CLINICAL
JOURNAL OF HYPERTENSION

EDITOR-IN-CHIEF
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OFFICIAL PUBLICATION OF

Hypertension Society India
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www.hsindia.org

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Are Genomics Essential in Essential Hypertension?

Nihar Mehta

The pathophysiology of Essential Hypertension is still elusive to physicians. The interplay between genetic and environmental factors result in hypertension. Certain facts about hypertension kindle the interest in the geneticists, a few of them being that hypertension is 2.4 times more common in people with both hypertensive parents[1] and family and twin studies have shown that the heritability of high blood pressure to be as high as 30-50%.[2,3] There is no 'Primary Hypertension Gene' which can be labeled the culprit for essential hypertension. The contribution of genes to hypertension is definite but the extent of effect they have on the actual blood pressure is debatable.

Essentially, blood pressure regulation is influenced by genetics in two fundamental ways.[4-6]

1. **Polygenic contribution to Essential Hypertension**: Multiple genetic variants (hundreds or thousands of single nucleotide polymorphisms - SNPs) can have a small individual effect on blood pressure to the tune of about 1 mmHg systolic and 0.5 mmHg diastolic. These are modulated by environmental factors like age, sex, body mass index, salt consumption, insulin resistance, dyslipidemia, among others, resulting in nothing more than a

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modest contribution of genetics to blood pressure. Genes that code components of the renin-angiotensin-aldosterone system (RAAS), angiotensinogen, angiotensin-converting enzyme (ACE) polymorphisms, AT_1 receptor, aldosterone synthase, atrial natriuretic peptide, and the β_2 adreno-recepto, may be related to the genesis of hypertension and to salt sensitivity of blood pressure.

2. **Monogenic hypertension**: Certain mutations can confer hypertension to individuals or families which is called Monogenic hypertension and this is appropriately labeled as Secondary Hypertension. Some examples are congenital adrenal hyperplasia due to 11-β-hydroxylase deficiency or 17-α-hydroxylase deficiency, Gordon's syndrome, Liddle's syndrome, etc. Most of these disorders are due to genetic defects affecting the kidney or mineralocorticoid pathway. Conversely, rare mutations lower the blood pressure such as the loss-of-function mutation of the thiazide-senitive Na-Cl co-transporter in Gitelman Syndrome. Monogenic hypertension contributes to <2% of hypertension.

Recent studies use markers to rapidly scan the genome to detect loci of blood pressure (hypertension loci) rather than individual genes using dense genotyping chips. Some studies also suggest the genetic determinants
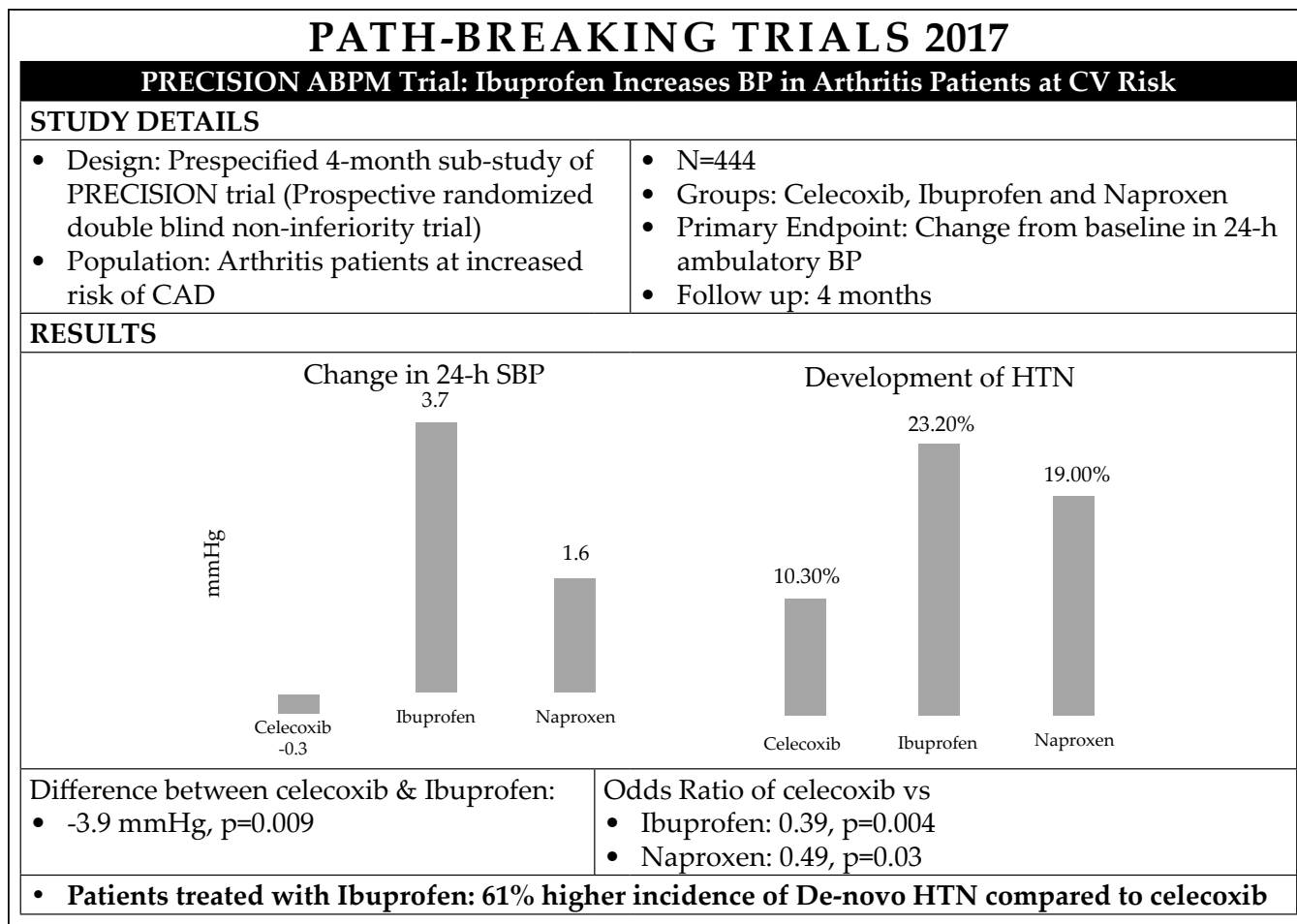
of target organ damage due to hypertension such as LV mass, nephopathy, strokes and ischemic heart disease.[7]

This edition of the Clinical Journal of Hypertension introduces the section on "Basics in Hypertension" with a detailed review of the "Genetics of Hypertension", especially focusing on the genetics of essential hypertension.

At present, genomic studies are not useful in predicting the risk of an individual to develop hypertension. However, in the future, it may be possible to predict the risk of hypertension, risk of target organ damage and the likely responders and non-responders to certain classes of antihypertensive drugs.

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PATH-BREAKING TRIALS 2017

PRECISION ABPM Trial: Ibuprofen Increases BP in Arthritis Patients at CV Risk

STUDY DETAILS

• Design: Prespecified 4-month sub-study of PRECISION trial (Prospective randomized double blind non-inferiority trial) • Population: Arthritis patients at increased risk of CAD	• N=444 • Groups: Celecoxib, Ibuprofen and Naproxen • Primary Endpoint: Change from baseline in 24-h ambulatory BP • Follow up: 4 months

RESULTS

Change in 24-h SBP

- Celecoxib: -0.3
- Ibuprofen: 3.7
- Naproxen: 1.6

(mmHg)

Development of HTN

- Celecoxib: 10.30%
- Ibuprofen: 23.20%
- Naproxen: 19.00%

Difference between celecoxib & Ibuprofen: • -3.9 mmHg, p=0.009	Odds Ratio of celecoxib vs • Ibuprofen: 0.39, p=0.004 • Naproxen: 0.49, p=0.03

• **Patients treated with Ibuprofen: 61% higher incidence of De-novo HTN compared to celecoxib**

Hypertensive Encephalopathy

Bhupendra Chaudhary[1], Amitabh Gautam[2]

Hypertensive encephalopathy is a neurological dysfunction induced by malignant hypertension. The term "hypertensive encephalopathy" was introduced to describe this type of encephalopathy by Oppenheimer and Fishberg in 1928. Hypertensive encephalopathy refers to the transient migratory neurologic symptoms that are associated with the malignant state in a hypertensive emergency and the clinical symptoms are usually reversible with prompt initiation of therapy. Hypertensive encephalopathy occurs in eclampsia, acute nephritis and crises in essential hypertension. Symptoms of hypertensive encephalopathy include headache, restlessness, nausea, disturbances of consciousness, seizures, bleeding in the retina, and papilledema. Focal brain lesions may be associated with specific neurological symptoms. These neurological impairments may culminate in a coma if not treated properly and adequately.

EPIDEMIOLOGY

Of the all people with hypertension, less than 1% develop a hypertensive emergency. The morbidity and mortality associated with hypertensive encephalopathy are related to the degree of target-organ damage. Without treatment, the 6-month mortality for hypertensive emergencies is 50%, and the 1-year mortality approaches 90%.

Hypertensive encephalopathy mostly occurs in middle-aged individuals who have a long-standing history of hypertension. Hypertension in general is more prevalent in men than in women. The frequency of hypertensive encephalopathy in various ethnic groups corresponds to the frequency of hypertension in the general population. Hypertension is more prevalent in black people, exceeding the frequency in other ethnic minority groups. The incidence of hypertensive encephalopathy is lowest in white people.

SIGNS AND SYMPTOMS

Hypertensive encephalopathy is most commonly encountered in young and middle-aged people who suffer from hypertension. Overall, the condition is rare even among hypertensive patients. Different clinicians reported that from 0.5 to 15% of patients with malignant hypertension developed hypertensive encephalopathy. With the development of methods for detection and treatment of hypertension, hypertensive encephalopathy has been becoming more rare.

Symptoms of hypertensive encephalopathy typically start to occur 12–48 hours after a sudden and sustained increase in blood pressure. The first manifestation of these symptoms is a severe headache. Headache

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occurs in more than 75% of patients. The patient becomes restless. Alterations in consciousness may follow several hours later, which include impaired judgement and memory, confusion, somnolence and stupor. If the condition is not treated, these neurological symptoms may worsen and ultimately turn into a coma. Other symptoms may include increased irritability, vomiting, diplopia, seizures, twitching and myoclonus of the limbs. Alterations in vision (vision blurring, hemivisual field defects, color blindness,cortical blindness) are common. Hemiparesis, intracerebral hemorrhage, aphasia may also occur, but they are less common. So, in the evaluation of an encephalopathic patient, it is vital to exclude systematic disorders and various cerebrovascular events that may present with a similar constellation or clinical findings.

PATHOPHYSIOLOGY

The clinical manifestations of hypertensive encephalopathy are due to increased cerebral perfusion from the loss of blood-brain barrier integrity, which results in exudation of fluid into the brain. In normotensive individuals, an increase in systemic blood pressure over a certain range (ie, 60-125 mm Hg) induces cerebral arteriolar vasoconstriction, thereby preserving a constant cerebral blood flow (CBF) and an intact blood-brain barrier.

In chronically hypertensive individuals, the cerebral autoregulatory range is gradually shifted to higher pressures as an adaptation to the chronic elevation of systemic blood pressure. This adaptive response is overwhelmed during a hypertensive emergency, in which the acute rise in systemic blood pressure exceeds the individual's cerebral autoregulatory range, resulting in hydrostatic leakage across the capillaries within the central nervous system (CNS). Brain MRI scans have shown a pattern of typically posterior (occipital greater than frontal) brain edema that is reversible. This usually is termed reversible posterior leukoencephalopathy or posterior reversible encephalopathy syndrome (PRES).

With persistent elevation of the systemic blood pressure, arteriolar damage and necrosis occur. The progression of vascular pathology leads to generalized vasodilatation, cerebral edema, and papilledema, which are clinically manifested as neurologic deficits and altered mentation in hypertensive encephalopathy.

ETIOLOGY

The most common cause of hypertensive encephalopathy is abrupt blood pressure elevation in a chronically hypertensive patient. Other conditions that can predispose a patient to elevated blood pressure and cause the same clinical situation include the following :

- Chronic renal parenchymal disease
- Acute glomerulonephritis
- Renovascular hypertension
- Sudden withdrawal of hypertensive agents (eg, clonidine)
- Encephalitis, meningitis
- Pheochromocytoma, renin-secreting tumors
- Sympathomimetic agents (eg, cocaine, amphetamines, phencyclidine [PCP], and lysergic acid diethylamide [LSD])
- Eclampsia and preeclampsia
- Head trauma, cerebral infarction
- Collagen-vascular disease
- Autonomic hyperactivity
- Vasculitis
- Ingestion of tyramine-containing foods or tricyclic antidepressants in combination with monoamine oxidase inhibitors (MAOIs)

TREATMENT

Approach Considerations

In patients without hypertension, cerebral autoregulation preserves a relatively constant cerebral blood flow (CBF) at a mean arterial pressure (MAP) range of 60-90 mm Hg. In chronically hypertensive patients, autoregu-

lation is altered and shifted upward to maintain a relatively constant CBF at a higher MAP range.

When therapy is initiated, it is important to consider the baseline blood pressure in order to avoid excessive blood pressure reduction and prevent cerebral ischemia. It is usually safe to reduce MAP by 25% and to lower the diastolic blood pressure to 100-110 mm Hg. This level of BP control will allow gradual healing of the necrotizing vascular lesions. More aggressive hypotensive therapy is both unnecessary and may reduce the blood pressure below the autoregulatory range, possibly leading to ischemic events (such as stroke or coronary artery disease).

Acute monitoring in an intensive care unit (ICU) with arterial blood pressure monitoring is required for adequate titration of pharmacologic agents and monitoring of end-organ function. Potential complications of medical therapy (e.g, overzealous reduction in blood pressure and adverse effects or toxicity of pharmacologic therapy) must be watched for.

Deterioration of clinical status despite therapy warrants immediate and further investigation into other possible etiologies or reevaluation of therapy for worsening hypertensive encephalopathy.

Pharmacological Therapy

Pharmacologic agents selected for use in hypertensive encephalopathy should have few or no adverse effects on the central nervous system (CNS). Avoid agents such as clonidine, reserpine, and methyldopa. Although the clinical impact of diazoxide has not been determined, this agent is avoided because of the impact of decreased CBF. An increasing number of authorities are considering labetalol, nicardipine, and esmolol as preferred initial agents.

Labetalol provides a steady consistent drop in blood pressure without compromising CBF. It is frequently used as initial therapy as intravenous bolus or infusion. Because of its nonselective beta-blocking properties, labetalol should be avoided in severe reactive airway disease and cardiogenic shock.

Nicardipine is a second-generation dihydro-pyridine-derivative calcium channel blocker, which has high vascular selectivity and strong cerebral and coronary vasodilatory activity. It has been shown to increase stroke volume and coronary blood flow.

Clevidipine, a short acting dihydropyridine calcium blocker. It reduces blood pressure without affecting cardiac filling pressures or causing reflex tachycardia.

Nitroglycerin has been used to provide a rapid reduction in elevated blood pressure complicating myocardial ischemia. The reduction in blood pressure may be severe and can cause further complications due to venodilatory effects in volume-contracted individuals.

Nitroprusside sodium and hydralazine pose a theoretical risk of intracranial shunting of blood. Accordingly, these agents should be avoided in patients suspected of having increased intracranial pressure (ICP), because the potential intracerebral shunting of blood can increase the ICP. Hydralazine has a limited role in this setting, owing to reflex tachycardia, and it should not be used in patients with suspected coronary artery disease (CAD). Diuretics should also not be used in these patients unless there is clear evidence of volume overload. This is due to pressure natriuresis that occurs and leaves these patients volume depleted. Volume repletion by itself can sometimes lower the blood pressure.

Oral agents : A slower onset of action and an inability to control the degree of BP reduction has limited the use of oral antihypertensive agents in the therapy of hypertensive crises. They may, however, be useful when there is no rapid access to the parenteral medications described above. Both sublingual nifedipine and sublingual captopril can substantially lower the BP within 10 to 30 minutes in many patients. A more rapid response is seen when liquid nifedipine is swallowed.

The major risk with oral agents is ischemic symptoms (e.g., angina pectoris, myocardial infarction, or stroke) due to an excessive and

uncontrolled hypotensive response. Thus, their use should generally be **avoided** in the treatment of hypertensive crises if more controllable drugs are available.

Now despite of all efforts if neurologic deterioration worsens with therapy, it is necessary to reconsider the extent of blood pressure reduction or to consider alternate diagnoses.

Once the BP is controlled, the patient should be switched to oral therapy, with the diastolic pressure being gradually reduced to 85 to 90 mmHg over two to three months. The initial reduction to a diastolic pressure of approximately 100 mmHg is often associated with a modest worsening of renal function; this change, however, is typically transient as the vascular disease tends to resolve and renal perfusion improves over one to three months. Antihypertensive therapy should not be withheld in this setting unless there has been an excessive reduction in BP. A change in medication, however, is indicated if the decline in renal function is temporally related to therapy with an angiotensin (ACE) converting enzyme inhibitor or angiotensin II receptor blocker, which can interfere with renal autoregulation and produce acute renal failure in patients with bilateral renal artery stenosis.

Prevention

Recommend lifestyle modifications, including weight reduction to decrease the patient's body mass index (BMI) to less than 27, moderation of alcohol and sodium intake, increasing physical activity, and avoidance of tobacco products.

Discharge patients on antihypertensives that were effective in maintaining an adequate blood pressure range during hospitalization. Emphasize the importance of adhering to antihypertensive therapy and scheduling reassessment at regular intervals to modify failing regimens.

Long-Term Monitoring

Because hypertension is a chronic problem, regularly reassessment is vital. Adequate control of hypertension is essential in preventing the progression of target-organ disease. High blood pressure has been associated with a rapid rate of cognitive decline and an increased risk of cardiac and neurologic events.

To guide the formulation of a more effective treatment plan, document prior hypertensive medication regimens that have failed.

Prognosis

Patients with hypertensive encephalopathy who are promptly treated usually recover without deficit. However, if treatment is not administered, the condition can lead to permanent neurological deficit or even death.

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Childhood Hypertension: An Overlooked Entity

Anuj Rastogi[1], Prashant Bendre[2], Bhupendra Chaudhary[3]

INTRODUCTION

It has become clear that hypertension (HTN) begins in childhood and adolescence and that it contributes to the early development of cardiovascular disease (CVD). In hypertensive adults, multiple randomized trials have shown that reduction of blood pressure (BP) by antihypertensive therapy reduces cardiovascular morbidity and mortality. Based upon these observations, identifying children with HTN and successfully treating their HTN should have an important impact on long-term outcomes of CVD. The etiologies of hypertension in children and adolescent are quite different than the adult population but the management strategies remains almost the same. The non-pharmacological methods to control blood pressure also holds true in this subset of population but relatively lesser intensified as compare to their counterparts. As a good number of children having underline hypertension remains undetected, they generally add the substantial burden to cardiovascular disease profile in their later age.

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DEFINITION

In children, the following definitions based upon the 2004 National High Blood Pressure Education Program Working Group (NHBPEP) are used to classify blood pressure (BP) measurements in the United States. BP percentiles are based upon gender, age, and height. The systolic and diastolic BPs are of equal importance; if there is a disparity between the two, the higher value determines the BP category. The age and height-specific blood pressure percentiles may be determined using calculators for boys for girls :

- Normal BP - Both systolic and diastolic BP <90th percentile.

- Prehypertension - Systolic and/or diastolic BP >90th percentile but <95th percentile or if BP exceeds 120/80 mmHg (even if <90th percentile for age, gender, and height).

- Hypertension - Hypertension (HTN) is defined as either systolic and/or diastolic BP >95th percentile measured on **three** or more separate occasions. The degree of HTN is further delineated by the two following stages.

  - **Stage 1 HTN -** Systolic and/or diastolic BP between the 95th percentile and 5 mmHg above the 99th percentile.

  - **Stage 2 HTN -** Systolic and/or diastolic BP >99th percentile plus 5 mmHg,

Table 1: Causes of secondary hypertension in children and adolescents

Renal disease	Psychologic causes
Pyelonephritis	Mental stress
Renal parenchymal disease	Anxiety
Congenital anomalies	**Pharmacologic causes**
Reflux nephropathy	Sympathomimetics
Acute glomerulonephritis	Corticosteroids
Henoch-Schonlein purpura	Stimulants
Renal trauma	Oral contraceptives
Hydronephrosis	Anabolic steroids
Hemolytic uremic syndrome	Cocaine
Renal stones	Phencyclidine (PCP)
Nephrotic syndrome	Licorice
Wilm's tumor	Nicotine
Hypoplastic kidney	Caffeine
Polycystic kidney disease	**Vascular disease**
Endocrine disease	Renal artery abnormalities
Hyperthyroidism	Renal vein thrombosis
Congenital adrenal hyperplasia	Coarctation of the aorta
Cushing syndrome	Patent ductus arteriosus
Primary aldosteronism	Arteriovenous fistula
Primary hyperparathy-roidism	**Other causes**
Diabetes mellitus	Neuroblastoma
Hypercalcemia	Heavy metal poisoning
Pheochromocytoma	Acute pain
Neurologic causes	Collagen vascular diseases
Increased intracranial pressure	Neurofibromatosis
Guillain-Barre syndrome	Tuberous sclerosis

ETIOLOGY

Childhood HTN is also divided into two categories depending upon whether or not an underlying cause can be identified :

• Primary HTN - No underlying cause is identified.

• Secondary HTN - An identifiable cause is determined. In children with secondary HTN, the underlying disorder may be curable with complete resolution of HTN.

Primary hypertension — Primary HTN is the most common cause of HTN in older children and is a diagnosis of exclusion. It is more likely in children who are postpubertal, have a family history of HTN, are overweight or obese, or have only mild hypertension (blood pressure [BP] at or just above the 95th percentile).

A family history of HTN is present in as many as 70 to 80 percent of all patients with primary HTN (also referred to as essential HTN), which has no identifiable underlying etiology, and in approximately 50 percent of hypertensive children.

In patients with primary HTN, elevated BP is thought to result from the interaction of multiple genes and environmental factors. It has been estimated that genetic factors account for approximately 30 percent of the variation in BP in various populations and as much as 60 to 70 percent of HTN in families.

Secondary hypertension — There are a number of causes of secondary HTN and specific symptoms and findings may point to a particular disorder. The three most common causes are renal disease, endocrinal causes and renovascular diseases. Almost all children younger than 15 years of age have secondary cause, whereas 75 percent of adolescents use to have primary HTN (Tables 1 & 2).

1. **Renal parenchymal disease** — A variety of intrinsic renal disorders is associated with HTN and includes the following :

   • **Glomerulonephritis -** HTN is a manifestation of both chronic and acute glomerulonephritis (GN). In children, the most common form of acute GN is post-streptococcal GN, which follows after a streptococcal infection. Henoch-Schonlein purpura (IgA vasculitis) can present with renal manifestations including HTN. In children, chronic glomerular disorders associated with elevated BP include IgA nephropaathy, membranoproliferative GN, or lupus nephritis.

   In children with glomerulonephritis, the most common mechanisms of HTN are volume expansion due to salt and water retention (as in acute poststrep-tococcal glomerulonephritis) and activation of the renin- angiotensin system. Other common presenting

Table 2: Distinguishing clinical features between primary (essential) and secondary pediatric hypertension

Clinical features	Primary HTN	Secondary HTN
Age : Prepubertal		HTN in prepubertal children is more likely due to secondary HTN
Adolescents	Adolescents are more likely to have primary HTN	
Severity	Usually stage 1 HTN	Severe HTN (defined as stage 2) is usually associated with secondary HTN
Diastolic HTN		Diastolic HTN is more likely to be associated with secondary HTN
Nocturnal HTN		Nocturnal HTN is more likely to be associated with secondary HTN
Overweight/ obesity	Overweight or obese children/ adolescents are more likely to have primary HTN	
Family history of HTN	Children with a positive family history of primary HTN are more likely to have primary HTN	Family history may be positive in some cases of secondary HTN due to a monogenic cause (eg, autosomal dominant polycystic kidney disease)
Symptoms of underlying disorder	Patients with primary HTN are typically asymptomatic	Patients with secondary HTN often have other symptoms related to the underlying cause (eg, headache, sweating, and tachycardia due to catecholamine excess in patients with pheochromocytoma)

features of glomerular disorders include hematuria, oliguria, peripheral edema, and an elevated serum creatinine or BUN.

- Renal parenchymal scarring can be a sequelae of acute pyelonephritis and may be associated with vesicoureteral reflux. It is also seen in children with congenital anomalies of the kidney and urinary tract, and those with irreversible renal injury from hemolytic uremic syndrome.

- **Polycystic kidney disease -** Polycystic kidney disease (PKD) is due to two genetic disorders, autosomal dominant and autosomal recessive PKD, that involve the formation of renal cysts. HTN is a common presenting sign in children with the recessive form of PKD.

- **Chronic renal failure -** Chronic renal failure (CRF) of any cause can be associated with HTN because of volume expansion. In addition, children who have undergone renal transplantation are at increased risk for HTN due to several different mechanisms including rejection or the administration of drugs that increase BP.

2. **Renovascular disease —** HTN due to renovascular disease is due to a decrease in renal blood flow resulting in increased plasma levels of renin, angiotensin, and aldosterone. Children with renovascular disease generally have stage 2 HTN.

Causes of renovascular disease in children include the following :

- Fibromuscular dysplasia - Fibromuscular dysplasia is the most common etiology of renovascular disease. It is characterized by arterial stenosis due to a non-inflammatory, non-atherosclerotic process.

- Umbilical arterial catheterization - During the newborn period, catheter-

ization of the umbilical artery may lead to a clot in the renal artery resulting in renal arterial injury and stenosis.

- Other causes of renovascular disease include neurofibromatosis, arteritis, renal artery hypoplasia, and midaortic syndrome (segmental narrowing of the proximal abdominal aorta).

Renal tubular disease — Rare Monogenic diseases in which tubular reabsorption of sodium or chloride is increased are associated with increased vascular volume and HTN, such as Liddle's syndrome, Type 1 pseudohypoaldosteronism, Type 2 pseudohypoaldosteronism, or Gordon's syndrome.

3. **Endocrinologic disease —** Endocrinologic conditions associated with HTN include the following :

- Catecholamine excess — Catecholamine excess that results in HTN occurs in patients with pheochromocytoma and neuroblastoma, and those who use sympathomimetic drugs including phenylpropanolamine, cocaine, amphetamines, phencyclidine, epinephrine, phenylephrine, and terbutaline and the combination of a monoamine oxidase (MAO) inhibitor plus ingestion of tyramine-containing foods.

- Corticosteroid excess — Corticosteroid excess is more commonly due to exogenous administration of glucocorticoids and rarely due to endogenous production of either glucocorticoids or mineralocorticoids. In both settings, corticosteroid excess results in HTN.

  - Corticosteroid excess may be seen in patients with Cushing's syndrome due to hypersecretion of adrenocorticotropic hormone (ACTH).

  - Mineralocorticoid excess that result in HTN may be seen in patients with congenital adrenal hyperplasia.

Other rare causes of HTN due to mineralocorticoid excess include aldosterone-secreting tumors and the monogenic disorder of glucocorticoid-remediable aldosteronism.

- Other endocrinologic disorders — Other endocrinologic abnormalities associated with HTN include thyroid disorders (hypothyroidism and hyperthyroidism), and hypercalcemia (e.g. hyperparathyroidism).

4. **Cardiac disease —** Coarctation of the aorta is the primary cardiac cause of HTN. The classic findings are HTN in the upper extremities, diminished or delayed femoral pulses, and low or unobtainable arterial blood pressure in the lower extremities. The diagnosis is confirmed by echocardiogram.

5. **Prenatal and neonatal factors —** There is increasing evidence that prenatal and neonatal factors contribute to higher BP. There are data demonstrating a role for low birth weight in the development of primary HTN.

In addition, a systematic review reported in utero exposure to preeclampsia was associated with an increase in systolic (mean 2.4 mmHg) and diastolic (mean 1.4 mmHg) BP, as well as an increase in BMI (mean 0.62 kg/m^2)

However, for children with chronic kidney disease, there appears to be no additional effect of an abnormal birth history on BP. This was illustrated in a report from the Chronic Kidney Disease in Children Study that found no difference in BP or the rate of chronic kidney disease (CKD) progression between patients with an abnormal birth history (birth weight <2500 g, gestational age <36 weeks, or small for gestational age) and those with a normal birth history.

Comorbid risk factors and diseases — HTN is one of several risk factors that increase the risk of premature atherosclerosis in childhood and of cardiovascular disease (CVD) in adults. These risk factors (eg, HTN, overweight/

obesity, dyslipidemia, and a family history of premature CVD) do not generally occur in isolation but are usually found concurrently, which further increases the likelihood of premature atherosclerosis and CVD. In addition, several childhood diseases such as type 1 and type 2 diabetes mellitus, and chronic kidney disease are associated with accelerated atherosclerosis and CVD.

INITIAL EVALUATION — The initial evaluation of the child with hypertension (HTN) includes history, physical examination, and laboratory tests and procedures.

History and physical examination — Symptoms consistent with hypertensive emergencies include headache, seizures, changes in mental status, vomiting, focal neurologic complaints, visual disturbances, and cardiovascular complaints indicative of heart failure (such as chest pain, palpitations, cough, or shortness of breath). These children require emergent evaluation and treatment.

Secondary versus primary hypertension — Secondary hypertension should be suspected in children with one or more of the following findings :

- Prepubertal, particularly younger than 10 years of age.

- A thin child with a negative family history for HTN.

- An acute rise in blood pressure (BP) above a previously stable baseline.

- Severe HTN defined as stage 2 HTN (BP >5 mmHg above the 99th percentile)

- Stage 1 HTN (BP > 95th percentile but less than stage 2) with finding(s) on history or physical examination that suggests systemic disease or a specific secondary etiology of HTN.

- Specific ambulatory blood pressure patterns, such as sustained diastolic hypertension, nocturnal hypertension, and/or blunted nocturnal dipping.

- Past history of urinary tract infection, especially pyelonephritis, or underlying congenital kidney or urologic anomalies raises the possibility of renal scarring.

- Symptoms suggestive of catecholamine excess include headache, sweating, and tachycardia in addition to HTN.

- Ambiguous genitalia may be suggestive of congenital adrenal hyperplasia with excess endogenous secretion of androgens and mineralocorticoids. Children with mineralocorticoid excess may develop hypokalemia.

- Edema and hematuria may be indicative of renal parenchymal disease. Initial laboratory testing demonstrating an abnormal urinalysis or elevated serum creatinine add further support for an intrinsic renal disease process.

- Patients with glomerulonephritis due to systemic disorders such as Henoch-Schonlein purpura (IgA vasculitis) or systemic lupus erythematosus have other clinical findings including arthritis, rash, and abdominal pain (the latter especially in Henoch-Schonlein purpura).

- A family history of chronic or congenital renal disease (such as polycystic kidney disease), or other genetic conditions that are associated with HTN, such as neurofibromatosis or tuberous sclerosis.

- Perinatal history including :
  - Umbilical arterial catheterization (UAC) as a neonate. UAC is a predisposing factor for renovascular disease.
  - Oligohydramnios
  - Perinatal anoxia

- The presence of an abdominal bruit raises the possibility of renovascular disease, but its absence does not exclude the diagnosis.

- The findings of hypertension in the upper extremities and low or unobtainable blood pressure in the lower extremities, significant difference between right and left arm BP, and diminished or delayed femoral pulses are suggestive of coarctation of the aorta, the primary cardiac cause of hypertension.

Physical findings of end-organ damage — In addition to obtaining height and weight, and calculating BMI, the physical examination should include a retinal examination to detect any retinal vascular changes due to HTN. Laterally displaced Apex beat may indicate left ventricular hypertrophy (LVH).

Laboratory evaluation and imaging — Initial laboratory evaluation in all children with persistent HTN is directed at determining the etiology of HTN, identifying other CVD risk factors, and detecting end-organ damage. The following approach is recommended by the 2004 National High Blood Pressure Education Program Working Group (NHBPEP) and the 2016 European Hypertension Society guidelines.

- Measurement of serum BUN, creatinine, and electrolytes, and collection of urine for urinalysis. These tests permit quick assessment of renal function and abnormalities in glucose (eg, diabetes mellitus), potassium homeostasis (eg, chronic kidney disease or congenital adrenal hyperplasia), or monogenic disorders (Liddle's syndrome, glucocorticoid remediable hyperaldosteronism etc). An abnormal urinalysis and/or an elevation in serum creatinine are suggestive of underlying renal disease.

- Complete blood count, looking for anemia that may reflect chronic diseases such as vasculitis and chronic kidney disease, or polycythemia.

- Measurement of fasting plasma glucose and lipids to identify children with diabetes mellitus and dyslipidemia. These tests should be performed in prehypertensive children who are obese, have a family history of premature CVD, or have chronic kidney disease.

- An echocardiogram to identify children with left ventricular hypertrophy (LVH) because clinical parameters, such as the severity of HTN, and electrocardiography do not accurately predict LVH. LVH is the most prominent manifestation of end-organ damage from HTN. LVH has been reported in 30 to 40 percent of children and adolescents with HTN and if present, is an indication to initiate or intensify antihypertensive therapy. Echocardiography should also be performed in prehypertensive children with obesity, hyperlipidemia, diabetes mellitus, or chronic kidney disease.

- Renal ultrasonography is used to determine the presence of both kidneys and presence of any other congenital anomaly, or disparate renal size.

Therapeutic interventions — Ambulatory treatment for persistent childhood HTN includes both non-pharmacologic and pharmacologic interventions.

- Non-pharmacologic therapy (i.e, lifestyle changes) includes weight reduction for children who are overweight, a regular aerobic exercise regimen, dietary measures (eg, salt restriction), and avoidance of alcohol consumption, caffeine, energy drinks, and smoking and incorporation of relaxation techniques in daily life.

- Pharmacologic agents used frequently in children that are efficacious and safe include thiazide diuretics, angiotensin converting enzyme (ACE) inhibitors, beta blockers, and calcium channel blockers (CCBs).

- Treatment is directed towards achieving the following blood pressure (BP) target goals recommended by the National High Blood Pressure Education Program Working Group (NHBPEP) and the European Society of Hypertension (ESH).

  - In children and adolescents with HTN and with no evidence of end-organ damage or comorbid CVD conditions, the targeted goal for blood pressure (BP) is less than the 95th percentile based upon age, height, and gender. The age and height-specific blood pressure percentiles may be determined using calculators for boys or for girls.

  - If there are comorbid CVD risk

factors (eg, obesity or dyslipidemia), or diseases associated with CVD (eg, diabetes mellitus), or chronic kidney disease, the BP targeted goal is lowered to below the 90th percentile for age, height, and gender and, for adolescents, a target BP <120/80.

Choice of antihypertensive agent — There are no long-term clinical outcome measures to evaluate the comparative effectiveness of specific antihypertensive drugs in children with HTN. Based upon data from adult studies, the following underlying medical conditions be treated with a specific class of antihypertensive drugs.

- In adolescents with primary HTN without end-organ damage, the choice of medication is dictated by the clinical setting and patient compliance. Low-dose thiazide diuretic therapy is administered to patients who are reliably compliant in taking their medication and adherent to sodium restriction. In other patients, ACE inhibitors/angiotensin-receptor blockers (ARBs) or CCBs are used as the first antihypertensive agent.

- In children with CKD, we suggest that ACE inhibitors be used as the initial antihypertensive agent. In patients who cannot tolerate ACE inhibitors, ARBs are a reasonable alternative.

- In children with either type 1 or type 2 diabetes mellitus, we suggest that ACE inhibitors be used as the initial antihypertensive agent. In patients who cannot tolerate ACE inhibitors, angiotensin-receptor blockers (ARBs) are a reasonable alternative.

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Alcohol and Hypertension Related Left Ventricular Systolic Dysfunction-Integrated Approach using Echocardiography

Suraj Kumar[1], Rohit Tandon[2], Gurpreet Singh Wander[3]

- Asymptomatic left ventricular systolic dysfunction (ALVSD) is defined as depressed LV systolic function in the absence of heart failure (HF).

- The rationale for early detection of asymptomatic left ventricular systolic dysfunction (ALVSD) is that appropriate pharmacologic therapy can significantly improve outcomes in patients with ALVSD with LV ejection fraction (LVEF) ≤35 to 40 percent. Also, outcomes are better in treated patients with ALVSD than in treated patients with heart failure with reduced ejection fraction.

Hypertension and alcohol abuse have been recognised as two major causes of asymptomatic left ventricular systolic dysfunction in the western world. In PIUMA study 3.6 % and Framingham Heart Study 4-6% participants had asymptomatic Left ventricular systolic dysfunction. the mean age in these studies was 50 to 70 years :

- LVEF ≤54 percent – 12.5 percent

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- LVEF ≤50 percent – 3.3 to 4.7 percent
- LVEF ≤40 percent – 0.9 to 2.1 percent
- LVEF ≤30 percent – 1.4 percent; almost all of these patients with severe LV dysfunction had evidence of coronary heart disease and/or hypertension

Subgroups have been identified that have higher rates of ALVSD with reduced LVEF These include men, older patients, and those with known coronary disease in whom the reported rate has ranged from 4.8 to 8.5 percent

The impact of risk factors on the prevalence of LV systolic dysfunction was illustrated by a screening study of adults ≥45 years of age that included 734 patients with varying risk who were randomly selected from a general practice population and 471 selected from a group deemed to be a high risk as defined by one or more of the following risk factors: ischemic heart disease, hypertension, diabetes mellitus, peripheral arterial or cerebrovascular disease, and excessive alcohol intake. Using echocardiography as the gold standard and defining ALVSD as an LVEF <45 percent, the following findings were noted:

- LV systolic dysfunction was present in
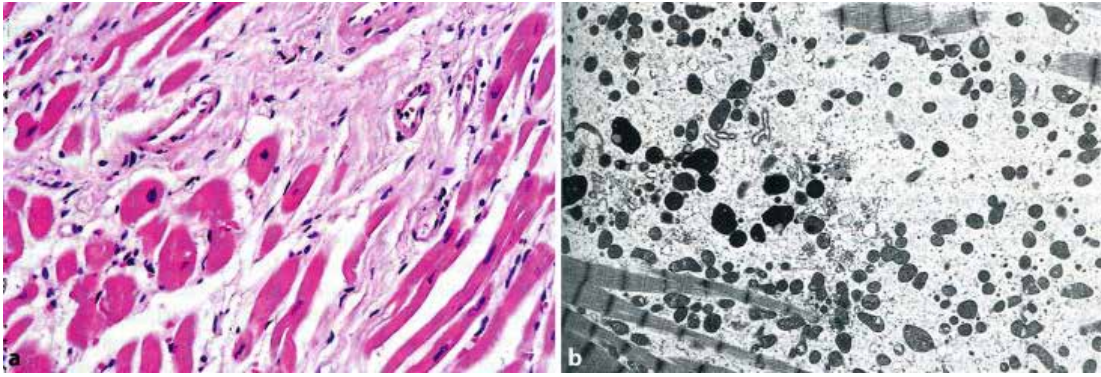
ALCOHOL

Alcohol consumption ↓ *> 90 gms > 5 years*

- Apoptosis (either directly via alcohol or indirectly via ↑ NE levels)
- ↓ synthesis and/or accelerated degradation of contractile proteins
- ↓ myofilament Ca^{2+} sensitivity
- Intrinsic myocyte dysfunction due to mitochondrial and sarcoplasmic dysfunction (due to Ca^{2+} overload, fatty ethyl esters or NE)

Cell drop out and weakly contracting mycocytes

Decreased cardiac output

- LV dilation to increase EDV (preload) to compensate for ↓ cardiac output, however this is may be accompanied by wall thinning due to cell drop out
- Hypertrophy of normal myocytes to compensate for weakly contracting neighboring myocytes

Continued drinking ↓ *> 15 years*

- Progressive LV dilation and wall thinning
- Activation of other neurohormonal systems
- Signs and symptoms of heart failure

Fig. 1 : Myocardial Structural and Functional Changes Associated with chronic alcohol abuse

64 patients, 24 of whom had a general practice diagnosis of heart failure (HF) or LV systolic dysfunction or were taking loop diuretics.

- LV systolic dysfunction was present in 3.5 percent of patients from the general
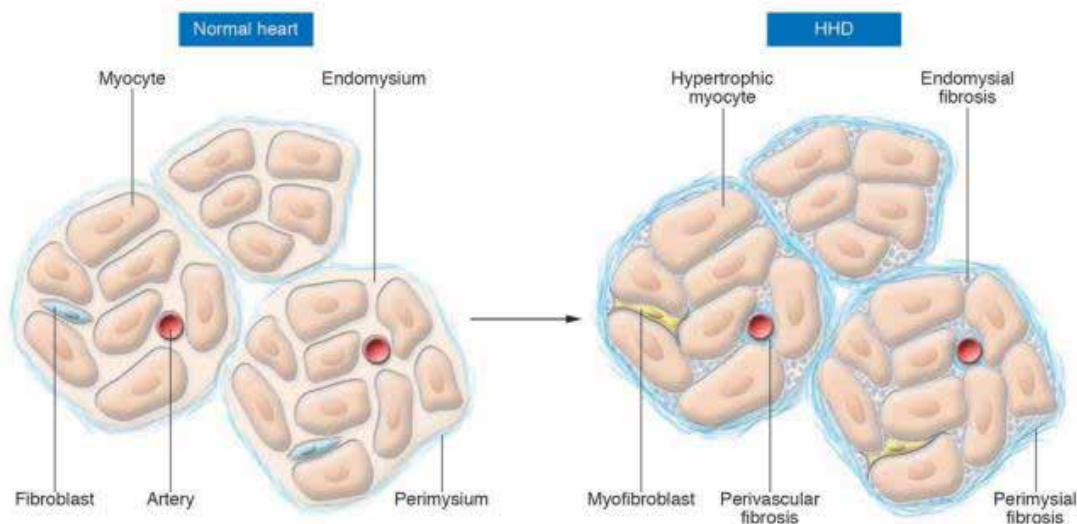
Fig. 2: Structural changes in Hypertensive Heart Disease

practice population; 96 percent of these patients had one or more of the above risk factors.

- LV systolic dysfunction was present in 8.5 percent of high-risk patients (one or more risk factors) compared with 0.2 percent of those at low risk (1 of 444 with no risk factors).

- Influence of western culture on Indian society have led to increased incidence of hypertension and is also facing a challenge of alcohol abuse. In our country during 1992-2012, per capita consumption of alcohol has increased by 55%, it is the third highest increase in the world [1] 30% of Indian population drink alcohol regularly, 11% Indians are moderate to heavy drinkers. Rural population consumption exceeds three times the average Indian consumption.

- Long-term heavy alcohol consumption of any beverage type is the leading cause of alcoholic cardiomyopathy (ACM). Prevalence ranges from 23 to 40% can present with either a preclinical (asymptomatic) or symptomatic stage. Men are more affected than women (14% cases reported in population studies)

- Asymptomatic alcoholic patients with

history of consuming > 90 g/d of alcohol for > 5 years start exhibiting structural changes in cardiomyocyte. The key variable linked to the development of heart failure appears to be the duration of heavy daily alcohol consumption. Alcohol is a causative factor for high blood pressure in up to 11% of men with hypertension in various population studies. Individuals who consume more than two drinks daily are 1.5 to 2 times more likely to have hypertension when compared with age- and sex-matched non drinkers. Heavy consumption and binge drinking leads to a substantial increase in systolic arterial pressure. Histo-pathologically both hypertension and alcohol have differential effects on cardiomyocyte structure and function. Newer Echocardiography modalities viz. Tissue doppler, strain are helpful to identify these changes in preclinical stages.

STRUCTURAL CHANGES WITH HYPERTENSIVE HEART DISEASE

Endomysial network in normal heart, thin layers of perimysium and endomysium surround myocytes and blood vessels walls (Fgure 1).
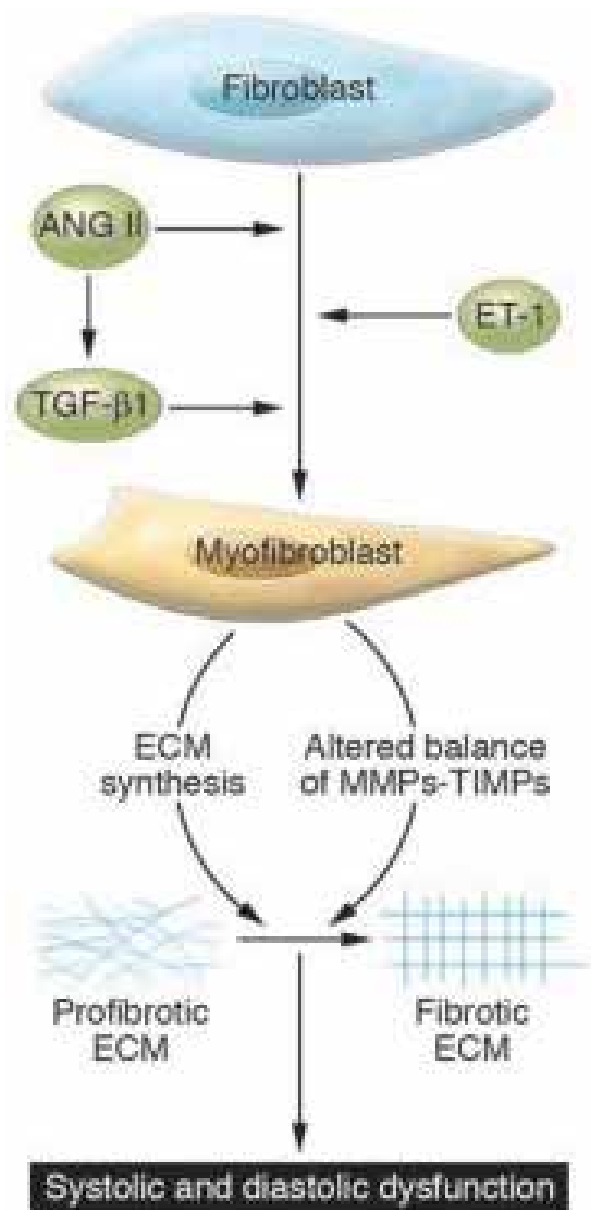
Fig. 3: Transition of Fibroblasts to Myofibroblasts

In HHD, there is hypertrophy of cardiomyocytes and transition of fibroblasts to myofibroblasts. These changes are associated in early disease with perivascular, endomysium and perimysium fibrosis (Figure 2).

MECHANISMS FOR TRANSITION OF FIBROBLASTS TO MYOFIBROBLASTS

Transition of fibroblasts to myofibroblasts is an early event in HHD, regulated in part by increased expression of the hormones of the RAAS system (renin, ANG II, and aldosterone), ET-1, and TGF-β1. Myofibroblasts express a gene program that contributes to a progressive profibrotic state. Changes occur due to an altered balance of MMPs and their inhibitors which lead to a stiffening and functional alterations in myocyte signalling which leads to progressive cardiac dysfunction (Figure 3).

LV hypertrophy is a complex phenotype that predicts adverse cardiovascular outcomes and may not be necessarily considered as an adaptive response to systemic hypertension. LV geometric patterns classified according to LVM, LV volume, and RWT.

For every 39 g m^{-2} increase in LV mass there is 40% rise in the risk of major adverse cardio-vascular events $_{\text{Data :MAVI study}}$

- Considerable inter individual variability exists in development and pattern of LVH in response to afterload secondary to hypertension and is dependent on multiple factors

- Blacks are predisposed to a concentric hypertrophic response compared with whites.

- Increasing age, diabetes, isolated systolic hypertension and women are more likely to develop concentric LVH.

- Obesity and moderate alcohol intake are characterized as a volume-overload state so associated with eccentric hypertrophy

- Subjects with concentric hypertrophy have

    - Higher systolic blood pressures

    - Total peripheral resistance

    - Higher ambulatory blood pressure

Those with eccentric hypertrophy and concentric remodelling are at an intermediate risk between concentric hypertrophy and normal geometry.

NATURAL HISTORY OF LV GEOMETRY IN HYPERTENSION

- In mild hypertension, LVH is usually absent and the first manifestation of hyper-
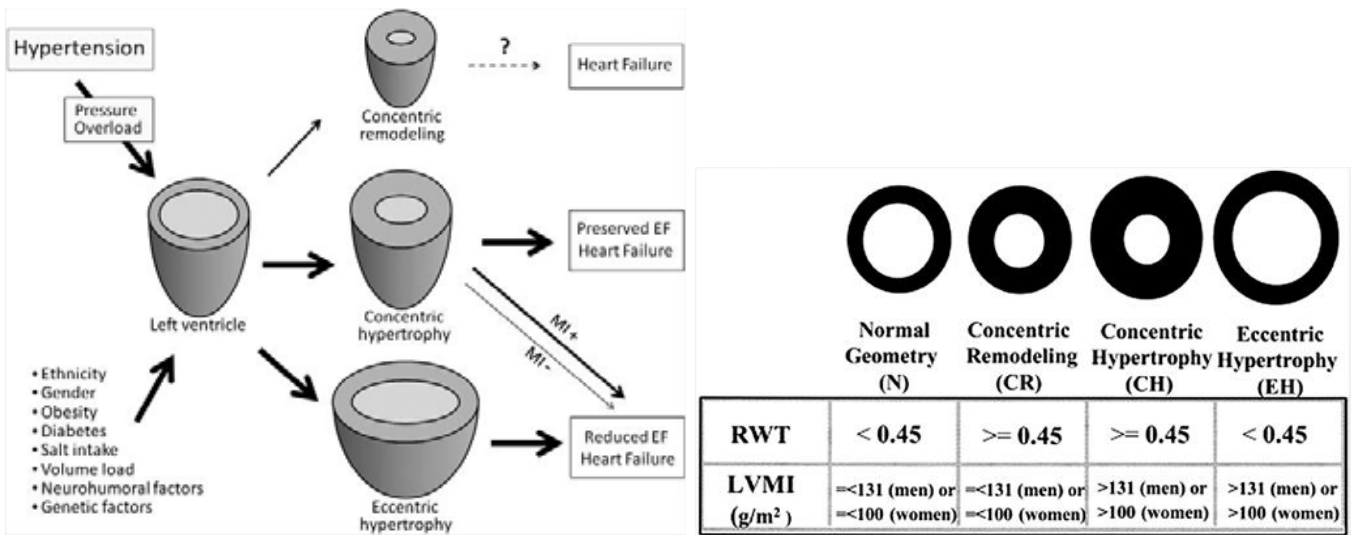
Fig. 4: L.V. Geometry in Hypertensive

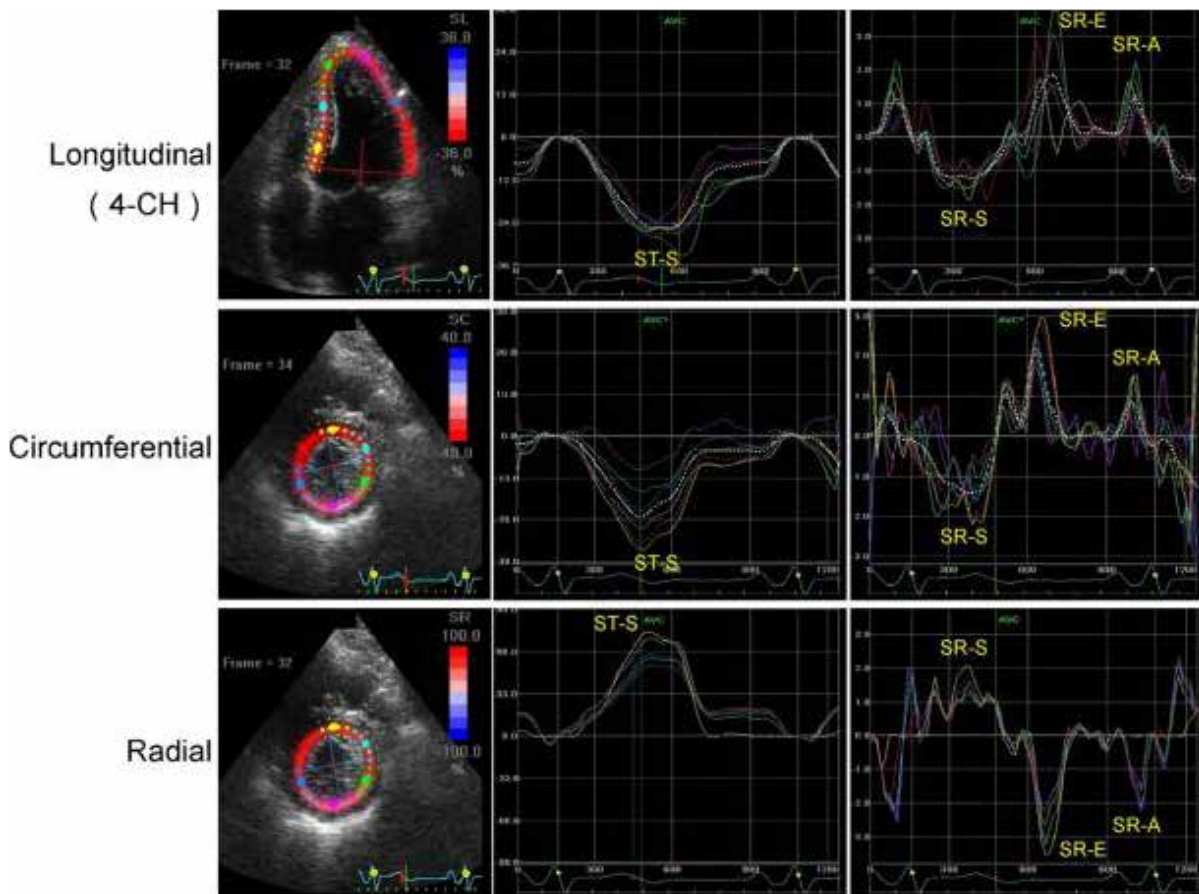|	Normal Geometry (N)	Concentric Remodeling (CR)	Concentric Hypertrophy (CH)	Eccentric Hypertrophy (EH)
RWT	< 0.45	>= 0.45	>= 0.45	< 0.45
LVMI (g/m^2)	=<131 (men) or =<100 (women)	=<131 (men) or =<100 (women)	>131 (men) or >100 (women)	>131 (men) or >100 (women)

Fig. 5: Longitudinal, Circumferential and Radial Strain in Tissue Doppler

tension is concentric remodelling with grade 1 diastolic impairment (impaired relaxation)

• In untreated hypertension, LVH is accompanied by increase in filling pressure and left atrial remodelling

• Eventually, LV dilatation occurs and left ventricular systolic dysfunction ensues

(Figure 4).

TISSUE DOPPLER

- s' helps to differentiate physiological LVH in athletes from LVH secondary to hypertension.

- Mean $s' < 9$ cm/s has shown to discriminate physiological from pathological LVH with a sensitivity of 87% and a specificity of 97%.

- Ratio of E/E' nowadays is used as prime determinant of LVEDP estimation

MYOCARDIAL STRAIN IN HYPERTENSION

- Longitudinal, circumferential and radial strain are impaired in patients with hypertension and concentric hypertrophy (Figure 5).

- LV torsion is preserved

- Peak systolic circumferential strain is an independent predictor related to LV ejection fraction

- Myocardial strain is sensitive in diagnosis of sub-clinical left ventricular systolic dysfunction

Deterioration of systolic longitudinal, circumferential, and radial myocardial deformation in hypertensive patients with preserved left ventricular pump function. (Journal of Cardiology-2010)

BIOMARKERS INDICATIVE OF INCIPIENT HYPERTENSIVE HEART FAILURE

- BNP and NT pro BNP lack sensitivity and specificity for use in hypertensive heart failure

- N-terminal propeptide of procollagen type III (PIIINP), is one of the biomarkers of extracellular matrix remodelling and holds promise for clinical use in hypertensive patients with mild left ventricular systolic dysfunction

CONCLUSION

- Hypertension and alcoholism can cause asymptomatic left ventricular systolic dysfunction both in association and isolation

- Although molecular mechanisms differ but phenotypes of end stage disease are similar.

- It is imperative for the physicians to identify early, the morphological changes occuring in left ventricle

- Echocardiography is the most routinely available clinical tool for physicians in evaluation of these cases

- Its the variety in presentation and different modes of phenotypic variability that exist which needs to be recognised

- Physicians should embrace newer echocardiography modalities (TDI,strain) so as not to miss the subtle cases of left ventricular systolic dysfunction.

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Best Practices in Hypertension-2017

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ABSTRACT

Change is the way of life. Everything in this universe changes, so also the best practices for hypertension keeps on changing to further optimize the results. It is important to bear in mind that the mortality in controlled hypertensive is not similar to a normotensive and is at least two times greater. This occurs due to 2 reasons, atherosclerosis which continues unabated even in controlled hypertensive and fibrosis in the left ventricle, left atrium, aorta and small vessels which contributes to increased morbidity and mortality Therefore the treatment of hypertension should not be BP centric but a disease centric approach should be employed. It is important to bear in mind that the office based readings of BP represents only a snapshot in time with low reproducibility. The ambulatory blood pressure monitoring provides an idea about the 24 hr BP profile. Besides this, it also gives an idea about the dipping patterns of blood pressure, the morning surges and the BP variability which has substantial prognostic and therapeutic implications. The goals of BP control are 140/90 mm Hg. but the SPRINT trial created flutter by showing benefits of add lowering of BP to 120 mm Hg compared to 140. It is important to bear in mind that BP measurement in this trial was unique and never done before ,i.e., unattended, automated, unobstructive with patient relaxing in an AC room for 5 minutes before recording the reading. Therefore it seems the reading of SPRINT 120 mm Hg mm Hg is equivalent to 130 mm Hg, if we record BP of the same patient in the conventional manner in the clinic. Therefore lower goal of 120 mm Hg systolic of SPRINT cannot be applied in real practice as such and 130 mm Hg may be appropriate for hypertensive patients at high cardio vascular risk. Among drugs used for hypertension, CTD and indapamide are preferred over hydrochlorthiazide, Azilsartan the new sartan, has additional advantages of producing greater fall in blood pressure with vasculoprotective properties and new CCBs Cilnidipine and Benedipine has additional advantage over amlodipine in that they provide renoprotection and has minimal chances of edema. Atenolol is out and currently vasodilatory betablockers like nebivolol are used for treatment of hypertension particularly when it is associated with coronary heart disease and heart failure.. Spironolactone is the fourth preferred drug in resistant hypertension. Angiotensin Receptor Neprilysin inhibitor is undergoing evaluation

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in hypertension with lot of excitement A panoply of interventional techniques including renal denervation been evaluated for treatment of hypertension but none of them have been approved for clinical use.

The last couple of years have witnessed spectacular advances in the field of hypertension, both in terms of enhanced understanding and in the availability of rich panoply of therapeutic options. Due to this, the best practices for hypertension keep on changing.

Hypertension is the biggest global cause of mortality. It is important to bear in mind that control of hypertension is not self sufficient to improve outcome of the disease because the mortality in a controlled hypertensive is at least two times that of normotensive. This occurs due to two reasons:

1. **Atherosclerosis**: Hypertension is self sufficient to initiate and perpetuate atherosclerosis and this continues unabated even after control of blood pressure. This is classically illustrated in specimen of aorta of coarctation in children who usually do not have risk factors for atherosclerosis. The aorta below the coarct segment is normal but there is extensive atherosclerosis above it. Interestingly the HOPE-3[1] trial has shown that when candesartan + hydrochlorthiazide is used with rosuvastatin in patients of hypertension who did not had cardiovascular disease and were at intermediate risk, there is a statistically significant reduction of 24% in the primary end point cardiovascular death, MI and stroke compared to the group receiving candesartan + hydrochlorthiazide alone.

2. Fibrosis in various parts of the cardiovascular system

   This has detrimental effects.

   a. **Fibrosis in myocardium**: The fibrosis in the myocardium can be beautifully seen with Late Gadolinium Enhancement (LGE) on Cardiac Magnetic Resonance (CMR). This makes the ventricle vulnerable for development of heart failure and is also a risk factor for development of ventricular arrhythmias and sudden cardiac death.

   b. **Fibrosis in the left atrium**: This predisposes for development of atrial fibrillation (AF) and stroke. This can be visualized by LGE on CMR and is also utilized in conjunction with CHA_2DS_2-VASc score for prediction of stroke in AF. Moreover those patients who have marked left atrial fibrosis, the recurrence after Radio Frequency Ablation (RFA) for atrial fibrillation for restoing sinus rhythm rhythm is high. In fact, most of the electrophysiologist before attempting RFA in AF, visualize fibrosis in left atrium by CMR.

   c. **Fibrosis in the Aorta**: In normal young individuals, the aorta is compliant and the aortic Pulse Wave Velocity (PWV) is about 8 mete /sec. but if there is fibrosis is in the aorta, this result in decrease compliance and the aortic PWV is increased. In normal individuals the pulse wave after travelling from aorta to periphery comes back to aorta in diastole and this result in augmentation of diastolic blood pressure and increase in coronary filling but in aortopathy because of increase in aortic PWV, the pulse wave traverses fast from aorta to periphery and comes back to aorta in systole itself. This exerts several deleterious effects on the aorta.

   i. Increase in central aortic systolic pressure.

   ii. Increased LV after load.

   iii. Increased pulsatile strain with chances of plaque rupture

   iv. No diastolic augmentation of pressure.

Table 1: Criteria for diagnosing hypertension

Category	SBP	DBP
Office BP Criteria		
Office BP	≥ 140	≥90
Ambulatory BP Criteria		
Daytime	≥135	≥85
Nightime	≥120	≥70
24-H	≥130	≥80
Home BP Criteria		
Home BP	≥135	≥85

v. Decreased coronary perfusion.

Aortopathy is a very important predictor of future cardiovascular events in hypertension

BLOOD PRESSURE RECORDING

For several years we have been utilizing office blood pressure for diagnosis and treatment of hypertension but it is important to remember that the office based readings represent only a single snapshot in time with low reproducibility. The Home BP measurement is also very useful in evaluation of hypertension.

The Ambulatory Blood Pressure Monitoring (ABPM) provides an idea about the 24 hour BP profile[2-4] (Table 1).

Besides this, it also gives vital information regarding several parameters mentioned below.

a. Nocturnal blood pressure: Normally the blood pressure falls in the night by 10% .If it does not dip in night than it is called non dipper pattern and this is associated with increased morbidity and mortality.[5-9] There are several types of nocturnal BP patterns as mentioned in (Table 2).

The important causes of non dippers include obesity, obstructive sleep apnoea (OSA), high salt intake in salt sensitive subjects, orthosthatic hypotension, autonomic dysfunction, chronic kidney disease (CKD), old age, diabetic neuropathy, old age etc.

b. **Morning surges of blood pressure:** Normally the BP starts rising 90 minutes before the expected arousal,the maximum rise being less than 35 mm Hg. If the surge

Table 2: Criteria for different types of dippers

Subset	Criteria	
	Nocturnal BP fall	Night to day time BP ratio
Normal dippers	>10%	0.8 to 1
Extreme dippers	>20%	<0.8
Non dippers	No fall	1.0
Reverse dippers	↑ BP during night	>1

is more this is associated with increased incidence of cardiovascular events[10-12].

c. **Blood pressure variability:** The BP variability is defined as the average variation of BP throughout 24 hrs. quantitated as the SD of ABPM readings and is usually around 10-15 mm Hg for the day and 5-10 mm Hg for the night time. If the BP variability is increased, this is associated with increased incidence of cardiovascular events. Interestingly, the use of calcium channel blockers like amlodipine is associated with decreased cardiovascular events.

Moreover the effect of BP lowering medicines is best assessed by 24 hour ABPM[13-14]

HYPERTENSION AND VASCULAR DISEASE

Hypertension no doubt is associated with increased macrovascular disease in coronary, cerebral and peripheral arteries but what is not being realized by many that hypertension is also a very important cause of cognitive decline due to microvascular disease in the brain particularly when it is associated with diabetes.

GOALS OF BLOOD PRESSURE CONTROL

The goals of BP are decreasing over the years. In JNC 4 and 5, the goal of SBP was 160, it decreased to 150 in JNC 6 and further dropped to 140 mm Hg in JNC 7.

The ACCORD BP trial[15] carried out in diabetic hypertensive patients showed that tight BP control is not beneficial. The ACCORDION trial[16] also did not favoured tight BP control. This is an extended study of 3957 patients
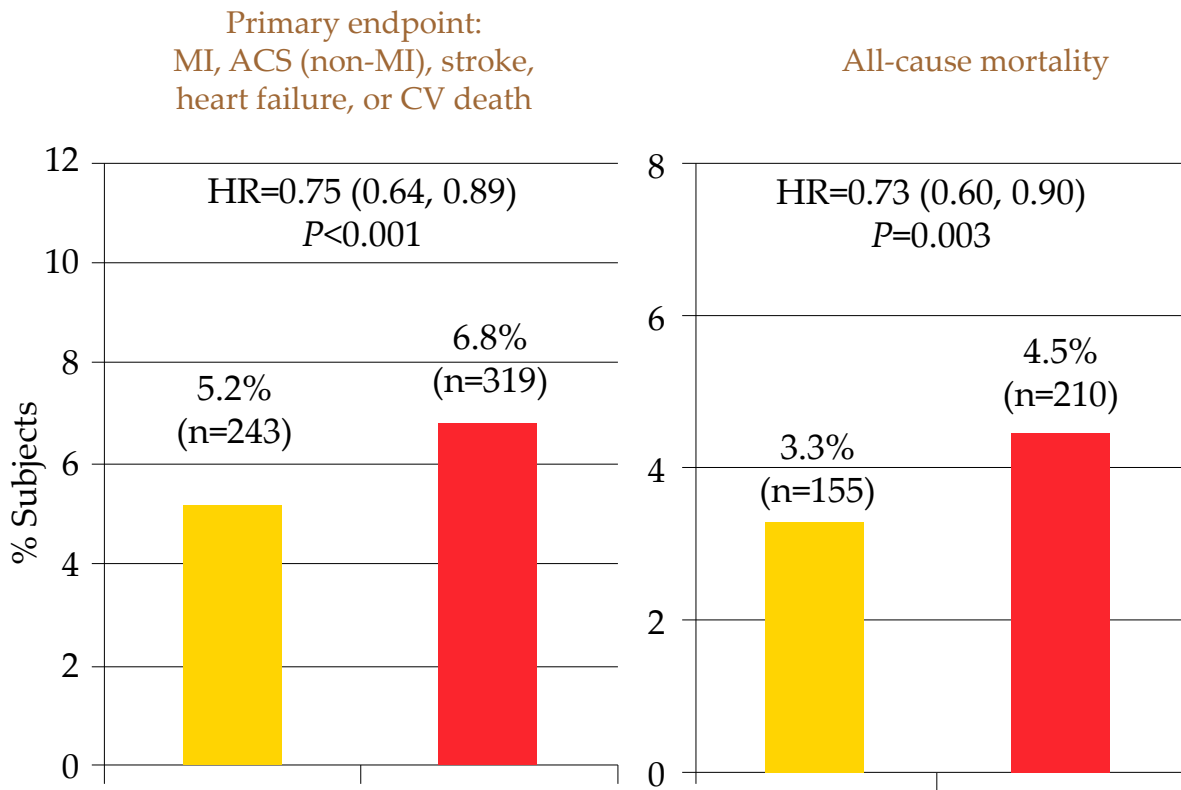
Fig. 1: **SPRINT Trial primary end point and all cause mortality**

of ACCORD trial who were followed for an additional 54-60 months. During this time, patients who had been in the intensive BP arm in the main trial were no longer aiming for the lower BP goals, so the difference in BP between the two groups narrowed from 14.5 mmHg at the end of the main trial to 4.2 mmHg at the end of the follow-up period. Results from the follow-up period showed a 9% non-significant reduction in the primary end point of major CV events over a median follow-up of 8.8 years from randomization. During the long-term follow-up, an inter-action between BP and glycemia interven-tions became significant (P for interaction 0.037), with evidence of benefit for intensive BP lowering in participants randomized to standard glycemia therapy (HR = 0.79, 95% CI 0.65–0.96).

The INVEST trial[17] showed that tight control of

BP (<130) in diabetics with CAD is associated with a trends towards all cause mortality compared to usual control (130-140). The extended follow up of INVEST trial[18] showed that in hypertensive patients with coronary artery disease, achieving a systolic BP of 130–140 mmHg seems to be associated with lower all-cause mortality after approximately 11.6 years of follow-up.

The SPRINT trial[19] however created a flutter by showing that 120 SBP was better than 140 mm Hg (Figure 1,2) .The trial showed a 25% reduction in the primary end point of MI, ACS (non-MI), stroke, heart failure or CV death, the all cause mortality and CV mortality decreased by 27 and 43 % respectively. The hospitalization for heart failure was decreased by 38%.

The SPRINT trial did show benefits of additional lowering of SBP to 120 mm Hg
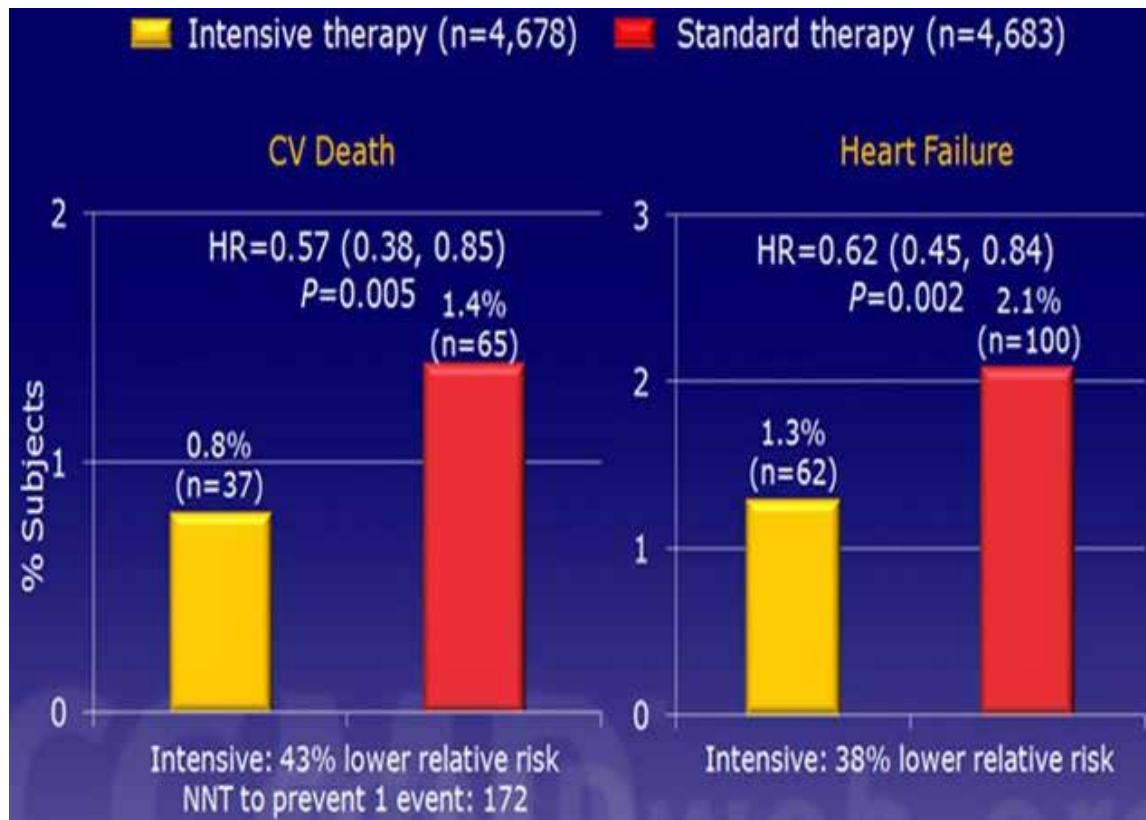
Fig. 2: SPRINT Trial CV death and heart failure

but is is important to bear in mind that the technique of BP measurement in this trial was unique and never done before, i.e., unattended, automated, unobstructive with patient relaxing in an AC room for 5 minutes before recording the reading. Due to this a lower reading of blood pressure by 8-10 mm is recorded. Therefore the reading of SPRINT 120 mm Hg is equivalent to about 130 mm Hg,if we record BP in the conventional manner in the clinic. Therefore lower goal of 120 mm Hg of this trial cannot be applied as such in real practice

The 2016 European Guidelines on CVD prevention in clinical practice therefore has not directly endorsed SPRINT trial but it says based on current data, it may still be prudent to recommend lowering SBP/DBP to values within the range 130-139/80-85 mm Hg, and possibly close to the lower values in this range, in all hypertensive. The AACE/ACE Consensus statement released in recent past has recommended a target of 130 /80 mm Hg. for diabetic patients.

The SPRINT trial also has several limitations.

1. It is an open label study

2. It represents only 20% of total hypertensive population as patients with diabetes, congestive heart failure, proteinura >1 gm/day, eGFR < 20 were excluded

3. The SPRINT trial cannot be applied to diabetics as the ACCORD BP and ACCORDION trial carried out in diabetic patients were negative.

4. It cannot be applied to frail elderly.

However SPRINT and the ACCORD trial had differences in several parameters and this may perhaps account for failure of ACCORD BP trial to show benefits of intensive BP lowering (Table 3).

EFFECT OF LOWERING BP IN TARGET ORGANS

Curiously enough, different organs behave differently to decrease in BP.

a. **Brain:** The dicta for brain is lower is better

Table 3: Comparison between ACCORD and SPRINT trials

Parameter	Accord	Sprint
Study Design	Complex factorial study design could have prevented a statistically significant difference	Randomized, controlled, open-label
Age	Mean age 62. Individual with age > 80 excluded and this led to younger group of patients	Older, mean age 68
CV risk	Lower risk patients because of lower age and dyslipidemic patients were assigned to lipid arm and excluded from BP arm	Higher risk patients
Diabetes	Only diabetics enrolled	Excluded
Diuretics	HCTZ often used	CTD often used
Intensive BP lowering	No effect on CV events	↓ CV events
Event rates	Lower than predicted because of lower CV risk profile	-
Microvascular disease	Common in diabetics and greater BP lowering may decrease perfusion pressure and increase CV events	Less common in non-diabetics

i.e. lower the BP, less is the incidence of stroke as shown by ACCORD BP and INVEST trial.

b. **Heart:** As the coronary arteries are filled in diastole, lower diastole blood pressure below 70 to 80 increases the incidence of acute myocardial infarction and this results in a J-shaped curved. Thus in patients with coronary artery disease, the blood pressure should be carefully lowered.

c. **Kidney:** In kidneys, it is the intraglomerular pressure that matters more than the BP in the renal arteries. If the intraglomerular pressure is increased, this results in proteinuria which adversely affects the kidneys. Therefore in renal hypertension, drugs which decrease intraglomerular pressure like ACEI / ARBS are preferred.

BP TARGETS IN DIABETICS

The BP targets in diabetics have been controversial. For several years a target of lower than 130 / 80 has been recommended and lower was considered better. The JNC-7 guidelines in 2003 for hypertension also endorsed this target. The concept of lower is better was prevalent based on observational data from MRFIT and other trials showing increasing levels of SBP to be associated with higher risk of macrovascular events but there is no evidence from observational or RCTs that achieving SBP lower than 130 with drugs is associated with decreased risk of cardiovascular events. The UKPDS 38[20], ADVANCE[21] and HOT[22] trials were also used in support of this recommendation but in UKPDS the BP achieved in the intensive arm achieved was only 144/82 and the advance trial recorded a systolic BP of 134.7 mm Hg. The hot trial subgroup which was targeted to achieve DBP < 80 actually achieved a reading of 81.1 mm Hg. Therefore the recommendation to lower BP < 130 /80 was not based on solid evidence. Moreover several trials like ONTARGET,[23] PROFESS,[24] TRANSCEND,[25] INVEST, ACCORD BP, ACCORDION and extended follow up of INVEST trial reported no benefit or even harm when lower BP target were achieved. These trials compelled the professional bodies to recommend less stringent targets (Table 4). As discussed earlier, the SPRINT trial reported enormous benefits with SBP of 120 compated to 140 although it was later realized that 120 SBP of this trial is equivalent to 130 SBP in office setting.

To solve the discrepancy between various studies and to detect an appropriate target several meta-analysis were examined.[26-31] Following their scrutiny, ADA 2017 has issued a consensus for BP targets in diabetics. There is irrefutable evidence that SPB > 140 mm Hg. is harmful. Therefore the goal of systolic BP should be <140 mm Hg. in most patients. A

Table 4: BP targets in diabetics as per various Guidelines

S. No.	Society	BP target
1	ESH/ESC 2013	140/85
2	JNC 8 2014	140/90
3	ACC/AHA 2014	140/90
4	ASH/ISH 2014	140/90

goal closure to 130 mm Hg is recommended for subset of patients who are at high risk of stroke or have albuminuria. Lowering BP below 130 does not improve outcome and may be detrimental. There is strong evidence that DBP > 90 mm Hg. is associated with harm. The goal of DBP in diabetic should be <90 but a goal closure to 80 mm Hg. may be recommended for patients at high risk of stroke or those who have proteinuria. Targeting BP to < 70 mm Hg. is harmful.

STATINS, HYPERTENSIVE PATIENTS AND CV EVENTS

In the recent Heart Outcomes Prevention Evaluation (HOPE)–3 trial 12,705 participants at intermediate risk who did not have CV disease were randomized to receive either candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day or placebo and were followed for 5.6 years. The first co-primary outcome was the composite of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke; the second co-primary outcome additionally included resuscitated cardiac arrest, heart failure, and revascularization. Therapy with candesartan plus hydrochlorothiazide was not associated with a lower rate of major CV events than placebo despite a BP decrease of 6.0/3.0 mmHg in the active treatment group. Addition of rosuvastatin showed a statistically significant reduction of 24% in the primary endpoint. The only subgroup who benefited from BP lowering was the subgroup of participants with initial systolic BP > 143.5 mmHg.[32]

CHRONIC KIDNEY DISEASE AND HYPERTENSION

The goals of blood pressure are outlined Table

Table 5: Targets for blood pressure in chronic kidney disease and hypertension

S. No.	Guideline	Subset	BP Goal	Initial drug treatment option
1	JNC VII 2003	CKD	<130/80	ACEI/ARB
2	ACC/AHA 2014	CKD	<140/90	ACEI/ARB
3.	ASH/ISH 2014	CKD	<140/90	ACEI/ARB
4.	ESH/ESC 2013	CKD no proteinuria	<140/90	ACEI/ARB
		CKD + proteinuria	<130/90	ACEI/ARB
5.	CHEP 2013	CKD	<140/90	ACEI/ARB

5. The cutoff point is 140/90 mm Hg. but if there is proteinuria lower BP goal i.e. 130/90 is beneficial. The AASK trial[33] showed no benefit in the primary outcome of progression of kidney disease in patients of CKD with hypertension but when the data was analysed on the basis of PC ratio, the subset of patient with PC ratio >0.22 showed benefit.

DRUGS FOR TREATMENT FOR HYPERTENSION

Commonly four groups of drugs are used for treatment of hypertension.

a. **Diuretics:** Chlorthalidone (CTD) is preferred over hydrochlorthizide (HCTZ) which we have been using for several decades. This is because CTD produces greater reduction in BP including nocturnal BP and is associated with decrease in the cardiovascular events (CVE). HCTZ has never been shown to reduce CVE. Indapamide is also a good diuretic and has no metabolic side effects.

b. **RAAS Blockers:** There are 3 types of RAAS blockers as mentioned below:

   i. **Angiotensin Converting Enzyme Inhibitors (ACEIs)**: These agents although they produce incomplete RAAS inhibition but have excellent outcome data.

   ii. **Angiotensin Receptor Blockers**

(ARBs): Telmisartan in the ONTARGET trial was found equivalent to ACE inhibitor Rampril and is approved for clinical use like the ACEI Rampril.

Azilsartan is a new sartan and has the advantage over other sartan that besides blocking AT1 receptors, it also activates ACE2, Angiotensin (1-7), mass pathways and provides vasculoprotective and vasodilatory effects. In terms of blood pressure reduction it is therefore more potent than the other sartans and provides good blood pressure control.

iii. **Direct Renal Inhibitors (DRI)**: These drugs despite a sound theoretical basis failed to produce outcome data in various trials and therefore they are not preferred.

c. **Calcium channel blockers (CCBs):** Amlodipine is a time tested CCB for treatment of hypertension and has been tested in several large scale trials with beneficial results. But the the main problem with amlodipine is pedal edema. Of late the fourth generation CCB cilnipipine is now commercially available. It has the advantage that it not only acts on the L-type calcium channel blockers but also blocks the N-type calcium channels which suppresses excess norepinephrine release from the sympathetic nerve endings. This provides cardio-protection[34] as it does not increase heart rate and cardiac contraction and also provide renal protection by decreasing proteinuria[35]. It also produces venodilation and decreases chances of pedal edema[36]. Of late, a new CCB benidipine is available with blocks the L,N and T type calcium channels. It follows the membrane approach which lead to long duration of action even after short half lie of 2 hours. It provides better BP control than other CCB like amlodepine and clinidipine and because of T-type calcium channel blockage, it significantly improves the UPE, provide better kidney protection

than amlodipine and Cilnidipine. Besides this benidipine also provides cardiovascular benefit by improving nitrous oxide and cGMP (vasodilation), reduce oxLDL level (anti-atherosclerotic action), reduce aldosterone level.[37]

d. **Beta blockers:** For several years beta blockers like atenolol has been commonly used for treatment of hypertension but the meta-analysis by Carlberg[38] showed that it increases all cause mortality and CV mortality by 13% and 16% respectively. It increased MI by 17% and curiously enough the strokes were increased by 30%. As a result the NICE guidelines for hypertension in 2011 degraded beta blockers to number four. Currently vasodilatory beta blockers like Nebivolol and carvedilol are used for treatment of hypertension. These have minimal side effects but long terms trials are lacking with these agents are lacking.

COMBINATION THERAPY

Most patient of hypertension in the long run requires combination therapy[39]. The desirable combinations are ACEI / ARB + Diuretics, CCB + Diuretics, ACEI / ARB + CCB, ACE / ARB + CCB +Diuretics.

RESISTANT HYPERTENSION

Hypertension uncontrolled (>140/90 mm hg) with triple combination i.e., ACEI/ARB +CCB + diuretics is categorized as resistant hypertension. Currently the most potent combination is Azilsartan + Benidipine + Chlorthalidone.

Depending on the population examined and the level of medical screening, the prevalence of resistant hypertension has been reported to range from 5–30% of the overall hypertensive population, with figures less than 10% probably representing the true prevalence. Resistant hypertension is associated with a high risk of CV and renal events[40-43].

But before labeling somebody as resistant hypertension, one should rule out the possibility of apparently difficult to control

hypertension due to inappropriate cuff size, pseudohypertension, non-adherence to drug therapy, unknowingly consuming large amount of salt, inadequately prescribed dosage or improper combinations, white coat hypertension, drug induced hypertension etc. If true resistant hypertension is present, one should exclude obstructive sleep apnoea (OSA), hypothyroidism, renovascular hypertension, primary aldosteronism, aortoarteritis, endocrinal hypertension etc.

WHAT SHOULD BE THE FOURTH DRUG IF BLOOD PRESSURE IS NOT CONTROLLED WITH ACE/ARB, CCB/CHLORTHALIDONE I.E. RESISTANT HYPERTENSION ?

This was tested in the PATHWAY 2 trial[44] which showed that spironolactone was distinctly superior to bisoprolol and doxazosin and therefore this should be the fourth drug of choice.

Other drugs that can be used include betablockers like nebivolol or bisoprolol, alpha blockers, like prazosin ,direct vasodilators like hydralazine, minoxidil, centrally acting drugs like clonidine, moxonidine etc

NEW DRUGS: ANGIOTENSIN RECEPTOR NEPRILYSIN INHIBITOR (ARNI)

This drug has already been approved for clinical use in patients with heart failure with reduced ejection fraction as Class-I (B) recommendation in various guidelines. The valsartan in ARNI produces RAAS blockade and the neprilysin inhibition with sacubtril results in increased bioavailability of natriuretic peptides, bradykinin and substance P, which produces natriuretic, vasodilatory and anti-proliferative effects.

ARNI is now being evaluated for treatment of hypertension. The PARAMETER study[45] showed favourable effects. This 52-week multi-center study randomized 454 patients with hypertension aged ≥60 years with a mean sitting systolic blood pressure (SBP) of ≥150 to <180 and a pulse pressure of >60 mm Hg to once daily ARNI (200 mg) or olmesartan (20 mg) for four weeks, followed by a forced titration to double the initial doses for the next eight weeks. At 12–24 weeks, if the BP target had not been attained, amlodipine (2.5–5 mg) and subsequently hydrochlorothiazide (6.25–25 mg) were added. The primary and secondary endpoints were changes from baseline in central aortic systolic pressure and central aortic pulse pressure at week 12, respectively.

Results showed that after 12 weeks, patients treated with ARNI had a 3.77 mmHg greater reduction in central aortic systolic pressure and a 2.4 mm Hg greater reduction in central aortic pulse pressure from baseline compared to patients treated with olmesartan. Additionally, the 24 hour ambulatory brachial and central SBPs were significantly reduced from baseline to 12 weeks in both treatment arms, with ARNI lowering brachial SBP by an additional 4.1 mmHg and central SBP by an additional 3.3 mmHg compared to olmesartan. This finding was most pronounced during the nighttime.

In other findings, a greater percentage of patients treated with olmesartan (47 percent) required additional hypertension medication at weeks 12–24 compared to patients in the ARNI group (32 percent). Investigators also noted that an exploratory analysis of the carotid-to-femoral pulse wave velocity indicated a trend toward greater improvement in a subgroup of ARNI treated patients with the stiffest arteries at baseline.

PARAMETER is the first randomized study demonstrating the ability of ARNI to significantly reduce central blood pressure and pulse pressure compared to an ARB in high-risk older patients with systolic hypertension and a wide pulse pressure. These data are important because lowering systolic and pulse pressure in older people with stiffened arteries is an unmet need in our endeavor to reduce the risk of cardiovascular disease and heart failure in older people. The results

Table 6: Ongoing trials of LCZ696 in hypertension

Trial number	Patient population	Brief title	Comparator
NCT01785472	Essential hypertension	Efficacy and Safety of LCZ696 in Comparison to Olmesartan in Asian Patients With Essential Hypertension	Olmesartan
NCT01599104	Essential hypertension	Efficacy and Safety of LCZ696 in Comparison to Olmesartan in Japanese Patients With Essential Hypertension	Olmesartan
NCT01870739	Essential hypertension	A Study to Evaluate the Effect of LCZ696 on Aortic Stiffness in Subjects With Hypertension	Olmesartan
NCT01615198	Essential hypertension	Efficacy and Safety of LCZ696 in Comparison to Olmesartan in Elderly Patients With Essential Hypertension	Olmesartan
NCT01681576	Salt-sensitive hypertension	Assessment of LCZ696 and Valsartan in Asian Patients With Salt-sensitive Hypertension	Valsartan
NCT01256411	Essential hypertension	A Long-term (12 Months) Safety, Tolerability and Efficacy Study of LCZ696 in Patients With Essential Hypertension	NA
NCT01601470	Mild-to-moderate hypertension	Evaluation of Drug-drug Interaction Between LCZ696 and Sildenafil in Subjects With Mild to Moderate Hypertension	Sildenafil
NCT01353508	Hypertension; heart failure and healthy volunteers	Sodium Excretion of LCZ696 in Patients With Hypertension; Heart Failure and Healthy Volunteers	Valsartan
NCT01692301	Hypertension	Study of the Safety and Efficacy of LCZ696 on Arterial Stiffness in Elderly Patients With Hypertension	Olmesartan, Amlodipine, HCTZ
NCT01663233	Essential hypertension	Efficacy and Safety of LCZ696 200 mg + Amlodipine 5 mg in Comparison With Amlodipine 5 mg in Hypertensive Patients Not Responding to Amlodipine	Amlodipine
NCT01646671	Severe hypertension	Safety and Tolerability and Efficacy of LCZ696 in Japanese Severe Hypertensive Patients	NA
NCT01631864	Hypertension, concurrent obesity	Evaluation of the Metabolic Effects of LCZ696 and Amlodipine in Obese Hypertensive Subjects	Amlodipine
ISRCTN11958993	Chronic kidney disease	Randomized multicentre pilot study of LCZ696 vs. Irbesartan in patients with chronic kidney disease: UK Heart And Renal Protection (HARP)-III	Irbesartan

suggest that ARNI has been able to achieve more in this regard than existing treatments and indeed this is an exciting advance.

The holy grail of systolic hypertension therapy is to achieve a 'destiffening' effect. The fact that release of BNP was reduced for ARNI provides indirect evidence that this may be occurring. Currently studies are

under way using MRI to directly measure changes in arterial distensibility following ARNI treatment.

Although ARNI has shown impressive reduction in systolic and diastolic blood pressure, the long-term antihypertensive efficacy of ARNI has not been fully evaluated. Moreover the effect of ARNI on cardiovascular outcomes in patients with hypertension is unknown. It is also to be seen whether ARNI also confers long-term prognostic benefits in patients with hypertension. Further studies need to be conducted to elucidate the role of ARNI in hypertensive patients with (i) diabetes, (ii) chronic kidney disease (iii) elderly (iv) resistant hypertension. Since blacks were underrepresented in the published hypertension trials, future trials should also include adequate black population. Most importantly, studies needs to be conducted comparing antihypertensive efficacy and outcome of ARNI with other drug classes such as ARBs, calcium-channel blockers and diuretics.

Besides PARAMETER trial, several other clinical trials are ongoing (Table 6)

INTERVENTIONAL THERAPY IN HYPERTENSION

Several interventions have been used for treatment of hypertension like carotid baroreflex activation, Iliac AV anastomosis and renal sympathetic denervation.

a. **Baroreflex activation**: It decrease blood pressure by vagal stimulation but the problem with this technique is that carotid stenosis is seen about 60% of patients and we do not know how to prevent it ?

b. **Iliac AV anastomosis**: In this external iliac artery connected to external iliac vein by a device. It decreases blood pressure by decreasing vascular resistance. This is associated with venous stenosis in 25% of patients but this can be treated by venodilatation.

c. **Renal sympathetic Denervation**: This was a very promising technique and the initial results with SYMPLICITY-1 and 2 were exciting but distressingly enough the SIMPLICITY HTN-3 trial[46] although it met the safety end point, it failed to show any reduction in blood pressure compared to the Sham control group. Therefore it has not been approved for clinical use. The failure of the trials was attributed to several reasons like operator inexperience/ failure, fault with the catheter and patient in the late stage of disease with burnt out sympathetic activity. The problem with the technique is that there is no parameter to document success of renal denervation / technical failure immediately after the procedure. New improved catheters for the procedure are being designed with circumferential denervation of renal artery and its branches and the initial result are exciting. It seems renal sympathetic denervation is still alive and not dead and may bounce back in future.

But we should not forget that the major battle for hypertension is to be fought outside the clinics and hospitals because the major chunk of hypertensive patients is still out of reach. This can never be done merely by the medical fraternity but requires cohesive efforts by the government, voluntary agencies, paramedical workers, electronic and print media etc.

SUMMARY

Hypertension is the commonest cause of cardiovascular morbidity and mortality throughout the globe including our country. Prevention should be the goal and indeed it is possible. For hypertensive patients, we have panoply of powerful antihypertensive drugs to control it. But for optimum treatment, a disease centric approach should be employed rather than merely a BP centric approach.

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Genetics of Hypertension

Prochi Madon

Hypertension is a complex multifactorial trait that is influenced by the interaction of both genetic and environmental factors. The hereditary nature of hypertension has been established in family and twin studies, where monozygotic twins show a greater concordance in blood pressure values compared to dizygotic twins.[1] The importance of genes in hypertension stems from the fact that hypertension is more common in subjects when both parents are affected. The risk of familial heritability of this condition is positively correlated with the number of hypertensive relatives. More than 80 loci have been examined in association studies with hypertension, such as those in the angiotensinogen (AGT) gene. The renin-angiotensin-aldosterone (RAA) system is thought to be of pathogenic importance in hypertension, hence genes for RAA elements are among the best studied candidates.[2]

The genetic contribution to blood pressure regulation is of two fundamentally different types:

a. Primary hypertension with common genetic variants and

b. Monogenic hypertension with rare genetic mutations

Numerous common genetic variants with

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small effects on blood pressure have been identified, as well as some rare genetic variants with larger effects on blood pressure.[3,4]

BASICS OF GENETIC TESTING

Genetic testing can identify changes in chromosomes, genes or proteins. DNA present in the nucleus of cells is very tightly coiled to form the chromosomes which are microscopically visible during cell division. Different methods are used for testing various genetic disorders.

Cytogenetics covers genetic study at the chromosome level. Gross chromosome anomalies are detected by karyotyping which is time consuming. The later technology of fluorescence *in situ* hybridization (FISH) can detect specific small deletions, translocations or aneuploidy of chromosomes rapidly. FISH is helpful in differentiating the type of cancer and judging the prognosis to decide on specific therapies. It is also used for rapid detection of common trisomies such as 21 (Down syndrome), 13 or 18 in pregnancies at high risk on USG and biochemical screening.

The more recent *molecular cytogenetic technique* of chromosome microarray (CMA) or array comparative genomic hybridization (aCGH) can detect minute duplications/gains or deletions/losses on chromosomes at the DNA level. These are also called copy number variations (CNVs). Changes known to be delete-

rious are termed 'pathogenic' while those commonly seen in normal individuals are termed 'benign'. Microarrays are a powerful tool for studying the genetics of hypertension as they facilitate the measurement of the expression of thousands of genes simultaneously.[5]

Molecular genetics comprises a study of mutations or deleterious changes in genes at the DNA level, using different techniques such as various types of polymerase chain reactions (PCR), Sanger sequencing, haplotyping, candidate gene and linkage analysis, genome wide association studies (GWAS) and next generation sequencing (NGS). The interpretation of the NGS raw data is largely based on bioinformatics. The classification of DNA sequence polymorphisms, single nucleotide polymorphisms (SNPs) or variants of unknown significance (VOUS) can change over a period of time as more studies are undertaken and new data is generated in different ethnic populations. The term genomics is now used for the study of the whole genome and proteomics for the large scale study of proteins and their functions. Genomics research makes use of the data collected to study disease predisposition, causation, prognosis, complications and treatment responses. The focus is now on common complex disorders such as hypertension, coronary heart disease, diabetes and obesity. Genes suspected to play a role in hypertension or any other disorder being studied, are called *candidate genes*.

A **genetic counselor** or geneticist helps by providing information of the appropriate tests to be used for studying different genetic conditions in individual families, explaining the risks of recurrence by studying the family history and offering ways to prevent transmission of specific genetic disorders in the immediate and extended family.

RESEARCH ON ANIMALS

Over 50 years ago, the research community, through selective breeding, developed many animal models of hypertension. In one of the classic experiments, spontaneously hyper-

tensive rats, Dahl salt-sensitive rats and Milan hypertensive rats were used to study essential hypertension in humans. Kidney cross-transplantation studies using hypertensive and normotensive rats derived from one single strain overwhelmingly demonstrated that the genotype of the donor kidney plays a principal role in determining chronic blood pressure levels in the recipient.[6] Other experiments were carried out between normotensive Wistair-Kyoto (WKY) rats and spontaneously hypertensive stroke-prone (SHRSP) rats using DNA fingerprinting and genetic linkage.[5] Adrenal gland secretory products, both medullary and cortical, are logical candidates for the study of hypertension since they can directly influence cardiovascular, endocrine and sympathetic nervous system functions.

The search for genes accounting for the susceptibility to hypertension has driven parallel efforts in human research. The identification of variant genes that contribute to the development of hypertension is complicated by the fact that the two entities that determine blood pressure (BP), namely cardiac output and total peripheral resistance, are themselves controlled by other intermediary phenotypes, including the autonomic nervous system, vasopressor/vasodepressor hormones, the structure of the cardiovascular system, body fluid volume and renal function.[7] Most of the data obtained from genome wide association studies requires functional validation in experimental models. Genome-wide linkage analysis predicts that multiple chromosomal regions may play a role in the development of human essential hypertension. Lack of consistency across earlier studies made it difficult to draw any general conclusions regarding the cause. However, through GWAS meta-analyses, numerous loci have now been robustly associated with BP.[8]

SEARCH FOR COMMON GENETIC VARIANTS

Ehret et al., in a large genome-wide association study of systolic BP and diastolic BP which used a multi-stage design in 200,000

individuals of European descent identified 16 novel loci, six of which contained genes previously known or suspected to regulate BP (*GUCY1A3-GUCY1B3; NPR3-C5orf23; ADM; FURIN-FES; GOSR2; GNAS-EDN3*); the other 10 provided new clues to BP physiology.[3] In this study, a genetic risk score based on 29 genome-wide significant variants was associated with hypertension, left ventricular wall thickness, stroke, and coronary artery disease, but not kidney disease or kidney function. Associations with BP in East Asian, South Asian, and African ancestry individuals were also observed. These findings provided new insights into the genetics and biology of BP, and suggested novel potential therapeutic pathways for cardiovascular disease prevention.

Recent candidate gene studies have taken advantage of advances in high-throughput genotyping technology to identify gene variants related to BP, utilizing cardiovascular gene-centric arrays which interrogate large numbers of variants in a multitude of genes and biological pathways. A large association study, examined ~ 50,000 single-nucleotide polymorphisms from ~2,100 candidate genes for cardiovascular phenotypes in 127, 505 individuals of European ancestry and identified two novel loci associated with blood pressure highlighting the potential of candidate gene studies in identifying genetic factors for complex disease by the use of stringent methodologies.[9] Using the HumanCVD BeadChip, which genotypes approximately 50,000 single nucleotide polymorphisms (SNPs) from 2,000 genes demonstrated to associate with CVD-related traits, Johnson and colleagues identified BP-related SNPs in the *LSP1/TNNT3, MTHFR-NPPB, AGT, ATP2B1, NPR3, HFE, NOS3* and *SOX6* genes among a discovery-stage sample of 25,118 participants and replication study of 59,349 participants.[10] Chromatin immunoprecipitation and transcript expression data highlight potential gene regulatory mechanisms at the MTHFR and NOS3 loci. Although variants identified in genome-wide association studies of blood pressure are associated with blood pressure and hypertension, the effect sizes are small and do not permit clinically relevant prediction of whether or not hypertension will develop in an individual.[11] Kato et al. showed that blood pressure SNPs are enriched for association with DNA methylation at multiple nearby CpG sites, suggesting that, at some of the loci identified, DNA methylation may lie on the regulatory pathway linking sequence variation to blood pressure.[12]

Liu et al. identified 31 novel loci in discovery among 146,562 individuals with follow-up and meta-analysis in 180,726 additional individuals (N_{total}=327,288). These blood pressure loci are enriched for known cardiometabolic trait variants. In addition, blood pressure associations at 39 previously reported loci were confirmed. The identified variants implicate biological pathways related to cardiometabolic traits, vascular function, and development. Several new variants are inferred to have roles in transcription or as hubs in protein-protein interaction networks. Genetic risk scores constructed from the identified variants were strongly associated with coronary disease and myocardial infarction. This large collection of blood pressure loci suggests new therapeutic strategies for hypertension emphasizing a link with cardiometabolic risk.[13] Even though much of the heritability of BP still remains unexplained, there is renewed optimism as we turn our attention towards next-generation approaches for the discovery of novel genomic determinants of this complex trait.

Polymorphisms in genes of renin-angiotensin–aldosterone system (*RAAS*) comprising angiotensinogen (*AGT*), angiotensin-converting enzyme (*ACE*), angiotensin II receptor type 1 (*AT1R*), and aldosterone synthase (*CYP11B2*) genes have been the most commonly studied for association with various aspects of hypertension.[14] The ACE gene polymorphism was specifically found to be associated with reduced diastolic blood pressure in men who were older than 50 years.[15] However, linkage with a site adjacent to the ACE and growth hormone (GH) genes does not prove

that either gene necessarily causes hypertension.[16] MTHFR and CYP17A1 (cytochrome P450, family 17, subfamily A) are other genes associated with hypertension.[14] Although variants identified in genome-wide association studies of blood pressure are associated with blood pressure and hypertension, the effect sizes are small and do not permit clinically relevant prediction of whether or not hypertension will develop in an individual.[17] The most immediate use of blood pressure loci identified by genome-wide association studies is to identify pathways involved in the pathogenesis of primary hypertension. Blood pressure genes that have been identified and the corresponding pathways might serve as targets for pharmacological intervention. One example of this in a related field of cardiovascular prevention is the development of anti-PCSK9 antibodies to reduce low-density lipoprotein (LDL)-cholesterol levels.[11]

RARE MONOGENIC HYPERTENSIVE DISORDERS

Genetic investigations in rare hypertensive families have detected mutations in a few genes which are responsible for a few syndromes which have a Mendelian pattern of inheritance.[18] These include early-onset autosomal dominant hypertension with exacerbation in pregnancy, glucocorticoid-remediable aldosteronism, congenital adrenal hyperplasia (CAH) due to 11-beta-hydroxylase deficiency with mutations of the *CYP11B1* gene, CAH due to 17-alpha-hydroxylase deficiency (CYP17A1), familial hyperaldosteronism type 3, Gordon's syndrome, Liddle's syndrome, and autosomal dominant hypertension with brachydactyly.[11] Mutations in the genes causing these disorders are sufficient to cause substantial blood pressure elevations. Most of the genes responsible for these disorders act in the kidney or in the mineralocorticoid pathways. Mitochondrial genome mutations in hypertensive patients have also been reported recently.[19]

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PATH-BREAKING TRIALS 2017

PRAGUE-15 Study: 2-year Outcomes

## Renal Denervatin Vs Intensified Pharmacotherapy in True Resistant HTN

STUDY DETAILS

- Design: Randomized, multicenter study

- Population: True resistant HTN

- N=106

- 2-year data=86

- Study Groups: Renal Denervation (RDN) (n=52) vs Spironolactone addition (n=54)

- Cross over at 1 years: After RDN to spironolactone in 23 and Spironolactone to RDN in 5 patients

- Outcome: 24-h SBP and Office SBP reduction

RESULTS

Baseline SBP: 159±17 in RDN and 155±17 mmHg in spironolactone	**Average no. of drugs:** 5.1 and 5.4, respectively

RDN   Spironolactone

-9.1
-10.9
-14.1
-17.7

■ 24.h SBP Reduction ■ Office SBP
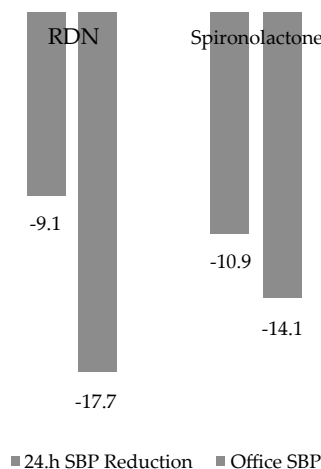
CROSSOVER ANALYSIS

After RDN, Spironolactone addition resulted in

- Non-significantly better BP reduction

  - 24-h SBP: 3.7 mmHg (p=0.27)

  - Office SBP: 4.6 mmHg (p=0.28)

- Increase in number of Antihypertensive drugs

  - +0.7 (p=0.001)

CASE REPORT

Giddiness Requires Vigilance

Hozefa Runderawala[1], Pratit Samdani[2]

ABSTRACT

Hypertension is the most common risk factor for ischemic stroke. Cerebellar strokes are uncommon cause of ischemic stroke and its sign and symptoms overlap with many benign conditions. The diagnosis of cerebellar stroke is important as delayed intervention or misdiagnosis can lead to lethal complications. We report a case of 68-year-old male who presented with complaints of giddiness diagnosed as left cerebellar infarct.

INTRODUCTION

Stroke is the third largest cause of mortality and single largest cause of adult disability. Cerebellar infarctions are the rare cause of stroke and forming approximately 2.3% of total stroke.[1] Hypertension is the most important risk factor for stroke. Cerebellar stroke needs vigilance as its symptoms overlap with benign disease like vestibular neuritis, benign paroxysmal position vertigo, and many more. Timely intervention in a case of cerebellar infarction is must as misdiagnosis or delayed diagnosis can lead to catastrophic complications.

CASE REPORT

68-year-old male, known case of hypertension for 20 years on regular treatment, presented with complaints of an episode of giddiness. It was associated with transient black out episode and mild loss of balance along with nausea. There was no h/o fever, vomiting or

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trauma. Patient also denies about tinnitus, loss of consciousness or any limb weakness. Giddiness was not accompanied with dysarthria, diplopia or hearing loss. There was no h/o diabetes mellitus, ischemic heart disease or cerebrovascular accident.

On examination, he was afebrile, pulse 74/ min, regular, BP- 184/110 mm of Hg, respiratory rate was 18/ min. There was no evidence of pallor, icterus or cyanosis. On central nervous examination, higher functions, sensory and motor examination and cranial nerve examination were normal. He had left finger-nose test and left heel-shin test positive. Also, left side dysdiadochokinesia, Romberg sign and tandem gait test was positive. Both plantar reflexes were downwards. Rest of the systemic examination was unremarkable.

On routine blood investigation, his haemoglobin was 14 gm%, total leucocyte count- 12490/mm^{3} with normal differentials. His serum electrolyte, calcium and creatinine level was within normal range. Lipid profile was deranged with raised triglycerides and

Fig. 1: MRI showing left cerebellar infarct of size 2 X 2.5 cm

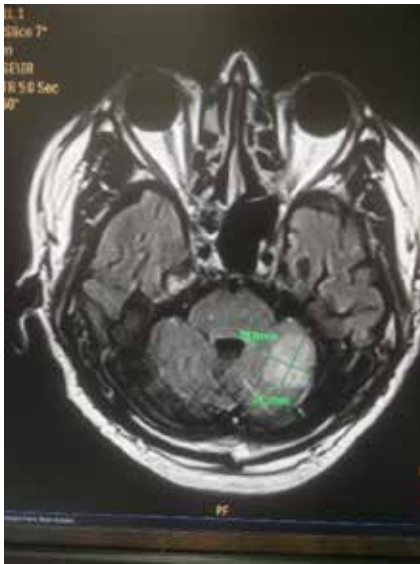**Fig. 2: Restricted diffusion showing left cerebellar infarct**

cholesterol level. MR angiography of the brain revealed fresh left cerebellar infarct of size 2.0 X 2.5 cm, neck vessels appear normal. 2D echocardiography of heart showed normal ejection fraction with normal atria, ventricles and atrial appendages.

He was treated with antiplatelet, statins and anti- hypertensives and was advised limb physiotherapy.

DISCUSSION

Cerebellar infarctions are not common type of stroke and constitute approximately 2.3% of overall acute stroke.[1] These can occur due to occlusion of the superior cerebellar artery (SCA), anterior inferior cerebellar artery (AICA) or the posterior inferior cerebellar artery (PICA). Approximately 10% of cerebellar infarction can present with isolated vertigo, i.e. vertigo without localising findings on sensory, motor, reflex, cranial nerve or limb coordination.

Vertigo is defined as a pathologic illusion of movement.[2] It is experienced as spinning sensation most commonly, it arises from a pathologic imbalance in peripheral or central vestibular system. Most of the patients who has presented with isolated vertigo have benign pathology, approximately 0.7-3% have
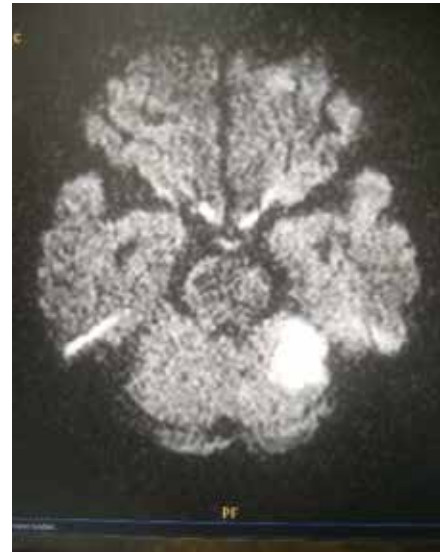
cerebellar infarction.[3,4] The common symptom of vertigo of cerebellar infarct has to be differentiated from other causes of vertigo as benign paroxysmal positional vertigo, Meniere's disease, migrainous vertigo or vestibular neuritis. The symptoms of cerebellar stroke overlap substantially with other benign condition hence it is often overlooked, with a misdiagnosis rate estimated at 35%.[4] Patients with missed cerebellar infarction in general are at higher risk of complications, with mortality rate possibly as high as 40%.[5] Hypertension and cardio aortic diseases are found in majority of the patients of cerebellar infarction and an embolic source is found in 24-40%.[1,6]

Hypertension is the main risk factor for stroke and can cause stroke through many mechanisms. A high intraluminal pressure will lead to extensive alteration in endothelium and smooth muscle function in intracerebral arteries. The increased stress on the endothelium can increase permeability over the blood-brain barrier and local or multifocal brain oedema. Endothelial damage and altered blood cell- endothelium interaction can lead to local thrombi formation and ischemic lesions. Fibrinoid necrosis can cause lacunar infarcts through focal stenosis and occlusion.[7]

The two most common easily overlooked sign in cerebellar infarction are ataxia and direction changing nystagmus. 71% of the patients with cerebellar infarction and isolated vertigo present with inability to walk without support and nystagmus found to be 56% sensitive for cerebellar infarction.[2,6] The inability to walk without support and direction changing nystagmus are important signs because they are commonly present even when no other findings of brainstem ischemia are present. At least one of these two signs are seen in 84% of the patients with cerebellar infarction and isolated vertigo.[6]

Neuroimaging for the vertiginous patients has not been clearly established. On the basis of currently available evidence, clear indication for neuroimaging include any focal neurological deficit, inability to walk without support, and direction changing nystagmus. When neuroimaging is indicated, diffusion weighted Magnetic Resonance Imaging (MRI) with magnetic resonance angiography is currently considered the optimal study. For ischemic stroke, MRI is clearly superior with an 83% sensitivity compared to 26% of Computed Tomography (CT).[8] CT therefore should not be relied to rule out cerebellar infarction.

Cerebellar infarction requires high index of suspicion and timely intervention because of danger of cerebral oedema within the posterior fossa. The cerebellum and brain stem are tightly constrained by the tentorium cerebelli superiorly and the occipital bone and foramen magnum posteriorly.[9] Within the posterior fossa, cerebral oedema can rapidly obstruct the fourth ventricle, causing hydrocephalus. In addition, cerebral oedema can compress the brainstem causing potentially fatal trans tentorial herniation of superior vermis through the tentorial notch or downward herniation of cerebellar tonsils through the foramen magnum.[10]

Management of cerebellar infarction is similar to infarcts of other areas of the brain. Thrombolysis is indicated in acute cases otherwise antiplatelet and statin are usual line of management. Close neurological monitoring is required and may require neurosurgical intervention because of the potentially fatal consequences of cerebral oedema in posterior fossa. Also, the associated condition and risk factor need to be diagnosed and treated accordingly.

CONCLUSION

Cerebellar strokes are rare cause of overall stroke with signs and symptoms mimicking other benign conditions. It requires vigilance and high index of suspicion and timely intervention to prevent fatal complications. Hypertension is one of the most common risk factor which need to be addressed appropriately.

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