment. The first influential study was SHEP in which patients age 60 or older with SBP >160 mm Hg were recruited and the trial finished with the mean SBP of 143 mm Hg. Chlorthalidone was compared with placebo which proved its efficacy and safety

in elderly individuals with 36% reduction in stroke and 27% reduction in CHD and 55% reduction in HF.[26] SHEP – long-term-follow up[7] with an aim to determine whether the effect of BP lowering during SHEP is associated with long-term [22 years] outcomes [CV and all cause mortality] and extended life expectancy.

Results

People on active therapy lived an average 516 days longer 205 days free of all-cause mortality not necessarily CV mortality. ACCOMPLISH study investigators looked at the event rates according to the SBP reduction. It was clearly seen that less number of events occurred when SBP was brought down between the ranges of 130 and 120 mm Hg. Events increased when SBP came down below 120–110 mm Hg. The same study also had shown maximum reduction in CV death for the same ranges of SBP reduction described above and CV death rates were higher when SBP was brought down below 120–110 mm Hg.[27]

Systolic Blood Pressure Intervention Trial (SPRINT)[28]

Current guidelines recommend SBP targets of <140 mm Hg in patients with hypertension and high CV risk. SPRINT was sponsored by the National Institutes of Health. Participants were at least 50 years of age with SBP of 130–180 mm Hg without diabetes and an increased risk of CV events. 9361 participants were assigned to an SBP target of either <140 mm Hg (the standard-treatment group) or <120 mm Hg (Intensive treatment group). Chlorthalidone was encouraged as the primary thiazide-type diuretic and amlodipine as the preferred calcium-channel blocker for this study. Primary composite outcomes: MI, ACS not resulting in MI, stroke, acute decompensated HF, or death from CV causes. Secondary outcomes: Individual components of the primary composite outcome, death from any cause, and the composite of the primary outcome or death from any cause.

SPRINT showed that among adults with hypertension but without diabetes, lowering SBP to a target goal of <120 mm Hg, as compared with the standard goal of <140 mm Hg, resulted in significantly lower rates of fatal and nonfatal CV events and death from any cause. Intensive treatment arm had a 25% lower relative risk of the primary outcome; in addition, the intensive-treatment group had lower rates of several other important outcomes, including HF (38% lower relative risk), death from CV causes (43% lower relative risk), and death from any cause (27% lower relative risk). Serious side effects such as hypotension, electrolyte abnormality, and acute kidney injury were noticed in few patients which were reversed. The trial was stopped early due to benefit after a median follow-up of 3.26 years. This study is an important landmark study which will pave the way for the guideline developers to recommend a lower SBP goal in people with hypertension and high CV risk in future guidelines.

BP Lowering for Prevention of CVD and Death[29]

A systematic review and meta-analysis which involved 123 studies with 613815 participants. The results provide strong support for lowering SBP <130 mm Hg and providing BP lowering treatment to individuals with a history of CVD, CHD, stroke, diabetes, HF, and CKD.

2017-ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high BP in adults Table 1.

Table 1: BP thresholds for and goals of pharmacological therapy in patients with hypertension according to clinical conditions

Clinical condition (s)	BP threshold, mm Hg	BP goal, mm Hg
General		
Clinical CVD or 10-year ASCVD risk ≥10%	≥130/80	<130/80
No clinical CVD and 10-year ASCVD risk <10%	≥140/90	<130/80
Older persons (≥65 years of age; noninstitutionalized, ambulatory, community-living adults)	≥130 (SBP)	<130 (SBP)
Specific comorbidities		
Diabetes mellitus	≥130/80	<130/80
CKD	≥130/80	<130/80
CKD after renal transplantation	≥130/80	<130/80
HF	≥130/80	<130/80
Stable ischemic heart disease	≥130/80	<130/80
Secondary stroke prevention	≥140/90	<130/80
Secondary stroke prevention (lacunar)	≥130/80	<130/80
Peripheral arterial disease	≥130/80	<130/80

CKD: Chronic kidney disease, HF: Heart failure, ASCVD: Atherosclerotic cardiovascular disease, BP: Blood pressure

Conclusions

Hypertension outcome trials which have been discussed above will pave the way for the clinicians to properly manage hypertension and its complications, including participants who are older and those with diabetes and CKD. Monotherapy may not be adequate in most of the patients and combination of antihypertensive drugs is needed to tackle not only complications of hypertension but also to reach the goals of BP in special situations.

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Review Article

Isolated Systolic Hypertension

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Abstract

Isolated systolic hypertension (ISH) is a problem of major public health concern as its incidence is increasing. It is difficult to control and is an important risk factor for cardiovascular disease. This article discusses the pathophysiology behind ISH and how to go about treating this condition. The article also discusses about ISH in the young, which is a totally different entity with respect to pathophysiology and treatment.

Key words: Hypertension, systolic, isolated

Introduction

Isolated systolic hypertension (ISH) is defined as systolic blood pressure (SBP) of >140 mmHg with a diastolic blood pressure (DBP) of <90 mmHg.[1] It is the most common and the most difficult form of hypertension and is a public health problem of major proportion. If we consider the frequency of untreated hypertension according to subtype and age, ISH is the most common form of untreated hypertension above the age of 50 years. Above the age of 80 years, more than 90% of all untreated hypertension is ISH.[2]

There are several unanswered questions about ISH. Does ISH develop *de novo* in older people or is it a naturally occurring stage in the hypertensive process? Data from Framingham study showed that about 40% of patients with ISH were conversion from untreated or poorly controlled diastolic HTN at young age. The majority acquired ISH without going through a stage of elevated DBP.[3]

SBP

Elevation of both SBP and DBP predicts an increased risk of cardiovascular (CV) events. However, raised SBP is more important and the prognostic value of SBP increases with age.[4] It becomes greater than DBP in the elderly individuals.[5] Raised SBP was once thought to be benign accompaniment of aging.

However, now, we know that it increases the risk of CV events. Recent guidelines, therefore, give more importance to SBP in the diagnosis and treatment of HTN, especially in the elderly.[6]

SBP increases progressively with advancing age, while DBP tends to decline from the sixth decade, irrespective of ethnicity and sex.[4] Thus, there is an increase in the prevalence of ISH with age. 60% of older patients with HTN have ISH. Elevated SBP is the key risk factor for CV disease, CV, and all-cause mortality and declines in renal function.[7] Lowering elevated SBP improves CV and renal outcomes regardless of any concomitant reduction in DBP.[8]

As SBP goes up and DBP comes down, the pulse pressure (PP) starts widening. For each 10 mmHg increase in PP, there was an 11% increase in the risk of stroke.

For each 10 mmHg increase in mean arterial pressure (MAP), there was an independent 20% increase in the risk of stroke. Thus, both PP and MAP are independent predictors of stroke and all-cause mortality.[9]

Independent predictors of incident ISH include older age, female gender, higher baseline SBP, lower baseline DBP, longer duration of hypertension, greater arterial stiffness, higher intima-media thickness of the carotid artery, and higher cardiac mass.[10]

DBP

The invariable result of aggressive control of SBP in ISH is the excessive fall in DBP. Secondary analysis of elderly SPRINT[11]

participants showed that DBP in the intensive-therapy arm fells to 62 mmHg. There was no trend toward myocardial damage or CHD among those with DBP <60 mmHg and SBP <120 mmHg. Maybe the low systolic pressure, by reducing the myocardial oxygen demand, protected against a low diastolic pressure.

Vascular Changes with Aging

Normal aging causes generalized arterial stiffening. Elastin becomes thinner, fragmented, and degraded and is replaced by collagen, which is much stiffer. Pressure wave now travels faster along the stiffened arterial system.

Vascular inflammation, fibrosis, hypertrophy, collagen deposition, and elastin degradation occur with aging. These processes dilate the vessel lumen and increase the wall thickness.[12] There are a loss of arterial elasticity and a reduction of compliance. There is also loss of endothelial function. This results in reduced production of vasodilator factors (nitric oxide, natriuretic peptides, and so on) and increased production of vasoconstrictor substances (endothelins, norepinephrine, and so on).[13] Alterations in large artery structure and function are accelerated by risk factors such as hypertension, diabetes, and dyslipidemias. This results in early vascular aging in people with uncontrolled risk factors.[14]

The Pulse Wave

The morphology of any pulse wave is the summation of incident (forward-traveling) and reflected (backward-traveling) pressure waves. Timing of backward travelling wave depends on the pulse wave velocity and the distance to the predominant or "effective" reflecting site. In young healthy adults, SBP and PP at the brachial artery are higher than in the ascending aorta. This is because the reflected wave reaches brachial artery earlier, in systole itself. By the time it reaches the ascending aorta, it has become diastole. Hence, the brachial artery systolic pressure is the sum of forward wave and reflected wave, while SBP in the ascending aorta is only forward wave. Hence, there is pressure amplification from the aorta to the brachial artery. The other reasons for the higher pressure in the brachial artery include the increase in arterial stiffness as we go from the elastic ascending aorta to the stiffer peripheral vessels and the smaller diameter of the peripheral vessels.[15] As age advances, vessels become stiff and inelastic. Hence, the SBP starts going up. The vessels cannot dilate to accept the cardiac output in systole without increasing the pressure. Furthermore, the inelastic vessels have a higher pulse wave velocity. The reflected wave, hence, reaches the ascending aorta in systole itself, augmenting the SBP. The DBP falls because the normal support given by the reflected wave is absent in diastole. The PP rises.

Impact on Target Organs

The high SBP and low DBP lead to excessive pulsatility. The high pulsatile BP/flow is not absorbed by the large artery walls and is transmitted to the microcirculation of the brain, kidney, and heart. This causes structural damage to the tissues and functional derangement of the organs.[16] An increase in SBP also increases left ventricle (LV) afterload and oxygen demands. Final result will be LV hypertrophy and failure, myocardial ischemia, chronic heart failure, and arrhythmias.[17]

The increased pulsatility and the reduced ability of the vessels to distend enhance the traumatic effect on the large artery wall and favor an increase in endothelial permeability and initiate formation of an atherosclerotic plaque.[13]

Evidence for the Benefits of Treatment in Ish

The first major trial in ISH was the systolic hypertension in the elderly program (SHEP).[18] This was the first clinical trial to demonstrate the beneficial effects of treatment in ISH. Chlorthalidone (with the addition of a beta blocker if needed) was the treatment regimen used. SBP was reduced by approximately 26 mmHg. There was a significant reduction in stroke (36%), coronary heart disease (25%), and heart failure (49%). Other important trials, which showed benefits of treatment, include systolic hypertension in Europe study,[19] systolic hypertension in China study,[20] the Swedish trial in old patients with hypertension (STOP-hypertension-2),[21] and hypertension in the very elderly trial.[22] Even though the drugs used in these trials were different, the results were identical. This proved that reducing SBP was important in the elderly with ISH, irrespective of the drug used. Substudy on the elderly in the SPRINT[11] also showed benefits of aggressive SBP reduction, especially in reducing the incidence of heart failure.

Management

Dihydropyridine calcium channel blockers (CCBs) and thiazide-like diuretics are the preferred first-line drugs. ACEI/ARB should be used in situations with compelling indications such as heart failure, post-myocardial infarction, or albuminuria. Beta-blockers are better avoided. Optimal blood pressure has not been well studied, but SBP goal of <140 mmHg is generally accepted. It is better to individualize the target for each patient depending on the comorbidities and the tolerability and the clinical response.[23]

Atrial Fibrillation (Af) and ISH

The prevalence of AF increases with age and approximately doubled for every 10-year increment in the age beyond 50 years. The prevalence is around 5% above the age of 70 years.[24]

Arterial hypertension is an independent risk factor for developing AF.[25] In the SHEP trial, 2.06% developed AF over 4.5-year follow-up, 1.82% in the active treatment group, and 2.32% in the placebo group ($P = 0.2$). The mean of all systolic BP measurements during 4.5 years of follow-up was significantly higher in the AF group. Poor blood pressure control increased the risk of developing AF. Subjects who developed AF were significantly older, had more electrocardiography abnormalities at baseline, and were more likely to experience CV events, left

ventricular failure, and rapid death. All-cause and total CV mortality were significantly increased in the hypertensives who developed AF at both 4.7-year and 14.3-year follow-up.[26]

ISH in the Young

Clinical significance of high SBP in the first decades of life is debatable. There is a lack of a consistent definition of young age. The prevalence of ISH in the general adult population follows a typical J-shaped pattern with a nadir in the fifth decade. There is a steep increase in SBP after 70 years of age. There is an earlier peak, though of lower magnitude, below 30 years of age. There is a steep increase in SBP during childhood, followed by a plateau phase between 20 and 40 years, and then a subsequent increase. PP decreases in the age range between 20 and 40 years.[27,28] Higher baseline SBP predicts steeper increases in aortic stiffening and the future risk of hypertension in both adolescence and adulthood.[29] ISH in individuals <16 years is defined as SBP at least 95th percentile and DBP <90th percentile for the age, sex, and height.[30] It is often correlated to overweight and obesity.

ISH in the young is thought to have different mechanisms than ISH of the elderly. It is a very heterogeneous condition and includes individuals with totally different genetic background and clinical characteristics. It remains unclear as to whether this condition implies a worse outcome or needs antihypertensive treatment. ISH in the young is associated with and caused by multiple factors that can operate in isolation or interact. These include a hyperkinetic heart, a selective increase in heart rate or stroke volume, and an increase in arterial stiffness above the values regarded as normal for young age ranges.[31]

Isolated SBP elevation at the level of the brachial artery with normal central BP did not exhibit a greater CV risk or progression to systolic–diastolic HTN. Antihypertensive treatment is recommended if target organ damage is present or if central aortic BP is also raised.[31] The 2013 European guidelines recommend following these people closely, modify risk factors by lifestyle changes, and avoid antihypertensive drugs.[6]

Conclusion

ISH is increasing in prevalence as the population of the elderly increases. It is difficult to treat and is an important risk factor for CV and renal diseases. The basic pathology is increased arterial stiffness. Several trials have shown benefit, even in the elderly, by treating ISH. Very low DBP is a concern, but elderly subgroup analysis of SPRINT showed no adverse effects with a DBP of 60 mmHg. CCBs and diuretics are the drugs of choice. ISH in the young is a different entity with different pathologies and different prognoses. ISH in the young has to be treated only if the central aortic blood pressure also is high or if there is evidence of target organ damage.

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*R*eview *A*rticle

How to Detect Early Kidney Disease in Hypertension?

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Abstract

There is high prevalence of kidney disease among hypertensive patients. Identifying kidney disease in hypertensive patients at the earliest is of paramount importance in preventing progression to ESRD. Simple and cost-effective techniques are available for screening kidney disease and all medical care professionals need to be sensitized to do an early screening for kidney disease in all hypertensive patients at presentation. Treating chronic kidney disease (CKD) significantly improves cardio-vascular mortality in hypertensive patients which increases exponentially when there is co-existing hypertension and CKD.

Key words: Chronic kidney disease (CKD), early screening, hypertension

Introduction

Hypertension and kidney disease have a "cause" and "effect" relationship. Majority of the kidney diseases cause hypertension and hypertension can induce kidney disease. Most often, kidney disease remains silent in the early stages. Early detection of kidney disease in hypertensives is of great significance.

"Hypertension" and "Kidney Disease" - "Cause" and "Effect" Relationship

Almost all the kidney diseases except some forms of chronic tubulointerstitial nephritis cause hypertension. Hypertension in kidney disease is multifactorial. Volume overload, activation of renin-angiotensin-aldosterone system, enhanced sympathetic activity, and altered vascular reactivity comprise the common mechanisms.

Hypertension *per se* can injure kidney. Benign nephrosclerosis and malignant nephrosclerosis are the two well-defined pathologies described. Hypertension, being a major risk factor for atherosclerosis, can contribute for "ischemic nephropathy" occurring due to atherosclerotic renal artery disease. Importantly, hypertension is an independent determinant of renal prognosis irrespective of the etiology of kidney disease!

The Concept of "Chronic Kidney Disease"

Kidney disease, in early stages, may remain silent. Subclinical early kidney disease often failed to get enough attention when the concept of "chronic renal failure" was in vogue. This formed the basis for the evolution of the concept of chronic kidney disease (CKD). CKD refers to any functional/structural alteration of kidney persisting for >3 months.[1] Glomerular filtration rate (GFR) is normal in Stage 1 CKD and serum creatinine starts rising only in Stage 3 CKD.

CKD stage	GFR (ml/min/1.73 m²)
I	≥90
II	60–89
III	30–59
IV	15–29
V	<15

Detection of Kidney Disease

There are two important tests to detect early kidney disease: (1) Urine test for the presence of protein and (2) estimation of GFR (eGFR).

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Proteinuria

Proteinuria is detected by urinary dipsticks. This is a semi-quantitative and fairly sensitive screening test for kidney disease.

Microproteinuria

Microproteinuria refers to increased urinary protein excretion, but, not sufficient enough to be detected by dipstick.

Proteinuria is not only a harbinger for progressive kidney disease but also is an indicator of cardiovascular disease risk.[2] Microalbuminuria is more specific than microproteinuria. Microalbuminuria is defined as urinary albumin excretion of 30–300 mg/day or 20–200 mcg/min or urine spot albumin-creatinine ratio of 30–300 mcg/mg of creatinine in two of three tests done over 6 months in the absence of the known causes of transient proteinuria such as fever, physical exertion, and urinary infection.[3]

eGFR

eGFR is preferred to measured GFR since the commonly employed test for measuring GFR, namely endogenous creatinine clearance, is fraught with inaccuracies and practical difficulties.

Estimation of GFR is done applying serum creatinine-based formulae. Cockcroft-Gault formula, which was widely adopted in the past, has become obsolete.

The two currently employed formulae are as follows: (a) Modification of diet in renal disease (MDRD) formula and (b) CKD-EPI (CKD Epidemiology Collaboration) formula. Both these formulae use four variables, namely (1) age in years, (2) gender, (3) race, and (4) serum creatinine (mg/dl). Of these, CKD-EPI formula is preferred.[4] Although these formulae have not been validated in Indian subjects, it is prudent to estimate GFR using these formulae rather than relying on serum creatinine alone due to the following reasons:

1. Serum creatinine is less sensitive in identifying renal failure in the early stages. Elevation in serum creatinine value occurs only when GFR has decreased by 50%.
2. The same value of serum creatinine denotes different GFR in different individuals.
   MDRD formula:
   GFR = 175 × (SCr)-1.154 × (age)-0.203 × 0.742 (if female) ×1.212 (if black)
   CKD –EPI Formula:[5]
   $$GFR = 141 \times \min (Scr/\kappa, 1)^{\alpha} \times \max (Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \, [\text{if female}] \times 1.159 \, [\text{if black}]$$
   κ = 0.7 if female
   κ = 0.9 if male
   α = −0.3229 if female
   α = −0.411 if male
   min = The minimum of Scr/κ or 1
   max = The maximum of Scr/κ or 1
   Scr = Serum creatinine (mg/dL)

These formulae ideally use standardized serum creatinine, i.e., serum creatinine assayed using methods that are traceable to IDMS (isotope dilution mass spectrometry).

Serum cystatin is a low-molecular-weight protein produced by all the nucleated cells of the body and degraded by the renal tubular epithelial cells. Its levels are not altered by inflammation, infections, dietary, and constitutional factors. Although CKD-EPI equation, based on serum cystatin, is believed to be more precise, there is no definite evidence for the same. Moreover, due to cost implication, serum cystatin may not be suitable for screening tests.

Various online calculators and mobile applications are available for calculating estimated GFR (https://www.kidney.org/professionals/KDOQI/gfr_calculator).

Significance of Early Detection of the Renal Disease in Hypertension

1. It provides an impetus for better control of hypertension. Most guidelines advocate a lower BP target in hypertensives with proteinuria as compared to non-proteinuric hypertensives.
2. Preferential use of angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists is advised since they are antiproteinuric and renoprotective.
3. Renoprotective strategies like correction of acidosis (if present) may be applied early.
4. Kidney disease in hypertensives confers added risk for cardiovascular disease. Appropriate risk reduction measures can be taken.
5. Nephrotoxic drugs/agents can be strictly avoided.

There are quite a few studies which have documented the prevalence of kidney disease among hypertensives.

I-DEMAND study (Italy-Developing Education and awareness on MicroAlbuminuria in patients with hypertensive Disease) illustrates significant prevalence of kidney disease among hypertensives.

It is an observational, cross-sectional, and multicentric study involving 3534 hypertensives. Of them, 37% had diabetes also. 27% of them had low GFR (eGFR <60 ml/min/1.73 m^2) and 26% of them had microalbuminuria (>2.5 mg/mmol [men]; >3.5 mg/mmol [women]) and 42% of them had both.[6]

European Society of Hypertension and European Society of Cardiology Guidelines on the management of hypertension emphasize to look for evidence for subclinical kidney damage in every hypertensive. Subclinical kidney disease, particularly microalbuminuria, is described as "renal window" opened on the cardiovascular system, signifying the heightened cardiovascular risk in microalbuminuric hypertensives.[7]

KHA-CARI an Australian working group advocates annual screening for CKD in hypertensive patients. The screening should include both urinary albumin: creatinine ratio to detect proteinuria and serum creatinine to determine eGFR every year.[8]

In the PREVEND-IT trial, which evaluated the effect of Fosinopril (ACE inhibitor) on the cardiovascular events, the

initial screening for albuminuria was done through postal survey. The study patients were instructed to send by return mail a "vial" containing a portion of the morning spot urine sample and estimation of protein by nephelometry in a nearby laboratory. This strategy can be a cost-effective strategy for screening large group of hypertensive patients for the presence of albuminuria.[9]

Indian guidelines on hypertension (I.G.H-III) recommends to screen all hypertensive patients with urine albumin-creatinine ratio and serum creatinine to identify patients with target organ damage and reserving urine microalbumin for risk stratification.[10]

Conclusion

The importance of early detection of the kidney disease in a hypertensive patient cannot be overemphasized. Physicians at all levels of health care need to be sensitized on screening for kidney disease in every hypertensive patient. There are simple and cost-effective techniques that can be performed without much additional resources. The professional bodies and all the stakeholders involved in formulating guidelines on the management of hypertension have to give special emphasis on this important recommendation.

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Review Article

Renovascular Hypertension

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Abstract

Renovascular Hypertension (RVH) is the most common cause of secondary hypertension. High index of suspicion is needed to diagnose this condition. Two major causes for RVH are renal artery stenosis (RAS) secondary to atherosclerosis (~90%) and fibromuscular dysplasia (~10%). Certain clinical clues for RVH are unprovoked hypokalemia, abdominal bruit, age of the onset of hypertension (<30 years or >55 years), the absence of the family history of hypertension, recent onset of hypertension (duration <1 year), difference of kidney size >1 cm, unexplained azotemia, recurrent flash pulmonary oedema, new onset azotemia with initiation of ACEI, and resistant or refractory hypertension. Revascularization by Percutaneous transluminal renal angioplasty (PTRA)/surgery as indicated should be instituted whenever there is medical failure or worsening of azotemia with maximal medical therapy for RVH.

Key words: Renovascular Hypertension, renal artery stenosis, percutaneous transluminal renal angioplasty

Introduction

Among the secondary causes of hypertension, the renovascular hypertension (RVH) tops the list. It accounts for 3% of hypertensive patients. Renal artery stenosis (RAS) progression has direct correlation with age and the grade of stenosis and has no correlation with BP control.

Etiology

Two major causes for RVH are RAS secondary to atherosclerosis (~90%) and fibromuscular dysplasia (~10%). The other causes are renal artery aneurysm, systemic vasculitis (polyarteritis nodosa and Takayasu arteritis), arteriovenous fistula (congenital or traumatic), acute arterial thrombosis or embolism, acute aortic/renal artery dissection, hypercoagulable state (antiphospholipid antibody syndrome), congenital bands, and radiation-induced fibrosis.

Atherosclerotic RAS (ARAS) occurs usually in elderly individuals and is associated with diffuse atherosclerosis in other vascular territories. It is commonly seen in aged males, diabetics, smokers, and patients with dyslipidemia. It involves the origin of the renal arteries and extends to proximal segment.

Fibromuscular dysplasia (FMD) occurs in young females, often with a history of smoking. It involves mid to distal portion of renal arteries and appears as string of beads appearance in angiography. Usually, renal function is not affected.

Prevalence

The prevalence of RAS increases with the age and in patients with known cardiovascular risk factors such as diabetes, hypertension, and dyslipidemia. The prevalence of RAS of >70% was 7.3% in patient who has undergone cardiac catheterization with resistant hypertension, renal impairment, flash pulmonary edema, or atherosclerosis in other vascular territories.[1] In our study,[2] the incidence of RAS was 7.7% by the routine drive-by angiogram, during coronary angiography for suspected CAD. In the general population, 2–5% of secondary hypertension is due to ARAS. In autopsy series, 27% had RAS of >50% in the group aged >50 years.

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Clinical Clues for RVH

Even though RVH is not easily distinguishable from essential hypertension, there are certain clinical clues such as unprovoked hypokalemia, abdominal bruit, age of the onset of hypertension (<30 years or >55 years), the absence of the family history of hypertension, recent onset of hypertension (duration <1 year), difference of kidney size >1 cm, unexplained azotemia, recurrent flash pulmonary edema, new onset azotemia with initiation of ACEI, and resistant or refractory hypertension.

Diagnosis of RAS

Non-invasive Test [Table 1]

1. Plasma renin activity
2. Renal vein renin ratio
3. Captopril renography
4. Renal artery Doppler
5. MR angiography of RA
6. CT angiography of RA.

Renal Doppler by Duplex Scan

It is the most commonly used non-invasive test to diagnose RAS. It is inexpensive, readily available. It is operator dependent and has limitation in patients with excess gaseous abdomen and obesity. Significant RAS with >60% stenosis can be diagnosed when peak systolic velocity is >200–320 cm/s, resistive index (RI) is <0.8%, RI difference >0.05, RAR (renal to aortic

RENAL DOPPLER
↓
PSV >200-320 Cm/s or RAR >3.5-3.8 plus RI difference >0.05 or ESP missing
↓
conventional angiography and PTRA(S) if pressure gradient significant

Figure 1: Assessment of renal artery stenosis by Renal doppler. PSV - Peak systolic velocity, RAR - Renal aortic ratio, RI - resistance index, ESP - Early systolic peak, PTRA(S) - Percutaneous transluminal renal angioplasty (with stenting)

pressure ratio) >3.5–3.8, and missing early systolic peaking and prolonged acceleration time [Figure 1]. The resistance index by renal Doppler test is the only parameter that predicts the blood pressure (BP) control and improvement in kidney function following percutaneous transluminal renal angioplasty (PTRA) with stenting and value >0.8 indicates non-responders.

CT Angiogram

Computerized tomography angiogram will provide accurate renal artery anatomy including accessory renal arteries and better visualization of soft tissue except with dense renal arterial calcification. Contrast-related allergy, nephrotoxicity, and radiation are the issue with this modality and hemodynamic significance of the stenosis cannot be assessed.

Magnetic Resonance Imaging (MRI) Angiogram

MRI provides high-quality imaging of renal arteries. Contrast-enhanced MRI using gadolinium improves image quality. Hemodynamic significance of the stenosis cannot be assessed in routine MRI angiogram. Gadolinium use has been shown to cause nephrogenic systemic fibrosis with incidence of 1–6% for dialysis patients.

Blood-oxygen-level-dependent MRI assesses the level of deoxyhemoglobin in the kidney and following furosemide challenge; there is a reduction in the level of deoxyhemoglobin in normal kidney and no response in atrophic kidney, which helps in planning decision regarding revascularization.

Invasive Test

Catheter angiography with digital subtraction angiography confirms the diagnosis of RAS and helps in assisting the hemodynamic significance of RAS by measuring the pressure gradients. Significant RAS diagnosis is defined as >50% diameter stenosis by eyeball technique, peak translesional gradient of >20 mmHg or >10% of peak systolic aortic BP or >10 mmHg mean translesional pressure gradient. The issues with the invasive angiography are contrast-induced nephropathy, allergy, radiation, and the cost.

Table 1: Accuracy of tests for renal artery stenosis

Test	Sensitivity (%)	Specificity (%)	Pretest probability for renal artery stenosis			
			20%		50%	
			Positive predictive value (%)	Negative predictive value (%)	Positive predictive value (%)	Negative predictive value (%)
Captopril renography	74	59	31	90	64	69
Duplex sonography*	76	75	43	93	75	76
Magnetic resonance angiography**	78	88	64	94	87	80
Computed tomographic angiography**	77	88	76	94	93	80

*Values chosen are intermediate between captopril renal scanning and average of values obtained for magnetic resonance angiography and computed tomography and based on the summary receiver-operator curves from Vasbinder *et al.* **Values reported for atherosclerotic renal artery stenosis

Translesional gradient can be measured using 4 French catheter or with 0.014-inch pressure wire. Gradient (Pd/Pa) across the lesion of <0.8 after intra-arterial papaverine (30 mg) or dopamine (50 mcg/kg) bolus indicates significant stenosis.

Drive by Renal Angiogram with Contrast Flush

It is useful in detecting ostial lesion and can avoid dissection of the origin of renal artery, spasm, atheroembolism, and missing out multiple renal arteries.

Treatment

Medical Therapy

Medical therapy with antihypertensive drugs can be continued indefinitely if BP control is good with stable renal function. Among the antihypertensive drugs, angiotensin convertase inhibitors are the most effective drugs in RVH except in patients with bilateral RAS or ipsilateral RAS with only solitary functioning kidney. Calcium channel blockers are the next choice followed by other groups of drugs. Patients with ARAS with hypertension should be kept on antiplatelet, statin in addition to antihypertensive drugs and smoking should be stopped.

Worsening of azotemia on initiating ACEI indirectly points to significant RAS in these patients. It occurs especially when there is severe congestive heart failure, use of high-dose diuretics, volume depletion, and baseline renal dysfunction. A significant >30% fall in GFR or >0.5 mg/dl rise in creatinine or >30% rise from baseline creatinine may be an indication to consider renal vascularization. Whenever patient does not tolerate ACEI due to hyperkalemia or cough, angiotensin receptor blockers can be substituted.

Revascularization by Angioplasty with Stenting

Revascularization by PTRA is aimed to retard the progression of azotemia, better control of BP, and relief of chronic angina, heart failure, and flash pulmonary edema (cardiac disturbance syndrome) in patients with hemodynamically significant RAS.

Following revascularization by PTRA in patients with RVH, there are four types of responses noted, namely cure, good responders, poor responders, and non-responders. Usually, BP response is seen within 48 h after PTRA. Predictors of the control of BP following revascularization are unilateral versus bilateral RAS, duration of hypertension, angiographic success,

and size of kidney by USG, resistance index difference, baseline serum creatinine level, and extent of atherosclerosis, advanced age, and presence of diabetes.

RVH secondary to FMD responds better than ARAS (60% vs. 30%). Cure is relatively rare (11%) in ARAS on follow-up over 2½ years. In our study,[3] cure was noted in 3.75% over 1-year follow-up [Table 2]. PTRA is considered treatment of choice in patients with RVH secondary to FMD with success rate of 82–100%. There is a risk of 10–11% restenosis after PTRA.

In patients with ARAS, PTRA should be followed by stenting, as there is more elastic recoil at the ostium of renal artery, dissection, and residual stenosis with plain PTRA, with a success rate of 94–100%. The rate of restenosis at the end of 1 year is 11–23%.

PTRA Benefit in Aras

1. >70% RAS by angiography in unilateral RAS/bilateral RAS/ solitary kidney with rapidly declining renal function
2. Unilateral ARAS with hypertension with renal insufficiency.

Responders

A hyperemic translesional systolic gradient of >20 mmHg following intrarenal papaverine or intravenous dopamine considered as a strong predictor of a positive response to PTRA in patients with unilateral RAS.[4] Those who have higher renal frame count and renal blush have good clinical response following vascularization.[5] The response to PTRA is good, whenever the ipsilateral kidney size is > than 7 cm.

PTRA does not help in patients with unilateral RAS with normal renal function or stable renal function, whose BP could be controlled easily. Subgroup of patients who are least likely to respond to PTRA is those with small kidney size, longer duration of azotemia, baseline creatinine of >3 mg/dl and a high baseline resistance index of >0.8, significant proteinuria, and high risk of atheroembolism. Patients with RAS with Pd/Pa of >0.9 with no rise in baseline renal vein renin level are unlikely to improve following PTRA.[6] A small percentage of patients will deteriorate in renal function after PTRA, possibly due to contrast nephrotoxicity, atheroembolism, and reperfusion injury and it is difficult to predict before the procedure.

A baseline creatinine concentration >130 μmol/L is the strongest independent predictor of death within 4 years after PTRA with stenting. Once azotemia starts worsening in RAS,

Table 2: BP response to PTRA-comparative trials

Author and year	Number of patients	Follow-up in months	Cure%	Improved%	Unchanged/worse%
Iannone *et al.* (1996)	63	11.3	3.7	35.2	61.1
Baumgartner (1997)	35	12	8.6	45.7	45.7
Rees CR (1999)	845	24	6	56	38
Vande Ven (1999)	41	6	4.8	43.9	51.3
Alberto Morganti (2000)	66	6	3	38	59
Stefanio Pinto (2002)	58	6	35	36	29
Sathyamurthy (2010)	80	12	4	55	41

for every 88 μmol/L increment from baseline creatinine, there is 2–3-fold risk of death.

Trial

Drastic trial showed no significant difference between the angioplasty and medical treatment at 1 year.

Astral trial

Angioplasty and stenting for renal artery lesion study[7] did not show any significant clinical benefit following PTRA in ARAS and there was substantial risk.

Flaws

1. RAS severity was possibly overestimated
2. 40% of patients in both the groups had RAS <70%
3. The success rate was 78.6%, which was far below the expected success rate of 96–98%.
4. The primary and secondary end points are poor outcome measures.

Star Trial

Stent placement in patients with ARAS and impaired renal function - a randomized trial[8] did not show any benefit on progression of impaired renal function following PTRA but led to a small number of significant procedure-related complications.

Coral Trial

Cardiovascular outcomes in renal atherosclerotic lesions study[9] did not show a significant benefit in preventing clinical events in patient with ARAS with hypertension or CKD when PTRA added to optimal medical therapy.

Two meta-analyses of these trials, independently reported that PTRA is more effective in controlling BP than medical therapy.

Great Trial

Only prospective study[10] comparing bare metal and sirolimus-coated low profile stent in RAS, showing a relative risk reduction of angiographic binary in-stent restenosis by 50%, which was statistically insignificant. The use of drug-eluting stent is not recommended, as there are no outcome data.

Resist Trial

It is a randomized trial,[11] wherein stenting in moderate RAS in patients with resistant hypertension found to reduce mean baseline transluminal gradient and a gradient of >20 mmHg is highly predictive of BP improvement after PTRA. However, there was no overall improvement in GFR with the use of distal protection device.

SPYRAL HTN-OFF MED[12] was a randomized, sham-controlled, single-blinded trial, found clinically meaningful BP reduction compared to sham control at 3 months in uncontrolled

hypertensive patients in the absence of antihypertensive medication with no major safety events.

SPYRAL HTN-ON MED[13] was a randomized, single-blinded, sham-controlled trial in patients with uncontrolled hypertension, aged 20–80 years, wherein 50% of maximum recommended dosage of antihypertensive medications were instituted and followed up for 6 months. Office and 24 h ambulatory BP decreased significantly from baseline at 6 months, which was statistically significant and there were no major safety events.

Sympathetic Nervous System for Kidney and RVH

There is direct relationship between sympathetic nervous system and BP, which was proved beyond doubt that beta-blockers are effective only when native kidneys have not been removed in renal transplant patients. Both efferent and afferent neuronal signals between the kidney and central nervous system create a loop of hemodynamic abnormalities that increase BP. This renal contribution to central sympathetic drive can be blended by deefferentiation of the renal nerve. This can be achieved by radiofrequency ablation, ultrasonic neuronal ablation, chemical neural ablation, cryoablation, and ionizing radiation neural ablation.

Symplicity HTN 3[14] was a randomized, sham-controlled, multicenter, blinded prospective trial. It was a negative trial, wherein denervation was not found superior to sham procedure and medical therapy in reducing office and ambulatory BP at 6 months in patients with severe resistant hypertension but found to be safe of 6 months with no excess increase in RAS.

DENERHTN[15] was a multicenter, open-label randomized, controlled trial in patients with resistant hypertension, wherein denervation found more effective at reducing ambulatory, but not office BP, compared with standardized antihypertensive treatment alone.

RADIANCE-HTN SOLO[16] was a randomized, sham-controlled trial in mild-moderate hypertension used endovascular ultrasound for renal denervation. There was significant reduction in daytime ambulatory BP in renal denervation group at 2 months with no safety issues.

However, ESC 2018 guidelines have given Class III B for device-based therapy for hypertension treatment, as still this modality is mostly investigational only.

Surgery

Surgical correction of RAS by aortorenal, mesenteric/celiac renal bypass is indicated only when patients are not candidates for PTRA or non-responders to PTRA and in whom maximum medical therapy has failed to control RVH. In the current practice, role of surgical treatment in RAS is very limited to a subset of patients where endovascular procedure has failed.

Conclusion

RVH is the most common cause of secondary hypertension. High index of suspicion is needed to diagnose this condition. Revascularization by PTRA/surgery as indicated should be

instituted whenever there is medical failure or worsening of azotemia with maximal medical therapy.

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Review Article

Diagnosis and Management of Pediatric Hypertension

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Abstract

Hypertension (HT), a modifiable risk factor in adults, is a major risk factor for cardiovascular disease. Blood pressure (BP) originates in childhood and tracks to adulthood and hence very important to diagnose and appropriately manage childhood HT for healthy adulthood. In this article, we have attempted to answer the following questions: (1) What is HT in children and adolescents? (2) When does it begin? (3) What initiates it? (4) Who is susceptible? (5) What can be done during childhood to prevent consequences of HT during adult life? The updates of the recent American Academy of Pediatrics 2017 guidelines on HT for children have been included with importance to the prevention of HT through healthy lifestyle and vigilant screening including 24 h ambulatory BP monitoring.

Key words: Adult hypertension, childhood blood pressure, obesity, pediatric hypertension, preterm, prevention, risk factors

Childhood Hypertension (Ht): A Window to Adult Ht

The first report on pediatric HT by the National Heart, Lung, and Blood Institute, published in 1977, declared that "detection and management of HT in children and the precursors of HT in adults are the next major frontier.[1] HT in adults is a major modifiable risk factor for cardiovascular disease and is often associated with other cardiovascular risk factors, including impaired glucose tolerance, obesity, and dyslipidemia.[2] The standard approach of treating high BP in middle and old age can help mitigate these risks, but considerable burden remains. An approach that identifies those at greatest risk of developing high BP much earlier in life could permit more effective risk reduction through earlier, age-appropriate prevention, and intervention strategies. This made Ellin Lieberman post a series of questions for pediatricians way back in 1974.[3] (1) What is HT in children and adolescents? (2) When does it begin? (3) What initiates it? (4) Who is susceptible? (5) What can be done during childhood to prevent consequences of HT during adult life? In this review, an attempt has been made to answer by presenting information for diagnosis, management, and preventive aspects of pediatric HT.

What is HT in Children and Adolescents?

HT is defined as average of three clinics measured systolic BP (SBP) and/or diastolic BP (DBP) ≥95th percentile on the basis of age, sex, and height percentiles. The classification of HT as per the recent American Academy of Pediatrics (AAP) 2017 Guidelines is shown in Table 1.[4] and Fig 1 shows the procedure for BP measurement and classification in children

In the recent AAP Guidelines of 2017, the normative data are based on the auscultatory findings obtained from 50,000 normal children and adolescence and carries a number of modifications. (1) The term "Prehypertension" has been replaced by "elevated BP" to be consistent with adult American Heart Association/ American College of Cardiology guideline. This change in terminology also conveys that BP is already abnormally elevated and the importance of lifestyle modifications to prevent HT. (2) Definitions that categorize BP values were modified into two age groups, for children and adolescents. (3) The staging criteria have been revised for Stage 1 and Stage 2 HT. (4) The classification of adolescent HT is aligned with adult guidelines for the detection of chronic elevated BP. (5) Unlike the previous guidelines, the BP tables are based on BPs from normal-weight children. This decision was taken as overweight and obesity

Table 1: Classification of HT in children and adolescents[4]

For children aged 1–13 years	For children aged ≥13 years
Normal BP: <90th Percentile	Normal BP: <120/<80 mmHg
Elevated BP: ≥90th percentile to <95th percentile or 120/80 mmHg to <95th percentile (whichever is lower)	Elevated BP: 120/<80–129/<80 mmHg
Stage 1 HT: 95th percentile–< 95th percentile+12 mmHg, or 130/80–139/89 mmHg (whichever is lower)	Stage 1 HT: 130/80–139/89 mmHg
Stage 2 HT: ≥95th percentile+12 mmHg, or≥140/90 mmHg (whichever is lower)	Stage 2 HT: ≥140/90 mmHg

HT: Hypertension

has a strong association for HT. (6) Emphasis on use of 24-h ambulatory BP monitoring to confirm the diagnosis of HT. (7) Added is a simplified screening table for ease of use in the consulting room [Table 2]. (8) The height centiles and the corresponding height in inches and centimeter have been included in the BP chart. Hence, BP staging can be directly plotted in the BP charts compared with the earlier guideline.

Primary and secondary HT in children

Primary HT in childhood was thought previously to be rare. Secondary HT is more common in adolescents than in infants, children, and preadolescents. At present, as with adults, children and adolescents with mild-to-moderate HT have primary HT in which a cause is not identifiable. The worldwide childhood obesity epidemic has had a profound impact on the frequency of HT and other obesity-related conditions with the result that primary HT should now be considered as a common health problem in the young.

Gupta-Malhotra *et al.* evaluated the etiology of HT among 423 children from a pediatric HT clinic. A total of 275 children were diagnosed with HT of whom 156 (57%) had an identifiable secondary cause; 119 (43%) had primary HT.[5] In a cross-sectional study a total of 1085 apparently healthy student, aged between 11 and 17 years from rural and urban schools in hills of northern India, were examined using standard methods. After two evaluations, HT was identified in 62 (5.9%) children and pre-HT in 130 (12.3%). Urban and rural children had comparable rates of high BP (HT and pre-HT). Rates of elevated BP were significantly higher (46.5% vs. 17%, *P* < 0.001) among those with high body mass index (BMI) (overweight and obese) compared to those with normal BMI. In conclusion, nearly 20% of the school children had high BPs.[6]

In a review publication from a developed country primary, HT was identified in 16% of cases and 70% had secondary HT.[7] In a study of 351 hypertensive children and adolescents it was observed that the younger children (<6 years of age) had higher secondary HT, were less obese, and had higher diastolic BP as compared to children in mid-childhood (age 6–<12 years) and adolescents (age 12–<17 years). Thus, secondary HT is more likely to be detected in non-obese younger children with higher BP, whereas, primary HT is more commonly found in late childhood and adolescence and is associated with overweight/obesity and modest BP elevations.[8]

General characteristics of children with primary HT include older age (≥6 years), positive family history of HT, and

Table 2: Screening BP values requiring further evaluation[4]

Age (years)	Boys (BP, mmHg)		Girls (BP, mmHg)	
	SBP	DBP	SBP	DBP
1	98	52	98	54
2	100	55	101	58
3	101	58	102	60
4	102	60	103	62
5	103	63	104	64
6	105	66	105	67
7	106	68	106	68
8	107	69	107	69
9	107	70	108	71
10	108	72	109	72
11	110	74	111	74
12	113	75	114	75
≥13	120	80	120	80

SBP: Systolic blood pressure, DBP: Diastolic blood pressure

overweight, and/or obesity. DBP elevation appears to be more predictive of secondary HT, whereas systolic HT appears to be more predictive of primary HT.[8]

Further, the data published documents a progressive increase in the frequency of primary HT at the varying period of time from different centers as shown in Figure 2.[9] Common causes of HT in children include renal and renovascular disease, coarctation of the aorta, and endocrine disease.

HT in neonates

HT is detected in 1–2.5% of all neonates admitted to the neonatal intensive care unit (NICU). In neonates, HT is defined as persistent SBP and/or DBP that exceeds the 95th percentile for postconceptional age.[10] Most hypertensive newborns are asymptomatic, and diagnosis is made by routine BP measurement. BP is measured by an oscillometric device after an appropriate sized BP cuff is positioned on the right upper arm and preferably 1.5 h after feed or medical intervention when the infant is in quiet state and either in prone or supine position. It is challenging to establish normative values for neonatal BP, especially in pre-term infants, due to the effects of gestational age and maturation on BP values. The 1987 "Report of the Second Task Force on BP control in Children" published curves of normative BP values in older infants up to 1 year of age which is currently being used.[11]
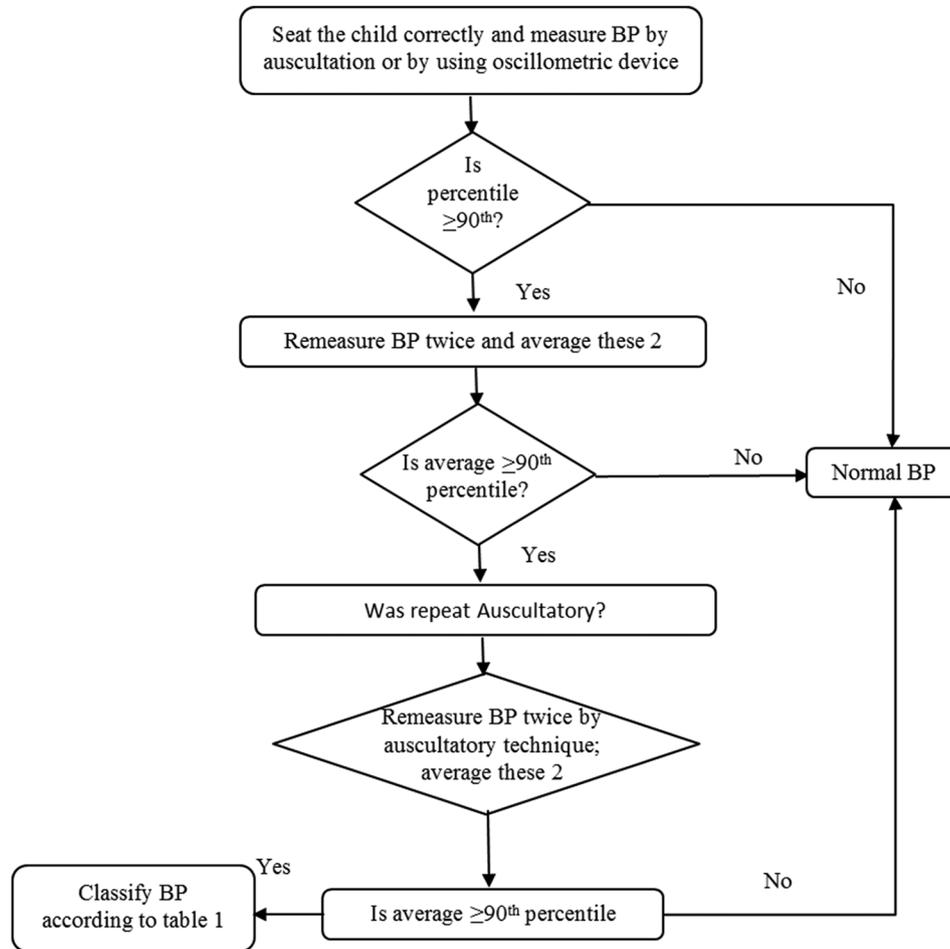
Figure 1: Flow chart reflecting the procedure for blood pressure measurement in children and classification[4]

Common causes of neonatal HT are umbilical artery catheter-associated thromboembolism, bronchopulmonary dysplasia, intraventricular hemorrhage, patent ductus arteriosus, and congenital renal structural malformation, renovascular diseases, acute kidney injury, and certain medications.[10]

Once the diagnosis of neonatal HT is confirmed, an evaluation is performed to identify the underlying cause of HT as in children, which may potentially be corrected. Angiotensin-converting enzyme inhibitors (ACE I) or angiotensin receptor blockers (ARB) are not recommended in neonates in view of potential side effects. Calcium channel blockers, vasodilators, and beta-blockers are used in the treatment of neonatal HT.

When Does it Begin?

Childhood BP originates in childhood and tracks to adulthood. In a review study, it has been reported that childhood HT ranges from 0.5% to 11.7% in Indian children.[12] Theodore *et al.* followed 975 subjects to identify childhood to early-midlife SBP trajectories. The BP data at ages 7, 11, 18, 26, 32, and 38 years from a longitudinal, representative birth cohort study was used
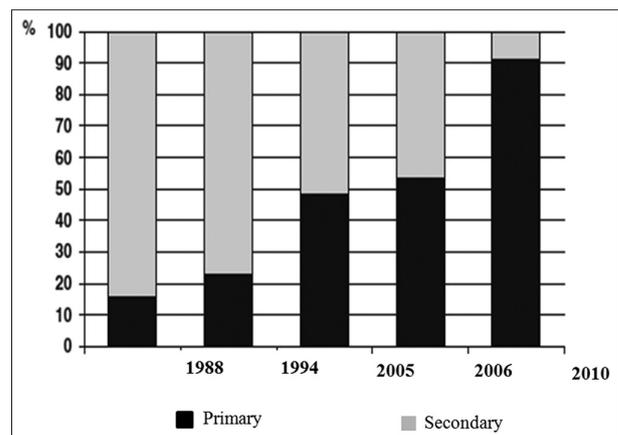
Figure 2: Bar diagram showing an increasing trend of primary hypertension in American youths[9]

to identify four distinct trajectory groups. Figure 3 shows the plotted predicted trajectory lines for each of the four groups which shows that each trajectory follows the same path from childhood to adulthood thus confirming that childhood BP
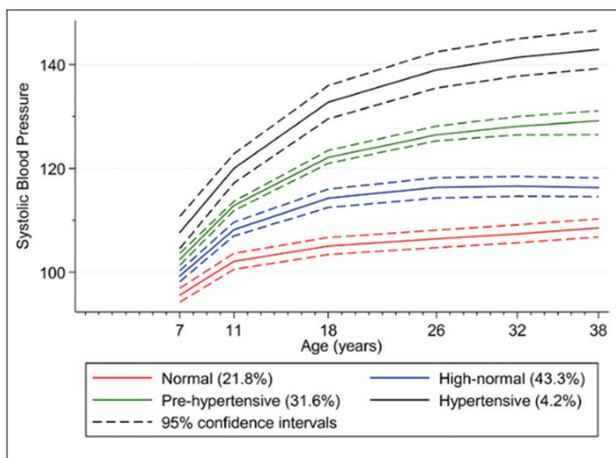
Figure 3: Blood pressure trajectory from childhood to early-mid adulthood[13]

tracks to adulthood. Prehypertensive and hypertensive trajectory groups had worse cardiovascular outcomes by early midlife. They concluded that harmful BP trajectories are identifiable in childhood, associated with both antecedent and modifiable risk factors over time, and predict adult cardiovascular disease risk. The means for all four groups significantly differed from each other at all ages, beginning at the age of 7 years. The normal group and high-normal group had mean BP in the normal SBP range (90–120 mmHg) as in adults. The prehypertensive group had a mean SBP within the prehypertensive range (120–139 mmHg) throughout adulthood. The hypertensive group had the highest mean BP at the age of 7 years and displayed the steepest rise in BP with mean BP in the hypertensive range at the age of 38 years (≥140 mmHg). Early detection and subsequent targeted prevention and intervention may reduce the life course burden associated with higher BP.[13]

What Initiates Pediatric HT?

Low birth weight (LBW)

Brenner *et al.* postulated that developmental programming in the intrauterine environment influences BP during adult life.[14] Barker *et al.* analyzed two large samples of 9921 children and 3259 adults in Britain and found that SBP was inversely related to birth weight. The association was independent of gestational age, and therefore, HT was attributed to reduced fetal growth.[15] Individuals with nephron numbers on the lower side of the spectrum are those at higher risk of HT and kidney disease.[16] Nephron numbers increase in proportion to birth weight and gestational age and vice versa in individual's born as LBW and prematurely.[17]

Prematurity

Prematurity increases the risk of HT through decreased glomerulogenesis independent of birth weight. A meta-analysis of 10 studies including 3083 individuals from eight countries reported the association of prematurity with adolescent or adult

BP (measured at an average age of 18 years). Those who were born premature had modestly but significantly higher SBP (by 2.5 mmHg), regardless of weight.[18]

Obesity

This is one of the major contributing factors in recent times to HT and the reason for the shift to an era of primary HT in children. Today, many tiniest neonates leave NICU without apparent morbidity, and adverse effects were marked among those who became overweight or obese.[19] In India, Patil *et al.* screened 1486 adolescents and found the prevalence of overweight and obesity to be 20% and 16%, respectively. The prevalence of pre-HT was noted in 7.5% and HT in 5.4% children.[20] Evidence shows that rapid "catch-up" growth with a body weight higher than expected leads to the development of high BP, insulin resistance, cardiovascular, and renal risk. Catch-up growth is necessary as it improves child survival, stunting, and malnutrition but not to an extent of obesity.

Sleep disordered breathing

Researchers in numerous studies have identified an association between sleep-disordered breathing and HT in the pediatric population.[21]

Other risk factors

Family history of high BP, male sex, high salt intake, first born added to LBW were associated with hypertensive group. Higher body mass index and cigarette smoking resulted in increasing BP across trajectories, particularly for the higher BP groups. Maternal malnutrition, gestational diabetes, gestational HT, maternal overweight and obesity, preeclampsia indirectly, through LBW, and prematurity, contribute to the development of HT. Congenital anomalies of the kidneys and urinary tract, and neonatal AKI, perinatal exposure to nephrotoxic drugs and primary renal disease, acquired and hereditary, contribute to renal injury, and HT.

Genetics of HT is complex and many genes react to different environmental stimuli and contribute to BP. About 30–50% of the variance of BP readings are attributable to genetic heritability and about 50% to environmental factors. Genetic studies have identified (a) specific enzymes, channels, and receptors implicating sodium handling in the regulation of BP, (b) genes involved with the renin-angiotensin-aldosterone system controlling BP and salt-water homeostasis, (c) proteins in hormonal regulation of BP, and (d) regulation of vascular tone through endothelins and their receptors.[22]

When to Measure BP and Who Are Susceptible to HT?

BP is measured annually in healthy children more than 3 years of age. In children <3 years of age BP is measured and at every health-care encounter in those with the history of (a) prematurity (<32 weeks) (b) very LBW, (c) neonates requiring NICU care, (d) overweight, obesity or diabetes, (e) associated renal, cardiac or neurological ailment, (f) systemic illness leading

to HT, (g) solid organ transplant, and (h) treatment with drugs known to cause HT.[4]

What can be Done During Childhood To PreventHT During Adult Life?

In 2013, the US Preventive Services Task Force presented a controversial statement that "the current evidence is insufficient to assess the balance of benefits and harms of screening for primary HT in asymptomatic children and adolescents to prevent subsequent cardiovascular disease in childhood or adulthood."[23]

The International Childhood Cardiovascular Cohort Consortium has, however, documented evidence that pediatric HT is predictive of adult BP and has a significant impact on the heart and blood vessels.[24] Left ventricular hypertrophy (LVH) has been identified as an important side effect with HT in children. It is estimated that 8–41% of hypertensive children have left ventricular mass of >95th percentile, adjusted for age, sex, and height, and roughly 10–15.5% of children have values >51 g/m^2, a level known to be associated with significant cardiovascular morbidity and mortality in adults.[25] HT during childhood has been shown to be associated with early markers of cardiovascular disease, including carotid intima-media thickness, arterial compliance, atherosclerosis, and diastolic dysfunction.[26,27] Likewise, retinal arteriolar narrowing and microalbuminuria have been documented.

Analysis of the National Childhood BP database found that 7% of adolescents with elevated BP per year progressed to true hypertensive BP levels.[28] Therefore, efforts should be made to prevent progression to sustained HT through: (a) Good antenatal care, (b) prevention of obesity, (c) vigilant screening for HT in high-risk children, and (e) prevent or control HT and target organ damage through healthy lifestyle and pharmacotherapy.

Good antenatal care
It is evident that kidney diseases including HT in adulthood often springs from childhood legacy. The care should start from the womb. Decreasing teenage pregnancy, empowering and educating girls and women, reducing maternal infections and malnutrition, appropriate antenatal care can reduce the risk of LBW, small for gestational age, preterm birth, pre-eclampsia, gestational diabetes mellitus, maternal and childhood obesity and hold promise of a positive impact on the renal health of future generations.[29]

Prevention and management of obesity
Weight loss is particularly important for children with obesity-related HT because it addresses the underlying etiology, improves comorbidities and reduces sympathetic overactivation, and leading to lowering of BP. Guidelines recommend a staged approach to obesity treatment, with weight loss recommended for children 6 years of age and above when BMI is in the obese category and weight maintenance for growing children when BMI is in the overweight category.[30]

Avoidance of sugar-sweetened beverages leads to weight loss among children. Sodium intake to <1.5 g/day has a significant impact on BP among children and adolescents who are overweight/obese.

A review of 9 studies of the physical activity interventions in children and adolescents with obesity suggested that 40 min of moderate to vigorous, aerobic physical activity at least 3–5 days per week improved SBP by an average of 6.6 mm Hg and prevented vascular dysfunction.[31] The 2017 AAP Guideline recommends moderate to vigorous physical activity of 30–60 min/session for 3–5 days/week to control HT in children and adolescents with elevated BP. ACE I or ARB is recommended as initial agents in the treatment of obesity-related HT. The added benefit is being able to target pathways leading to elevated BP, and beneficial effects on comorbidities, diabetes, and dyslipidemia.

Vigilant screening
In addition to screening children who are susceptible to HT as above, ambulatory BP monitoring (ABPM) is a recent tool being used in the pediatric population for confirming HT. According to the 2017 AAP guidelines, ABPM is recommended in children >5 years with the following indications: (a) White-coat HT (WCH), (b) masked HT, (c) to confirm diagnosis and before initiating pharmacologic therapy, (d) assess BP control in children on antihypertensive, and (f) follow-up of secondary HT. The diagnosis of WCH is relevant due to risk for cardiovascular damage. Current knowledge does not recommend treatment. Pharmacological therapy is advised in the presence of LVH, changes in intimal/medial wall thickness of carotid arteries and microalbuminuria. Mark *et al.* did a cross-sectional analysis of BP and cardiac structure in a large population of children with chronic kidney disease (CKD) as a part of the observational CKD cohort study. On the basis of the combination of ambulatory and casual BP assessment ($n = 198$), 38% of children had masked HT and 18% had confirmed HT. If ABPM was not used, then 38% of the children would have missed the diagnosis of HT. LVH was more common in children with either confirmed (34%) or masked HT (20%). In conclusion, casual BP measurements alone are insufficient, and ABPM should be performed routinely.[32]

Lifestyle modification
The Dietary Approaches to Stop Hypertension (DASH) diet with specific elements is the recommended dietary strategy for HT. These elements include a diet that is high in fruits, vegetables, low-fat milk products, whole grains, fish, poultry, nuts, and lean red meats; it also includes a limited intake of sugar and sweet along with lower sodium intake. The current recommendation for salt intake for normal children is <1.2 g/day for children aged 4–8 years and <2.5 g/day for 8–16 years.

Pharmacologic management
In both primary and secondary HT, if lifestyle modification is unsuccessful in BP control, it is necessary to initiate pharmacologic therapy along with lifestyle modification. The frequency of repeat BP measurement and pharmacologic therapy initiation is shown in Table 3 and Figure 4.[33]

Evidence has emerged that markers of target organ damage, such as increased left ventricular mass, can be detected among some children with BP >90th percentile (or >120/80 mmHg) but <95th percentile. The goals of therapy for the treatment of HT are for achieving a BP level that reduces the risk for target organ damage. In the recent AAP 2017 guidelines, optimal BP level to be achieved with the treatment of childhood HT is <90th percentile or <130/80 in >13 years of age. Children with CKD, HT should be treated to lower 24-h MAP to <50th percentile by ABPM. Alternately guideline recommends, in children with non-dialysis CKD particularly those with proteinuria, BP to be lowered to achieve systolic and diastolic

readings less than or equal to the 50th percentile for age, sex, and height.[34] First line pharmacologic agents to control BP, in children and adolescents are Angiotensin converting enzyme inhibitor (ACE I) and angiotensin receptor blocker (ARB), long-acting calcium channel blockers or thiazide. Other antihypertensive medications should be reserved for children who fail to achieve adequate BP control with two or more of these preferred agents.[35]

In conclusion, the current focus is early identification of HT in asymptomatic, healthy children and adolescents and those with secondary HT. Barriers for early identification in clinical practice are poor knowledge of normal BP range, lack of awareness of previous BP readings and the need to synthesize multiple BP readings over time to make a diagnosis of HT. The current scenario is around the epidemic of obesity in children, obesity-related HT, and primary HT. The increasing survival of newborns from pregnancy, prenatal and perinatal complications due to improved maternal and NICU care would indicate an increase in childhood HT and its consequences in adulthood. In future, this form of non-communicable disease would be dominant in pediatrics. Hence, physicians who care for children should have before them Table 2 (screening BP values requiring further evaluation of AAP Guidelines 2017). Oscillometric devices may be used for BP screening in children and adolescents. The update recommends increased use of ABPM for diagnosis and for assessing therapeutic response. Treatment goal with non-pharmacologic and pharmacologic therapy should be a reduction in SBP and DBP to 90th percentile for children and <130/80 for adolescents of 13 years and above. Prevention of predisposing causes and early identification of elevated BP in children would serve the foundation for battling the impending storm of HT in children.

Table 3: Frequency of BP measurement and timing of pharmacologic therapy initiation[33]

Types of HT	Stage of HT	BP measurement frequency	Pharmacologic treatment
Primary	Elevated BP	Initiate lifestyle changes Repeat in 6–12 months	After 12 months if not controlled with lifestyle changes
	Stage I	Initiate lifestyle changes Recheck in 1–2 weeks (twice) Sooner if the patient is symptomatic Repeat after 3 months and refer to a specialist if high	Symptomatic After 3 months if lifestyle changes fail in asymptomatic children
	Stage II	Initiate lifestyle changes If asymptomatic, repeat in week and evaluate or refer to a specialist	Symptomatic or acute severe HT If repeat values are high
Secondary		Initiate lifestyle changes	Initiate treatment

HT: Hypertension, BP: Blood pressure
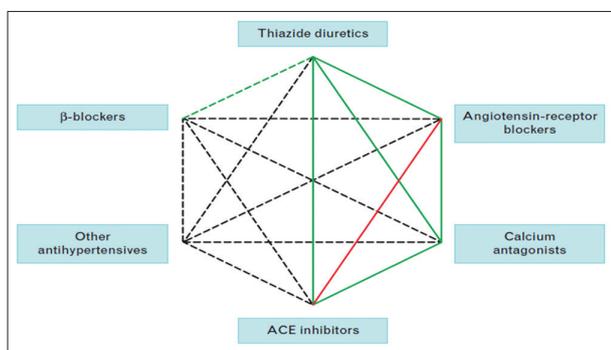
Figure 4: Recommended combination of antihypertensives.[33] Green/continuous: Preferred. Green/dashed: Useful (with some limitations). Black/dashed: Possible but less well tested. Red/continuous: Not recommended. Only dihydropyridines to be combined with beta-blockers. Thiazides and beta-blockers increase risk of new onset diabetes mellitus. angiotensin-converting enzyme inhibitors and angiotensin receptor blockers combination discouraged

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Review Article

Central Aortic Blood Pressure: An Evidence-based Approach

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Abstract

The conventional brachial blood pressure measurement remains as a principle tool to assess cardiovascular risks and monitor the effect of drug therapies. The convenience of measuring the blood pressure in the brachial artery and its cost-effectiveness made it a gold standard for measuring the blood pressure across the world. Even though the diastolic pressure and mean arterial pressure are close to constant throughout the arterial tree, the systolic pressure is not. The systolic pressure widely varies in different segments of the arterial system. This makes the measured brachial pressure inaccurate reflection of load in the central hemodynamics. All the major end organs such as the heart, brain, kidneys, and large arteries, which bear the brunt of hypertension, actually perceive the pressure on the central elastic arteries and certainly not on the brachial artery. Due to the complex mechanism of the presence of wave reflection, pulse pressure amplification, and arrival of the reflected wave to the aorta, the central aortic systolic pressure and brachial pressure were never identical. To add to this complexity, the drug has a differential effect on the brachial and central aortic pressure. In future, the management of hypertension will revolve around central blood pressure and central aortic pressure waveform analysis.

Key words: Central blood pressure, wave reflection, pressure amplification, arterial stiffness, cardiovascular events

Introduction

Hypertension is one of the major causes of cardiovascular death and disability across both developed and developing nations.[1] Blood pressure, measured in brachial artery over the forearm, has firmly established itself as a routine clinical tool in the cardiovascular risk assessment and managing hypertension. Predicting future cardiovascular events in asymptomatic individuals and patients with cardiovascular disease made brachial blood pressure not only a routine but also a superior clinical tool. In the past couple of decades, several studies have shown patients with diagnosed hypertension; if their brachial blood pressure is lowered by hypertension drugs, this can positively influence the future cardiovascular event rates. Inadvertently, all these successes with brachial blood pressure have left it unchallenged for more than 100 years and have been slowly accepted as a surrogate measure of pressure in the central elastic artery, such as central aortic blood pressure. When diagnostic cardiac catheterization came into practice in the late 1940s, it became increasingly evident that the pressure in the arterial tree was different at different segments of the artery due to arterial stiffness and wave reflections.[2] This questions the basic assumption that brachial pressure as a surrogate measure of central aortic blood pressure was not accurate. In many instance the difference between the central and brachial pressure vary widely from 20 to 40 mmHg.[3-5] Furthermore, the pressure in the central elastic artery, where all the major organs were exposed to, was never the reflection of pressure in the peripheral brachial artery. The future of blood pressure management will be based on the accuracy of measuring the central blood pressure noninvasively. Currently, there are a number of clinical data to show the superiority of central blood pressure over brachial pressure in predicting future cardiovascular events. Studies also showed targeting and reducing the central blood pressure results

in greater reduction of cardiovascular events.

Historical Perspective

Historically for thousands of years, palpating the pulse in the radial artery was practiced in the Eastern countries including Greek, Egypt, China, and India. The palpation of the radial artery was done to assess the characteristics of the pulse. The change in pulse contour in health and in disease status was well recognized during these civilizations at a very early date. This practice reached western countries only in the 18th century. In the 1860s, palpation of the radial artery was advanced and the recording of this pulse waveform from the radial artery was made possible through a device called the sphygmograph [Figure 1].

Thus, the art of interpretation of the pulse waveform in different disease conditions had began and popularized.[6] One of the many pioneers Akbar Mahomed, the grandson of a Bengali Indian restaurant owner, who was considered as a visionary, wrote in 1871 in his paper "The pulse ranks first among our guides; no surgeon can despise its counsel, no physician shut his ears to its appeal…we should study the pulse in its marvelous changes of character and form." However, by the early 19th century, the sphygmograph was slowly replaced by the sphygmomanometer due to this new device's ability to quantify blood pressure in numbers. This new device was able to provide numbers for the two extreme measure of the waveform, namely systolic and diastolic pressure. This, indeed, revolutionized the management of hypertension, which was actively encouraged by the Life Insurance Companies as a risk assessment tool for its policyholders. This ultimately resulted in the shift from pulse waveform interpretation to systolic and diastolic numbers of interpretation. The waveform which carries remarkable information about the ventricular interaction with the vascular system, reflecting the compliance of the systemic vessels, was abandoned in favor of two simple numbers. From early 19th century to the 20th century, sphygmomanometer was unchallenged. Now, for the past two decades, there was a renewed interest among researchers and clinicians to move toward arterial waveform and arterial stiffness assessment rather than fully depending on brachial systolic and diastolic pressure. This derived central aortic blood pressure waveform noninvasively from peripheral artery is a more accurate reflection of the real pressure load on the major target organs of hypertension, namely
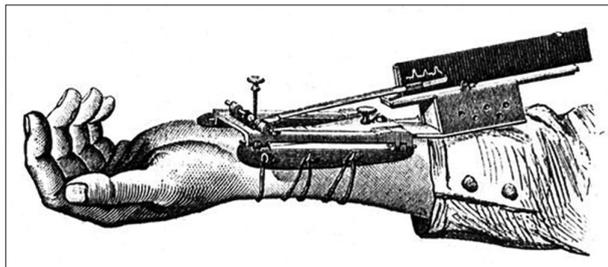
Figure 1: Sphygmograph original equipment, showing amplified pulse recorded in the smoked paper

the brain, kidneys, and heart. The forearm-based brachial blood pressure measure is devoid of the waveform which can provide crucial information on wave reflection and its effect on central hemodynamics. Newer devices can now derive central blood pressure noninvasively by applying a tonometer in the radial artery or by blood pressure cuff in the brachial artery as accurate as invasive measurement through cardiac catheterization.[7]

Effect of Wave Reflection on Central Aortic Pressure

In an arterial tree from the proximal aorta to the femoral artery, the pressure waveform contours and peak systolic pressure change throughout the vascular system. However, the diastolic and mean arterial pressure is relatively constant. In young individuals, the peak systolic pressure increases and the waveform contour changes significantly as the pressure waveform moves from the center to the periphery. In middle age and older individuals, the increase in peak systolic pressure is comparatively lower and the waveform contour changes also less significant as the pressure wave moves toward the periphery in the vascular system [Figure 2].

This change in the peak systolic pressure and wave contour is due to the wave reflection. This phenomenon of an increase in systolic pressure from the center to peripheral is called systolic pressure amplification. Sometimes, it is referred as pulse pressure amplification, which is defined as the ratio of peripheral to central pulse pressure. This systolic pressure amplification is not constant and can vary between individuals, and it is inversely proportional to arterial stiffness and vessel diameter. Many other factors such as age, gender, height, ethnicity, and heart rate affect it.[8-10] The reason for high systolic pressure amplification in the younger age group is due to compliant or lower stiffness in the arteries, leading to a slower travel velocity of the reflected wave. Hence, in the peripheral muscular brachial artery, since the reflective site is closer, the wave will arrive during the systolic phase, thereby increasing the brachial systolic pressure. Hence, the systolic pressure measured in the brachial artery is higher or amplified. However, by the time the reflected wave arrives at the central elastic aorta, it reaches later during the diastolic phase, so it will not contribute to an increase in systolic pressure. This explains why the central aortic blood pressure is always lower than the brachial blood pressure. This amplification of systolic and pulse pressure causes the overestimation of pressure by the sphygmomanometer in the younger age group patients (without arterial stiffness). Hence, in the younger age group, raised systolic pressure may not be a good indicator for risk assessment but raised diastolic pressure does.[11] In this group of patients, there are no clinical data available to substantiate the use of antihypertensive drugs, since published prospective data have shown that they do not proceed to systolic or diastolic hypertension in the near future.[12] Hence, this is a gray area, where brachial systolic pressure may not increase the risk of cardiac events since the corresponding derived central blood pressure may sometimes be normal. This was endorsed by the European Society of Cardiology/European Society of Hypertension 2013 guidelines.
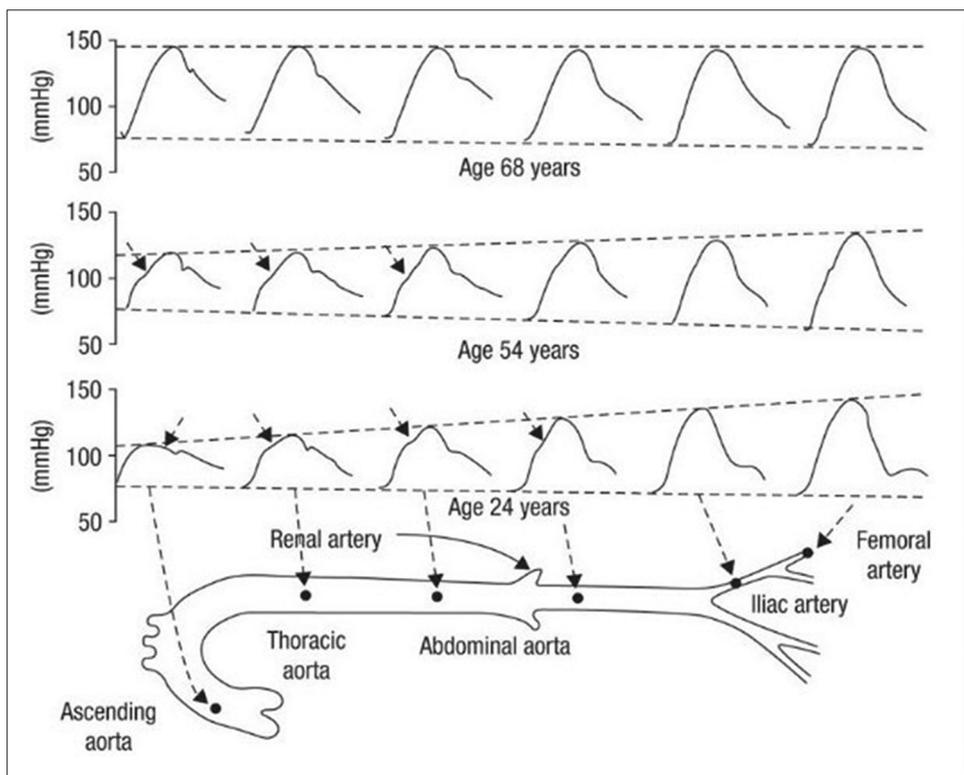
Figure 2: Systolic pressure amplification in different age groups from central aorta to peripheral femoral artery. Note, the pressure amplification is higher in younger age group when compared to older age group

Ventricular Vascular Interaction

When the ventricle contracts during systolic phase, it does not only eject the end diastolic volume into the aorta but also generate pressure wave that propagates along the vascular system. This forward travelling pressure wave moves through the large elastic artery, muscular artery, and the high resistance arterioles. Along the pathway, it gets reflected wherever there is impedance mismatch. The major reflective sites are the branching points of distal arteries and high-resistant arterioles. The velocity of this forward traveling and the reflected waves depends on resistance offered by these following pathways. A large elastic artery plays an important role of buffering the pulsatile blood flow due to the systolic and diastolic phase of the cardiac cycle. When advancing age is couples with cardiac risk factors, the calcification of aorta with loss of elasticity will contribute to increase in the forward and reflected wave velocity and widening of the pulse pressure due to loss of buffering function of the aorta. The muscular artery provides an increased resistance due to endothelial dysfunction, which leads to vasoconstriction and will increase the wave reflection. Finally, the smaller arterioles which are responsible for majority of peripheral vascular resistance due to vasoconstriction will lead to an increase in wave reflection velocity. All these segments of the vascular system contribute to the forward and reflected wave velocity and this may impact on the central aortic pressure. If the vascular system is a complaint, then the reflected wave comes to the central

aorta when the ventricle is still at the diastolic phase. This provides additional advantage, as this wave can boost the coronary perfusion further and help to improve myocardial blood flow. If the vascular system is non -complaint or stiff, then the pressure wave travels with high amplitude and velocity, so it arrives at the central aorta, when the ventricle is still at the systolic phase. This is detrimental as the natural boost done by the reflective wave in boosting coronary perfusion is lost and also the early reflective wave can cause raise in central aortic systolic pressure and increase the left ventricular afterload. These changes in the central hemodynamic and reflective wave impact on central blood pressure make central aortic blood pressure a better reflection of ventricular-vascular interaction, which cannot be appreciated in brachial pressure.

Measuring Central Blood Pressure

The most direct and accurate method of measuring the central blood pressure in the ascending aorta can be done through an invasive catheter, tipped with a pressure sensor. This method cannot be applied for routine use of blood pressure measurement in hypertension management. However, the central blood pressure and waveform can be derived from the peripheral radial artery through a pressure sensor tipped applanation tonometer. The handheld tonometer is placed over the radial artery mildly flattening it over the underlying bone, and the intraarterial pressure is measured [Figure 3].

This pressure waveform using a validated generalized transfer function is used to estimate the central pressure waveform.[13] This derived central pressure waveform not only provides the central systolic, diastolic, and pulse pressure but also provides various indices which carry information on vascular status and ventricular ejection duration. The increase in central systolic pressure due to the reflected wave is called augmentation pressure. This reflects the ventricular load or the pressure; the ventricle has to generate to eject the blood into the aorta. The augmentation index is the ratio of augmentation pressure to the central pulse pressure and is usually expressed in percentage. Subendocardial viability ratio is the measure of myocardial supply divided by demand. Poor subendocardial viability ration can happen due to no diastolic augmentation, which occurs due to the absence of a reflected wave. This can precipitate subendocardial ischemia on exertion.

Central Blood Pressure in Patient Management

Patients with hypertension and blood pressure reduction measured in brachial artery *per se* are considered as the major determinant of reducing the cardiovascular events both in young and older patients. This outcome is not related to the choice of antihypertensive drugs used to reduce the pressure.[14] However, some of the published studies challenged this simplistic view as different antihypertensive drugs have shown to influence the outcome differently. When this was placed carefully on investigation, it was shown that the blood pressure reduction *per se* matters rather than the choice of antihypertensive drugs, but the difference in outcome is due to the differential effect of the hypertension drugs on aortic and brachial artery pressures. Hence, it is the ability of the drug to reduce the central aortic pressure, which determines the outcome. In ASCOT study, the amlodipine-/perindopril-based regimen is compared with

the standard atenolol-/bendroflumethiazide-based regimen.[15] Even though the brachial systolic pressure reduction is similar in both these regimens, the amlodipine/perindopril group has better reduction in all-cause mortality, stroke, non-fatal MI, and cardiovascular mortality. This trial was prematurely stopped due to significant increase in mortality in the atenolol-based regimen. The CAFE trial is a major substudy of the ASCOT trial, which was designed to answer why there is a difference in the clinical outcome between these two drug regimens, even though the reduction in brachial systolic pressure is similar in both of these drug arms.[16] It has been observed that the aortic systolic pressure and pulse pressure were around 4.3 mmHg and 3.0 mmHg lower in amlodipine-based treatment regimen. This reduction in the central pressures was the reason behind the observed differences in outcome. The same trend was previously shown in an another randomized double-blind study called REASON.[17] In this study perindopril and diuretic drug, indapamide combination is compared with the beta-blocker atenolol. The brachial blood pressure reduction was superior in perindopril based arm around 6 mmHg, but when the central aortic pressure is measured, it showed a much greater reduction in the perindopril arm when compared to the atenolol arm as much as 13 mmMg. When these patients are followed up for 1 year, the left ventricular mass regression was more pronounced in the perindopril treatment arm.[18] This shows that the ventricular load is dependent on the central aortic pressure and not on brachial pressure. Furthermore, in this study, it is very clear that the brachial pressure has significantly underestimated the efficacy of pressure reduction by perindopril/indapamide combination in the central aorta.

Beta-blockers in Hypertension

Cardioselective beta blocker especially atenolol has shown less effective in reducing central blood pressure when compared to
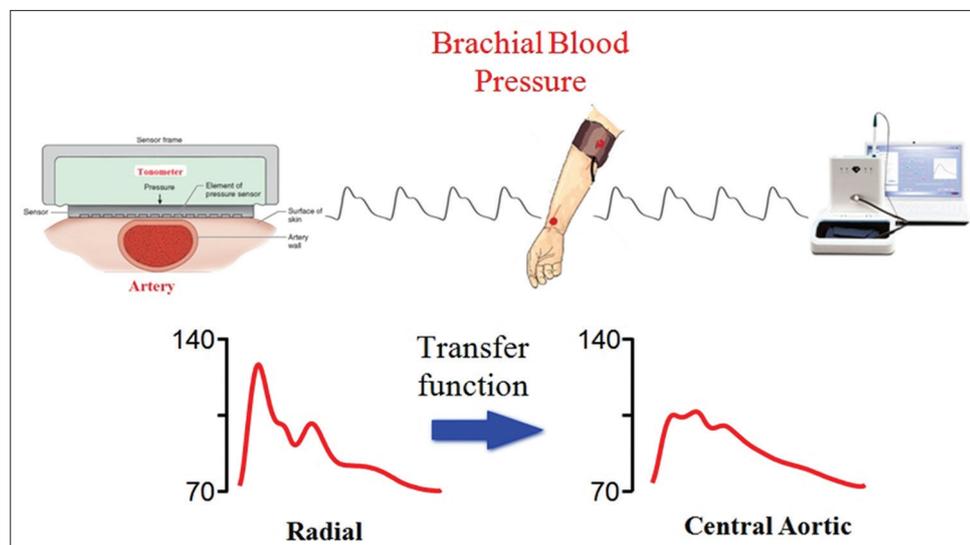
Figure 3: Applanation tonometer is used to derive the central aortic pressure by measuring intra-arterial pressure in the radial artery by applying validated general transfer function

other antihypertensive drugs. Still, Its brachial pressure reduction is comparable, which is evident from the above-mentioned trials. Atenolol failure to reduce the central blood pressure is possible due to the lack of vasodilatory property. Another main action of the beta-blockers, which may affect the central blood pressure reduction efficacy, is the reduction of heart rate. When heart rate decreases, it increases the systolic ejection duration, thereby allowing the reflective wave to fall on the systolic ejection time due to prolong systolic phase. This results in the augmentation of central pressure. Furthermore, beta-blockers reduce the cardiac output triggering compensatory increase in peripheral vascular resistance. These combined effects of reduced heart rate, cardiac output, and raised peripheral vascular resistance make cardioselective beta-blocker not a good drug of choice for primary hypertension. It has been postulated that this probably may not be a case if the beta-blocker has a vasodilatory effect. Arterial vasodilatation causes a decrease in amplitude and velocity of the reflected wave preventing central pressure augmentation due to the early arrival of the wave. A newer drug, Nebivolol, a different class of beta-blocker with vasodilatory effect when compared to another cardioselective beta-blocker metoprolol has shown to reduce the central blood pressure and left ventricular wall thickness better than metoprolol.[19] Even though the heart rate reduction is similar in both these groups, the reduction in central blood pressure is significant in the nebivolol group. This shows somehow the deleterious effect of reduction in heart rate on central pressure is offset by the vasodilatory effect. This shows that drugs such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, nitrates, and vasodilating beta-blockers will have a much-pronounced effect in central blood pressure.[20-24] This is predominantly due to its reduction in peripheral vascular resistance by vasodilating the arterioles and also moving the reflective site to the distal. This late arrival of the reflected wave may cause a reduction in the left ventricular myocardial demand or LV after load.

Central Pulse Pressure

In another pivotal study called strong heart, the relation of central and brachial systolic and pulse pressures toward outcome was studied in a larger sample size.[25] It is the pulse pressure which shows more significant when compared to the systolic pressure of both brachial and central. When mutual adjustments were made, it became clear that it is the central pulse pressure and augmentation index, which are the predictor of cardiovascular outcome than the brachial pulse pressure. Furthermore, the central pulse pressure and the augmentation index are strongly related to carotid intimal-medial thickness and carotid plaque score. When antihypertensive medication is added to this model, the predictive value of brachial pulse pressure becomes non-significant and only the central pulse pressure remains so as a sole predictor of outcome. This disappearance of the brachial pulse pressure predictive value after adding the hypertension

medication shows the lowering of the brachial systolic pressure higher than the central systolic pressure. In the subsequent analysis of Strong Heart study,[26] its shown that the central pulse pressure >50 mmHg possesses a greater risk for cardiovascular events and serves as a target for reduction by antihypertensive medications.

Conclusion

The treatment of hypertension, a modifiable cardiac risk factor, has shown to reduce the occurrence of future cardiovascular events. To measure and monitor the reduction of blood pressure, measuring brachial pressure at the arm has been practiced for more than a century without any change. Recent accumulating data have shown that the brachial systolic and pulse pressure may not be an accurate reflection of pressure in the central aorta. From a younger to an older age group, the central systolic and pulse pressure was never identical to the peripheral systolic and pulse pressure. These differences are attributed to pulse pressure amplification and due to the presence of strong wave reflection in the arterial tree. Antihypertensive drugs are also shown to have a differential effect in the peripheral and central systolic pressure. Many times, brachial blood pressure either underestimates or overestimates the blood pressure reduction in central hemodynamic and these may influence class of antihypertensive drugs used and cardiovascular outcomes. Newer concepts such as pulse pressure amplification, wave reflection, and augmentation index will be implemented in the future to manage hypertension effectively. The central pressure-based treatment strategy will help to better manage hypertension. However, in spite of the overwhelming evidences, its unlikely brachial blood pressure will be replaced sooner by central blood pressure. This is not due to the lack of evidence but due to the ease of using sphygmomanometer and the practice which lasted more than a century will be difficult to change, so it will be gradual.

Acknowledgment

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

Resistant Hypertension 2018

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Abstract

Resistant hypertension (HT) (RH) is defined as blood pressure (BP) that remains elevated above the target despite simultaneous treatment with three antihypertensive agents of different classes, at maximum or maximally tolerated doses and at the appropriate dosing frequency. Patients requiring four or more antihypertensives to achieve BP targets are also included. About 12–15% of individuals treated for high BP would have RH. They are at higher risk of cardiovascular morbidity and mortality. White coat effect and pseudohypertension should be ruled out before diagnosing RH. Drug compliance and assessment for comorbidities such as sleep disturbances, obesity, diabetes, and secondary HT are important. The treatment is primarily lifestyle and risk factor modification as well as pharmacotherapy. Diuretics, especially spironolactone and eplerenone, should be used appropriately. Divided dosing, bedtime dosing, and use of fixed-dose combinations should be applied. Renal artery stenting for significant renal artery stenosis is useful in carefully selected subsets. Among interventional approaches, renal denervation (RDN) showed initial promise, but sham-controlled trial could not prove a significant benefit. Modifications of the RDN techniques hold promise. Other interventional techniques such as baroreceptor activation therapy still need further studies. In addition, clinical inertia by the physician should be avoided.

Key words: Resistant hypertension, hypertension, secondary hypertension, renal artery stenting, renal denervation, target blood pressure

Introduction

Non-communicable diseases are becoming the leading cause of morbidity and mortality worldwide. Hypertension (HT) is a major cause of cardiovascular disease, especially stroke, myocardial infarction, and renal failure. The incidence of HT *per se* is increasing and stricter and lower definitions of HT is also contributing to it. Resistant HT (RH) is a challenging subgroup with a worse prognosis.

Terminologies

Varied terminologies have been used in relation to RH. Controlled, uncontrolled, apparent, true, easy to treat, and difficult to treat are some of the different terminologies used in relation to RH. Uncontrolled HT is not synonymous with RH. It includes subjects who do not achieve blood pressure (BP) targets on treatment. This includes those with poor adherence and undetected secondary HT, those on insufficient treatment protocols, and those with true treatment resistance. RH forms only a small but very significant proportion of uncontrolled HT.

Definitions

BP that remains above the goal despite compliance with full doses of three or more antihypertensive drugs of different classes (one of the three being a diuretic) with the treatment plan also including adequate lifestyle modifications can be considered as RH. This includes patients who achieve targets with four or more antihypertensive agents.

The AHA scientific statement 2018 defines RH as "above-goal elevated BP in a patient despite the concurrent use of 3 antihypertensive drug classes, commonly including a long-acting calcium channel blocker, a blocker of the renin-angiotensin

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system (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker), and a diuretic. The antihypertensive drugs should be administered at maximum or maximally tolerated daily doses. RH also includes patients whose BP achieves target values on ≥4 antihypertensive medications. The diagnosis of RH requires assurance of antihypertensive medication adherence and exclusion of the "white-coat effect (WCE)" (office BP above goal but out-of-office BP at or below target)."[1]

The 2018 ESC/ESH Guidelines for the management of arterial HT definition of RH is similar to the AHA scientific statement 2018 except that the treatment goal was set as <140/90 mmHg instead of <130/80 mmHg as per the ACC/AHA guidelines.

Apparent Treatment RH (aTRH) is a term used when either medication dose, adherence or out-of-office BP is missing, thereby making pseudo resistance non-excludable.[2] BP should be measured using correct methodology before labeling as RH. Ambulatory BP measurements (ABPM) or home BP monitoring (HBPM) allows WCE to be ruled out. Patients with WCE have a prognosis similar to that of controlled hypertensives. Suboptimal adherence is seen in a large majority (50–80%) of HT patients on antihypertensive medications.[3] ABPM, correct technique for BP measurement and confirming drug compliance, helps to rule out pseudo resistance. Marked arterial stiffening may be seen in the elderly, especially those with heavy calcification of arteries. This can prevent occlusion of the brachial artery, resulting in pseudo-HT.

Prevalence

The prevalence of aTRH in hypertensive adults on treatment varies in the population from 12% to 15% in population-based studies and 15–18% in clinic-based studies.[1] In the Spanish data, RH was 12.2% of the total treated population, of which 7.6% were true RH and 4.6% WCE.[4]

Pathophysiolgy

The exact mechanism of resistant HT is unknown, but it is most likely multifactorial with the interplay of an enhanced sympathetic tone and fluid retention. Aldosterone likely has an important role in RH. Hyper-enhanced adrenergic state is present along with impaired baroreflex activity.

Prognosis of RH

Combined outcomes of death, myocardial infarction, heart failure, stroke, or chronic kidney disease (CKD) over a follow-up of a median of 3.8 years in a retrospective study of >200,000 patients with incident HT were 47% more likely in RH.[5] The effect of BP control on hypertensive patients with RH and without RH is different. A 13% reduction of risk of incident stroke, coronary heart disease, or heart failure was seen in RH compared with a 31% lower risk in those without RH.[6] It is

possible that the benefit of BP lowering may be less in patients with RH compared with hypertensive non-RH patients.[1]

Patient Characteristics

Obesity, diabetes mellitus, undiagnosed DM, metabolic syndrome, advancing age, albuminuria, CKD, left ventricular hypertrophy, higher Framingham 10-year risk score, obstructive sleep apnea, excess salt intake, depression, and African American ancestry have been associated with RH. Up to 60–84% of RH patients have sleep apnea. Sleep deprivation including shorter sleep duration, reduced sleep efficiency, and less rapid eye movement sleep has been reported to be associated with RH.[7] A genetic link to RH has also been postulated. However, only candidate gene studies have been performed for RH and included only small samples.[8]

Diagnosing RH

Identifying and correcting non-adherence to medication

Adherence to and persistence of therapy and lifestyle modifications are of utmost importance in the management of RH. Pill counts, self-report medication adhesion assessment tools, pharmacy databases, pharmacodynamic parameters (heart rate and B-blockers), witnessed intake of medication, event monitoring systems, urine and blood metabolite assessment, urine fluorometry, and electronic pillboxes have been tried with varying success. Useful techniques include a patient-centric approach to reduce pill burden, using low-cost and generic drugs and fixed dose combinations. Effective strategies include improving adherence by once-daily dosage of antihypertensives when possible instead of multiple daily doses as also using fixed-dose combination agents. White coat effect and poor BP measurement techniques need to be identified and addressed.

Clinical inertia

This is the failure of health-care providers to initiate or intensify therapy when indicated. Clinical inertia is due to at least three problems: Overestimation of care provided; use of "soft" reasons to avoid intensification of therapy; and lack of education and training aimed at achieving therapeutic goals. It is an important reason for not attaining treatment goals in RH. Therapeutic drug monitoring has a potential for monitoring and tailoring treatment.

Lifestyle factors

Alcohol, obesity, dietary sodium, physical inactivity, and dietary patterns all contribute to RH.

Drugs and other substances with a potential to induce or exacerbate elevated BP and HT

This includes NSAIDs, oral contraceptives, sympathomimetics, cyclosporine, tacrolimus, erythropoietin, VEGF inhibitors,

alcohol, cocaine, amphetamines, antidepressants, glucocorticoids and mineralocorticoids, oral contraceptives, and hormone replacement.

Diagnosis and management of secondary HT

Primary aldosteronism

Primary aldosteronism is particularly common with a prevalence rate of approximately 20% in patients with confirmed RH.[9] Screening for primary aldosteronism should be conducted using the plasma aldosterone concentration to plasma renin activity ratio from a morning blood sample obtained after the patient has been in a seated position for at least 30 min before sampling.[1] Unilateral laparoscopic adrenalectomy offers a complete cure in >50% or improvement (≈50%) in BP control. Half of the unilateral disease is caused by aldosterone-producing adenoma, and unilateral hyperplasia is rare. Mineralocorticoid receptor antagonists (MRA) such as spironolactone or eplerenone give good control of BP in subjects with bilateral disease (idiopathic hyperaldosteronism).[10]

Renal parenchymal disease

CKD is both a cause and a complication of poorly controlled HT.[1] Target BP goal of <130/80 is more often attained in stage 1 CKD (49.5%). The control rate drops to 30.2% at stage 4. The overall control rate in CKD as a whole is 44.6%, even though antihypertensive medications are used more frequently in CKD. When the ESC target of ≤140/90 mmHg was used, it was attained in only 66.5%.[11] Loop diuretics are often needed as the renal function declines.

Renal artery stenosis

Secondary causes form 12.7% of the total in a HT specialty clinics referral analysis. Occlusive renovascular disease formed 35% of this subgroup.[12] Non-dipper BP profile, sudden deterioration of renal parameters especially after RAS inhibitors and abrupt progression of HT mandate screening for renal artery stenosis. Atherosclerosis is the etiology in majority of the cases of renal artery stenosis. Other less common causes including a variety of fibromuscular dysplasias, renal artery dissection or infarction, Takayasu arteritis, radiation fibrosis, and renal artery obstruction from aortic endovascular stent grafts should be considered and ruled out.[1] In general, ACE inhibitor or ARB therapy is tolerated well by the majority of patients with renovascular disease without adverse renal effects. The clinician should be aware that a small number (10–20%) will develop an unacceptable rise in serum creatinine. Volume depletion and presence of bilateral renal artery stenosis could be the trigger for this rise and should be avoided or corrected.[1] The pendulum for renal artery stenting (RAS) for the treatment of RH has swung from broad endorsement to calls for an almost complete moratorium. This extreme swing has been due to the highly publicized release of two RAS trials (ASTRAL and cardiovascular outcomes with renal artery lesions [CORAL]). However, these studies did not focus on the population that would benefit most from RAS, i.e., hemodynamically significant renal artery stenosis with RH. RAS took a backseat after ASTRAL and CORAL trials. However, a subset of medically treated patients with renal artery stenosis may benefit with RAS and includes those who have worsening HT, renal insufficiency, or fluid overload ("flash pulmonary edema"). These are conditions with higher risks of death. RAS is also a good option for patients with atherosclerotic severe renal artery stenosis (either >70% angiographic diameter or 50–70% stenosis with hemodynamic confirmation of lesion severity) with true resistant HT or with HT and intolerance to medication. SCAI expert consensus statement for RAS appropriate use 2014 gave Class II a: LOE B for RAS in accelerated, resistant, or malignant HT. A mortality benefit of revascularization was seen in the *post hoc* analysis of the CORAL trial data for atherosclerotic renal artery stenosis in patients without proteinuria compared with medical therapy.[13] A short period of pressure elevation after revascularization is a reliable predictor for effective BP reduction in the long term.[1]

Pheochromocytoma/paraganglioma

Even though the classical feature is paroxysmal HT, elevated BP levels may be sustained in up to 50% of high norepinephrine-producing tumors. Orthostatic fluctuations in BP should lead to a suspicion of epinephrine-predominant tumors. The symptoms of headache, palpitations, pallor, and piloerection ("cold sweat") in patients should be sought for and the index of suspicion should be high.[1] Measurement of circulating catecholamine metabolites is the screening test of choice for pheochromocytoma/paraganglioma.

Cushing's syndrome, coarctation of the aorta, and other rarer causes of secondary HT should not be forgotten during evaluation.

Evaluation of RH

The focus for evaluation should be on confirmation of true treatment resistance, identification of causes contributing to resistance (including secondary causes of HT), and documentation of complications of the hypertensive disease process. Algorithm for evaluation as per the AHA scientific statement 2018 on RH is given in Table 1.[1]

Management of RH

Management approach can be broadly divided into lifestyle interventions, pharmacotherapy, and device therapy.

Lifestyle interventions

Weight reduction, lowering salt intake, DASH diet, and exercise are traditional lifestyle modifying measures. Alternative measures include acupuncture and yoga. Other modalities, including transcendental meditation, device-guided slow-breathing, and isometric handgrip exercise, have been tried with varying success. Isometric handgrip, typically performed for 12 min 3–5 times/

Table 1: Treatment approach to resistant hypertension as per aha 2018 guidelines

SUSPECT RH	RULE OUT PSEUDO RH	RULE OUT CAUSES FOR SECONDARY HT	CHECK FOR TARGET ORGAN DAMAGE
When BP >130/80mm Hg in a patient on maximum/ maximal tolerated doses of ≥ 3 antihypertensives including long acting calcium channel blocker, RAS blocker and a diuretic	By confirming adherence to therapy and ruling out white coat hypertension using 24hr ABPM and/or home BP monitoring (HBPM)	Primary aldosteronism, CKD, renal artery stenosis, pheochromocytoma/ paraganglioma, Cushing syndrome, Obstructive sleep apnea syndrome, coarctation of the aorta and other rare endocrine causes	Eye: Hypertensive changes Heart: Left Ventricular Hypertrophy, coronary artery disease Kidney: Proteinuria, decreased glomerular filtration rate Peripheral arterial disease: Ankle/ brachial index

week, lowers BP by 5.2/3.9 mmHg.[1] The role of improving sleep quality and avoiding environmental triggers such as cold, noise, and pollution appears promising.

Pharmacological approaches

Diuretics

For true RH, the first approach would be to optimize diuretics. MRAs (spironolactone 25–50 mg daily or eplerenone 50–100 mg daily) are the current mainstay. Increasing the dose of the existing diuretic or switching to a more potent thiazide-like diuretic (chlorthalidone or indapamide) should be done. A loop diuretic should replace thiazides/thiazide-like diuretics if the eGFR is <30 ml/min. The use of spironolactone for resistant HT should usually be restricted to patients with an eGFR ≥45 ml/min and a plasma potassium concentration of ≤4.5 mmol/L. Amiloride (10–20 mg/day) has been shown to be as effective as spironolactone (25–50 mg daily) in reducing BP in the PATHWAY-2 study. The PATHWAY-2 study also evaluated bisoprolol (5–10 mg/day) or doxazosin modified release (4–8 mg/day) as alternatives to spironolactone. Thus, bisoprolol and doxazosin though not as effective as MRA have an evidence base for the treatment of resistant HT when spironolactone is contraindicated or not tolerated.[14] Frusemide or bumetanide should be given twice or thrice daily as they have a shorter duration of action. Once-daily dosage of frusemide is associated with intermittent natriuresis and consequent sodium retention mediated by RAS increase. Torsemide has a longer duration of action and may be given once or twice daily. The 2018 ESC/ESH recommendations on RH are given in Table 2.[14]

Choice of other antihypertensives is also important. The more potent drug of each class should be chosen. Among ARBs, azilsartan in ABPM studies has been shown to have further 4–8 mmHg reduction in SBP compared to valsartan, olmesartan, or ramipril.[1] Long-acting formulations of nifedipine may have better BP lowering effect than amlodipine but at the expense of increasing edema.

Divided doses and nocturnal or bedtime dosing may be, especially, useful. Additional drugs that can be used depend

on the sympathetic drive and tolerability. B-blockers, centrally acting drugs clonidine or moxonidine, can be tried. Clonidine tablets should be used with caution due to the risk of rebound HT. The next line of drugs that can be utilized are hydralazine and minoxidil. However, minoxidil increases sympathetic tone and sodium avidity and a background B-blocker and diuretic therapy may be needed. An algorithm for managing RH as per the AHA 2018 guidance is given in Table 3.[1]

Renal Denervation (RDN)

Although most of the early studies showed great promise and generated considerable interest, these were uncontrolled and did not use ABPM. The first sham-controlled prospective randomized study in the field of renal ablation therapy (SYMPLICITY HTN-3) showed little to no effect of RDN therapy in a severely drug-resistant population setting.[1] There may be many reasons why SYMPLICITY HTN-3 failed to demonstrate the expected benefit, one being possible incomplete denervation. There is a greater concentration of nerves in the proximal and middle segments of the renal artery, and the nerves in the distal segment lie closer to the lumen (30% of proximal vessel fibers are found between 4 and 9 mm from the lumen, which is too far to be reached by low-energy radiofrequency ablation). Other possible causes of the negative result could be the difference in population cohorts and Hawthorne effect. HT-1 had no controls, and HT-2 was not sham controlled. The greater effect on BP control in the control population may be at least partially explained by the fact that they were participants in the trial.

Future for RDN

Although the efficacy of RDN is under serious debate, safety in the short term and medium term is well established. There is a low risk of procedural complications. SPYRAL HT global clinical trial program using symplicity spyral multielectrode RDN catheter having multiple circumferential electrodes that can deliver radiofrequency energy to multiple segments of the vessel wall at the same time and the DENERHTN trial showed

Table 2: 2018 ESC/ESH recommendations on RH

Diagnosis of RH (LOE 1C)
- Clinic SBP ≥ 140 and/or DBP ≥ 90mm Hg in a patient on optimal/ best tolerated doses of an appropriate treatment strategy which should include a diuretic (typically ACE inhibitor/ARB + CCB + thiazide/ thiazide like diuretic).
- ABPM or HBPM should confirm inadequate BP control.
- Pseudo RH (especially poor medication adherence) and secondary HT should be ruled out

Treatment for RH (LOE 1B)
- Lifestyle modification with emphasis on sodium restriction
- Addition to existing treatment of:
  - Diuretics:
    - Low dose spironolactone
    - In case of spironolactone intolerance, addition of eplerenone, amiloride, higher dose thiazide/ thiazide like diuretic or loop diuretic
  - Or Bisoprolol or Doxazosin

Table 3: Algorithm for management of resistant hypertension (AHA 2018 guidelines)

STEP 1
Rule out other causes of HT: Medication non-adherence/ white coat HT/ secondary causes

+

Low sodium diet (<2400mg/d)

Maximum LSM:

6 hrs uninterrupted sleep/day

Overall dietary pattern

Weight loss

Exercise

+

Optimize 3 drug regimen

3 anti-HT of different classes (RAS blocker, CCB, diuretic) at maximum/ maximum tolerated dose

* Diuretic to be appropriate for renal function

STEP 2
Substitute optimally dosed thiazide like diuretic: Chlorthalidone/ indapamide for prior diuretic

STEP 3
Add mineralocorticoid receptor antagonist (MRA): Spironolactone or eplerenone

STEP 4
If HR>70/min add B-blocker.If contra-indicated add centrally acting agents . If they are not tolerated consider once daily diltiazem

STEP 6
Substitute hydralazine with minoxidil. If still not reaching targets , refer to hypertension specialist and/or experimental protocols

STEP 5
Add hydralazine, If associated heart failure co-administer isosorbide mononitrate

that RDN may still be effective. Non-invasive RDN using several piezoelectric transducers to direct high-frequency sound waves causing thermal effects that lead to highly specific ablation of target tissue is also in the pipeline. Transcatheter perivascular alcohol denervation provides an interesting safety/efficacy profile. RADIOSOUND-HT study randomized patients with RH to receive either RDN of the main renal arteries (RFM-RDN) or radiofrequency RDN of main renal arteries, side branches and accessories (RFB-RDN) or endovascular ultrasound based RDN of the main renal artery. The results indicated that, in RH, RDN using the Paradise endovascular ultrasound RDN system resulted in greater reduction in ambulatory SBP at 3 months compared with RFM-RDN but not RFB-RDN. This difference may be due to deeper penetration of energy and more complete sympathetic ablation.[15]

Baroreceptor activation therapy

The Mobius HD carotid bulb expansion device is a small endovascular implantable device that works by stretching the carotid artery at the bulb, thereby activating baroreceptors to lower BP.[1] It is sympathomodulatory, and an increase in the carotid bulb strain causes durable amplification of baroreceptor feedback and BP reduction. The CALM-FIM_EUR study has recently demonstrated in patients with RH that endovascular baroreflex amplification with the Mobius HD device substantially lowered BP with an acceptable safety profile. CALM-FIM_US is an ongoing study.[1]

Devices in the pipeline for RH

Central arteriovenous anastomosis
Central AV iliac anastomosis with ROX AV coupler targets mechanical aspects of circulation and lowers BP through effectively

reducing the arterial volume and systemic vascular resistance. There is a 30% incidence of ipsilateral venous stasis. Risk of high output states is low. There are no long-term safety data.

Carotid body ablation

Unilateral carotid body ablation reduces sympathetic vasomotor tone without affecting respiratory drive. There is proof of concept studies with surgical ablation in RH. Endovascular approach for the same is being explored. It appears effective only in those with high carotid body tone, and screening for which is, therefore, essential before employing this modality of management. Endovascular approach has the challenges of difficulty in accessing the target and damage to adjacent structures.

Deep brain stimulation

This is a sympathomodulatory measure. Electrical stimulation of the dorsal and ventrolateral periaqueductal gray region within the midbrain reduces the BP through mechanisms not clearly elucidated. This technology was primarily developed for movement disorders and chronic pain syndromes. However, there are isolated reports of lowering of BP independently. It has limited efficacy/safety data.

Drugs in the pipeline targeting RAS and NP systems

Finerenone (MRA), osilodrostat (LCI 699- 11B hydroxylase inhibitor), RhACE2 (ACE2 activator), RB 150 (aminopeptidase A inhibitor), valsartan-sacubitril (dual ARB-neprilysin inhibitor already approved in heart failure), daglutril (dual ECE-neprilysin inhibitor), and PL3994 (NP A agonist) are some of the medications in the pipeline for RH. VIP receptor 2 agonists, intestinal Na/H exchange inhibitions, DBH inhibition, and vaccines against Ang-II are also under early trial stages.

Pharmacogenomics

The response to equivalent doses of ACE inhibitors varies considerably among individuals. An ACE gene polymorphism (287 Bp insertion in Intron16) accounts for approximately 50% of the genetic variance in serum ACE levels. Approximately 20% of individuals have the 287 Bp insertion. Caucasian patients with the 287 Bp insertion have a poor response to ACE-inhibitors.

Ten Practical Points on RH

1. Exclude pseudo resistance. Evaluate for white coat effect, pseudo-HT. Use ABPM and HBPM.
2. Lifestyle factors are important. Diet and exercise are important. Avoid hidden sources of salt.
3. Check medications: Adherence, persistence, optimum dose, and use of right combinations.
4. Look for associated conditions and secondary HT: Sleep study, renal artery Doppler, hyperaldosteronism.
5. Diuretics: Given in divided doses. Spironolactone/

eplerenone very important.
6. Use of more potent drugs of each class.
7. Bedtime dosage.
8. Old may still be gold: Moxonidine, hydralazine, minoxidil.
9. RAS in selected cases.
10. RDN: Down but not totally out.

Conclusions

Resistant HT remains a challenging condition with poor prognosis. It includes high-risk patients who need effective strategies. ABPM and HBPM are a necessary part of workup and control of variables such as modifications in lifestyle and treatment regimen as well as ascertaining adherence to treatment is fundamental. Pharmacological treatment with diuretics, especially MRA, remains the mainstay but is often unsuccessful in reaching target goals. RDN remains worthy of continuing investigation.

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ℛeview ℛrticle

Rare and unusual causes of hypertension

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Abstract

Background: Hypertension in most cases is primary, the exact etiology not known but there may be risk factors such as salt excess, obesity, lack of physical activity, genetic factors, metabolic syndrome, and diabetes. However, there exists a subgroup of patients with hypertension with underlying etiology, referred to as secondary hypertension, and constitutes about 5–10% of patients with hypertension. The importance of diagnosis of the secondary causes of hypertension is to detect a potentially reversible etiology. Some of these causes are rare and unless looked for, can be easily missed.

Methods: A review of age-specific causes, approach, rare diseases of the aorta, endocrine, renal, iatrogenic, and substance abuse have been discussed. The importance of suspecting unusual causes in patients with uncontrolled hypertension, hypertension in the young, in the presence of target organ damage is emphasized. Case reports of rare cases have been included.

Conclusion: A systematic approach and knowledge of various rare causes will help suspect and lead to the correct diagnosis in many cases of secondary rare causes of hypertension. It gives a unique opportunity to cure hypertension in some cases and if the underlying cause is undiagnosed may result in morbidity and even prove fatal in some cases.

Key words: Secondary hypertension, renal artery stenosis, coarctation of aorta, pheochromocytoma, pseudopheochromocytoma, hyperaldosteronism

Introduction

Hypertension in >90% of cases is primary hypertension with the interaction between genetic and multiple environmental cardiovascular risk factors. Some of the underlying etiologies of hypertension are rare and may go undiagnosed unless a systematic approach and targeted testing are done. Many secondary causes are underlying etiology of resistant hypertension and passed off as essential hypertension in the absence of a careful clinical and diagnostic evaluation.[1]

Clinical Examination

A thorough clinical examination may give some pointers to secondary hypertension. Some clinical findings which may be helpful to detect the secondary causes of hypertension include presence of radio femoral delay suggests coarctation of aorta.

Differences in limb blood pressure, the presence of vascular bruit - may unveil coarctation of aorta, Takayasu's arteritis or Peripheral vascular disease which may be associated with atherosclerotic renal artery stenosis (RAS).

An abdominal bruit is often present in RAS, especially in fibromuscular dysplasia in young postural hypotension - 40% of cases of the pheochromocytoma are associated with postural hypotension, paroxysmal hypertension is common in pheochromocytoma, pseudopheochromocytoma, and panic disorder.

Clinical features of hyper or hypothyroidism, cushingoid features may be suggestive of underlying endocrine disorder obesity, excess snoring with day time somnolence is suggestive of obstructive sleep apnea (OSA).

Diagnostic approach

An age-specific approach is recommended

In patients in early childhood, secondary causes are underlying in 70–85% of cases.[2] The most common causes are renal causes. Reflux

uropathy is common in young boys. In adults >18 years, renal causes and coarctation of aorta are the common secondary causes in about 10–15% of cases of the hypertension. In young adults, RAS due to fibromuscular dysplasia should be considered along with coarctation of the aorta and other renal causes. In the middle-aged, renal causes, thyroid disorders, OSA, and primary hyperaldosteronism are some of the secondary causes, whereas in the elderly renal causes and atherosclerotic RAS are important to be considered [Table 1].

Investigations

The basic investigations include:
- Blood sugar
- Lipid profile
- Blood urea, serum creatinine, serum electrolytes, and serum calcium
- ECG
- X-ray chest
- ECHO
- Ultrasound abdomen
- Renal Doppler
- Thyroid function test
- Urinary 24 h metanephrine, plasma metanephrine
- Plasma aldosterone/renin ratio
- Serum cortisol
- Polysomnography
- Computer tomography (CT)/Magnetic resonance imaging (MRI)/CT or MRI angiogram/metaiodobenzylguanidine (MIBG) scan in special situations
- Invasive angiogram, usually when planned for intervention
  Evaluation for secondary causes is recommended in the following situations[3]
  1. Hypertension in age <40 years > Grade 2, and no genetic or overt risk factors, and hypertension in childhood
  2. Severe hypertension and hypertensive emergencies

3. Hypertension with target organ damage
4. Lack of control in previously well-controlled hypertensive
5. Evidence of abnormal renal function, electrolytes, or abnormal endocrine tests.
6. Presence of bruit, murmur, absent pulses, and variation in blood pressure in the limbs.
7. Paroxysmal hypertension.
8. Clinical features of OSA.
9. Deterioration of renal function on the initiation of angiotensin-converting enzyme inhibitors (ACEI) or ARB drugs.

Secondary causes of hypertension

Renal causes
Two major types of renal diseases - renal parenchymal disease or RAS cause secondary hypertension. Renal parenchymal diseases include glomerulonephritis, polycystic kidney disease, diabetic kidney disease, and chronic pyelonephritis. Reflux uropathy is an important cause in pediatric age group boys. RAS in younger individuals is usually due fibromuscular dysplasia which response very well to interventional therapy. It can also be secondary to Takayasu's arteritis. In older adults, it is usually atherosclerotic in origin. Renal angioplasty has doubtful benefits in atherosclerotic long-standing RAS. It is reserved for patients with uncontrolled hypertension, flash pulmonary edema, bilateral RAS, or sudden deterioration in renal function. Whenever there is a deterioration of renal function following use of ACEI or ARB's; it is important to look for RAS. RAS can be diagnosed by renal Doppler, CT, or MRI angiogram. In individuals with raised serum creatinine noncontrast, MRI angiogram can be done.

Disorders of aorta

Coarctation of aorta is the second most common etiology of secondary hypertension next only to renal causes in pediatric and

Table 1: Age-based diagnostic approach of secondary hypertension

Age group	Common etiology	Initial investigations	Percent of hypertensive patients with secondary cause (%)
<12 years	Renal causes Reflux uropathy COA	Urine analysis Renal function test Usg abdomen	70–85
12–18 years	Renal causes COA	Urine analysis Renal function test USG Abdomen ECHO	10–15
Young adults 19–40 years	Renal parenchymal diseases RAS-Fibro muscular dysplasia COA	Renal function tests Renal doppler ECHO	5–10
Middle-aged - 40–65 years	Primary aldosteronism Renal parenchymal disease OSA Thyroid disorders	Aldosterone/renin ratio Polysomnography Thyroid function tests	5–15
Old age >65 years	Renal parenchymal disease RAS-Atherosclerotic Thyroid disorders	Renal function test Renal Doppler CT/MRI Renal angiogram Thyroid function test	5–10

young adults. The most important sign is a radio-femoral delay and difference in pressure between the limbs. It can be diagnosed by ECHO, MRI angiography, or CT aortogram. Council of Architecture (COA) patients benefit from aortoplasty and stenting or surgical repair. The usual lifespan of uncorrected COA is about 50 years with complications due to hypertension, dissection, or heart failure.

We had a 65-year-old patient detected to have coarctation during evaluation of severe bicuspid aortic stenosis who underwent successful coarctation angioplasty and stenting.

Takayasu's arteritis is rare non-specific arteritis involving aorta and its branches. It is a chronic granulomatous arteritis involving large muscular arteries and results in areas of stenosis, occlusion, dilatation, and aneurysms. The disease occurs in young women predominantly in the second or third decades and is associated with hypertension in two-thirds of patients. Absent upper limb pulses, subclavian bruit, and high blood pressure more often in lower limbs are present, hence called "reversed coarctation." The cause of hypertension in Takayasu's disease may be RAS, atypical coarctation or diffuse aortic narrowing. Renal angioplasty or aortic angioplasty can be done in Takayasu's arteritis as well, but they are more hard and fibrotic lesions and generally need higher inflation pressures or cutting balloon angioplasty. The reported success is about 85–90% with an incidence of restenosis in about 15–20% [Figure 1].[4]

We had a 45-year-old female with Grade 2 hypertension with left renal artery total occlusion, right renal artery 80% stenosis, diffuse aortic narrowing, and aneurysmal dilatation of right iliac artery. She underwent percutaneous transluminal renal angioplasty (PTRA) of the right renal artery.

Autoimmune arteritis like polyarteritisnodosa (PAN) can involve renal arteries. PAN is often associated with hepatitis B infection in close to 10% of cases. PAN may be associated with renal artery aneurysms and stenosis combined. PAN needs immunological treatment, renal angioplasty, and hepatitis treatment combined in these cases [Figure 2].

Endocrine causes

The most common endocrine cause is a hyperaldosteronism. Hyperaldosteronism can be due to unilateral macroadenoma or bilateral diffuse adrenal hyperplasia. It is more common in middle-aged adult men between 40 and 65 years. Unprovoked hypokalemia, though suggestive is present only in 30% of the cases. Diuretic-induced hypokalemia or low normal K+ <3.9 in the presence of ACEI/ARB therapy should also lead to suspect and evaluate for hyperaldosteronism. Any case of resistant hypertension should have an evaluation for primary hyperaldosteronism. It is diagnosed by doing a plasma aldosterone/renin ratio after correcting hypokalemia and patients should not be on aldosterone antagonist therapy. CCB, hydralazine, and prazosin can be used for hypertension control without interfering with the test. Aldosterone/renin ratio >20 ng/dl with aldosterone level >15 ng/dl is suggestive of the diagnosis.[5]
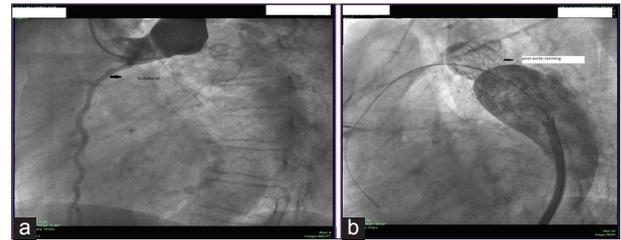
Figure 1: Aortogram of council of architecture, (a) diagnostic, (b) post stenting
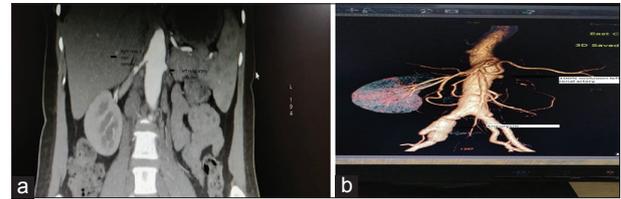
Figure 2: (a) Computer tomography abdominal aortogram, (b) Diagnostic renal angiogram-renal angiogram post percutaneous transluminal renal angioplasty of right renal artery

The treatment is surgical for macroadenoma and use of aldosterone antagonists for microadenoma.

We had a 65-year-old gentleman with Grade 3 hypertension, hypokalemia of 1.9, elevated aldosterone and suppressed renin levels, CT imaging failed to detect a tumor, a diagnosis of microadenoma was made, treatment started with aldosterone antagonist spironolactone 25 mg and losartan 50 mg and he responded well to treatment with correction of hypokalemia and blood pressure control and doing well on >15 years follow-up.

Hyperaldosteronism can also be familiar. There are four types described. Type 1 is an autosomal dominant condition, glucocorticoid-responsive disorder, associated with severe hypertension, young age, and family history. Hypokalemia is less common and cerebrovascular complications and rupture of intracranial aneurysms are common. The treatment is low dose steroids in the night to suppress ACTH surge in the morning along with mineralocorticoid receptor antagonists.[6]

Type 2 is a chromosomal defect, bilateral and clinically similar to sporadic type, type 3 is due to a potassium channel defect, and type 4 is due to calcium channel defect.

Gordon's syndrome: It is a rare monogenic disorder affecting NA-CL cotransporter in the distal renal tubule. It is associated with short stature, mental retardation, dental abnormalities, severe hypertension, hyperkalemia, hyperchloremia, and metabolic acidosis.

It responds to thiazide diuretics. It is also called as pseudohypoaldosteronism, it is associated with normal aldosterone and renin levels.[7]

Geller syndrome is a rare autosomal dominant disorder with hypertension exacerbated in pregnancy due to abnormalities of mineralocorticoid receptor interaction with progesterone.[8]

Congenital beta- or alpha-hydroxylase deficiency and glucocorticoid-resistant hyperaldosteronism (Chrousos

syndrome) - ACTH overactivity with the resistance of the glucocorticoid receptor, are some of the rare congenital defects associated with secondary hypertension.

Thyroid disorders

Both hypothyroidism and thyrotoxicosis can be associated with hypertension. Hypothyroidism causes diastolic hypertension; thyrotoxicosis causes systolic hypertension.

Hyperparathyroidism

Hyperparathyroidism causes secondary hypertension, hypercalcemia, vascular calcification, bone pains, and renal calculus.

Cushing's syndrome

It is usually due to steroid use but can be due to adrenal tumors or ACTH producing pituitary tumors, usually diagnosed by the presence of cushingoid features, striae, and purpura. Evaluation is by measurement of 24 h cortisol levels.

Pheochromocytoma

It is a rare cause - 0.5% of secondary hypertension, suspected by the presence of flushing, sweating, palpitation, headache, and labile hypertension. Use of beta-blockers, tricyclic antidepressants, and metoclopramide, and sympathomimetic drugs can precipitate hypertensive surges. It is a catecholamine-secreting tumor from adrenal medulla or extra-adrenal sympathetic ganglia. The adrenal tumor can be a unilateral macroadenoma or bilateral diffuse adrenal hyperplasia. 40% of pheochromocytoma is familial, which is more often bilateral or extra-adrenal. Pheochromocytoma is present in 50% of patients with multiple endocrine neoplasia type 2, 10–20% of patients with Von Hippel-Lindau syndrome, and 0.1–5% of patients with neurofibromatosis.[9]

6 P's characteristic of pheochromocytoma is as follows:

1. Paroxysmal hypertension
2. Palpitation
3. Perspiration
4. Postural hypotension
5. Pounding headache
6. Pallor

It is diagnosed by measurement of 24 h urinary metanephrines or plasma free metanephrines. Ultrasound may not be able to delineate the tumors well. CT or MRI imaging is required for detection of tumor masses, MIBG scan is used to diagnose extra-adrenal paragangliomas. 10% of pheochromocytoma is malignant with renal or bone metastases. Delayed recurrence can occur after several years; hence, periodic surveillance is recommended. Surgical removal of a tumor can cure hypertension. Adequate alpha-blockade by the use of phenoxybenzamine or prazosin followed by beta-blockade is essential before surgery. Calcium channel blockers only can be used in mild cases and metyrosine in severe cases [Figure 3].
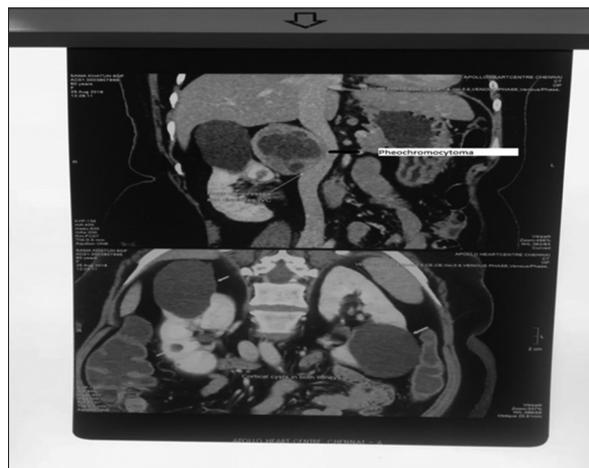
Figure 3: Computer tomography imaging of a case of pheochromocytoma

Pseudopheochromocytoma

Pseudopheochromocytoma is a cause of paroxysmal hypertension caused by catecholamine excess, mimics pheochromocytoma but does not have the biochemical or imaging features of pheochromocytoma. Pseudopheochromocytoma is more common in women, and the acute elevated blood pressure is accompanied by chest pain, nausea, dizziness, palpitation, and lasts for few minutes to several hours. It differs from panic attack as there is no definite anxiety or fear preceding the episode, though childhood trauma or underlying psychosocial stresses have been found in many cases. These patients respond to clonidine and clonazepam. Anxiety and psychosocial counseling help in prevention of the paroxysms.[10]

Liddle's syndrome

It causes hypokalemia but is associated with normal or low aldosterone and low renin levels. It is due to an autosomal dominant condition resulting in overactivity of the epithelial sodium channel in the luminal side of collecting tubule of kidney leading to sodium retention, hypokalemia, metabolic alkalosis, and hypertension. It is diagnosed by the presence of hypokalemia with low renin and aldosterone levels and increased urinary sodium levels. This hypertension responds to amiloride or triamterene, and mutual eecognition agreement drugs have no role in this condition. A case of known Liddle's syndrome successfully managed during pregnancy with amiloride has been reported.[11]

Reninoma

It is a rare benign renin-producing juxtaglomerular tumor produces renin, causes secondary hyperaldosteronism with hypokalemia and metabolic alkalosis and hypertension and it responds to RAS inhibitors, and the definitive treatment is surgical removal. The diagnosis is suspected due to headache with severe hypertension, hypokalemia with metabolic alkalosis, usually in young adults,

investigations show high renin and aldosterone levels and the tumor is detected by imaging by CT or MRI. Excess renin by renin vein sampling can be used for lateralization of the tumor.[12]

Acromegaly

Excess growth hormone can produce hypertension.

Sleep-apnea

It is a common cause of resistant hypertension in obese older adults. It is diagnosed by polysomnography. It is cost-effective to initially screen using sleep apnea scale and nighttime pulse oximetry. Weight reduction and continuous positive airway pressure therapy in moderate-to-severe sleep apnea can help controlling secondary hypertension.

Iatrogenic

Drugs causing hypertension include
- NSAIDs are one of the common drugs causing hypertension
- Steroid therapy for autoimmune, skin diseases
- Oral contraceptive pill with estrogen can cause usually mild, but rarely severe hypertension
- Nasal decongestants-phenylephrine
- Liquorice - can stimulate mineralocorticoid receptor causing hyperaldosteronism
- Cancer chemotherapy agents - antiangiogenic drugs - VEGF inhibitors such as bevacizumab, and tyrosine kinase inhibitors such as sunitinib and sorafenib
- Immunosuppressant like cyclosporine.
- Erythropoietin
- Vitamins and herbal drugs such as ginseng, ephedra, and mahuang.

Substance abuse

Alcohol is one of the most commonly abused agents causing hypertension. Alcohol causes hypertension through multiple mechanisms. Increased sympathetic activity, cortisol release, endothelial injury, and activation of renin-angiotensin system, activation of endothelin, loss of endothelial nitric oxide release, and activation of calcium channels have been proposed.

The treatment is cessation or reduction in alcohol use, ACEI/ARB, and calcium channel blockers.[13] Cocaine, methamphetamine is some of the other agents causing hypertension.

Miscellaneous

ACTH producing lung tumors, brain neoplasms can cause hypertension.

Carcinoid syndrome can cause flushing with hypertension.

Guillain-Barre syndrome, tetraplegia due to autoimmune and loss of CNS control respectively can cause neurogenic hypertension.

Conclusion

Secondary hypertension needs an age-based approach in the evaluation. An awareness of common and rare disorders is required to make the correct diagnosis. A careful history of symptoms, family history of rare disorders, a careful clinical examination, and judicious use of diagnostic tests can unravel the underlying cause in many patients and help to decrease the incidence of a missed diagnosis.

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