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Abstract
Home blood pressure measurement (HBPM) is self-measurement of blood pressure. Because easy technique, accepted by majority of people and awareness of complication of hypertension patient get adhere to treatment of hypertension. The International Society of Hypertension also recognized usefulness of HBPM in the management of hypertension. HBPM improves adherence to drug treatment. HBPM helps treating doctors to modify or reduced the doses of antihypertensive drugs.

Introduction
Hypertension is major cause of morbidity and mortality worldwide. Accurate and reproducible of blood pressure measurement by reliable and authentic blood pressure devices is an important clinical skill, which every clinician should acquire it. The correct diagnosis of hypertension is based on proper measurement of blood pressure (Fig. 1). The complication of raised blood pressure if someone aware than he will be more adherence to the treatment of hypertension, and further hypertension management is easy and can avoid, delay the complication of hypertension.

Since 1960, the pioneering work by George Pickering and Maurice Sokolow, the several techniques developed to the measure blood pressure like clinic/office BP, 24-hr ambulatory blood pressure (ABPM), and home blood pressure. Out of these, home blood pressure is gaining important method because of easy technique, self-monitoring blood pressure, wider acceptance, and availability of HBPM devices also increasing awareness of importance of regular blood pressure monitoring and early recognition of morbidity due to hypertension (Fig. 2).

Why we should Know about Hypertension?
Hypertension is silent killer often patients are asymptomatic and when symptomatic it may be too late to revert the progress of disease process. Increased blood pressure may be leading cause of death globally.

Most guidelines recommended that when person’s SBP ≥ 140 mm Hg and DBP ≥ 90 mm Hg then the condition termed as hypertension.

American College of Cardiology (ACC) and American Heart Association (AHA) recently gave guidelines that when SBP > 120 mm Hg and DBP > 80 mm Hg have hypertension. White coat hypertension-office blood pressure more than home blood pressure. Mask hypertension when office or clinical blood pressure is normal and home blood pressure is more (10–15%).

Patients with hypertension are often asymptomatic and disease progress so much that complications slowly and silently develop like stroke, heart failure, CAD, and sudden death. Hence, every effort should be made to protect people at large by creating awareness of hypertension, educating them, train them in taking home blood pressure measurement (HBPM), aware them classification, and complication of hypertension.
Hypertension is major cause of morbidity and mortality globally account for 10.4 million death/year (Fig. 3). There for (KSH) International Society of Hypertension has develop worldwide practice guidelines for clinician in 2020 for uniform and better management of hypertension in adult age 18 years and above.\textsuperscript{5,5} There is clear shift of trend of hypertension from high income group to low income group\textsuperscript{6,7} due to education, awareness improved living conditions, and following lifestyle measurement.

These large disparities in regional load of hypertension is due to low level of awareness, non-adherent to treatment and low control rates of hypertension in these groups. Therefore, the International Society of Hypertension launched the global campaign to increase awareness of hypertension mainly the May measurement month initiatives along with Hypertension Society India, Association of Physicians of India, and other hypertension societies took several initiative like lifestyle modification, home blood pressure monitoring, and meditation to reduce mental stress level and regular follow-up with appropriate lab investigation to treating physicians.

To describe hypertension and its complication and management is beyond the scope of this topic; therefore, we restrict our self to “Home Blood Pressure Measurement”, that is, how to measure blood pressure, what is proper technique, how to create awareness of hypertension in

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**Fig. 2:** Vascular complications of hypertension

Hypertension

1. Stroke
2. Heart failure
3. Cerebral haemorrhage
4. Chronic kidney failure
5. Hypertensive encephalopathy
6. Peripheral vascular disease
7. Retinopathy
8. Aortic aneurysm
9. Left ventricular hypertrophy
10. Myocardial infarction
11. Coronary heart disease

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**Fig. 1:** Technique blood pressure measuring at home

- Quiet room, comfortable temperature
- No smoking, coffee, exercise for 30 min
- Empty bladder
- Relax for 3–5 min
- Take 3 measurements at 1 min intervals
- Use the average of the last 2 measurements

1. For manual auscultatory devices the inflatable bladder of the cuff must cover 75–100% of the individual’s arm circumference.
2. For electronic devices use cuffs according to device instructions.
masses and high-risk populations, how the standard method should be applied for measuring blood pressure. The good equipment, appropriate blood pressure cuff and proper training of personnel are very important. Lastly, compare these HBPMs with other standard method like ambulatory blood pressure measurement. These devices should be calibrated regularly with mercury sphygmomanometer once in 6 months or 1 year.

The measurement of blood pressure is the clinical procedure of greatest important that is performed in the sloppiest manner (Norman Kaplan). Equipment for HBPM—the fully automatic with big screen should be used, brachial artery (arm) should be used for blood pressure measurement. Wrist or other Oscillometric devices may not work well with patient in atrial fibrillation.

**Types of Blood Pressure Measurement**
- Home blood pressure measurement
- Average blood pressure measurement
- White coat hypertension
- Mask hypertension

In some patient’s non adherent to treatment, hypertension and diabetes mellitus, anxiety prone patients s/s hypotension, smoker, obese, hypercholesterolemia and non-dipper the ambulatory blood pressure measurement is more useful than HBPM.

High blood pressure is single major cause of death globally accept 10.4 million death/year.

In 2010 the estimated figure was 1.39 billion had high blood pressure.
In recent years, raised blood pressure (hypertension) clearly shifted from high-income groups to low-income groups.\(^8,^9\)

- Checking blood pressure yourself at home is the first important step in management of hypertension which raised your confidence for correct diagnosis of hypertension.
- It is low cost, easy acceptance of techniques, and reproducible.
- Home blood pressure monitoring is more closely related to office blood pressure which induces target organ damage and better predictor of CV events.
- It detects marked hypertension, white coat hypertension.
- It improves adherence to antihypertensive therapy.
- It improves closing of antihypertensive drugs.

### Guidelines for Home Blood Pressure Measurement

- Checking blood pressure yourself at home is the first important step in management of home blood pressure, which will help to raise your confidence, awareness, and help to consult your treating doctor early.
- Thirty minutes before taking home blood pressure avoid Tea, Coffee, Smoking, Tobacco, Alcohol, Food, Physical exercise, and Medication.
- Sit 5 minutes in upright chair quietly with feet flat on floor before measuring blood pressure.

Once you know correct technique and choose proper device, it is easy help you and your physician to control hypertension reduce cost and visit to clinical for measuring blood pressure.

Blood pressure reading should be taken twice daily. Two readings should be taken with a gap of 3–5 minutes. In irregular heart rate HBPM may not give correct Blood pressure measurement other method (tentative) or blood pressure true should be used for getting current blood pressure reading.

HBPM improve the patient’s compliance adherence to treatment helps in preventing complications of hypertension.

In some patients non-adherence to treatment, hypertension, and diabetes mellitus anxiety prone patients e/o hypertensive s/s, smoker, abase, hypercholesterolemia and non-dipper average blood pressure measurement is more useful than HBPM.

### What is the Value of Home Blood Pressure Monitoring?

It is inexpensive to monitor blood pressure at home, especially before and after changing the therapy. It is more accurate than office blood pressure monitoring. It helps to confirm the smooth control of blood pressure with therapy. It correlates more closely with ambulatory blood pressure monitoring than clinical blood pressure measurement. It helps to confirm diagnosis of hypertension in untreated patient.

Five prospective studies have compared home blood pressure monitoring, office blood pressure monitoring for predicting CVS outcome. All studies have found that home blood pressure monitor is significant predictor of CVS outcome, than office blood pressure monitoring. Home blood pressure monitoring product is better TOD than office blood pressure monitoring. Home blood pressure monitoring is reproducible, it differentiate between White coat, sustained hypertension, and detect mask hypertension.

In older people where blood pressure variable is high and WCH is common and in DM, CKD blood pressure control is very important to reduce complication of hypertension home blood pressure monitoring is very helpful.

Home blood pressure is also helpful in pregnancy for early detection of pre-eclampsia, in CKD blood pressure fluctuation is very high; in patients with hypertension for early detection and diagnosis home blood pressure is helpful.

Despite of advances made in treatment of hypertension over last 60 years. There is still room for improvement in the management of hypertension.

Home blood pressure readings are very often lower than office blood pressure readings, that is, <135/85, or <130/80 mm Hg in high risk group.

### Indications for ABPM

- Suspected White coat hypertension
- Suspected masked hypertension (normal clinic blood pressure and elevated ABPM)
- Suspected nocturnal hypertension or non-dippers
- Suspected episodic hypertension (e.g., pheochromocytoma)
- Resistant hypertension
CHAPTER 12

Home Blood Pressure Measurement

- Titrating antihypertensive therapy
- Hypotensive symptoms while taking antihypertensive medications
- Autonomic dysfunction
- Hypertension detected early in pregnancy
- Suspected or confirmed sleep apnea

**ABPM:**
- Can be expensive
- Should be comfortable for patient to wear (light and quiet)
- Use of correct cuff size
- Need to be familiar with equipment
- Time to instruct patient, full explanation to patient of what is required
- Requires patient cooperation in order to obtain as many readings as possible
- Twenty-four-hour blood pressure correlates most closely with TOD (compared to clinic or casual blood pressure)
- Higher incidence of cardiovascular events when blood pressure remains elevated at night (non-dippers)
- Blood pressure variability is an independent determinant of TOD
- Highest incidence of cardiovascular events occurs in morning hours
  The upper limit of normal for home blood pressure monitoring is 135/89 mm Hg. It corresponded to 140/90 mm Hg.

**Equipment:**
- Fully automated monitors that use the Brachial Artery (Arm) for measurements are the most reliable
- Wrist monitors are not recommended
- Proper documentation of reading by patient/automated by machine—*Date, Time, and blood pressure*
- Oscillometric devices may not work well with patients who have atrial fibrillation or other arrhythmias
- Patients HBP monitoring device should be calibrated against mercury sphygmomanometer every 6–12 months

**Equipment cuff size:** See Table 1.

**Benefits:**
- HBPM is easy to use, more reproducible, more accurate, and has higher prediction of target organ damage than clinic blood pressure (Class IIa LOE B)
- Differentiates between White coat HT and Sustained HT
- In patients with prehypertension, detects masked HT
- Used to determine response to treatment
- Improves adherence (patients who use HBPM are more likely to take medications regularly)
- Improves quality of treatment and reducing the cost

**Benefits in special subsets:**
- Elderly: Blood pressure variability tends to be high, and White coat hypertension is common.
- Diabetics: Tight blood pressure control is important and home monitoring may help achieve this.
- Pregnancy: The early detection of pre-eclampsia might be facilitated by HBPM.
- Chronic kidney disease: Blood pressure may fluctuate a lot and home monitors help with management.
- Children: White coat hypertension occurs in children, and there are some data on normal home blood pressure levels at different ages.

### Support for Home Blood Pressure Measurement

- Measurements taken by patients at home are often lower than readings taken in the office and closer to the average blood pressure recorded by 24-hour ambulatory monitors.
- Home blood pressure reading predicts risk better than office blood pressure
- In a 2005 Gallop poll:
  - 35% of hypertensive patients now check their blood pressure at least once per week.
  - 86% of patients who had been advised to purchase a blood pressure monitor had done so.
  - 55% of patients were monitoring their blood pressure an increase of 17% from 2000.

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**TABLE 1** Equipment cuff size

<table>
<thead>
<tr>
<th>Cuff name</th>
<th>Bladder width</th>
<th>Bladder length</th>
<th>Mid arm circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small arm</td>
<td>10</td>
<td>24</td>
<td>22 to &lt;27 cm</td>
</tr>
<tr>
<td>Average arm</td>
<td>13</td>
<td>30</td>
<td>27 to &lt;33 cm</td>
</tr>
<tr>
<td>Large arm</td>
<td>16</td>
<td>38</td>
<td>33 to &lt;41 cm</td>
</tr>
<tr>
<td>Extra large</td>
<td>17</td>
<td>43</td>
<td>41 to &lt;52 cm</td>
</tr>
</tbody>
</table>

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**TABLE 1** Equipment cuff size
Conclusion

- Home blood pressure monitoring is very important for controlling the hypertension in masses. Therefore, the education of masses and training of taking home blood pressure to individual are also essential. The treating physician is also getting help for changing therapy for hypertension.
- ABPM can be regarded as the gold standard for the prediction of risk related to blood pressure.
- ABPM predicts clinical outcome better than clinic blood-pressure measurements.
- It is recommended that HBPM should become a Routine Component of blood pressure measurement in the majority of patients with known or suspected hypertension.
- HBPM has minimal cost, enhances self-confidence and compliance.
- HBPM can improve blood pressure control.
- HBPM Correlates More Closely with the results of Ambulatory blood pressure monitoring than clinic blood pressure.
- HBPM is more Predictive of Adverse Outcomes [e.g., stroke, end-stage renal disease (ESRD)] than clinic blood pressure.

References

Abstract
Orthostatic hypotension (OH) is an important but underrecognized entity. It is associated with an increased risk of cardiovascular diseases, and contributes to recurrent falls, syncope, and mortality, more so in the elderly population. A fall of 20 mm Hg or more in systolic blood pressure and/or 10 mm Hg or more in diastolic blood pressure is termed as Orthostatic hypotension. It can be a sign of autonomic dysfunction (neurogenic OH) or intravascular volume depletion (non-neurogenic OH). Orthostatic hypotension may also be classified into initial, classic, and delayed. Diagnosis of OH can be made using the bedside standing test, head-up tilt table test, and the 24-hour ambulatory blood pressure measurements. Management of OH can be difficult, and constitutes both pharmacologic (midodrine, droxidopa, and fludrocortisone) and non-pharmacologic measures.

Introduction
Orthostatic hypotension (OH) or postural hypotension is an important, though an underrecognized entity in clinical practice. Its importance is evident because of its association with increased risk of cardiovascular diseases, recurrent falls, syncope, and mortality. Besides, it is also associated with prothrombotic state, chronic kidney disease, fragility fractures, and cognitive decline. However, in the SPRINT trial, OH was not found to be associated with a higher risk of CVD events, falls, or syncope.

A recent meta-analysis demonstrates that OH affects nearly one in five older persons living in the community, and almost one in four persons living in long-term residential care facilities. It is common in patients with diabetes, affecting an estimated 30% of individuals with type 1 diabetes and 25–30% of individuals with type 2 diabetes. In the in-patient setting, prevalence as high as 64% can be observed.

Definition of OH
It is defined as a fall of at least 20 mm Hg in systolic blood pressure (BP) and/or of at least 10 mm Hg in diastolic BP within 3 minutes of active standing or head-up tilt table testing (HUTT) at an angle of at least 60°. However, this traditional definition of OH is recommended for normotensive persons. In hypertensive individuals, a reduction in systolic BP of 30 mm Hg is required to define OH. In addition, European Society of Cardiology proposed an additional criterion for OH: a fall in systolic BP to <90 mm Hg irrespective of magnitude of the BP drop.

Clinical Features
The inability to tolerate the upright posture because of signs and symptoms, which are relieved by recumbency is termed orthostatic intolerance (OI). OI generally results from either ineffective regulatory mechanisms or environmental conditions that exceed the ability of these
homeostatic mechanisms to compensate appropriately for the environmental stress. The clinical manifestations can be:

- Light-headedness or woozy sensation
- Visual (blurring/dimming) and hearing difficulties
- Syncope/presyncope
- Deficits in memory, reasoning, information-processing speed, and concentration
- Fatigue
- Headache
- Tremulousness
- Sweating
- Weakness
- Neck cramping or “coat-hanger headache,” due to hypoperfusion of the trapezius and shoulder girdle muscles
- Nausea and chest/abdominal pain
- Exercise intolerance

**OH Classification**

According to the period of occurrence, OH is classified as initial, classic, and delayed.

**Initial OH** is defined as a transient drop of >40 mm Hg in systolic BP and/or >20 mm Hg in diastolic BP within 15 seconds of active standing. The proposed underlying pathophysiologic mechanism is a temporal and abrupt mismatch between cardiac output and total peripheral resistance. Initial OH is frequently symptomatic and a common cause of situational syncope, which may be underrecognized.

**Classic OH** is the most common and typical variant of OH. It is defined as a sustained decline in systolic and/or diastolic BP (according to the current criteria for OH) within 30–180 seconds of active standing or HUTT. Classic OH is caused by decreased total peripheral resistance and/or an excessive fall of cardiac output, such that compensatory vasoconstrictor mechanisms are not sufficient to restore postural BP decline.

**Delayed OH** is defined as a sustained fall in BP (according to the current criteria for classic OH) occurring after 3–45 minutes of active standing or HUTT. The possible pathophysiologic mechanisms of delayed OH include increased pooling in the lower body capacitance vessels and gradual impairment of compensatory mechanisms during prolonged orthostatic stress, resulting in slow progressive declines in venous return to the heart, cardiac output, and BP. Delayed OH is considered a mild form of classic OH and may progress to classic OH.

OH can also be classified based on underlying pathophysiologic mechanisms as neurogenic or non-neurogenic.

**Neurogenic OH** is due to primary neurological disorders like Parkinson’s disease, multisystem atrophy, pure autonomic failure, Lewy body dementia or secondary polyneuropathies like endocrine disorders (diabetes mellitus, adrenal insufficiency, and hypothyroidism), malignant diseases (amyloidosis, multiple myeloma, and paraneoplastic syndromes), autoimmune diseases (lupus, Sjögren’s syndrome, rheumatoid arthritis, celiac disease, Guillain–Barré syndrome and multiple sclerosis), toxins (alcoholism, chemotherapy, and poisoning by industrial chemicals), nutritional deficiencies (vitamins B1, B6, B12, and E), infections (herpes zoster, human immunodeficiency virus), uremia, and cirrhosis.

The causes of **non-neurogenic OH** are aging, volume depletion (blood loss, dehydration), venous pooling (prolonged immobility, deconditioning, postprandial, exposure to hot and humid environment, varicose veins), cardiovascular disorders (hypertension, heart failure, cardiac arrhythmias, aortic stenosis, hypertrophic obstructive cardiomyopathy), renal failure, medications like diuretics, vasodilators (alpha-receptor blockers, calcium channel blockers, hydralazine, nitrates, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), central sympathetics, beta-receptor blockers, psychotropic agents (antidepressants, tranquilizers, antipsychotics), and anti-Parkinsonian agents.

**Diagnosis of OH**

The clinician should have a high degree of suspicion and careful history should always be obtained. The three recommended methods to evaluate OH are explained below.

- **Schellong test or bedside standing test:** The test is named after Fritz Schellong, a European pioneer of cardiovascular autonomic neuroscience. Active standing-up from the supine position is the "gold standard" method for initial evaluation of OH. There is no universal standardized protocol for performing a standing test, although this usually consists of a supine phase of 5–10 minutes, followed by an active standing phase of at least 3 minutes, ideally 5–10 minutes.
Blood pressure and heart rate are measured at the end of the supine phase and at 1-minute intervals during the orthostatic challenge. If the patient is unable to stand up from the supine position, a sitting-to-standing protocol is acceptable, although less sensitive than the supine-to-standing one. A sustained decrease of at least 20 mm Hg in systolic blood pressure or at least 10 mm Hg in diastolic or an absolute systolic blood pressure below 90 mm Hg after 3 minutes standing qualifies for OH.

- **Head-up tilt table test (HUTT):** It is a specialized method which largely depends on an expert to interpret the findings. It is performed if bedside standing test is negative in presence of strong clinical suspicion of OH. Moreover, its methodology is not standardized, and it is a less sensitive test. Protocols for performing HUTT vary in the durations of the supine pre-tilt and the passive head-up tilt, the tilt angle, and the monitoring of hemodynamic parameters.

- **24-hour ambulatory blood pressure measurements (ABPM):** Diagnosis of OH by ABPM is based on diurnal variation of systolic and diastolic BP. Reduced dipping (night/day fall 10% in mean values of BP) and reverse dipping (night/day increase in average BP levels) are patterns of diurnal BP variation that associate strongly with OH. ABPM may be helpful for diagnosing masked OH (OH that is not detected in the office) and postprandial OH. In addition, ABPM is recommended for patients with established OH, for assessment of nocturnal hypertension, drug induced OH and OH severity, and for tailoring treatment and diagnosing of additional comorbidities such as obstructive sleep apnea.

**Treatment**

It consists of both pharmacological and non-pharmacological measures.

**Non-pharmacologic Measures**

Patient education is the cornerstone of the management of neurogenic OH. The provocative factors that might precipitate or exacerbate OH [e.g., warm ambient temperatures; hot baths or showers; straining, especially with breath holding (the Valsalva maneuver); sudden moves from the supine or seated position to the upright position; and ingestion of large meals] should be sought for. Physical activity and exercise should be encouraged to avoid deconditioning. Simple activities like leg-crossing; stooping; squatting; and tending of the muscles of the legs, arms, abdomen, buttocks, or whole body reduce venous pooling and thereby increase central blood volume and cardiac filling, with resultant increases in cardiac output, BP, and cerebral perfusion. Additional non-pharmacologic measures include increased salt and water intake, slow rising, raising the head of the bed during sleeping, and the use of compression garments on the abdomen or lower extremities. Rapid ingestion of approximately 500 mL of tap water (e.g., over 3–4 minutes) elicits a marked press or response and improvement in symptoms in patients with neurogenic and non-neurogenic OH. In fact, acute water ingestion is the only class I recommended treatment for OH. All other measures (including pharmacologic treatment as well) have class II recommendations.

**Pharmacologic Measures**

**Midodrine (class IIA):** Patients with neurogenic OH report improvement in symptoms after taking midodrine. A dose-dependent effect is seen, usually corresponding to an increase in standing blood pressure. Though an important drug, several side effects may limit its use. Some of them are supine hypertension, scalp tingling, piloerection, and urinary retention. The dose usually used ranges from 5 to 10 mg per oral three times a day (the last dose at least 3 hours before bedtime).

**Droxidopa (class IIA):** It is mainly used for neurogenic OH that occurs in patients suffering from Parkinson’s disease, pure autonomic failure, and multiple system atrophy. According to some small studies droxidopa might reduce falls. Concomitant use of carbidopa in patients with Parkinson’s disease may decrease the effectiveness of droxidopa. Some side effects such as supine hypertension, headache, dizziness, and nausea may limit its use and titration. Usual dose is 100 mg per oral three times a day slowly increased to 600 mg three times a day over 3–7 days.

**Fludrocortisone (class IIA):** The improvement of symptoms of OH is primarily seen due to increases in plasma volume. If taken regularly, at least in astronauts after space flight, fludrocortisonemaypreventOH.Sincsupinehypertension is a limiting factor for its use, other medications should be used before fludrocortisone. Commonly seen side effects
include edema, hypokalemia, and headache. Adrenal suppression and immunosuppression, which are serious side effects can also occur with doses >0.3 mg daily. The starting dose is 0.1 mg per oral daily, maximum being 0.3 mg daily.

Pyridostigmine (class IIB) and octreotide (Class IIB) may be beneficial in certain refractory cases.

**Conclusion**

OH is an important diagnosis, which is likely to be missed in day-to-day clinical practice. A high index of suspicion, with good history and evaluation, is helpful in confirming the diagnosis. Apart from patient education and other non-pharmacological strategies, acute water ingestion is the recommended Class I treatment. Certain medications (Class IIA) like midodrine, droxidopa, and fludrocortisone form the basis of adjunct therapies in managing OH.

**Suggested Readings**

Abstract
Edible oil is an essential component of daily Indian food. However, there are a lot of wrong notions about the relative health benefits of different cooking oils. In a culturally diverse country like India, people in different communities have been using different sources of vegetable oil for hundreds of years and it is very difficult to come to a consensus for 1.4 billion people. In this article, the authors have discussed the biochemistry of edible oils including smoke point, the Omega 3:6 ratio, presence of phytosterols and the merits and demerits of refining these oils. Without selecting any particular oil, the authors have tried to discuss the health benefits and risks of various types of vegetable oil with special emphasis on the PUFA and MUFA content, the importance of omega-3 fat and the presence of saturated fat. The scientific basis of health risks associated with saturated fat and trans-fat has also been touched upon. The authors have also discussed the harmful effects of the commonly used cooking medium, Vanaspati. Finally, the authors have also discussed in brief, the problem of edible oil adulteration in India. There is no one correct option when it comes to choosing cooking oil. Sometimes, mixing two oils or using particular varieties of oil on particular weekdays may be the answer.

Introduction
The daily diet in India usually has curries as an indispensable component. Boiled, grilled, or steamed food, although popular for occasional feasts, is not preferred as daily food in India and most Indians prefer cooked items.

But India is a land of diversity. There are many tribes of Northeast India who prefer boiled food. In their cuisine, there is often very little oil. We must be aware of this culinary tradition of our country too. Thus, generally, the cooking medium, viz. oil, is an integral component of quotidian Indian diet. This is one of the main sources of fat in Indian food.

However, there is almost no scientific study or rational discussion on this indispensable dietary element and most Indians get their half-baked ideas on cooking oil either from family tradition or from the so-called “diet experts” online. The void left by the lack of proper scientific discourse is filled by pseudoscientific gibberish or advertisement gimmicks released by the processed food industry. The Indian cuisine varies radically throughout the length and breadth of this incredibly diverse country and any discussion on the “Indian” diet must be aware of this diversity. Otherwise, making just one dietary recommendation for the entire country is likely to be eschewed by various cultural groups and will never be acceptable for all sections of the population. The authors of this article recognize this dietary multiplicity of the country and will shape their discussion in an inclusive manner.

The Indian Culinary Culture
First of all, the authors will describe the prevailing culinary culture of the country with reference to cooking oil. But
it must be remembered that the choice of cooking oil is shaped by a lot of factors like family tradition, education level, socioeconomic status, place of residence, and accessibility. The Indian media or movies have a harmful tendency of clubbing various cultures of this country together as "North India" or "South India". But clubbing such diverse cultures as Malayali, Konkani, or Tamil together under the broad heading of "South Indian culture" is like describing British, French, and Italian cultures together. In the southern part of the country, in Kerala, coconut oil is the most popular cooking oil. They would never think of using mustard oil. But in the eastern part of the country, in Bengal, mustard oil is the oil for popular fish or meat dishes. Again, in Tamil Nadu, the state bordering Kerala and having a lot of cultural similarities, they prefer sunflower oil, groundnut, and sesame oil, but not coconut oil. If you go to Gujarat, you encounter sunflower oil and ghee for cooking. In Kerala or Tamil Nadu, mustard oil is used for pickles only, not for cooking. Similarly, in Bengal or Gujarat, coconut oil is used for applying on hair, not for preparation of food. Ghee is popular in Punjab, Haryana, and Madhya Pradesh for cooking. Groundnut oil is also used in Karnataka. In Goa, for the traditional dishes, they use coconut oil but for daily cooking, sunflower oil is preferred.

However, the cooking habit of urban Indians is radically changing with time. All across India, the upwardly mobile middle class is now shifting toward safflower oil, olive oil, rice bran oil, or soyabean oil. The earlier popularity of cottonseed oil or rapeseed oil is now dwindling. This is not specific to any culture and mainly reflects Western influence. Especially, the use of olive oil is seen as a status symbol by many Indians; but as subsequent discussions will show, this really does not have much health benefit to justify the cost. Over the last two decades, India has been importing millions of tons of palm oil as a cheap vegetable oil. This oil is used for making roadside food, biscuits, and many packaged food items. Millions of Indians are unknowingly consuming palm oil every day, although they don’t buy it for their home. Vanaspati, hydrogenated vegetable oil, is used in many hotels or restaurants of India. This is mainly prepared by processing palm oil. Thus, while discussing the cooking oil of Indians, not only the domestic food but also the outdoor food items must be discussed.

The discussion below is designed to be a scientific discourse on the pros and cons of various cooking oils and is not intended to be judgmental on any culture.

**Some Important Physical and Chemical Properties**

If the reader wants to make an informed choice about his/her cooking oil, then some preliminary knowledge on the biochemistry of this product is needed. Some important terms are discussed first.

### Smoke Point

This is the temperature at which oil starts to emit smoke or starts to burn. If the smoke point is low, that oil will burn in the frying pan easily. This gives a bad smell, bad taste, and also can generate free radicals. Thus, if the reader wants to deep fry something, obviously oil with high smoke point will be needed. Otherwise, the oil will burn and the frying will be half-done. Table 1 gives the smoke point of some commonly used cooking oils.

The authors would like to discuss two points on this table. Firstly, as seen here, butter is not a good frying medium. It has low smoke point and will burn easily. On the other hand, ghee has smoke point of 480°F. Thus, ghee can be used safely for frying. Secondly, the term “refined” is very important while discussing the smoke point. Unrefined safflower oil has smoke point of 225°F, while refined one has smoke point of 510. Thus, the final smoke point is also dependent on the degree of refining of the oil. This is one of the advantages of refining oil, although the disadvantages of refining will be discussed later.

### PUFA

These are organic acids with more than one double bond in their backbone. Many of them are essential in nutrition. These acids are further divided into Ω-3 and Ω-6 acids.
They will be described later. In high temperature cooking, the polyunsaturated fatty acids (PUFA) in cooking oil can degrade into hydroperoxide and other harmful products. Some studies have found cardiovascular benefit with consumption of some varieties of PUFA, like the Ω-3 variety. This is thought to be due to the antiatherogenic effect of long chain Ω-3 PUFA. Also, it raises HDL and lowers triglyceride in blood. The LDL particles in blood are also modified with alteration in their apolipoprotein levels, which make them less atherogenic. It is also thought that these varieties of PUFA may alter gene expression in the early stages of atherosclerosis.

In the website of the American Heart Association, three oils are mentioned as good sources of PUFA: soybean oil, sunflower oil, corn oil. Of these, corn oil is not found in India till now. But in the future, it may be imported and sold here. Also, the AHA recommends nuts like Walnut and soybean as sources of good PUFA. But there is a problem with PUFA-rich vegetable oils. During the process of refining, the PUFA in these oils may be oxidized, which may be harmful for the body.

MUFA
These are fatty acids that have only one double bond in their carbon skeleton. Some studies have shown decrease in blood LDL levels with monounsaturated fatty acids (MUFA) intake. But studies on diet are at best imperfect and it is often impossible to separate the relative benefits of each dietary component. The Mediterranean diet is rich in MUFA. Some studies have found that high MUFA intake may be associated with decreased risk of malignancy, diabetes, and neurodegenerative diseases.

Food rich in MUFA: Olive, Avocado, Cashew nut, tea-oil, whole grain wheat.

Cholesterol
Cholesterol is a compound which is found only in animal sources of food. Any plant product is expected to be free of cholesterol. Thus, the advertising gimmick of brandishing vegetable oil as “cholesterol-free” is basically a redundant message. Rather, if vegetable oil was not cholesterol free, it would be abnormal and we would suspect contamination with some animal fat!

Saturated Fat
Saturated fat is the type of lipid which contains no double bond in the carbon skeleton. Usually, these are solid at room temperature (although this is not universally true). Animal products like ghee are usually high in saturated fat. Saturated fat is considered to be bad for the vascular system. A Cochrane database review, published in May, 2020 found that cutting down on saturated fat led to a significant reduction in cardiovascular events.

Food high in saturated fat: butter, ghee, coconut oil (87%), palm oil (50%), sausage. All the commonly used vegetable oils contain very little saturated fat except rice bran oil, which has 25% saturated lipids.

Interesting fact: Ghee, constituted of 62% saturated fat, has a very long shelf life. That is why, in the Ayurvedic system of medicine, old Ghee was considered a valuable component. In India, two types of Ghee are in use: Cow and Buffalo products. Both are similar in fat content and only difference is the high carotene content in Cow milk Ghee.

Trans-fat
A trans-fatty acid is an unsaturated fatty acid in trans-geometric configuration. Trans-fatty acids have no known metabolic function in human body. They increase LDL in blood. This is produced mainly as a result of hydrogenation of vegetable oil. In the USA, the government has issued a guideline that there is no safe limit of consumption of trans-fat. It is to be completely eliminated from diet. Studies have shown that the concentration of trans-fat in adipose tissues of individuals who died of IHD were 8–10% higher compared to others. Studies in New York have shown that restriction of trans-fat in food industry led to significant reductions in the incidence of AMI and CVD mortality. The effects of trans-fat are shown in Figure 1.

Common food with trans-fat: Margarine, butter, some cake products. In Indian context, trans-fat is mainly found in foods that are cooked with reused oil. In roadside eateries of India, it is very common to find the same oil being used to fry a variety of products throughout the day. Constant reheating of oil produces trans-fat. Vanaspati, hydrogenated vegetable oil, is used commonly in India as a cheap substitute of ghee. This product contains trans-fat and is harmful. The reader of this article should be aware that Vanaspati is the commonest cooking medium in hotels and cafes and thus many Indians are unknowingly consuming the trans-fat of Vanaspati every day in canteens. Deep fried commercial food also contains trans-fat. For large multinational food companies, the quality of food is improved by regulation. But in the small scale industries
in remote parts of the country, the quality of local food industry is largely unregulated and those items may have trans-fat.

**Oryzanol**

This is a product of rice bran. Thus, Oryzanol is available only in rice bran oil. This is sometimes marketed as a health supplement but benefits are doubtful. It may have some antioxidant action.

**Ω-3 and Ω-6 Ratio**

As discussed earlier, these are varieties of PUFA. A particular specimen of oil (any oil) contains various types of PUFA. The nomenclature is based on the position of the double bond in the carbon skeleton. For example, Ω-3 acids are those where the double bond is three atoms away from the terminal methyl group.

Ω-3 acids include DHA, EPA, and alpha linolenic acid (ALA). Common sources are flaxseed oil, hemp oil, fish oil, and eggs. Animal sources are the sole supplier of EPA and DHA, while plant sources supply ALA. ALA can be converted into the other forms. Thus, vegetarian diet is enough to get the required Ω-3 acids. *The enzymes required for conversion of ALA to other PUFA are δ desaturase and elongase in the liver endoplasmic reticulum.*

Ω-6 acids include linoleic acid, calendic acid, etc. Most of the vegetable oil contain Ω-6 acids.

Ω-9 acids include oleic acid, erucic acid. *These are MUFA, not PUFA like the two previous ones. Sources include mustard, olive, and rapeseed.*

The reader must not assume that one particular oil contains one type of PUFA or MUFA. Usually, it is a combination and the relative percentages vary with processing. For example, mustard oil contains 60% MUFA (erucic acid etc.), 21% PUFA (Ω-6 more than Ω-3), and the rest saturated fat.

Ω-3 fatty acids are considered to be better for our health. Oil like hemp oil is rich in this variety, but it is not popular for cooking due to low smoke point. So, some authors have suggested blending two or more varieties of oil to make a more nutritionally healthy mixture. This can also overcome the problem of low smoke point.

The main aim is to increase the proportion of Ω-3 acids in our diet. Some cooking oil with good Ω-3 content are: canola oil and ghee. Fish oil, like cod liver oil, contains excess Ω-3 fraction. But fish oil is not used for cooking in India. Fish oil, like cod liver oil, is also a rich source of vitamins A and D. *But in India, fish oil is not popular due to its smell and also due to vegetarian culture of many communities in the country.* Coconut oil does not contain any Ω-3 acid. Sunflower oil, the most popular oil in urban India, has very high Ω-6 to Ω-3 ratio. Ω-6 acids are proinflammatory and thus, may have adverse effects on the blood vessels. But they don’t act in isolation. Other dietary factors are also responsible in tandem for the cardiovascular morbidities. Thus, it may be a suggestion to mix sunflower oil with some other oil like canola oil to improve Ω-3 content.

**Tocotrienols**

When oil is extracted from seeds, along with the lipids, some other compounds also get extracted. One of them is tocotrienols, a type of tocols (which also include tocopherols). It is mainly found in palm oil, rice bran oil, wheat germ oil and soybean oil. These are one of the most important antioxidants in vegetable oil. If a sample of oil is high in tocols, then the PUFA in that oil will resist oxidative damages. α-tocopherol are the major tocols in most oils like almond, olive or sunflower. In some varieties like soybean and canola oil, γ-Tocopherol is higher. Palm oil, although considered a cheap and inferior quality of edible
Cooking Oil: Making the Right Choice

Tocopherol content of some common edible oil

<table>
<thead>
<tr>
<th>Oil</th>
<th>Tocopherol (mg/100 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheat germ oil</td>
<td>150–190</td>
</tr>
<tr>
<td>Sunflower</td>
<td>33–60</td>
</tr>
<tr>
<td>Safflower</td>
<td>37–50</td>
</tr>
<tr>
<td>Coconut</td>
<td>0.2–2</td>
</tr>
</tbody>
</table>

Cold Pressing

Cold pressing is the process of extracting oil from plant seeds like olive by pressing at room temperature, without applying any extra heat. This prevents thermal degradation of phenolic and other useful compounds. However, the yield of oil is less and thus, for a burgeoning consumer market of India, quicker heat extraction method is preferred. Some consumers also prefer the better smell and taste of heat-pressed oil. Only olive oil and sesame oil are suitable for cold press production on a large scale.

Making the Right Choice

So, in the preceding discussion, the reader has been introduced to the essential principles based on which edible oils should be chosen. There is no single correct answer for this topic. Besides the scientific points mentioned above, the other important factors in the choice of any food are cultural, tradition, smell, taste, etc. Those issues cannot be neglected because they influence human behavior to a large extent. It must be remembered that any oil or ghee is 100% lipid by chemical composition and yields 9 kcal/g when metabolized. So, there is no “low-fat” oil and all varieties of oil, whether high in PUFA or high in saturated fat, yields the same number of calories.

Mustard oil is preferred in parts of Eastern India due to its distinctive smell and taste. This pungent smell is due to allyl isothiocyanate. This compound has no nutritional value. Mustard oil has about 21% PUFA, which is higher than coconut oil (2%). But mustard oil has high erucic acid, which is not digested by human intestine. This can also cause other metabolic problems. That is why the USFDA has banned the import of mustard oil in their country. Coconut oil, on the other hand, contains medium chain triglycerides, which have better absorption and metabolism. Also, these MCTs are less likely to be stored as fat and there is less weight gain.

Olive oil is the staple component of Mediterranean diet. It has high MUFA, which is good for the heart. Also, it contains other beneficial compounds like tocopherols. But Ω-3:Ω-6 ratio of olive oil is not optimal. Soybean oil has good PUFA content. But one disadvantage is that it gets rancid very quickly. Mustard oil also has high PUFA but due to presence of other antioxidants, it can be stored without rancidity for long. Safflower oil has high smoke point which is good for frying. But it contains high PUFA oil, contains high quantity of all types of tocopherols. The α-tocopherol content of some common oils that are given in Table 2.

Tocols have neuroprotective and anti-cancer properties and also prevents vascular changes in diabetes. However, during the refining process of vegetable oil and the deodorizing process, tocopherols are lost. The only exception being extra-virgin olive oil, which is prepared by a separate method without heat application. This retains the tocopherol content. Physical refining of oil reduces phenolic compounds more than chemical refining.

Phytoesterol

Phytosterols are plant compounds which are analogous to animal cholesterol. It has beneficial effect on blood cholesterol and reduces LDL levels. It is a good antioxidant and may also be beneficial in reducing the incidence of cancers. During lipid extraction from plant seeds, phytosterols are also added to the oil.

Rich sources of phytosterol include corn oil (990 mg/100 g), rapeseed oil (893 mg/100 g) and sunflower oil (253 mg/100 g). Prolonged cooking and high temperature food processing reduces the phytosterol content in oil.

Carotenoids

These are another group of important compounds in edible oil. Cold-pressed oil is a better source of carotenoids than heat-extracted variety. Palm oil is a good source of carotenoids. There is a variety called red palm oil, which has particularly high carotene content. But it is costly due to its rarity. Carotenoids are good antioxidant and have a role in diet complementary to tocopherols.

In a recent study, it was found that only cold-pressed oils contain appreciable amount of carotenoids. The oils with higher carotene content are rapeseed oil, soybean oil and linseed oil.
and this can be oxidized to toxic compounds in prolonged cooking. Also, high PUFA content means that it gets rancid very easily. In this context, coconut oil is better for frying as it has high saturated fat and is thus, less prone to oxidation.

Palm oil has high saturated fat. But it also has high levels of tocopherols which are essential for human body. Avocado oil and peanut oil are high in MUFA content but these are not popular in India till now.

So, how should a consumer make the choice? It is often a delicate balancing act. For example, ghee is high in saturated fat, which is bad for the cardiovascular system. But at the same time, ghee has long shelf life, high smoke point and Vitamins A and D, which are points in its favor. Similarly, mustard oil has high smoke point, contains 21% PUFA but it has erucic acid, which is not digested in our intestine. Again, the Ω-3:Ω-6 ratio in mustard oil is better than most other oils. This is how a consumer will have to make the choice. If a consumer cannot make a single choice, then it may be advisable to mix two or three oils. For example, 3 days a week the cooking may be done with mustard oil and the rest 4 days, olive oil can be used. Or if the vitamin content of ghee is considered important, occasional ghee products may be consumed. This is how a diet plan is made.

Last but not the Least: The Problem of Adulteration

In India, one major problem is food adulteration.1 Consumers here have very little say over the quality of food items they get, especially outside the metro cities. Some common adulterants used in edible oil in India are:

- Since palm oil is cheaper, it is often added to costlier oils like groundnut oil or sunflower oil
- Liquid paraffin in coconut oil
- Argemone to mustard oil
- TOCP (an incident of TOCP addition to rapeseed oil led to mass paralysis in west Bengal in the 1980s, this is one reason why rapeseed oil is not popular in India)
- Coloring chemicals

Thus, a consumer of India, while selecting edible oil, has to remember not only the chemical properties or cultural factors, but also the problem of adulteration.

Conclusion

The choice of oil for cooking is a contentious issue. A lot of considerations like cultural acceptability, cost, availability, and health effects are taken into account while making the choice. Some people consider mixing a variety of oils for the optimum health benefit. Some people also consider opting for exotic varieties like olive oil or peanut oil. The final decision should be based on informed choice and scientific judgment.

References

Abstract
Hypertension is a major risk factor for cardiovascular (CV) disease, cerebrovascular accidents, chronic kidney disease, peripheral vascular disease, and heart failure. As per the recommendation of latest guidelines, monotherapy may not work in most patients, and to achieve optimal BP targets, most of the hypertensive patients eventually require a combination of two or more antihypertensive drugs. The combination therapy looks like a lucrative option than increasing the dose of single agent and offers several advantages over high dose monotherapy to treat hypertension. The aim of a physician treating hypertension should always be a cost-effective, long-term therapy to control BP with drugs that are effective, safe, well tolerated, and must also actually reduce the CV risk.

Introduction
Hypertension is a tremendous public health burden globally affecting millions of patients. It is estimated that 26% of the world’s population suffer from hypertension, and the prevalence is expected to increase to 29% by 2025, mainly attributed to increase in economically developing countries. Hypertension is a major risk factor for cardiovascular (CV) disease, cerebrovascular accidents, chronic kidney disease, peripheral vascular disease, and heart failure. Significant reduction in clinical CV end points can be achieved with meticulous control of blood pressure (BP) in hypertensive patients, more importantly in the presence of comorbidities like diabetes mellitus, chronic kidney disease, etc. In recent times, newer antihypertensive agents have come on the scene and there has been a rise in awareness among both patients and physicians, but a significant percentage of hypertensive patients continue to have suboptimal BP control.

Recently, evidence suggests that for control of hypertension, monotherapy may not work in most patients, and to achieve optimal BP targets as per the recommendation of various guidelines, most of the hypertensive patients eventually need a combination of two or more antihypertensive drugs. The fact that multiple factors are involved in etiology of hypertension also favors the use of combination drugs acting through different mechanisms to control the BP. Latest international guidelines also recommend to initiate a double-drug combination therapy for patients with a systolic BP (SBP) more than 20 mm Hg and/or a diastolic BP (DBP) more than 10 mm Hg above the target BP and also for those patients who are at increased CV risk.

Combination Therapy: Need of the Hour
The rise in BP is controlled by diverse mechanisms. The three factors that primarily determine the BP are: renal sodium excretion and resultant plasma and total body volume, cardiac output, and vascular tone. The sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) chiefly control these parameters on a real-time basis. Apart from that BP in
individual patients is also influenced by diet, genetic, and environmental factors. Due to this multifactorial etiology involved in genesis of hypertension, many a times it is very difficult, if not impossible, to control the BP by using a single antihypertensive drug. On the other hand, combination of two drugs with different mechanisms of action can provide two to five times greater antihypertensive effect than with monotherapy.  

Various clinical trials report that achieving BP goals is usually not possible with monotherapy. As per the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), only 26% of the patients could achieve target BP with a single drug—despite the fact that the goal BP for diabetics (36% of the patient population) was <140/90 mm Hg rather than <130/80 mm Hg as per recommendations of latest guidelines.  

In the Losartan Intervention for Endpoints Reduction (LIFE) trial, more than 90% patients with left ventricular hypertrophy needed at least two antihypertensive drugs to achieve target BP of <140/90 mm Hg. In the Hypertension Optimal Treatment (HOT) trial, the target BP (diastolic only) with a single drug was achieved by only 33% patients, 45% needed two drugs, and 22% required three agents. The average SBP at the end of the study was 141 mm Hg, indicating that even a greater number of patients would have required combination therapy as per current treatment guidelines.  

Apart from achieving target BP control, time taken to achieve it is also important in patients having hypertension with high CV risk. As demonstrated in a post hoc analysis of the Valsartan Antihypertensive Long Term Use Evaluation (VALUE) trial, patients who reached their BP goals at 6 months had less subsequent CV events. In a randomized controlled trial in patients with hypertension and metabolic syndrome, starting treatment with a combination of valsartan and amlodipine achieved BP goal more rapidly than initiating with a high dose of valsartan monotherapy. In a cohort study of hypertensive patients 34% risk reduction in CV events was mainly attributed to the more rapid achievement of BP target with combination therapy. Combination therapy can even be effective in hard-to-treat patients in achieving normal BP. This early normalization of BP also motivates the patients to be more compliant to lifelong treatment. Single pill combinations (SPCs) containing two or three drugs in the same tablet offer additional advantage by improving adherence and potentially reducing the cost of therapy.

### Theoretical Considerations of Combination Therapy

#### Efficacy

By combining drugs that either effectively block the counter-regulatory responses or interfere with clearly different pressor mechanisms, BP lowering is possible to a greater extent than with monotherapy. Usually combining agents from harmonious classes is about 5 times more effective in reducing BP than increasing the dose of one agent. Another important need to make a good combination is that the combined-drug administration should produce additive and continuous BP reduction throughout the dosing interval.  

The beta-blocker/calcium channel blocker (CCB) combination is a good example to show the harmonious action of two agents where on one side beta-blocker attenuates the CCB-induced activation of the sympathetic nervous system, and on the other hand, the vasodilatory effect of CCB weakens the alpha-mediated reflex vasoconstriction induced by beta-blockers.  

#### Tolerability

Most drug combinations are designed so as to improve the tolerability of therapy by neutralizing the dose dependent side effects (that occur due to use of higher doses) of a single agent, by the pharmacologic effects of an added drug. For example, hypokalemia produced by thiazide diuretic can be counter-balanced by addition of a potassium-sparing diuretic, such as amiloride, triamterene, or spironolactone, or a RAAS inhibitor.  

#### Adherence

Combination therapy can improve the adherence and compliance to treatment by simplifying regimen in terms of reducing the number of medications, frequency of dosing, and also being cost effective most of the times. This definitely helps in control of BP. In a meta-analysis of nine studies, the adherence rate was improved by 26% in patients receiving SPCs in comparison to those taking their components separately.

### Table 1 summarizes
the benefits and drawbacks of various drug prescribing strategies in hypertension management.

**Indications of Combination Therapy**
- Unable to achieve the target BP with monotherapy.
- Presence of adverse effects of single drug that may be improved by the addition of a second agent (e.g., adding an angiotensin-converting enzyme inhibitor to a CCB to reduce peripheral edema).
- The SBP is ≥20 mm Hg and/or DBP is ≥10 mm Hg above the target BP.
- Presence of convincing indications that may get benefitted from different mechanisms of action of multiple antihypertensives.

**Advantages of the Combination of Antihypertensive Drugs**
The combination therapy looks like a lucrative option than increasing the dose of single agent. The advantages of combination therapy are summarized in **Box 1**.

**Specific Drug Combinations Available**
Various trials have been used and studied different classes of drugs in combination for treatment of hypertension. Angiotensin receptor blockers (ARBs), thiazide diuretics, alpha and beta-blockers, calcium channel blockers (CCBs), and angiotensin-converting enzyme inhibitors (ACEIs) are the most commonly used classes of antihypertensive agents for combination therapy. On the basis of these large, result oriented trials, various international guidelines have classified the different available combinations as preferred, acceptable, or not acceptable (**Box 2**).

**TABLE 1** Comparison of various hypertension treatment strategies

<table>
<thead>
<tr>
<th></th>
<th>Low-dose monotherapy</th>
<th>High-dose monotherapy</th>
<th>Free combination therapy</th>
<th>Single-pill combination therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effectiveness</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Tolerability</td>
<td>✓</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Adherence</td>
<td>✓</td>
<td>✓</td>
<td>x</td>
<td>✓</td>
</tr>
<tr>
<td>Convenience</td>
<td>✓</td>
<td>✓</td>
<td>x</td>
<td>✓</td>
</tr>
<tr>
<td>BP variability</td>
<td>x</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Flexibility</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Fast attainment of target BP</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

**BOX 1** Advantages of combination therapy
- Rapid and sustained control of blood pressure due to additive effect of combined drugs
- Minimization of the dose dependent side effects that occur due to use of higher doses of a single agent thus improving the tolerability of therapy
- Many other pathophysiological mechanisms of increased blood pressure are simultaneously blocked
- Much better protection to target organs
- Other beneficial effects independent of antihypertensive action of drugs:
  - Anti-inflammatory action
  - Metabolic anti-counter regulatory actions
  - Nephro- and cardiovascular protection
- Homologous blood pressure lowering and good safety profile
- Reduced pill burden and most of the times economically effective

**RAAS Inhibitors (ACEI/ARB/DRI) + CCB**
The addition of RAAS inhibitors to a DHP-CCB leads to greater degree of BP reduction and increased tolerability by significantly reducing the incidence of tachycardia and peripheral edema observed with CCB monotherapy. In the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial, the ACE inhibitor/CCB combination was found to reduce the CV complications and stroke incidence by 20% as compared to the ACE inhibitor/diuretic combination.

**RAAS Inhibitors (ACEI/ARB/DRI) + Diuretics**
The RAAS inhibitor reduces the incidence of diuretic induced hypokalemia and new onset glucose intolerance. Most outcome trials have shown the thiazide-like
**SECTION 2**

**Hypertension**

**BOX 2** Specific drug combinations used in hypertension\(^{17,18}\)

**Preferred:**
- ACEI/DHP (dihydropyridine) CCB
- ARB/DHP CCB
- ACEI/Diuretic
- ARB/Diuretic

**Acceptable:**
- Beta-blocker/Diuretic
- DHP CCB/Diuretic
- DHP CCB/Beta-blocker
- Thiazide diuretic/Potassium-sparing diuretic
- Direct renin inhibitor (DRI)/DHP CCB
- DRI/Diuretic

**Not acceptable:**
- Centrally acting agent/Beta-blocker
- CCB (non-dihydropyridine)/Beta-blocker
- ARB/Beta-blocker
- ACEI/Beta-blocker
- ACEI/ARB

**Other Combinations**

Other drug combinations like Centrally acting agent + Beta-blocker, CCB (non-dihydropyridine) + Beta-blocker, ARB + Beta-blocker, ACEI + Beta-blocker, and ACEI + ARB are considered as non-acceptable or ineffective either because of increased incidence of some serious side effects or inability to produce significant additive BP reduction when they were used in various clinical studies.

**Single Pill Combinations**

Single pill combinations (SPCs) offer several potential advantages, including simplification of the treatment regimen, convenience, and sometimes decreased cost of therapy. The choice of combined agents can be used to minimize the adverse effects of each individual agent. The disadvantage like the risk of causing orthostatic hypotension is mainly observed in older patients and patients with diabetic autonomic neuropathy.

After the success of two drug combinations, researchers are moving toward three-drug therapy at a lower dose. In a 2018 study in Sri Lanka, treatment with a three-drug SPC in mild hypertensive patients resulted in 15% better BP control in the combination group without any statistically significant difference in adverse effects after 6 months of therapy.\(^{21}\)

In the TRINITY (triple therapy with Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide in hypertensive patients study) trial, at 12 weeks, the triple-combination therapy resulted in significantly more BP reduction when compared with three different dual combinations, made by using two of these three drugs, with no significant difference in adverse events in patients with moderate to severe hypertension.\(^{22}\)

A simple algorithm for the use of monotherapy and combination therapy has been depicted in **Flowchart 1**.

**Effects of Combination Therapy Independent of Antihypertensive Action**

**Anti-inflammatory Effects**

Studies have shown that combination of an ACEI with a CCB is more protective than monotherapy in decreasing the various inflammatory mediators such as interleukins, tumor necrosis factor, etc.\(^{23}\)
**Flowchart 1: Algorithm for management of hypertension using combination therapy**

- **Hypertension**
  - **Stage 1**
    - **Question:** Whether patient is at high CV risk?
      - **No**
        - Treatment with monotherapy or low dose combination therapy* 
          - Along with lifestyle modifications
        - Still target BP not achieved?
          - Switch to full dose dual combination therapy
          - Target BP yet not achieved
          - Start triple combination therapy as SPC**
      - **Yes**
        - Initiate treatment with dual combination therapy* 
          - Along with lifestyle modifications
        - Still target BP not achieved?
          - Switch to full dose dual combination therapy
          - Target BP yet not achieved
          - Start triple combination therapy as SPC**

*Preferred and acceptable dual-combination should be used only (Box 2).

**If BP goal is not reached on triple SPC, consider secondary causes of hypertension and add a fourth BP-reducing drug if required.

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**Hemodynamic Effects**

Matsui et al. in their study showed that the combination of the ARB plus CCB reduced the central aortic pressure to a greater extent than the combination with the diuretic agent.24

**Nephroprotective Effect**

Studies have found that the combination of an ACEI with a CCB was better than ACEI monotherapy in reducing proteinuria and taper down rate of renal deterioration in hypertensive patients who do not respond to monotherapy.25

**Uricosuric Effect**

It has been consistently shown in studies that the combination of losartan plus a CCB more significantly reduce uric acid levels than the combination of losartan plus HCTZ providing additional benefits in hypertensive patients with hyperuricemia.26

**Metabolic Effects**

Among the various antihypertensive agents, ACEIs and ARBs improve insulin resistance whereas beta-blockers and diuretics are associated with insulin resistance and increased glucose intolerance. CCBs increase high-density lipoprotein levels while beta-blockers and thiazides raise triglyceride levels.27 These pleiotropic effects were also observed when these drugs were used in combination therapy.

**Vascular Effects**

In a study, combination of benazepril plus amlodipine more effectively resulted in improved arterial compliance,
reduced arterial stiffness, and decreased left ventricular mass than high doses monotherapies of both drugs.\textsuperscript{20}

\textbf{Conclusion}

The goal of a physician treating hypertension should always be a cost-effective, long-term therapy that controls BP with drugs that are effective, safe, and well tolerated and should also actually reduce the CV risk. All major current guidelines suggest that ≥1 antihypertensive agent is needed in most hypertensive patients to reach desired BP targets. \textit{Summarized recommendations are as follows:}

- Combination therapy must be routinely used to achieve BP goals.
- Initiate combination therapy in patients who require ≥20/10 mm Hg decrease in BP to achieve desired BP.
- Preferred or acceptable drug combinations should be maximally used.
- Combination therapy in stage 1 patients should be started, especially when the second drug improves the tolerability of initial therapy along with additive BP reduction.
- Use SPCs rather than separate individual agents to improve convenience and compliance of treatment.
- Triple therapy including a RAAS inhibitor, a CCB, and a diuretic should be initiated in those patients who do not respond to dual therapy in 6–8 weeks.

Although the basis of treatment is guideline recommended medical therapy, still individualized treatment and expert advice should be preferred because each and every patient is a unique subject with a specific CV profile and not merely a statistically derived number in clinical trials.

\textbf{References}

CHAPTER 16
Management of Hypertension with Increased Sympathetic Activity—A New Way Forward

BB Thakur, Smita Thakur

Abstract

Hypertension is one of the most important preventable causes of morbidity and mortality across the globe. It is estimated that 25–35% of modern population suffer from hypertension and is estimated to cause over seven million deaths each year. Evidence from randomized controlled trials (RCTs) has shown benefit of antihypertensive drug treatment in improving outcomes in persons with hypertension. Since hypertension does not have any specific symptom and most of the time, the symptoms do not cause any inconvenience, it remains an insufficiently treated disease with only 10–20% patients having controlled blood pressure in spite of availability of so many drugs.

It has long been known that Sympathetic Nervous system plays a crucial role in blood pressure control through several reflex and non-reflex mechanisms including its effect on renal sympathetic outflow. It plays an important role in the development and progression of the essential and all grades of hypertensive state and end-organ damage. We now know conclusively that Sympathetic over activity is the leading cause of stroke, chronic kidney failure, left ventricular hypertrophy, and sudden cardiac death.

Some pharmacologic classes of antihypertensive drugs (such as beta-blockers, ACE-inhibitors, and angiotensin II receptor blockers) may elicit profound sympathoinhibitory effects, while long-acting CCBs have no effect on it and diuretics and short-acting calcium antagonists further increase the adrenergic cardiovascular drive.

The unmet need of controlling blood pressure in those patients whose pressure is not controlled to target with usual drugs may be addressed, in part, by developing new drugs and devices/procedures to treat hypertension and its comorbidities.

Alongside pharmacological therapy, device-based approaches to modulate SNS have demonstrated beneficial effects on BP control. In the past few years, two new procedures have been developed for the treatment of resistant hypertension by modulating SNS: catheter-based renal denervation and electrical stimulation of carotid baroreceptors. However, the interventional procedures are still in experimental stage.

Introduction

Hypertension is a complex and progressive cardiovascular syndrome of multiple etiologies that result in functional and structural changes in the heart and vascular system and it remains one of the most important preventable contributors to disease and death in the world.1,2

Most patients with hypertension have other risk factors including lipid abnormalities, glucose intolerance and diabetes, family history of early cardiovascular events, obesity, and tobacco use with or without alcohol excess.

There is unholy alliance between obesity, type 2 diabetes, the sympathetic nervous system (SNS), and hypertension in young/middle-aged subjects.

It is estimated that one-fourth to one-third of the population is afflicted with this condition3-5 and is estimated to cause over seven million deaths each year, which is about 13% of the total number of deaths worldwide.6 According to a review on “The Global Burden of Hypertension,” the estimated prevalence of hypertension (in people aged 20 years and over) in India
in the year 2000 was 20.6% among males and 20.9% among females and is projected to increase to 22.9% and 23.6% respectively by year 2025. These trends are increasingly been seen with aging populations. Evidence from randomized controlled trials (RCTs) has shown benefit of antihypertensive drug treatment in improving outcomes in persons with hypertension. Since hypertension does not have any specific symptoms, and most of the time, the symptoms do not cause any inconvenience, it remains an insufficiently treated disease with only 10–20% patients having controlled blood pressure levels.

SNS has always been implicated in causation of hypertension, but there has been a renewed interest because of:

- Sympathetic abnormalities influence the development and progression of TOD;
- New therapeutic approaches for control of blood pressure have been developed by modulating SNS; and
- SNS overdrive has impact on morbidity and mortality in CVD.

Sympathetic overactivity is presently recognized as a major contributor to development and sustenance of hypertension. Several pathophysiological changes lead to increased vascular tone and resistance, tachycardia, compromised central and peripheral hemodynamics, renal vasoconstriction, oxidative stress, metabolic abnormalities, and adverse remodeling of cardiac and vascular smooth muscle. Notably, many antihypertensives result in reflex SNS activation, which can result in elevated resting heart rate, and this is one of the newly recognized cardiovascular risk factors. Secondary causes of hypertension can also increase sympathetic activity.

It is well acknowledged that sympathetic overactivity is the leading cause of stroke, chronic kidney failure, left ventricular hypertrophy, and sudden cardiac death. Understanding the mechanisms involved in the regulation of the SNS has currently lead to novel approaches in hypertension treatment (Fig. 1).

A distinct feature of the SNS is the immediate regulation of peripheral vascular resistance through modulation of the vascular tone. In addition, the release of sympathetic neurotransmitters contributes to adaptive mechanisms through regulation of cell proliferation, transformation, and apoptosis, and these are all blood pressure independent.
The renin-angiotensin-aldosterone system (RAAS) is responsible for the central nervous feedback in sympathetic activation, angiotensin II and nitric oxide (NO) are important effectors of this system. In chronic kidney disease, RAAS inhibition leads to decrease in efferent sympathetic activity. All RAAS inhibitors do not have the capability to penetrate through the blood-brain barrier; therefore, it is likely that peripheral actions of angiotensin II modulate afferent signal transduction.

Renal ischemia releases adenosine as a paracrine transmitter, leading to potent activation of afferent neurons. Severing afferent and efferent sympathetic nerve fibers prevent no hypertension in animal model with chronic kidney injury. Independent from CNS-effects, chronic kidney injury leads to a neither increase of presynaptic or epinephrine release in the heart and kidney. This might be due to an increase in angiotensin II through RAAS activation.

Multiunit sympathetic nerve activity (MSNA) is equivalent to the sympathetic activity. This can be measured as "bursts" per minute, and helps establish the concept of kidney as a pacemaker of sympathetic activity. Converse et al. analyzed the sympathetic activity in dialysis patients versus healthy controls. Interestingly, in kidney transplant patients with normal serum levels of creatinine and urea, the sympathetic overactivity persisted. Only bilateral nephrectomy was able to abolish the pathologic sympathetic overactivity.

**Sympathetic Overactivity**

The SNS plays a pivotal role in rapid adaptation of the body to ongoing events, orthostatic reaction is a glorious example of its instant activation. However, it is the long-term gradual modification in the sympathetic activity, which contributes to development of hypertension. There is an increase in sympathetic activity with an increase of MSNA of 1 burst/min per year, with advancing age. Female subjects have a lower MSNA, but they exhibit more significant annual increase, compared to their male counterparts. A good correlation between blood pressure and MSNA has been observed above 40 years of age, which does not exist in younger patients. Diminished compensatory mechanisms in the elderly population (endothelial dysfunction, diminished baroreflex, etc.) could be the reasons. Sympathetic overactivity could be the underlying factor linking heart failure, sleep apnea, metabolic syndrome, and hypertension.

**Sympathetic Overactivity in Sleep Apnea**

Sleep-related respiratory dysfunction is much more common in patients with hypertension compared to the common population. Sleep apnea patients demonstrate an increased blood pressure. Apnea causes an immediate rise in sympathetic activity that leads to increase in blood pressure. In chronic sleep apnea, this activation of the SNS persists during daytime also which results in increased MSNA and norepinephrine release. Denervation of the carotid body abolishes the blood pressure increase after hypoxia. Desensitizing chemoreceptors through respiration of 100% oxygen lead to a decrease in sympathetic activity, heart rate, and blood pressure in wake sleep apnea patients but not in healthy controls. Dysfunction of baroreceptors also exists in sleep apnea patients, similar to what is observed in chronic heart failure patients.

**Sympathetic Overactivity in Metabolic Syndrome**

Baroreflex dysfunction could be the cause of sympathetic overactivity in overweight patients. Accumulation of visceral fat is associated with an increase in MSNA and greater cardiovascular risk. An increase in MSNA is often observed in type 2 diabetes patients. Overweight people suffer more from hypertension and type 2 diabetes, thus interlinking together to manifest as metabolic syndrome. Administration of an increasing dose of insulin increased MSNA in euglycemic individuals, suggesting that hyperinsulinemia plays an important role.

**Sympathetic Overactivity in Hypertension**

Almost all studies measuring microneurographic sympathetic nerve activity in hypertensive patients could demonstrate the central role of sympathetic overactivity. MSNA increase is more pronounced in patients with observable target organ damage. The associated conditions with hypertension like chronic kidney disease, heart failure, obesity, and sleep apnea are all associated with increased sympathetic overactivity and tend to coexist. It is postulated that sympathetic reactivity might be genetically determined. Children of hypertensive individuals show normal MSNA levels, but when subjected to mental stress show...
a significantly increased MSNA, compared to children of non-affected parents.38

Diastolic (± systolic) hypertension in young/middle-age is accompanied by increased sympathetic nerve activity, particularly in presence of metabolic syndrome or type 2 diabetes. Hypertension in preeclampsia39 or pulmonary arterial hypertension39 also shows an increased activity in microneurography.

Currently chronic kidney injury is conclusively linked to pathogenesis of hypertension. As seen in Figure 1, activation of afferent neurons in the injured kidney leads to increased sympathetic activity through central nervous mechanisms. It is well established that there is reduced norepinephrine clearance and an increase of serum norepinephrine levels in chronic kidney failure.40 Kidney through release of a soluble monoamine-oxidase (Renalse) degrades circulating catecholamines and thereby might regulate blood pressure.41

**Therapeutic Approach**

**Non-pharmacological Treatment**

Aerobic exercise training and calorie restriction both inhibit SNS activity, and are the two most commonly applied and effective non-pharmacological therapies for hypertension. This is especially important for metabolic syndrome and obesity-related hypertension, where there is a contribution of sympathetic inhibition for reductions in both blood pressure and insulin resistance.42 Another non-pharmacological approach with an antiadrenergic component is the regular application of continuous positive air pressure (CPAP) ventilation in patients with obstructive sleep-apnea-related resistant hypertension at night. This therapeutic approach has been shown to prevent nocturnal obstruction of upper airways, reduce sympathetic activity, and favor blood pressure reduction.43-46

**Pharmaceutical Approach**

In patients with chronic renal failure, the severity of disease correlates very well with sympathetic activity.47 An increase of MSNA of 10 bursts/min increases the event rate by 60%. Adverse cardiovascular events are also increased in these patients (Fig. 3).

Some pharmacologic classes of antihypertensive drugs (such as beta-blockers, ACE-inhibitors, and angiotensin II receptor blockers) may elicit profound sympathoinhibitory effects, while long-acting CCBs have no effect on it and diuretics and short-acting calcium antagonists further increase the adrenergic cardiovascular drive.
Pharmacological intervention can be achieved with RAAS-blockade (Renin- or ACE-inhibitors, or AT1-blockers), which leads to a reduction in the efferent sympathetic activity. However, normalization of sympathetic activity can only be achieved if a central sympatholytic drug (moxonidine) is added to this treatment.

The initial antihypertensive drugs had antiadrenergic effects and were potent, but their side effects made them fall out of favor. Beta- and alpha-adrenergic blocking drugs are similar and effective. Centrally acting sympathetic suppressants, imidazoline-binding agents, such as moxonidine and rilmenidine can be prescribed in patients with essential hypertension as both produce the desired sympathetic inhibition in the sympathetic outflows to the heart, kidneys, and skeletal muscle vasculature. Moxonidine also has renoprotective properties in chronic renal failure and reduces MSNA, independent of blood pressure reduction. These are largely free of the side effects witnessed with clonidine, most notably rebound hypertension seen with clonidine when doses were missed.

In patients with resistant hypertension, target goal of <140/90 mm Hg cannot always be achieved using oral antihypertensive medication. Therefore, alternative approaches for blood pressure control have been researched, especially concentrating on novel treatment strategies to alter sympathetic overactivity.

**Antiadrenergic Devices**

Alongside pharmacological therapy, device-based approaches to modulate SNS have demonstrated beneficial effects on BP control.

In the past few years two new procedures have been developed for the treatment of resistant hypertension: catheter-based renal denervation and electrical stimulation of carotid baroreceptors.

**Renal Denervation Therapy**

Traditional surgical sympathectomy proposed in early forties has been discarded due to unacceptable severe side effects like voiding dysfunction, intestinal dysfunction, impotence and orthostatic dysregulation, and operative risks. Due to pharmaceutical alternatives, surgical sympathicolysis was replaced by antihypertensive drugs. This novel and recently introduced therapeutic approach (Flowchart 1) to RH involves bilateral destruction of the renal nerves travelling along the renal artery, using percutaneous catheter-based radiofrequency ablation (Fig. 4) via femoral artery. The basis for renal denervation lies in the importance of sympathetic influences on renal vascular resistance, renin release, and

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**Flowchart 1**: Scheme illustrating the possible mechanisms through which renal denervation may exert blood pressure-lowering effects: increase (up arrow) and reduction (down arrow)
sodium reabsorption, the increased sympathetic tone to the kidney and other organs displayed by hypertensive patients\textsuperscript{65-67} and the pressor effect of renal afferent fibers, seen in experimental animals.\textsuperscript{68,69}

The Symplicity HTN-1 and HTN-2 trials have shown substantial blood pressure reductions in response to renal denervation,\textsuperscript{70} in the order of 30/15 mm Hg, maintained beyond 2 years. Although renal denervation resulted in improved blood pressure control, the patients continued to take antihypertensive drugs at a reduced number or dose.

However, surprisingly, the very recently reported Symplicity HTN-3\textsuperscript{71} has failed to achieve its primary efficacy endpoint and has not found favor on merit and it is still under scrutiny.\textsuperscript{72} Following the initial hype\textsuperscript{73} on the basis of initial results of Symplicity HTN-1 and HTN-2, the Symplicity HTN-3 study\textsuperscript{74} was terminated in February 2014 by Medronic, because the primary endpoint that is lowering of the systolic occasional blood pressure by \(\geq 5\) mm Hg—was not achieved after 6 months compared with a control arm. The study, published online in March 2014, showed only a difference of 2 mm Hg for office and 24-hour ambulatory systolic blood pressure.\textsuperscript{75} The European Society of Hypertension and national expert teams have not come out so far regarding the indication for this interventional method.\textsuperscript{76-79} A subsequent position paper statement by the European Society of Hypertension Working group\textsuperscript{80} has very elegantly summarized the current status of this therapy and ways forward. Currently one should refrain from referring further patients for treatment with this method. As there is no safety concerns except for vascular issues and no major complications (impairment of renal function, renal artery stenosis/thrombosis) have been reported,\textsuperscript{75} the method may be useful for the small patient population with true treatment resistance, provided all contraindications are observed and after rigorous investigations and treatment.

Although there remain many questions to be answered regarding its long-term success, clinical outcomes, and technical issues, further renal denervation therapy trials are very likely to be conducted with new devices at various stages of development.

**Carotid Baroreceptor Stimulation**

Another invasive method is baroreflex stimulation (electrical stimulation of the carotid sinus nerve), which underwent a revival based on two studies.\textsuperscript{3,82}

Dysfunction of the baroreceptor reflex causes an increase in sympathetic activity in a variety of diseases such as sleep apnea and chronic heart failure. This option (Flowchart 2) allows appropriate physiologic adaptation to elevated SNS activation and reduced parasympathetic activation by electrically stimulating the carotid baroreflex, the carotid sinus nerves via implanted devices (baroreflex activation therapy—BAT). This device-based therapy (Fig. 5) has proved very effective in lowering blood pressure\textsuperscript{56} and recently been reported to reduce SBP and DBP in resistant hypertensive individuals also\textsuperscript{56,81,82} the reduction was quite marked when initial BP values were very high and the effect included ambulatory BP and persisted for up to 53 months. However, long-term observations have so far involved only a restricted number of patients and further data on larger numbers of individuals with an elevation of BP unresponsive to multiple drug treatments are necessary to confirm the persistent efficacy of this procedure. It seems to be safe with only a few remediable and local side-effects (infection, nerve damage, pain of glossopharyngeal nerve origin) and no effect on renal function\textsuperscript{83} and even a positive effect on structural and functional cardiac parameters was demonstrated.\textsuperscript{84} Previously, baroreflex activation therapy...
Flowchart 2: Possible mechanisms by which electrical stimulation of carotid baroreceptors might help lower blood pressure

Baroreflex activation therapy

- Baroreflex improvement
  - Blood pressure reduction
  - SNS inhibition and vagal activation
  - ↓ TOD

- Baroreflex impairment
  - Blood pressure increase
  - SNS activation and vagal inhibition
  - ↑ TOD

Fig. 5: This device-based treatment consists of an implantable pulse generator; bilateral carotid sinus leads to stimulate the area of greatest response. There is an external programmable device for noninvasive control of the pulse generator. Carotid sinus stimulation acts via a negative loop mechanism via central nervous system, leading to reflex blood pressure lowering.

required bilateral carotid preparation and implantation of electrodes and the corresponding pacemaker aggregate. Due to the approach of bilateral activation, battery power of pacemakers lasts only for 2 years with the need of replacement after this period. Ongoing technical innovations to reduce the inconvenience caused by the surgical implantation of the stimulating devices, and to prolong the duration of the battery providing the stimulation, are being studied.

Baroreflex stimulation has been approved in Europe for the treatment of patients with resistant hypertension and a high-cardiovascular risk, however, it should be applied in selected centers with great expertise in the treatment of hypertension and undertaken in close collaboration with vascular surgeons.

In contrast to renal sympathetic denervation, baroreflex stimulation is a reversible procedure; the system can be switched off in the event of hypotension or shock and be adapted to the requirements of a circadian blood pressure rhythm by external programming via radiofrequency telemetry.

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Slow Breathing Technique

Non-pharmacological approaches are recommended for all individuals with hypertension, regardless of drug therapy. Among several behavioral interventions, the device-guided slow breathing (SLOWB) exercise using RESPeRATE (Intercure, Ltd. Northern Industrial Area, Israel) has been introduced as a non-pharmacological approach in the prevention or treatment of elevated BP. It has been suggested that a decrease in breathing frequency may have beneficial effects on BP and autonomic CV regulation through the modulation of central mechanisms at the brainstem integrating cardiopulmonary receptors, arterial baroreceptors, and efferent sympathetic outflow.
RESPeRATE aims to lower BP with ad hoc regular paced therapeutic breathing (slow and deep breathing) below 10 breaths per minute accumulating ≥40 minute of therapeutic breathing training per week. Madanmohan et al. (1983) studied the effect of shavasan and savitri pranayam (a yoga-breathing technique characterized by slow, rhythmical and deep breathing cycles) in trained subjects (yoga training >1 year) and found significant decrease in oxygen consumption, heart rate, and diastolic blood pressure. They attributed it to the ability of the subjects to achieve a state of deep psychosomatic relaxation. Shavasan alone has been shown to be effective in the treatment of hypertension (Datey et al., 1969; Patel and North, 1975). This was attributed to a decrease in the frequency and intensity of proprioceptive and enteroceptive impulse traffic reaching the hypothalamus. Practice of yoga has been found to be beneficial in many current trials.

Whether the device-paced breathing represents an adjunctive treatment to state-of-the-art drug therapy for hypertension requires further clinical investigation in a larger patient cohort. However, this method appears unlikely to reduce sympathetic activity alone over the longer term.

**Deep Brain Stimulation**

Deep brain stimulation (DBS) is an exciting interventional therapy designed to modify pathological activity within the SNS. This approach has gained significant recognition in the treatment of Parkinson’s disease, recently entering clinical practice. Besides the promising therapeutic effects in a wide range of neurological disorders, DBS of the ventrolateral periadeququotal grey/periventricular grey matter has been successfully demonstrated in refractory hypertension. While this approach was primarily performed to treat chronic central pain syndrome that was unresponsive to pain-relief drugs, there was also an unexpected effect of sustained BP lowering. While costly, and associated with a 1% stroke risk, DBS appears to be an attractive approach for treating severe forms of uncontrolled hypertension in patients unresponsive to device-based interventional strategies. Whether DBS may be offered widely as a therapeutic tool for RH to improve CV outcomes merits further investigation.

**Conclusion**

Hypertension is one of the most significant health burdens in present day societies, affecting 25–35% of the population. Due to increasing life expectancy, incidence of hypertension is likely to increase in the future. The associated diseases (obesity, diabetes, and CKD) are also on rise. Despite the wide range of available non-pharmacological and pharmacological BP lowering approaches, hypertension is poorly controlled worldwide with a substantial impact on morbidity and mortality.

There is a distinct correlation between sympathetic activity, stage of disease, and hypertension. Almost every hypertensive subject shows sympathetic overactivity that correlates well with the adverse cardiovascular event rates (heart failure, myocardial infarction, and stroke).

Kidney plays an important role in the control of sympathetic nerve activity. There is increased sympathetic nerve activity in chronic heart failure, sleep apnea, and obesity also that can be measured by microneurography.

The well established contribution of sympathetic overactivity to human hypertension has led to the development of novel device-based and procedural interventions that favorably modulate autonomic neural mechanisms underlying hypertension. An additional approach currently being investigated to attain BP control in patients with RH is carotid body removal. Given the invasiveness, the cost of device-based strategies, and the different responsiveness of different patients, pre-procedural markers to stratify patients for the specific approach need to be identified. Future large scale clinical trials will determine the long-term safety and effectiveness of these various antihypertensive approaches in terms of BP control, hypertension-related end organ damage, and hard CV endpoints including death, myocardial infarction, and stroke.

**References**


Abstract
Morning surge hypertension (MSH) is among one of the most important hypertensive variabilities and its attenuation is very important. It is a short-term hypertensive variability. It is mainly controlled by the sympathetic neural output to the cardiovascular system, which is influenced by circadian rhythm. It seems like MSH is the main culprit behind the highest occurrence of cardiovascular and cerebrovascular events in the morning hours. For diagnosing MSH, ambulatory BP monitoring (ABPM) is the most appropriate method. Home blood pressure monitoring (HBPM) 2 hours after awakening is the practically available and largely affordable means in our country for MSH. Morning HBP recording in standing posture is a better predictor of MSH than morning HBP recording in sitting posture. For managing MSH, long acting antihypertensive a better choice. Long acting CCBs (especially amlodipine) are better than all other drugs. Long acting ACEIs, ARBs, β-blockers like nebivolol, etc. are good alternatives. For better management of MSH antihypertensives should be given in evening.

Introduction
Hypertension is a well known cause of cardiovascular, cerebrovascular, and all cause mortality and target organ damage (TOD). It is also among one of the most important preventable causes of death globally. Blood pressure is not always the same rather it varies from time to time. This hypertensive variability is an independent risk factor for TOD and cardiovascular and cerebrovascular events. Thus, while choosing antihypertensive therapy, attenuation of hypertensive variability must be kept in mind. Morning surge hypertension (MSH) is among one of the most important hypertensive variabilities and its attenuation is very promising.

Blood Pressure Variability
We all diagnose and treat hypertension on the basis of clinic blood pressure measurement, but researchers showed that assessment and quantification of blood pressure variability (BPV) is of paramount importance. Ample evidences are there which show that increased BPV is independently associated with increased risk of TOD, cardiovascular events, and mortality. Hence, for reducing hypertensive complications (e.g., cardiovascular and cerebrovascular events and TOD), attenuation of BPV is also required with reduction in average blood pressure values. BPV is directly proportional to mean BP values, and hence it is more in higher stages of hypertension as compared to lower stages of hypertension. White-coat hypertension and masked hypertension are well known BPV and there clinical and prognostic significance are well recognized.

On the basis of timing of changes in blood pressure, BPV can be divided into three types:
- Very short-term BPV (beat to beat oscillations in blood pressure)
- Short-term BPV (oscillations in BP within a day)
- Long-term BPV (oscillations in BP on day to day, visit to visit, or seasonal variation).
Causes and prognostic significance of all types of BPV differ with each other. According to definition MSH is a short-term hypertensive variability. Other short-term hypertensive variabilities are morning hypertension, nocturnal dipping, and nocturnal hypertension.

The circadian pattern in BP is well recognized. In night time during sleeping, BP values are usually low, which rise in early morning post-awakening period and usually coincides with transition period from sleep to wakefulness. A moderate rise in BP in morning hours is physiological, but if it became much more then it is pathological and is termed as MSH, morning blood pressure surge (MBPS), or morning hypertension.

In the normal individuals, BP usually falls by 10–20% during sleep and this phenomenon is known as nocturnal dipping. In hypertensives this dipping status differs and on the basis of this difference they are categorized into four different groups namely:

- Dippers—in whom BP falls in the range of 10–20% during sleep
- Extreme dippers—in whom fall in BP is more than 20% during sleep
- Non-dippers—in whom fall in BP is less than 10% during sleep
- Reverse dippers or risers—in whom instead of falling BP rises during sleep

The suprachiasmatic nucleus (SCN) situated in hypothalamus is the master body clock. It has direct control over peripheral molecular clocks present in almost every cell of our body. Due to a complex interaction of SCN with environmental and behavioral factors, a definite circadian pattern occurs in almost all physiological functions of our body. The SCN receives inputs from our body (behavioral factors) from environment (temperature and light) and from cerebral cortex and then synchronizes autonomic output, hormone secretion, and behavior. At the morning hours or arousal time certain neurohormonal changes occur in our body. The most important among them are the activation of sympathetic nervous system. The MSH is mainly controlled by the sympathetic neural output to the cardiovascular system, which is influenced by circadian rhythm. The occurrence of major cardiovascular and cerebrovascular events, e.g., myocardial infarction (MI), angina, stroke, transient ischemia attack (TIA), and sudden cardiac deaths are more common in morning as compared to other parts of the day. The exaggerated morning BP surge further increases the existing TOD in hypertensives. This might be the reason behind increased cardiovascular and cerebrovascular events in the morning. It seems like MSH is the main culprit behind the highest occurrence of cardiovascular and cerebrovascular events in the morning hours.

The most widely accepted definition of MBPS is given by Kario et al., which can be calculated as follows:

- Sleep-trough MBPS—For getting it we have to take two values. First one is an average of the mean SBP of 2 hours after awakening and second one is an average of 3 lowest SBPs in the night. The difference is the sleep-trough MBPS.
- Prewaking MBPS—Here we again take two values. First one is a mean of SBP of 2 hours after awakening and second is mean SBP of 2 hours before awakening. The difference is prewaking MBPS.

For diagnosing MSH, ambulatory BP monitoring (ABPM) is the most appropriate method. Unfortunately, ABPM is neither available at every corner of our country nor is affordable by everyone. Home blood pressure monitoring (HBPM) 2 hours after awakening is the practically available and largely affordable means in our country for MSH.

We can diagnose morning hypertension if the clinic BP values are more than or equal to 140/90 mm Hg in the morning or HBP values are more than or equal to 135/85 mm Hg in the morning. One can also diagnose MSH, if the difference in morning and evening BP is more than 15 mm Hg, or if the difference in morning and nocturnal BP is between 35 and 55 mm Hg. Nocturnal hypertension is diagnosed if average nocturnal BP is more than or equal to 120/70 mm Hg. Usually it is found in non-dippers or reverse-dippers due to failure of nocturnal dipping. In the beginning, night BP or BP during sleep could only be recorded by ABPM but now, with the development of newer home BP monitoring devices, which can intermittently (2, 3, and 4 AM) record nocturnal BP accurately during sleep, it is possible to get nocturnal hypertension by home BP monitoring also.

According to consensus statement of the Asian expert panel, BP should be recorded two or three times every morning for 5–7 days and then average of these values should be used for evaluations. According to the Japanese Society of Hypertension guidelines, morning HBP should be recorded within 1 hour after awakening and passing urine but before doing exercise or taking medicine or meal and evening HBP should be recorded just before going...
to bed. Morning HBP recording in standing posture is a better predictor of MSH than morning HBP recording in sitting posture.

**Pathophysiology of MSH**

Many physiological changes occur in the morning but they themselves only are not capable of producing MSH or increased incidence of cardiovascular and cerebrovascular events in the morning. MSH and increased incidence of cardiovascular and cerebrovascular events in the morning occur due to a complex interaction among physiological, environmental, and behavioral factors.

**Physiological Factors**

These include hemodynamic, vascular, and hemorrheological changes.

**Hemodynamic changes:** In the morning, the most important hemodynamic changes are increase in heart rate and BP. Morning hours are also associated with increased cortisol secretion, activation of renin-angiotensin-aldosterone system (RAAS), and enhanced systemic vascular resistance. In the morning atherosclerotic plaques become more vulnerable to rupture and may cause thrombosis due to decreased vagal tone, increased catecholamine levels, and activation of RAAS. This may be the reason behind increased incidence of cardiovascular and cerebrovascular events in the morning.

**Vascular changes:** The main vascular changes in the morning are increased vascular tone and increase in the sensitivity of vascular receptors.

**Hemorrheological changes:** In the morning platelet aggregability is increased. According to Brezinski et al., assumption of upright posture itself in the morning after sleep is responsible for increase in platelet aggregability. Other important hemorrheologic changes in the morning are increase in blood viscosity and decrease in fibrinolytic activity. These physiological changes all together make early morning prothrombotic state.

So, in the morning hours, physiologically there is:
- early morning prothrombotic state
- the existing atherosclerotic plaques are more vulnerable to rupture, which may lead to thrombosis, and
- there is increase in vascular tone and vascular receptor sensitivity, which further increases the danger.

The physiological changes in the morning are like fuel ready to burn out, which needs only egretter (behavioral and environmental factors) to kindle the fire (producing cardiovascular or cerebrovascular events).

**Behavioral and Environmental Factors**

The most important factors are start of activity, heavy physical exertion, psychological stress, bursts of anger, smoking, alcohol consumption or salt intake, and cold temperature. Preexisting cardiovascular risk factors like aging, hypertension, dyslipidemia, and glucose abnormality further increases the risk. Increase in sympathetic nervous system activation and endothelial dysfunction, which may lead to increased surge in morning BP, may also be caused by poor sleep quality, sleep apnea or nocturnal hypoxia. Otto et al. reported impaired endothelial function in morning hours in normal individuals. This impaired endothelial function reduces capacity for vasodilation, which further increases the risk.

According to Kario vascular damages like small artery disease (increased vascular tone) and endothelial dysfunction and large artery disease (arterial stiffening) and baroreflex dysfunction are not only the consequence of exaggerated BP but are also the leading cause of exaggerated surge in morning BP and produces a vicious cycle of further damage. If BP is increased in normal individuals then vasodilation of small arteries occur which counter-balance the rise in BP, but in hypertensives this buffering capacity is reduced due to remodeling of small arteries, and hence lead to exaggerated surge in morning BP. In response to any surge in BP in normal individuals baroreceptor-reflex, due to stretching of arterial baroreceptors situated in aortic arch and carotid arteries, occur which reduces BP but in cases of arterial stiffening this baroreceptor-reflex is impaired due to reduced stretching of baroreceptors, and hence will not be able to reduce surge in BP. Okada et al. observed an association between morning BP surge and arterial stiffening in elderly hypertensives.

As most of the hypertensives take their drugs just after breakfast, so its effect is minimal in the morning and may lead to MSH. If the person is taking short-acting or intermediate-acting antihypertensive drug after breakfast then on next morning the effect will be lost and result in MSH.
The concept of morning hours is different in our country as compared to western world due to differences in climatic, geographical, and sociocultural factors. Most of the western researchers of circadian pattern divided the whole day into 4, 6 hourly quadrants and inferred that maximum cardiovascular and cerebrovascular events occur in second quadrant of the day (0600–1200 hours). This pattern is not suitable for our country. For circadian pattern study in our country the whole day should be divided into 6, 4 hourly intervals from 0000 to 2400 hours. The factors responsible for morning events depend upon timing of awakening rather than an hour or quadrant of the day. Ridker et al. observed that the risk of MI is twice more common within 3 hours after awakening than any other time of the day. Rocco et al. found maximum number of transient myocardial ischemic attacks in 1–4 hours after awakening than any other comparable part of the day. Above studies show importance of time of awakening. In our country, the time of awakening is in between 4 and 5 AM in rural and in between 5 and 6 AM in urban areas as compared to late awakening in western world. Most of the cardiovascular and cerebrovascular events in our country occur in between 6 and 7 AM (4 and 8 AM), that is, in between 2 and 3 hours after awakening.

Management

If we keep a target of morning HBP values less than 135/85 mm Hg then it will produce a strict 24-hour BP control and also provide a better effective protection than clinic BP values with same target. For managing MSH long-acting antihypertensives are better choice. Long-acting CCBs (especially amlodipine) are better than all other drugs. CCBs have a unique BP reducing property. It reduces higher BP values more than lower BP values, hence reduction in morning BP values is more as compared to night BP values, which results in higher reduction in surge in morning BP. Long-acting ACEIs, ARBs, β-blockers, like nebivolol etc. are good alternatives. As diuretics predominantly reduce night BP more than morning BP, hence they are not suitable for control of MSH. Timing of antihypertensive drug is very important. For better management of MSH antihypertensives should be given in evening. Kario et al. observed a significant reduction in morning BP values and albuminuria by adding bed time doxazosin (α-blocker) on the top of base line antihypertensive therapy.

Conclusion

Cardiovascular and cerebrovascular events occur more commonly in morning, which may be due to MSH. Proper management of MSH is essential to prevent these complications and TOD. Long-acting CCBs (especially amlodipine) is best among all drugs. Others are long-acting ACEIs, ARBs, Nebivolol, etc. For better results antihypertensives should be given in evening.

References

Abstract
The most rapid section is the elderly population and for the development of hypertension, age is a major risk factor. Variations in SBP/PP depend on various factors like arterial aging, frailty, multimorbidity, and polypharmacy.

Evaluation: Diagnosis of hypertension depends on various ways in assessment of blood pressure, cardiovascular (CV) risk factors, secondary causes, comprehensive geriatric assessment (CGA), etc.

Therapy: Lifestyle modifications and pharmacological treatment.

Conclusion: Elderly patient is the most rapidly increasing section in the society and age is a major risk factor for the development of hypertension. These population are associated with multiple comorbidities, frailty, cognitive decline, and loss of autonomic functions and has to be managed from a life-course perspective with proper investigations and timely treatment of high BP as compared with younger age groups.

Introduction
Elderly patients represent the most rapid increasing section of the population. For the development of hypertension (mainly systolic), age is a major risk factor. The rising number of older population (especially over 80 years) also leads to elevated blood pressure (BP) as well as at the same time they are more prone to multimorbidity, frailty, cognitive dysfunction, multiple medications, and partial/complete loss of autonomic functions.1,2

During aging, high BP (mainly systolic) is a clinical expression of arterial stiffness3,4 and some studies have also indicated the association of neurocognitive disorders, like Alzheimer and vascular types, with elevated BP.5

According to some data, risks and benefits of correction of high BP are obtained in younger as well as selected older individuals.6

There are two major differences between these two age groups:

- The incidence and prevalence of comorbidities, frailty, and loss of autonomy increases mostly after 80 years; and
- In the “younger” old patients (60–70 years), evidence supports benefits of reducing BP, while there are limited evidence in patients (over 80 years).

Therefore, the management of older patients with high BP must be the following differences as compared with younger age groups.

Elevation in Systolic BP in Older Age Groups: Due to Arterial Aging
Both (systolic blood pressure) SBP and (diastolic blood pressure) DBP are independent predictors of cardiovascular disease (CVD) in younger age groups (<50 years), epidemiological studies suggest that SBP is a strong risk factor and DBP is inversely related with the risk in age group of 50 years or more.4
Increase in Pulse Pressure with Age

Both SBP and DBP increase as individuals get older. In the majority of cases, SBP and pulse pressure (PP) increase disproportionately to DBP with age and the most common cause is progressive stiffening of arterial wall.3,7

Causes like hypertrophy of wall, deposits of calcium, changes in the extracellular matrix, which include increase in collagen, fibronectin, fragmentation, disorganization of the elastin network, nonenzymatic crosslinks, and cell-matrix interactions, are responsible for decrease in elastic properties as well as the development of artery wall stiffness.8 The duration of the diastolic interval and the rate at which pressure falls helps in determination of the DBP. The speed of propagation of the pressure wave of artery (pulse wave velocity-PWV) and the timing of the reflections of the wave also depend on the viscoelastic properties of the arterial walls.

So the stiffening of the arteries increases PWV and there is an early return of the waves which are reflected, and then overlap with the incidental pressure wave, which further contributes to the increment in SBP and PP.3,7

Diabetes is also responsible for accelerated aging of arteries (due to increase in arterial stiffness) leading to an increase in PP as compared with nondiabetics.9,10

Increase of SBP/PP in Old Age

As SBP and PP better reflect the CVD risk in older age, whereas DBP better reflects the risk in younger age.4 DBP in young patients is mostly depends on peripheral resistance (PR), and hence low DBP reflects low PR. In addition to this, there is hyperkinetic circulation in young age, so, DBP is less variable than SBP, thus reflects better CV risk.

In old age groups, a low DBP may reflect high arterial stiffness (major manifestations as compared to low PR).3,7

Few Terms: Frailty, Multimorbidity, and Polypharmacy

Frailty is a syndrome (biological) of decrease in reserve and resistance to stress factors, which result from collective decline across multiple physiological systems and cause adverse outcomes.1

It increases mostly after the age of 80 years. Susceptibility to stress factors is also influenced by behavioral, environmental, social, and biological risks, consequently resulting in an increase in multiple adverse health outcomes.

Few studies have indicated that there is increase in morbidity and mortality in very old frail subjects and are mainly observed in treated hypertensives (mostly on several antihypertensives) and not in normotensives.11,12

Polypharmacy (taking more than 4 drugs) and side effects related to drugs are major problems in this age group that may contribute to morbidity, increased rates of hospital admissions, as well as mortality.

Clinical Evaluation

- Diagnosis of hypertension should be based on:
  - At least three different BP measurements, which should be taken on two visits of office separately.
  - At least two measurements, which should be obtained while the patient is sitting comfortably for 5 minutes with the support of back, feet on the floor, arm in horizontal position, and the BP cuff (of adequate size) at the level of heart.
  - Assessment of BP by self at home and 24-hour ambulatory BP measurements, if needed, can contribute in detection of white coat hypertension and recognition of CV risk related to high BP levels.
  - White coat hypertension (exaggerated BP measurements) in the office is more common in older subjects.

- Secondary hypertension is uncommon; therefore, extensive workup for every old patient with hypertension is not needed. But if there is, sudden deterioration of hypertension (previously well controlled), resistant hypertension, etc., then the causes which are reversible should be investigated.

- CV risk factors and target organ damage should be assessed to check the overall risks of CVD.

- Physical examination, which includes fundus examination, abdominal bruits auscultation, peripheral pulses, and palpation of abdomen, should be done thoroughly.

- BP should be taken in supine position in older hypertensives (independent of the symptoms suggestive of orthostatic hypotension).

- An ECG should be done (to look for LVH, IHD, arrhythmias, and conduction disturbances) and urine examination for determination of concentration of albumin should be done.
Comprehensive geriatric assessment (CGA), a proposed methodology to provide an approach (globally) to complex older age groups and their related problems, and allowing a specific and organized plan of care, which should be implemented for each and every patient.

- CGA permits for a complete assessment of drugs, which recognize and prevent drug-related problems and improve the quality of prescription.

**Antihypertensive Therapy**

**Lifestyle Modifications**

- Changes in lifestyle are beneficial for older patients who are being treated for hypertension.
- In obese patients, reduction in weight is the most effective intervention for lowering of BP.
- As older patients are more prone to have salt-sensitive hypertension; so sodium restriction is recommended.
- The Dietary Approaches to Stop Hypertension (DASH), reduction in alcohol intake (as it can lead to increased risk of falls and confusion), and increase in physical activity should be recommended. Weight reduction alone without exercise should not be recommended as it could induce loss of muscle mass and even can lead to cachexia.

**Pharmacological Treatment**

**Few Trials**

Clinical trials (meta-analysis) as shown in Table 1, indicated that antihypertensive treatment in patients (>65 years) produces similar proportional reductions in the CV risk as that of in young patients, but in older patients, the immediate benefits of treatment were more pronounced (because of a more average risk).

**Target BP**

In European-2013 guidelines, which stated higher SBP (>160 mm Hg), a definite evidence for reduction of SBP between 150–140 mm Hg is present.

Later these were challenged by SPRINT Trial, which was conducted in patients (with high CV risk and using antihypertensive drugs already), showed that keeping SBP of 120 mm Hg resulted in lowering of CV events and the total mortality as compared with patients with the target SBP of 140 mm Hg.

Further it indicated that keeping a target of 120 mm Hg showed a significant rise in adverse effects in very old patients and frail patients like hypotension, syncope, dyselectrolytemia, failure of kidney, etc.

A group of experts on hypertension and geriatric medicine proposed few rules for the hypertension management in very old patients with partial/complete loss of autonomy. It suggested that decisions regarding therapy should be taken after proper information of cognitive status, functional capacity, multi drug intake, frailty status, etc. of the patient. It also suggested keeping SBP (on treatment) between 150–130 mm Hg is safe range.

**Older Hypertensives: Any Specific Drugs?**

- JNC-7 recommended five drug classes (thiazides/thiazide-type diuretics, ACEIs, beta-blockers, CCBs, and ARBs) to be used initially.
- JNC-8 recommended four drug classes specifically (ACEIs, ARBs, CCBs, and diuretics).
- Additionally, the JNC-8 recommended these classes based on the evidences like race, CKD, and diabetics. So, the change between these two (JNC-7 & JNC-8) was the non-inclusion of beta-blockers in the 1st list treatment of JNC-8 with the exception like presence of associated indications (history of MI, chronic angina, or heart failure). It suggested that the beta-blockers may not be as beneficial as compared to other classes in the reduction of stroke, mostly in older patients.

- Majority of older patients require dual antihypertensives but it is preferable to initiate with a single drug.
- Increased risks of adverse effects are there with combination drug therapy, mostly among very older age patients with comorbidities.
- Cautious addition and titration of drugs are important, especially in the groups of older age, renal failure, or associated with hypotension and falls.

**Other Issues in Older Hypertensives**

**Postural Hypotension and Nocturnal Dipping of BP**

Older individuals are more prone to orthostatic hypotension, which is frequent with increasing age, and is associated with increased risk of death, CV events, and falls.
TABLE 1
Design and main results of placebo-controlled trials designed to evaluate the benefits of treatment in individuals 60 years and older with systolic-diastolic hypertension or isolated systolic hypertension

<table>
<thead>
<tr>
<th></th>
<th>EWPHE</th>
<th>MRC</th>
<th>STOP</th>
<th>SHEP</th>
<th>SYSTEUR</th>
<th>HYVET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects and age at enrollment</td>
<td>n = 840 Age &gt; 60</td>
<td>n = 4396 Age = 65–74</td>
<td>n = 1627 Age = 70–184</td>
<td>n = 4736 Age &gt; 60</td>
<td>n = 4695 Age &gt; 60</td>
<td>n = 3845 Age &gt; 80</td>
</tr>
<tr>
<td>Active treatment medication</td>
<td>HCTZ + triamterene</td>
<td>Atenolol or HCTZ + amiloride</td>
<td>Beta-blockers or diuretics</td>
<td>Chlorthalidone ± atenolol</td>
<td>Nitrendipine ± enalapril</td>
<td>Indapamid ± perindopril</td>
</tr>
<tr>
<td>Goal SBP levels (mm Hg)</td>
<td>SBP &lt; 150 or SBP &lt; 160</td>
<td>&lt; 160/95</td>
<td>&gt;20 from BL or SBP &lt; 160</td>
<td>&gt;20 from BL or SBP &lt; 150</td>
<td>&lt;150/80</td>
<td></td>
</tr>
<tr>
<td>BP reduction (mm Hg) with active tt compared with BL</td>
<td>30/15</td>
<td>33/15</td>
<td>28/15</td>
<td>27/9</td>
<td>23/7</td>
<td>29.5/12.9</td>
</tr>
<tr>
<td>BP reduction (mm Hg) (Active tt vs. Placebo)</td>
<td>20/9</td>
<td>13/10</td>
<td>19.5/8.1</td>
<td>12.4</td>
<td>10.5</td>
<td>15.0/6.1</td>
</tr>
<tr>
<td>Achieved BP (mm Hg) with active treatment</td>
<td>150/85</td>
<td>152/76</td>
<td>167/87</td>
<td>143/64</td>
<td>151/79</td>
<td>144/78</td>
</tr>
<tr>
<td>Mean follow-up (years)</td>
<td>4.3</td>
<td>5.8</td>
<td>2.1</td>
<td>4.5</td>
<td>2.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Percent reduction in events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>36</td>
<td>25*</td>
<td>47*</td>
<td>33</td>
<td>42*</td>
<td>30</td>
</tr>
<tr>
<td>CAD</td>
<td>20</td>
<td>19</td>
<td>13*</td>
<td>27</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>CHF</td>
<td>22</td>
<td>–</td>
<td>51*</td>
<td>55*</td>
<td>29</td>
<td>64*</td>
</tr>
<tr>
<td>All CVD</td>
<td>29*</td>
<td>17*</td>
<td>40*</td>
<td>32*</td>
<td>31*</td>
<td>34*</td>
</tr>
</tbody>
</table>

*Statistically significant
*Myocardial infarction only
BL, baseline; BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; CVD, cardiovascular disease; EWPHE, European Working Party on Hypertension in the Elderly; HCTZ, hydrochlorothiazide; MRC, Medical Research Council; SBP, systolic blood pressure; STOP, Swedish Trial in Old Patients; tt, treatment.
Hence, the suggestion of standing BP measurement and its evaluation and use in treatment goals in older age groups was given by National High BP Education Working Group. 23

Antihypertensives should be started in low doses and later titrated and added cautiously in older patients (as compared with young patients) in view of postural hypotension, syncope, and falls and frailty.

Some older patients on antihypertensives may have an increased nocturnal dipping of BP, which may lead to cerebral hypoperfusion so BP is routinely measured in waking hours. These patients have more risks of CV events.

Cognitive Impairment

Many studies have suggested an association between elevated BP in mid-age groups and the impaired cognition risk.

Duration of hypertension, levels of BP, cognitive profile, and testing may contribute in the discrepancy in the relationship between hypertension and decline of cognition.

Few studies have shown that markers of aging of arteries may recognize patients at higher risk of cognitive decline, whereas BP alone does not appear in having a significant predictive value. 24-26

Conclusion

Elderly patients are the most rapidly increasing section in the society and age is a major risk factor for the development of hypertension. These population are associated with multiple comorbidities, frailty, cognitive decline, and loss of autonomic functions.

For diagnosis, clinical examination, physical examination, lab investigations, as well as complete geriatric assessment should be done properly.

While treating the patients, lifestyle modifications should be advised initially. Later, drug therapy should be started after consideration of factors like age, sex, comorbidities, frailty, and cognitive status. Adverse effects of the drug should be kept in mind while starting the drugs and the patient should be continuously monitored.

So finally, it should be noted that hypertension in older age groups has to be managed from a life-course perspective with proper investigations and timely treatment of high BP as compared with younger age groups. 27

References


CHAPTER 19

Apparent Treatment Resistant Hypertension—What a Physician Needs to Ponder

Amitesh Aggarwal, Ankur Chikara

Abstract

Treatment resistant hypertension (TRH) and apparent treatment-resistant hypertension (aTRH) are two different identities. Compared to overall hypertensives, people with TRH have more poor outcomes, and hence BP control is much more important in such population. Low adherence to the medication intake is the major modifiable patient-related barrier in achieving controlled blood pressure. aTRH is used when issues of dosing, medication adherence, and white coat hypertension have not yet been ruled out, and have measurements as systolic BP ≥140 mm Hg and/or ≥90 mm Hg diastolic on ≥3 BP medications. The prevalence of controlled hypertension in India is 35% and, in the world, it ranges between 6% and 17%. MMAS-8 (Morisky Medication Adherence Scale) with 93% sensitivity and 53% specificity is used in validating medication non-adherence in very low-income patients who were being treated for hypertension in routine care clinic setting. The patients with aTRH were significantly associated with older age groups (>55 years), obesity (BMI >27.5 kg/m²), diabetes mellitus, prolonged hypertension (>10 years), female sex, black race, and comorbidity like ischemic heart disease, depression as risk factors as compared to patients with non-resistant hypertension. The prognosis of the patients suffering from aTRH compared with controlled hypertension should be impaired in aTRH as such patients typically have longstanding history of sub-standardly controlled BP and usually have other associated comorbidities and cardiovascular risk factors like diabetes, obstructive sleep apnea, left ventricular hypertrophy, and/or chronic kidney disease. Among aTRH patients, decrease adherence to antihypertensives is a significant problem and, spreading awareness for better medications adherence and proper measurement of BP can easily tackle it. This article discusses about the various causes of aTRH, role of medication adherence in aTRH, and factors affecting it, risk factors of aTRH and workup of aTRH in detail.

Introduction

Treatment resistant hypertension (TRH) and apparent treatment-resistant hypertension (aTRH) are two different identities. Term aTRH is used when issues of dosing, medication adherence and white coat hypertension have not yet been ruled out. The prevalence of TRH and aTRH internationally is found to be 11.8% and from 6% to 17%, respectively. More poor outcomes are noted in TRH patients compared to the overall hypertensive population, and hence BP control is much more important in such population. Low adherence to the medication intake is the major modifiable patient-related barrier in achieving controlled blood pressure. This article mainly focuses on various aspects of evaluation of a case of aTRH.

Definition

Hypertension by definition is an office systolic blood pressure (SBP) more than equal to 140 mm Hg and/or diastolic blood pressure (DBP) more than 90 mm Hg. Treatment resistant hypertension (TRH) by definition is blood pressure reading more than 140/90 mm Hg in spite of simultaneous use of three antihypertensive
medications of various classes. Ideally one drug should be diuretic and all the three antihypertensives must be taken in their optimal doses. This number of medications is arbitrarily and not scientific. It is to note that patients having controlled blood pressure (i.e., <140/90 mm Hg) with ≥4 antihypertensive drugs should also be categorized as having TRH.

Apparent treatment-resistant hypertension (aTRH) is used when issues of dosing, medication adherence, and white coat hypertension have not yet been ruled out. In different studies, uncontrolled aTRH has been described as systolic BP ≥140 mm Hg and/or ≥90 mm Hg diastolic on ≥3 BP medications. Controlled aTRH by definition is BP <140 mm Hg systolic and <90 mm Hg diastolic on ≥4 antihypertensives drugs unless specified otherwise. Optimum dose of a medication is the quantity of the drug that will produce the desired effect without any unfavorable side effects. It is not necessarily a maximum dose.

The purpose of defining TRH and aTRH is to find out patients having reversible causes of hypertension and who will be benefitted with special diagnostic and therapeutic considerations.

Prevalence of TRH and aTRH

The prevalence of true TRH is unknown. Nearly 10% of the patients with diagnosed hypertension have true TRH. Above the BP value of 120/70 mm Hg, cardiovascular diseases (CVDs) mortality doubles usually with every 10 and 5 mm Hg increase in SBP and DBP respectively.

Prevalence of aTRH: International Scenario

The prevalence of aTRH varies from 6% to 17% (Table 1).

aTRH: Indian Scenario

The prevalence of controlled hypertension in India is 35%. Since at present there is unavailability of good and robust data from India, thus the exact prevalence of resistant hypertension is difficult to quote. In a study by Mandal et al. in Kolkata, among 300 hypertensive subjects, 23.33% were identified as aTRH.

Causes for aTRH and TRH

The causes of resistant hypertension are divided into apparent cause and true cause (Table 2).

Role of Medication Adherence in Hypertension

Adherence to medication is a crucial part of patient care and indispensable for reaching goals. Medication adherence is defined as “The extent to which the medication taking behavior of a patient corresponds with agreed recommendations from the health-care provider.” The different factors that affect patients’ adherence to the drugs are demographic features, disease severity, complexity of drug regime (number and frequency of the drug prescribed), drug classes (tolerability and side effects profile of the drug), patients’ forgetfulness, and lack of understanding on the nature of disease.

### TABLE 1

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Study location</th>
<th>Study period</th>
<th>Prevalence of aTRH % (N=sample size)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushman et al. ^2</td>
<td>North America</td>
<td>1994–2002</td>
<td>9.4% (N=33,357)</td>
</tr>
<tr>
<td>INVEST ^2</td>
<td>Canada, South Africa, United States, Spain, Mexico, New Zealand, Israel, Italy, Australia, Germany, France</td>
<td>1997–2003</td>
<td>12.9% (N=22,576)</td>
</tr>
<tr>
<td>McAdam-Max et al. ^4</td>
<td>United States</td>
<td>2002–2005</td>
<td>12.4% (N=29,474)</td>
</tr>
<tr>
<td>Persell ^5</td>
<td>United States</td>
<td>2003–2008</td>
<td>9.2% (N=15,968)</td>
</tr>
<tr>
<td>Sim et al. ^6</td>
<td>United States</td>
<td>2006–2007</td>
<td>9.4% (N=470,386)</td>
</tr>
<tr>
<td>Sarganas et al. ^7</td>
<td>German</td>
<td>2008–2011</td>
<td>6.8%, (N=7,115)</td>
</tr>
<tr>
<td>Choi et al. ^8</td>
<td>Korea</td>
<td>2015</td>
<td>11.9% (N=2,439)</td>
</tr>
</tbody>
</table>
## Hypertension

### TABLE 2  

<table>
<thead>
<tr>
<th>Apparent cause (Pseudoresistance or aTRH)</th>
<th>True cause (True TRH)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pseudoadherence</strong> to antihypertensive drug therapy</td>
<td><strong>High risk patients—which includes following:</strong></td>
</tr>
<tr>
<td></td>
<td>• Female sex</td>
</tr>
<tr>
<td></td>
<td>• Elderly</td>
</tr>
<tr>
<td></td>
<td>• Black race</td>
</tr>
<tr>
<td></td>
<td>• Comorbidities like obesity, diabetes mellitus, chronic kidney disease, left ventricular hypertrophy, and high baseline blood pressure</td>
</tr>
<tr>
<td><strong>Improper technique</strong> to record BP</td>
<td><strong>Lifestyle which include:</strong></td>
</tr>
<tr>
<td></td>
<td>• Increase dietary salt intake (&gt;10 gm/day)</td>
</tr>
<tr>
<td></td>
<td>• Increase alcohol consumption</td>
</tr>
<tr>
<td></td>
<td>• Lack of exercise</td>
</tr>
<tr>
<td><strong>White coat hypertension</strong></td>
<td><strong>Drug related cause which include:</strong></td>
</tr>
<tr>
<td></td>
<td>• Following medications can cause difficulty in controlling BP—</td>
</tr>
<tr>
<td></td>
<td>• Non-steroidal anti-inflammatory agents—Aspirin</td>
</tr>
<tr>
<td></td>
<td>• Selective COX-2 inhibitors</td>
</tr>
<tr>
<td></td>
<td>• Sympathomimetic agents—decongestants, diet pills, cocaine</td>
</tr>
<tr>
<td></td>
<td>• Stimulants—amphetamine, modafinil, methylphenidate, methamphetamine</td>
</tr>
<tr>
<td></td>
<td>• Alcohol</td>
</tr>
<tr>
<td></td>
<td>• Erythropoietin</td>
</tr>
<tr>
<td></td>
<td>• Cyclosporin</td>
</tr>
<tr>
<td></td>
<td>• Natural licorice</td>
</tr>
<tr>
<td></td>
<td>• Oral contraceptives</td>
</tr>
<tr>
<td></td>
<td>• Herbal compounds—ma-huang or ephedra</td>
</tr>
</tbody>
</table>

| Secondary causes include: |
| • Renal parenchymal disease |
| • Primary aldosteronism |
| • Obstructive sleep apnea |
| • Renal artery stenosis |
| • Drug induced or heavy alcohol use |
| • Thyroid disorders |

| | • Genetic causes—CYP3A5 allele (CYP3A5*1)

Adherence to treatment can be measured using different methods:
- Pill counting
- Drug concentration in the body fluids and response to therapy.
- Measures which involves Electronic Medication Packaging (EMP’s) devices, clinician assessments and self-report.

World Health Organization (WHO) reports that secondary to substandard availability and accessibility of medications and health-care services, adherence to drugs in patients who are chronically ill averages nearly 50% in developing countries. The asymptomatic nature of the disease augments the issue of non-adherence to medications in hypertension.

In cohort study, which retrospectively studied the variance in medication adherence among hypertensive patients, it was noticed that the factors like duration of hypertension (shorter duration corresponds with better adherence) and use of newer agents (like calcium channel blockers and ACE inhibitors) had the strongest positive effect on medication adherence.

### Choosing a Suitable Medication Adherence Measure

An ideal medication adherence measure should have the following characteristics—low cost, practical, user friendly, highly reliable, easy to carry out and flexible. Eight-item MMAS-8 (Morisky Medication Adherence Scale) is the one easy and validated tool. In 2008 using Medication Adherence Questionnaires (MAQ), Morisky et al, developed this 8-item MMAS (MMAS-8) tool which has 93% sensitivity and 53% specificity in validating...


**TABLE 3**

<table>
<thead>
<tr>
<th>Studies (reference)</th>
<th>Results as percentage of non-adherence to medication</th>
<th>Factors responsible for non-adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irvin et al.21</td>
<td>The distribution of MMAS scores of 0 (best adherence) and 1, 2, 3, or 4 (worst adherence), was 68.8%, 24.1%, 5.0%, and 2.0%, respectively</td>
<td>After adjustments for age/gender/geographic region of residence, blacks were found to have low medication adherence. Also women compared to men, have low drug adherence</td>
</tr>
<tr>
<td>Pandey et al.22</td>
<td>Adherence score less than 6 was seen in 26% of patients. The actual prevalence of non-adherence using therapeutic drug monitoring was 51%</td>
<td>This study suggested that there is limited accuracy of the MMAS-8 tool in detecting drug adherence in patients of aTRH</td>
</tr>
</tbody>
</table>
| Hema et al.23        | Adherence was seen as—  
|                      | • High—15.3%  
|                      | • Low adherence—(62%, n=248) (majority of study population)  
|                      | • Medium adherence—22.7% (n=91) | Higher adherence was found in—  
|                      | • 50 years & above age group (46.6%)  
|                      | • Among females (51.6%)  
|                      | • Among nuclear families (47.1%)  
|                      | • Among literates (44.2%) |
| Nagarkar et al.24    | Using MMAS-8, 23.4% were high adherent and 76.5% showed low adherence to the medication | Medication adherence was found—  
|                      | • Significantly associated with age, family type, and experience of symptoms  
|                      | • Not associated with gender, education, frequency, and number of medications |
| Behnood-Rod et al.25 | 49.6% showed MMAS-8 score less than 6 | Following has been noted—  
|                      | • Negative linear association between systolic BP as well as diastolic BP  
|                      | • Factors recognized to have statistically significant association with the MMAS-8 score were—overweight/obesity/previous history of admission to emergency services due to hypertensive crisis/getting medication directly from drugstore without revised prescription |

**TABLE 4**

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Method of non-adherent assess</th>
<th>Baseline blood pressure</th>
<th>Non-adherent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yakovlevitch and Black26</td>
<td>New Haven, CT, USA</td>
<td>MD interview</td>
<td>176/103</td>
<td>9/91 (9.9%)</td>
</tr>
<tr>
<td>De Souza et al.27</td>
<td>São Paulo, Brazil</td>
<td>Pill count</td>
<td>163/103</td>
<td>16/44 (36%)</td>
</tr>
<tr>
<td>Cereal et al.28</td>
<td>Prague Czech R</td>
<td>Serum level</td>
<td>171/97</td>
<td>55/84 (65.5%)</td>
</tr>
<tr>
<td>Jung et al.29</td>
<td>Frankfurt, Germany</td>
<td>Urine level</td>
<td>Not stated</td>
<td>40/76 (53%)</td>
</tr>
<tr>
<td>Blinker et al.30</td>
<td>Dallas, TX, USA</td>
<td>Urine level</td>
<td>169/103</td>
<td>23/40 (57.5%)</td>
</tr>
</tbody>
</table>

medication non-adherence in very low-income patients who were being treated for hypertension in routine care clinic setting. Soon similar success was obtained in validating MMAS with high reliability in patients with other chronic illnesses (Table 3).

**Role of Medication Adherence in aTRH**

There is risk of poor outcomes in patients with aTRH. Drug adherence and intensification ameliorate BP control in the patients who receive pharmacological treatment; however, less is studied about the outcomes of these processes in aTRH. Substandard adherence or failing to take ≥75% of prescribed drug, influence ~10–60% of aTRH (Table 4).

**Factors Affecting Medication Adherence in aTRH**

There are very few studies which studied about factors affecting medications adherence in aTRH. Table 5 comprises few studies which have studied these factors.
Alsabbhag et al. extracted data of 40 cohorts in 30 studies reporting socioeconomic status (SES) variable and did a structured review and meta-analysis study to discover the relationship between SES with adherence to antihypertensives. They noticed that higher SES was associated with a lower risk of non-adherence in 31 cohorts (77.5%), with no difference in 1 cohort, and with an increased risk of non-adherence in 8 cohorts. A study by Siegel et al. entitled “Antihypertensive medication adherence in the department of veterans affairs,” which comprised of 95% of all patients included in this review noticed that patients with an ICD-9 diagnosis of depression were found to be less likely adherent to medication in multivariate analysis.

### TABLE 5

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Year of study</th>
<th>Results as prevalence of non-adherence (%)</th>
<th>Results as factors responsible for poor adherence of the medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhandari et al.33</td>
<td>2015</td>
<td>≥80</td>
<td>The following patients were more likely to be adherent to treatment:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Patients hypertensive for ≥5 years (2.98 times)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Whose hypertension was detected during checkups for conditions related to hypertension (2.35 times)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Patients living with ≤4 family members (2.01 times)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Family income of ≥3,000 rupees (2.56 times)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Who were getting free drugs (4.16 times)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Patients perceiving current blood pressure to be under control (2.23 times)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Those satisfied with current treatment (3.77)</td>
</tr>
<tr>
<td>Venkatachalam J34</td>
<td>2015</td>
<td>24.1</td>
<td>Adherence was found to be higher in following groups:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Age groups 30–39 years (27%) and above 60 years (27.1%) as compared with other age groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Among female (25.5%) respondents than male respondents (22.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Married (24.8%) respondents than unmarried respondents (21.1%)</td>
</tr>
<tr>
<td>Patel and Taylor35</td>
<td>2002</td>
<td>32</td>
<td>No statistically significant differences in medication adherence based on:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Age</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Gender</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Education</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Total household income</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Living arrangements</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Total number of years with hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Number of medications</td>
</tr>
<tr>
<td>Karakurt et al.36</td>
<td>2012</td>
<td>57.9</td>
<td>Significant association between old age and non-adherence</td>
</tr>
<tr>
<td>Ramli et al.37</td>
<td>2012</td>
<td>46.6</td>
<td>Female were one and a half times more adherent than male</td>
</tr>
<tr>
<td>Gupta et al.38</td>
<td>2016</td>
<td></td>
<td>• Age has an inverse association with non-adherence to antihypertensive treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Every 10-year increase in age was associated with more than 30% reduction in the odds of non-adherence in the UK and the Czech populations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Females were found to be more non-adherent compared to males</td>
</tr>
<tr>
<td>Yang et al.39</td>
<td>2016</td>
<td>43.5</td>
<td>Better medication adherence seen in:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Older participants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Patients having more knowledge of hypertension</td>
</tr>
</tbody>
</table>

### Risk Factors for aTRH

The patients with aTRH were significantly associated with older age groups (>55 years), obesity (BMI >27.5 kg/m²), diabetes mellitus, prolonged hypertension (>10 years), female sex, black race, and comorbidity like ischemic heart disease, depression as risk factors as compared to patients with non-resistant hypertension.

### Workup to Differentiate aTRH from TRH

#### Pseudo or aTRH

In clinical practice it is the most common form of resistance. It inferred absence of true resistance to drugs and is due to either wrong technique of measuring...
BP, substandard adherence to treatment or white coat hypertension.

**Poor Measurement Technique**

Faulty measurement techniques can result in false high readings of BP and thus can result in aTRH. The two most common mistakes in clinical scenario are—
- Measuring the BP immediately and not allowing the patient to sit calmly
- Use of inappropriate size cuff
  This results in falsely high BP readings of the patients who otherwise are having normal or controlled BP.

**Substandard Adherence**

One of the major reasons of inadequate BP control is poor adherence to antihypertensives. It is seen that substandard adherence is usual at primary care level and it is less frequent among patients who are being treated by specialists. Inadequate BP control and treatment resistance are two different identities. Before labeling failed antihypertensive regimen, it is mandatory and wise to ensure that the regimen was taken correctly as advised by the treating physician.

**White Coat Effect**

White coat hypertension is persistently higher values of clinic BP while home recordings are significantly lower. Studies specify that significant white coat effect is as usual in aTRH patients as in more general hypertensive population. Patients of resistant hypertension on the basis of white coat effect show less severe target organ damage and have less cardiovascular risk compared with patients who have persistently higher ambulatory BP values.

**Fragmented Health Services**

India like other developing countries is facing an important problem of lacking access to chronic care. Patients shift to different physicians at will and the majority of primary and secondary care physicians have no robust system to track patient’s data. This effects in inappropriate care, substandard lifestyle advice, and revising pharmacological therapy with substandard BP control.

**Workup for TRH/aTRH**

Workup of TRH and aTRH is summarized in Table 6.

**Guiding Principles or Clinical Pearls to Evaluate Resistant Hypertension**

What a clinician should know to evaluate a case of resistant hypertension is summarized below:

1. **Confirm TRH**—
   - Clinic BP >130/80 mm Hg
   - Patient taking >3 antihypertensive agents (including a long acting calcium channel blocker,

<table>
<thead>
<tr>
<th>TABLE 6</th>
<th>Resistant hypertension (TRH and ATRH ) workup</th>
</tr>
</thead>
</table>
| Find out and correct pseudohypertension (aTRH) | • Properly measure BP  
• Check white coat effect with help of authentic home or 24-hour ambulatory BP measurements  
• Evaluate treatment adherence and boost it with—education and awareness  
• Prescribing cost effective drug regimen  
• Prescribing drugs with least and tolerable adverse effects  
• Prefer once daily fixed-dose combination products |
| Life style changes | • Whether patient is using any pharmacological/herbal substances that may cause increase in BP—if yes, remove it  
• Find out the amount of daily alcohol intake and advise to cut down it to zero or recommended daily intake  
• Find out daily dietary salt intake and recommend sodium restriction to <100 mmol (2.4 gm) per day  
• Evaluate the degree of obesity, abdominal obesity, and physical activity. Also advise weight reduction and regular aerobic exercise (at least 30 min/day, most days of the week) |
| Find out contributing factors to true resistant hypertension | • Evaluate renal function (estimate glomerular filtration rate) and modify treatment accordingly  
• Find out causes of secondary hypertension |

Treatment should be customized as per the patient characteristics with optimal doses of suitable medications. Refer to the hypertension specialist if everything fails.
a blocker of renin-angiotensin system, and a diuretic)
- Medications are at maximal or maximally tolerated doses
- Assess for pseudo or aTRH—
  - Confirm adherence to antihypertensive treatment
  - Monitor 24-hour ambulatory BP to eliminate white coat effect
  - Use home BP monitoring in case of non-availability of 24-hour ambulatory BP monitoring
- Assess for secondary hypertension—look for the following—
  - Primary aldosteronism
  - Renal parenchymal disease
  - Renal artery stenosis
  - Pheochromocytoma/paraganglioma
  - Cushing syndrome
  - Obstructive sleep apnea
  - Coarctation of aorta
  - Other endocrine causes like—hypothyroidism, hyperthyroidism, hypercalcemia, and primary hyperparathyroidism, congenital adrenal hyperplasia, acromegaly
- Assess for target organ damage—
  - Ocular: fundoscopic exam
  - Cardiac: left ventricular hypertrophy, coronary artery disease
  - Renal: proteinuria, decreased glomerular filtration rate
  - Peripheral arterial disease: ankle/brachial index

**Prognosis**

The prognosis of the patients suffering from aTRH compared with controlled hypertension has not been particularly studied in detail. Uncertainly but likely, prognosis should be impaired in aTRH as such patients typically have longstanding history of sub-standardly controlled BP and usually have other associated comorbidities and cardiovascular risk factors like diabetes, obstructive sleep apnea, left ventricular hypertrophy, and/or chronic kidney disease. It is also unknown so far that post-successful treatment of aTRH in such patients, how much this cardiovascular risk will reduce. However, the advantage of successful treatment is likely considerable as suggested by hypertension outcome studies in general and by the early Veterans Administration cooperative studies, which illustrated a 96% reduction in cardiovascular events over 18 months with help of triple antihypertensive regimens compared with placebo in patients with severe hypertension (diastolic BP 115–129 mm Hg).41

**Conclusion**

Spreading awareness for better medications adherence and proper measurement of BP can easily tackle the aTRH, which is otherwise a significant issue. Among aTRH patients, decrease adherence to antihypertensives is a significant problem. Thus, it is emphasized that health-care professionals should pay attention to this fact while developing a treatment program for aTRH patients in order to enhance adherence to antihypertensive medications and improve health outcomes.

**References**

7. Sarganas G, Neuhauser HK. Untreated, Uncontrolled and Apparent Resistant Hypertension; Results of the German Health Examination Survey, 2008-2011.
CHAPTER 19

Apparent Treatment Resistant Hypertension—What a Physician Needs to Ponder


Abstract
Resistant hypertension refers to elevated blood pressure above the target level in spite of concurrent use of three antihypertensive agents from three different classes (including a diuretic) in the maximum tolerated/recommended doses. It is important to exclude pseudo-resistant hypertension before making a diagnosis of resistant hypertension. Adverse cardiovascular event rate is almost 50% higher in cases of resistant hypertension than in general hypertensive patients. Chlorthalidone/indapamide is the agent of first choice while selecting a diuretic. It is important to uptitrate the doses of three existing antihypertensive agents to the maximum permissible/tolerable levels before adding the fourth agent. The fourth preferred agent of choice is spironolactone provided the serum potassium is ≤4.5 mmol/L. Next comes the role of beta blockers, alpha blockers, centrally acting agents, direct vasodilators, and direct renin inhibitors. Device-based therapies like renal denervation and carotid baroreceptor stimulation have a very limited role restricted to highly specialized centers.

Introduction
Hypertension is one of the most common ailments seen by a primary care physician and failure to detect and treat it timely leads to many complications like stroke, myocardial infarction, and chronic kidney disease. It is unfortunate that in spite of having well established diagnostic and therapeutic protocols, more than half of patients are not controlled to target levels. Resistant hypertension refers to elevated blood pressure above the target goal of 140/90 mm Hg in spite of using three antihypertensive agents from three different classes, including a diuretic, in the maximum permissible/tolerable doses. Target goal of blood pressure is 130/80 mm Hg for patients of chronic kidney disease and established cardiovascular disease. Here, it is worth mentioning that a proper combination means a combination of three antihypertensive drugs having synergistic action—angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blocker (ARB) plus a calcium channel blocker (CCB) and a thiazide like diuretic.

Prevalence
Exact prevalence of resistant hypertension is not known but 20–30% of patients become resistant to treatment with the passage of time. In largest hypertension trial (ALLHAT), only 67% patients attained a systolic blood pressure of less than 140 mm Hg and 92% attained a diastolic blood pressure of less than 90 mm Hg. Refractory hypertension is not synonymous to resistant hypertension as refractory hypertension is much more severe form of disease where the blood pressure cannot be controlled even with five or more drugs including spironolactone and have to be referred to specialized centers for more invasive/devised based therapies.

Pseudo-resistant Hypertension
As the name indicates it is not truly resistant, but looks like resistant and one must rule it out before making a diagnosis of resistant hypertension. Important causes of pseudo-resistance are as follows:
• Improper blood pressure measurement technique or inappropriate sized blood pressure cuff.
• Poor compliance to prescribed medicines due to cost, side effects, or inadequate counseling. A renal denervation trial revealed that only 20% of patients were adherent to the prescribed medicines.³
• Inadequate/suboptimal doses or improper combination of drugs. A general practitioner’s prescription review of uncontrolled hypertensive patients revealed that only 18% of these patients were prescribed three antihypertensive agents including a diuretic.⁴
• Non-adherence to diet and lifestyle modification like reduction of salt intake, cessation of cigarette smoking, and moderation of alcohol intake.
• White coat hypertension—here the blood pressure is high in doctor’s chamber but otherwise it is normal. Best way to diagnose white coat hypertension is either ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM). White coat hypertension should be suspected in patients having orthostatic hypotension and in those having very high blood pressure readings in the absence of target organ damage.

Medications Interfering with Hypertension Treatment
A variety of drugs can raise the blood pressure or interfere with the working of antihypertensive drugs making them less effective.⁵ Commonly used such drugs are:
• NSAIDs
• Oral contraceptives
• Glucocorticoids
• Sympathomimetics including nasal decongestants
• Antidepressants
• Cocaine
• Erythropoietin
• Amphetamine

Secondary Hypertension
About 5% to 10% of total hypertensive patients have secondary hypertension and it is more prevalent in resistant hypertension.⁵ Common causes of secondary hypertension are obstructive sleep apnea (OSA), renal artery stenosis (RAS), chronic kidney disease (CKD), primary aldosteronism. Less common causes are pheochromocytoma, Cushing’s syndrome, hyperthyroidism, hypothyroidism, coarctation of aorta, and drugs.

Obstructive Sleep Apnea (OSA)
Clinical features of OSA are obesity, snoring, and day time sleepiness. Sleep apnea is more severe and more common in men than women.⁶ Sleep apnea gives rise to hypoxia which stimulates sympathetic nervous system and is responsible for resistant hypertension.

Continuous positive airway pressure (CPAP) is the treatment of choice for OSA. Once OSA is treated with CPAP, the blood pressure starts coming down and lesser and lesser medicines are required to control blood pressure.

Primary Aldosteronism
As the name indicates, primarily there is excessive production of aldosterone from the adrenal cortex. Control of hyperaldosteronism can control the blood pressure to a reasonable level. It is of two types:
• Bilateral adrenal hyperplasia or idiopathic hyperaldosteronism (IHA)
• Unilateral aldosterone producing adenoma (APA) Bilateral hyperplasia (IHA) is much more common than unilateral adenoma (APA). 10% to 20% patients of resistant hypertension are found to have primary aldosteronism.⁷

Clinical indicators of primary aldosteronism include:
• Hypertension with hypokalemia
• Adrenal mass on ultrasound in patients with hypertension
• Resistant hypertension especially in young individuals

Usually there is high plasma aldosterone concentration (PAC) and low plasma renin activity (PRA), and therefore PAC/PRA ratio is elevated. Aldosterone antagonists like spironolactone or eplerenone can effectively control blood pressure in such cases. Surgical treatment is restricted to patients who do not respond to medical management and have unilateral adrenal mass.

Renovascular Hypertension⁸
Overall prevalence of significant renovascular disease is 6–8%. Here the hypertension is due to an obstructive lesion in the renal artery.
Atherosclerotic RAS—this is the main cause of RAS found in 80–90% of cases. It is typically seen after the age of 55 years and is usually associated with atherosclerotic lesions elsewhere like coronary or cerebral vessels.

Fibromuscular dysplasia—this is second most important cause of RAS, responsible for 10–20% cases of RAS. It is more common in young females.

Clinical indicators of RAS:
- Onset of high blood pressure after 55 years of age
- More than 25% increase in serum creatinine after starting ACE inhibitors or ARBs
- Unexplained atrophic kidneys or difference of 1.5 cm or more in the size of two kidneys
- Abdominal bruit

Diagnosis is confirmed by renal Doppler studies and CT/MR angiography.

Aim of treatment is to control blood pressure mainly with the help of antihypertensives like ACE inhibitors or ARB, diuretics, especially chlorthalidone or indapamide and CCBs, keeping a close watch on serum creatinine and serum potassium.

Stenotic lesions unresponsive to medical treatment are treated with revascularization. However, ASTRAL study could not produce evidence that interventional therapy with angioplasty is a better choice.

Chronic Kidney Disease (CKD)
CKD has a very strong association with resistant hypertension. It is both a cause and complication of resistant hypertension. Resistant hypertension in cases of CKD is due to salt retention, increased action of renin angiotensin aldosterone system, and increased activity of sympathetic nervous system. ACE inhibitors and ARBs are the drugs of first choice. Initially, there is mild increase in serum creatinine/serum potassium levels after starting these agents and the same needs to be monitored closely. Diuretics along with fluid and salt restriction are also very effective. However, thiazides lose their potency once the GFR is below 40 mL and should be substituted with loop diuretics.

Other Causes of Secondary Hypertension
See Table 1.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing’s syndrome</td>
<td>Moon shaped facies, obesity, hirsutism, and hyperglycemia along with hypertension</td>
</tr>
<tr>
<td>Coarctation of aorta</td>
<td>Higher blood pressure in arms and lower blood pressure in legs</td>
</tr>
<tr>
<td></td>
<td>Weak femoral pulses</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Weight gain, fatigue, anorexia, dry skin</td>
</tr>
<tr>
<td></td>
<td>Amenorrhea</td>
</tr>
<tr>
<td></td>
<td>Increased TSH</td>
</tr>
<tr>
<td></td>
<td>Decreased free T4</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Fatigue, constipation, joint pains</td>
</tr>
<tr>
<td></td>
<td>Nephrolithiasis, heartburn, polydipsia</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Paroxysmal hypertension</td>
</tr>
<tr>
<td></td>
<td>Spikes of headache, sweating, tremors, and palpitations</td>
</tr>
</tbody>
</table>

Work Up for a Patient of Resistant Hypertension

Once the diagnosis of resistant hypertension is made, it is very important to record a detailed history and clinical examination to exclude pseudo-resistant hypertension.
- Confirm that the patient is taking all prescribed medicines
- Review the prescription for proper drug combination and doses
- Confirm adherence to lifestyle measures
- Exclude white coat effect by ABPM or HBPM
- Look for consumption of excessive salt or alcohol or smoking
- Look for consumption of offending drugs like NSAIDs, oral contraceptives, or corticosteroids
- Look for secondary causes of hypertension

Management
Non-pharmacological Intervention

Lifestyle modifications can significantly decrease the blood pressure.
- Dietary sodium—it has been found that restriction of sodium to 2.4 gm/day or salt to 6 gm/day reduces both systolic and diastolic blood pressure by reducing extracellular volume.
- Restrict the use of alcohol and smoking.
Weight loss if overweight.
Consume high fiber and low fat diet.
Increase physical activity.

**Antihypertensive Drugs**

It is presumed that when the patient is diagnosed as having resistant hypertension, he is already taking a synergistic combination of three antihypertensive drugs, that is, a combination of ACE inhibitors or ARB plus a CCB plus a thiazide like diuretic.

First of all, one should optimize the doses of the three antihypertensive agents as a large majority of patients are taking suboptimal doses. It is worth mentioning that chlorthalidone is twice as potent as hydrochlorothiazide and so, those patients who are taking hydrochlorothiazide should be changed to chlorthalidone or indapamide.

**Spironolactone**

Spironolactone is the fourth agent of choice in resistant hypertension provided serum potassium is ≤ 4.5 mmol/L. Its dose is usually 12.5–50 mg/day. It has got a long half-life and maximal effect is seen after 3–4 weeks. Therefore, dose titration needs to be done every 4–6 weeks. It has an additional property of regressing left ventricular hypertrophy. The main side effect of spironolactone is breast tenderness and hypertrophy which is both dose and duration dependent, and is reversible once the drug is withdrawn. The second important side effect is hyperkalemia, especially in combination with ACE inhibitor or ARB. It is important to monitor serum potassium before starting and 2 weeks after drug initiation. Another side effect is hyponatremia, especially in elderly population after long-term use.

**Beta Blockers**

A beta blocker like metoprolol, nebivolol, or carvedilol is the next choice in resistant hypertension. These agents are of special use in cases of coronary artery disease, heart failure, and tachyarrhythmias.

**Alpha Blockers**

An alpha blocker can be used especially in the presence of benign enlargement of prostrate.

**Centrally Acting Agents**

Centrally acting agents like clonidine and alpha methyldopa can also be used in the management of resistant hypertension if the patient is refractory to other classes of drugs. Rebound hypertension can occur if the drug is suddenly stopped.

**Direct Vasodilators**

A vasodilator like hydralazine is the next agent to be used. Main side effect of hydralazine is fluid retention and tachycardia, and therefore concomitant therapy with a diuretic and beta blocker is usually required.

**Direct Renin Inhibitors**

Aliskiren is particularly useful in patients of resistant hypertension associated with features of metabolic syndrome.

**Newer Drugs for the Management of Resistant Hypertension**

Endothelin receptor antagonists like darusenatan gave promising results initially but could not show similar results in subsequent studies. Nitric oxide donors are other promising agents for the management of resistant hypertension. Nitrates with phosphodiesterase-5 inhibitors showed good results in a small study of six patients suffering from resistant hypertension. However, these agents can drastically lower the blood pressure, and hence are to be used with great caution.

**Night Time Administration of Antihypertensives**

Early morning fall of blood pressure (nocturnal dipping) is a normal physiological process and this is impaired in all hypertensive patients and more so in cases of resistant hypertension. Night time administration of at least one antihypertensive medication can restore the impaired night time dipping and reduces cardiovascular risk. American Diabetes Association in 2013 recommended in its guidelines to administer at least one antihypertensive medication at bedtime in cases of resistant hypertension.

**Procedures and Devices for Resistant Hypertension**

**Renal Denervation (RDN)**

As the name indicates, this procedure involves bilateral destruction of renal nerves travelling along the renal arteries using radio frequency ablation. The underlying principle is to decrease the renal sympathetic tone and thereby reduce the renal vascular resistance.
The initial Simplicity HTN-1 and HTN-2 RDN trials showed quite good results and the blood pressure was reduced by 30/15 mm Hg and the results were maintained for more than 2 years. However, the subsequent trial (Simplicity HTN-3) did not show any significant reduction in blood pressure after 6–12 months of renal denervation.

**Carotid Baroreceptor Activation**

It has been observed that carotid baroreceptor activation by implanting an electrical device (Baroreceptor Activation Therapy—BAT) in the carotid sinus can significantly reduce both systolic and diastolic blood pressure. Moreover, this procedure gives an additional benefit of reducing left ventricular hypertrophy and arterial stiffness. However, these studies have involved only a limited number of patients. This is an expensive and invasive procedure and more randomized controlled trials with larger number of individuals are required to establish the safety and beneficial effects of this procedure.

**Conclusion**

Resistant hypertension is an established entity and it is important to diagnose it because of its close association with the complications of hypertension. One should exclude pseudoresistant hypertension especially white coat hypertension and up titrate the doses of all the three existing antihypertensive agents to the maximum recommended/tolerable levels before labeling resistant hypertension. Compliance to treatment need to be re-emphasized along with lifestyle changes before adding further antihypertensive agents. Role of procedures like renal denervation and carotid baroreceptor stimulation is still in the experimental stage and large randomized controlled studies are required to establish their usefulness.

**References**

CHAPTER 21

Role of ARB in Hypertension

Sangram S Biradar

Abstract
Hypertension being one of the important diseases and risk factors of CVD and stroke in India. In management of hypertension all Indian guidelines recommend (ARBs) as an initial angiotensin receptor blockers or add-on drugs therapy. Hence, ARBs have demonstrated evidence-based benefits in management of hypertension, heart failure, and diabetic renal disease. ARBs are very well tolerated as monotherapy as well as in combination with other antihypertensive medications that improve adherence to therapy and have become a mainstay in the treatment of stages 1 and 2 hypertension.

Introduction
Hypertension is one of the risk factors of (CVD) and leading to disability and death in spite progresses happened in management in past three decades. In India up to 33% of urban and 25% of the rural population are afflicted with the disease. Attainment of (BP) goals in the population at large is a major challenge and area of focus of health systems worldwide.

Angiotensin II receptor blockers (ARBs) are advocated for people with stage I-II hypertension and type 1 or 2 diabetes. Since 1995, the role of ARBs has been in clinical use. ARBs are supposed to be better antihypertensive agents with good tolerance. ARBs have additive BP-lowering effects when they are combined with thiazide diuretics and dihydropyridine calcium channel blockers (CCBs), ARBs have proven mortality and morbidity effects in heart failure and chronic renal disease, particularly when associated with T2DM, concerns were raised surrounding the association of ARBs with development of solid cancers and coronary artery disease.

Pharmacology of Angiotensin Receptor Blockers
The renin–angiotensin–aldosterone system has been a major target pathway for development of antihypertensive medications. The major four groups of medications, like ARBs aldosterone antagonists, and direct rennin inhibitors, and ACE inhibitors, act on the same pathway. The interest in this pathway is due to the action of angiotensin II on the vascular system, renal sodium and water handling, and cellular proliferation. Inhibition of ACE only partially inhibits formation of angiotensin II. Angiotensin II activates two types of angiotensin II receptors (ATR): ATR1 and ATR2. ATR1 are abundant in the vessels, brain, heart, kidney, adrenal gland, and nerves, while ATR2 are prominently expressed in the fetus but decrease in number during the postnatal period, where they are only available in small numbers in the adult kidney, adrenal gland, heart, brain, uterus, and ovary. Activation of ATR1 increases inositol triphosphate and various arachidonic acid metabolites, and decreases cyclic adenosine monophosphate.

1,2
The mechanism of generalized vasoconstriction of vascular smooth muscle from contraction, which intern increases aldosterone thereby increase in reabsorption of sodium in the proximal tubal and cell growth in arteries and heart occurs. Therefore, angiotensin II which facilitates release of catecholamine from adrenal medulla and nerve endings thereby increasing hyperactivity from sympathetic nervous system occurs. Angiotensin II is believed to have an important mechanistic role in promoting CV diseases that is unrelated to its effect on BP.

Several animal studies have shown that it causes cardiac hypertrophy in the absence of elevated BP. Individuals with a high renin–sodium profile have a greater risk of myocardial infarction than those with a normal or low profile. The function of ATR2 (Alderman) remains unclear, but it inhibits cell growth by stimulation and differentiation of cell and apoptosis leads to vasodilation. However, ATR2 studies in animal show cardiac function improvements by stimulation and thereby preventing remodeling of cardiac post-myocardial infarction (Table 1).

### Angiotensin Receptor Blocker Available

Presently ARBs available in the market for hypertension and cardiac indications, that is, losartan, valsartan, candesartan, eprosartan, irbesartan telmisartan, olmesartan, and azilsartan. All these above are accepted for hypertension treatment.

Losartan and irbesartan are approved in diabetic nephropathy, losartan in stroke prophylaxis, candesartan and valsartan for heart failure and also reduce CV mortality in left ventricular failure patients or left ventricular dysfunction followed by myocardial infarction. ARBs also have demonstrated reducing proteinuria by preserving kidney function in diabetic patients and also decreasing endothelial dysfunction thereby increasing fibrinolysis and have demonstrated their effectiveness in preventing atheromas.

The eight ARBs approved for use in the USA and Europe are nonpeptide compounds having biphenyl, tetrazole, benzimidazole or non biphenyl non tetrazole groups. Candesartan, olmesartan, valsartan, losartan, and irbesartan have a common tetrabenzoliphenyl structure; telmisartan, and candesartan have a benzimidazole in common group; and eprosartan has a nontetrazole and nonbiphenyl, chemical structure. Whereas the irbesartan as an exception, and all have free carboxylic acid group. ARBs have more affinity for ATR1 than for ATR2 and can block the activities of angiotensin II on ATR1 regardless of whether it was created from ACE or other enzymes such as cardiac chymase (Table 2).

### TABLE 1: Pharmacological characteristics of angiotensin receptor blockers

<table>
<thead>
<tr>
<th>ARB</th>
<th>Half-tife (h)</th>
<th>Tmax (h)</th>
<th>Bioavailability (%)</th>
<th>Route of elimination: renal % (R) biliary/faecal % (B)</th>
<th>Food interaction</th>
<th>Drug interaction</th>
<th>CYP metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan</td>
<td>2</td>
<td>1–1.5</td>
<td>33</td>
<td>35 R; 60 B</td>
<td>Yes</td>
<td>None</td>
<td>2C9, 3A4</td>
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<tr>
<td>Candesartan</td>
<td>9</td>
<td>2–5</td>
<td>42</td>
<td>33 R; 67 B</td>
<td>No</td>
<td>None</td>
<td>2C9 (negligible)</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>5–9</td>
<td>1–3</td>
<td>63</td>
<td>7 R; 90 B</td>
<td>Yes</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>11–15</td>
<td>1.3–3</td>
<td>60–80</td>
<td>20 R; 80 B</td>
<td>No</td>
<td>None</td>
<td>2C9, 3A4 (negligible)</td>
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<tr>
<td>Telmisartan</td>
<td>24</td>
<td>0.5–1</td>
<td>43</td>
<td>&lt;1 R; &gt;97 B</td>
<td>No</td>
<td>Digoxin</td>
<td>No</td>
</tr>
<tr>
<td>Valsartan</td>
<td>6</td>
<td>2–4</td>
<td>23 (capsule) 50 (capsule)</td>
<td>13 R; 83 B</td>
<td>Yes</td>
<td>None</td>
<td>2C9 (weak)</td>
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<tr>
<td>Olmesartan</td>
<td>12–14</td>
<td>1.7–2.5</td>
<td>26</td>
<td>35–50 R; 50–65 B</td>
<td>No</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>Azilsartan</td>
<td>12</td>
<td>1.5–3</td>
<td>60</td>
<td>42 R; 55 B</td>
<td>No</td>
<td>None</td>
<td>2C9, 286 (negligible), 2C8 (negligible)</td>
</tr>
</tbody>
</table>

---

**Angiotensin Receptor Blocker Available**

Presently ARBs available in the market for hypertension and cardiac indications, that is, losartan, valsartan, candesartan, eprosartan, irbesartan, telmisartan, olmesartan, and azilsartan. All these above are accepted for hypertension treatment.

Losartan and irbesartan are approved in diabetic nephropathy, losartan in stroke prophylaxis, candesartan and valsartan for heart failure and also reduce CV mortality in left ventricular failure patients or left ventricular dysfunction followed by myocardial infarction. ARBs also have demonstrated reducing proteinuria by preserving kidney function in diabetic patients and also decreasing endothelial dysfunction thereby increasing fibrinolysis and have demonstrated their effectiveness in preventing atheromas.

The eight ARBs approved for use in the USA and Europe are nonpeptide compounds having biphenyl, tetrzole, benzimidazole or non biphenyl non tetrzole groups. Candesartan, olmesartan, valsartan, losartan, and irbesartan have a common tetrabenzoliphenyl structure; telmisartan, and candesartan have a benzimidazole in common group; and eprosartan has a nontetrazole and nonbiphenyl, chemical structure. Whereas the irbesartan as an exception, and all have free carboxylic acid group. ARBs have more affinity for ATR1 than for ATR2 and can block the activities of angiotensin II on ATR1 regardless of whether it was created from ACE or other enzymes such as cardiac chymase.
TABLE 2  Doses for hypertension and other indications of the angiotensin receptor blockers⁵

<table>
<thead>
<tr>
<th>ARBs</th>
<th>Starting dose (mg/day)</th>
<th>Maximum dose (mg/day)</th>
<th>Dosing interval</th>
<th>Other approved indications, apart from hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan</td>
<td>50</td>
<td>100</td>
<td>Once daily or twice daily</td>
<td>Diabetic nephropathy when serum creatinine is increased and proteinuria is present in patients with hypertension and type 2 diabetes; stroke reduction in patients with hypertension and left ventricular hypertrophy (non-black only)</td>
</tr>
<tr>
<td>Candesartan cilexetil</td>
<td>16</td>
<td>32</td>
<td>Once daily or twice daily</td>
<td>Treatment of heart failure (NYHA classes II-IV)</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>600</td>
<td>800</td>
<td>Once daily or twice daily</td>
<td>None</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>150</td>
<td>300</td>
<td>Once daily</td>
<td>Diabetic nephropathy when serum creatinine is increased and proteinuria is present in patients with hypertension and type 2 diabetes</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>40</td>
<td>80</td>
<td>Once daily</td>
<td>Cardiovascular risk reduction in patients unable to take ACE inhibitors</td>
</tr>
<tr>
<td>Valsartan</td>
<td>80 or 160</td>
<td>320</td>
<td>Once daily</td>
<td>Treatment of heart failure (NYHA classes II-IV); reduction of cardiovascular mortality in clinically stable patients with left ventricular failure or dysfunction following myocardial infarction</td>
</tr>
<tr>
<td>Olmesartan medoxomil</td>
<td>20</td>
<td>40</td>
<td>Once daily</td>
<td>None</td>
</tr>
<tr>
<td>Azilsartan medoxomil</td>
<td>40 or 80</td>
<td>80</td>
<td>Once daily</td>
<td>None</td>
</tr>
</tbody>
</table>

TABLE 3  Blood pressure reductions in randomized controlled trials of angiotensin receptor antagonists⁵

<table>
<thead>
<tr>
<th>Study and year</th>
<th>Duration (weeks)</th>
<th>Titration type</th>
<th>Drug</th>
<th>Dosage (mg)</th>
<th>Sample size (n)</th>
<th>Mean baseline BP (mm Hg)</th>
<th>Mean BP reduction (mm Hg)</th>
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</thead>
<tbody>
<tr>
<td>Telmisartan (TEL) versus other ARBs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mallion et al.</td>
<td>6</td>
<td>None</td>
<td>Telmisartan Telmisartan Losartan</td>
<td>40</td>
<td>57</td>
<td>162/101</td>
<td>14/19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Telmisartan Losartan</td>
<td>80</td>
<td>54</td>
<td>164/102</td>
<td>16/10</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Telmisartan Eprosartan</td>
<td>50</td>
<td>57</td>
<td>164/100</td>
<td>10/16</td>
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<tr>
<td>Lee et al.</td>
<td>4</td>
<td>Optimal</td>
<td>Telmisartan Losartan</td>
<td>40–80</td>
<td>86</td>
<td>154/101</td>
<td>17/9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Telmisartan Losartan</td>
<td>50–100</td>
<td>90</td>
<td>155/102</td>
<td>14/9</td>
</tr>
<tr>
<td>Derosa et al.</td>
<td>54</td>
<td>None</td>
<td>Telmisartan Eprosartan</td>
<td>40</td>
<td>40</td>
<td>143/92</td>
<td>8/8</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>600</td>
<td>39</td>
<td>144/91</td>
<td>7/4</td>
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<tr>
<td>Zhu et al.</td>
<td>8</td>
<td>Optimal</td>
<td>Telmisartan Losartan</td>
<td>40–80</td>
<td>164</td>
<td>149/99</td>
<td>13/11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Telmisartan Losartan</td>
<td>50–100</td>
<td>166</td>
<td>165/100</td>
<td>9/9</td>
</tr>
<tr>
<td>Calvo et al.</td>
<td>12</td>
<td>None</td>
<td>Telmisartan Valsartan</td>
<td>80</td>
<td>34</td>
<td>152/89</td>
<td>11/8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Telmisartan Valsartan</td>
<td>160</td>
<td>36</td>
<td>157/92</td>
<td>19/12</td>
</tr>
<tr>
<td>White et al.</td>
<td>8</td>
<td>Forced</td>
<td>Telmisartan Valsartan</td>
<td>40/80</td>
<td>244</td>
<td>154/99</td>
<td>12/8</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Telmisartan Valsartan</td>
<td>80/160</td>
<td>246</td>
<td>153/99</td>
<td>11/7</td>
</tr>
</tbody>
</table>
ARBs and their Pharmacological Characteristics

The mechanism of action of ARBs is by blocking the angiotensin II via the AT1 receptor irrespective of the biochemical pathway lead by angiotensin II formation.

ARBs cause a several-fold rise in circulating angiotensin II levels, AT2 receptors are activated by ARBs. Because AT1 receptors are blocked by ARBs, the increase level of angiotensin II activates AT2 receptors. Hence, AT2 receptor is thought to activation the opposite effect of AT1 receptor, which are protective for cardiovascular system and for protection of target organs damage.5,6

Pharmacokinetic Considerations

Lithium is increased by affect of all ARBs in renal reabsorption; hence, ARBs with concomitant use with lithium should be avoided.

Peak action of ARBs on BP occurs at 3–6 hours after intake. Losartan metabolism occurs in liver via CYP system to its metabolite EXP3174, which has 10–40 times potent than IV losartan; hence, its dose is given half in severe hepatic impairment.

Although food delays its absorption and reduces its maximum plasma concentration (Cmax), this is not clinically significant. As such, any CYP2C9 enzyme inhibitors or inducers may reduce the effectiveness of losartan, and this must be considered during drug selection.

The ARBs (olmesartan medoxomil, candesartan cilexetil, and azilsartan medoxomil) require GIT and liver for activation as all three are prodrugs (olmesartan, candesartan, and azilsartan, respectively). The drug irbesartan has highest bioavailability among the ARBs. Telmisartan has longest action available in the market with half-life of 24 hours and has mechanism action rapidly about 0.5–1.0 hour (Table 3).5

BP Reductions Trials in ARBs

In patients with T2DM with proteinuria and/or renal insufficiency, ARB-based treatment is recommended because these agents delay the progression of nephropathy.

ARBs in Diabetic and Kidney Disease

The intraglomerular hypertension is reduced in patients with diabetic nephropathy by ARBs. By reducing the gradient in glomerulus and thereby fibrosis of the nephron is averted (IRMA 2) that over 1 year trial.

The endpoints of reduction in NIDDM with angiotensin II antagonist losartan (RENAAL) trial showed losartan reduced incidence of doubling of serum creatinine (risk reduction 25%, p=0.006), 35% proteinuria reduction occur in end-stage renal disease (risk reduction 28%, p=0.002). Except for lowering the rate of first hospitalizations for heart failure (risk reduction 32%, p=0.005), the composite endpoint was similar after 3.4 years of therapy.1,3,8

CKD and ARBs

The important aim was preservation of renal function. In 2007, a scientific statement by AHA developed on treating hypertension and CKD population as a high (CAD) risk group as recommended blood pressure less than 130/80 mm Hg as goal. (ACEIs) or (ARBs) antihypertensive drugs were preferred agents CKD.9

Post-MI Survival

After acute MI, approximately 50% of patients show signs and symptoms of heart failure and approximately 10% have asymptomatic LV systolic dysfunction. Post-MI patients with heart failure, LV dysfunction, or anterior Q-wave MI have poor prognosis. Although large clinical trials show that ACE-inhibitors can reduce mortality and cardiovascular events, the prognosis of these high-risk patients is not satisfactory.10

Vascular Remodeling

Most vascular actions of angiotensin II are mediated through the AT1 receptors located on vascular smooth muscle and endothelial cells. The hallmark of vascular injury by hypertensive patients and vascular hypertrophy indeed may involve AT1 activation of receptor. And novel mechanism of AT2 receptor is by nitric oxide generation which promoted by AT2 receptors, which help in and induce apoptosis.3
Conclusion

All ARBs are highly proven effective class of drugs in treatment of hypertension and its associated comorbid condition from two decades. Presently there are eight ARBs approved for treatment of hypertension. There longer half-lives and high potency made BP reductions into enhanced duration of action, combining ARBs with other antihypertensive drugs like beta-blocker nebivolol made better BP control in some studies.

While there are added benefits by combining ARBs with ACEi (e.g., reduction in proteinuria), whereas some studies show combining these demonstrated increases in adverse renal events. Therefore, no clinical benefits seen by combining ARBs with ACE inhibitors (or direct rennin inhibitors) in treatment of hypertension.

The excellent safety and tolerability profile of the ARB class have improved the adherence to antihypertensive therapy and enhanced our ability to manage hypertension in those patients with sensitivities to other antihypertensive drug classes, including ACE inhibitors.

References


9. Division of Cardiovascular Medicine, Department of Internal Medicine (P.M.G., J.B.B.) and University of Michigan Hypertension Center (J.B.B.), University of Michigan, Ann Arbor; Division of Nephrology, Department of Medicine (G.M.C., V.B.) and Stanford Hypertension Center (G.M.C., V.B.), Stanford University School of Medicine, CA.

**Abstract**

Novel calcium channel blockers have shown a promising role in management of hypertension due to their antisympathtic actions and their renoprotective, cardioprotective and neuroprotective effects. There are six subtypes of calcium channels L, N, P, Q, R, and T-type. They are differentiated on basis of their electrophysiological properties. N type calcium channels are found at nerve endings. T-type Ca channels are found in pacemaker cells, atrial cells, purkinje fibres, juxtamedullary efferent, and afferent arterioles. The novel calcium channel blockers predominantly act on N and T type calcium channels along with L type calcium channels and decreases norepinephrine release which leads to vasodilatation, decrease in heart rate, and increase in renal blood flow.

**Introduction**

Hypertension accounts for major stroke and cardiovascular deaths all over the world. Globally an estimated 26% of world population has hypertension and prevalence is expected to increase to 29% by 2025. Hypertension is widely prevalent in India with significant variations in urban and rural population and regional variations. Prevalence is 20–40% in urban and 12–17% in rural adult population in India. But it is also the most modifiable factor with effective lifestyle changes and pharmacotherapy. A 2-mm Hg decrease in blood pressure can prevent 1,51,000 stroke and 1,53,000 coronary heart disease deaths in India.

Calcium channel blockers (CCBs) are one of the first-line drugs used in hypertension. Novel CCBs have further shwon a promising role in the management due to their antisympathtic actions. Further their renoprotective, cardioprotective, and neuroprotective effects have also been demonstrated with lesser side effects.

**Classification of Calcium Channels**

There are six subtypes of calcium channels L-, N-, P-, Q-, R-, and T-type. They are differentiated on basis of their electrophysiological properties. The T-type Ca$^{2+}$ channels are low voltage activated Ca$^{2+}$ channels that activate and deactivate slowly and other five types of Ca$^{2+}$ channels are high voltage-activated Ca$^{2+}$ channels, which depolarize approximately at ~40 mV. These channels consist of four subunits, α1, α2-δ, β, and γ. An α1 subunit is the most dominant component of the calcium channels. Each α1 subunits are of 10 different types and each of them has specific distribution in body and ion conductance of its channels as mentioned (Table 1).

**Calcium Channel Blockers: Classification and Mechanism of Action**

CCB are classified into three categories:

- Benzothiazepines (e.g., diltiazem)
Phenylalkylamines (e.g., verapamil)

Dihydropyridines.

Dihydropyridine are classified into four generations:

- First generation—Nifedipine, Nicardipine
- Second generation—
  - Slow release formula—Nifedipine SR (slow release), Felodipine ER (extended release)
  - Newer chemical structures—Benidipine, Manidipine, Nilvadipine, and Nitrendipine.
- Third generation—to avoid reflex tachycardia:
  - Long acting—Amlodipine
  - Lipophilic—Lercanidipine, Lacidipine, and Azelnidipine
- Fourth generation—block multiple calcium channels:
  - Cilnidipine and Efonidipine

CCBs bind to α1 subunit and prevent release of internal calcium stores into cytosol of cell thus inhibiting cell excitability. Traditionally CCB acted on L-type calcium channels which are predominantly expressed in heart and vessels so they regulated cardiac contractility, sinus node function and vascular tone. Novel CCBs act on N- and T-type calcium channels also. N-type calcium channels are found at nerve endings so they regulate the release of neurotransmitters norepinephrine. Hypertension is closely related to increase sympathetic nerve activity so decrease in norepinephrine release helps in decreasing blood pressure and their other effects.

T-type Ca channels are found in pacemaker cells, atrial cells, Purkinje fibers, juxtamedullary efferent and afferent arterioles and regulates afferent and efferent arteriole and adrenal secretion. Table 2 shows different CCB and types of calcium channels blocked.

**Novel Calcium Channel Blockers**

**Cilnidipine**

Cilnidipine has got both L- and N-type channel blocking property. It prevents excitation and contraction coupling in vascular smooth muscle cell leading to arterial vasodilatation with reduction in peripheral resistance, same mechanism in cardiac muscle leads to negative ionotrophic effect, results in slowing of sinus rate and inhibits the release of sympathetic neurotransmitter norepinephrine. Recommended dose is 5–20 mg once daily.

Morning hypertension involves increased sympathetic activity and the renin-angiotensin system (RAS). In ACHIEVE-ONE trial, 2,319 hypertensive patients were divided into four quartiles depending upon baseline SBP and were treated with cilnidipine for 12 weeks. Cilnidipine reduced both morning SBP and PR more markedly in patients with higher baseline morning SBP and PR. Cilnidipine independent BP- and PR-lowering effects were due to neuronal N-type Ca channel blocking. In ACHIEVE-ONE subanalysis hypertensive patients were classified into four groups according to nocturnal SBP reduction rate (%), extreme dippers, a nocturnal SBP reduction rate of 20%, dippers, a nocturnal SBP reduction rate of 10% to <20%, nondippers, a nocturnal SBP reduction rate of 0% to <10% and risers, a nocturnal SBP reduction rate of <0%. Cilnidipine reduced nighttime BP more than daytime BP in risers, nighttime and daytime BPs equally in nondippers, and daytime BP more than nighttime

### Table 1

<table>
<thead>
<tr>
<th>Current</th>
<th>α1 subunit</th>
<th>Channel</th>
<th>Distribution</th>
</tr>
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<tr>
<td>P</td>
<td>α1A</td>
<td>CaV.2.1</td>
<td>Neurons</td>
</tr>
<tr>
<td>Q</td>
<td>α1A</td>
<td>CaV.2.1</td>
<td>Neurons</td>
</tr>
<tr>
<td>N</td>
<td>α1B</td>
<td>CaV.2.2</td>
<td>Neurons</td>
</tr>
<tr>
<td>R</td>
<td>α1E</td>
<td>CaV.2.3</td>
<td>Neurons</td>
</tr>
<tr>
<td>L</td>
<td>α1S</td>
<td>CaV 1.1</td>
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### Table 2

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<th>Drugs</th>
<th>L-type</th>
<th>T-type</th>
<th>N-type</th>
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<tr>
<td>Nifedipine</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cilnidipine</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Efonidipine</td>
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<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Azelnidipine</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Benidipine</td>
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</table>
BP in dippers. It does not cause reflex tachycardia as it attenuates norepinephrine release.

Cilnidipine dilates afferent and efferent arterioles by inhibiting N-type Ca channels and causing no increase in intraglomerular pressure. It causes reduction in urinary protein excretion and suppression of any serum creatinine increase. A study comparing cilnidipine and amlodipine effect on renal function and proteinuria showed significant decrease in proteinuria in cilnidipine group at 12 months of treatment. It causes less pedal edema as it causes venodilation so that the pressure in the afferent capillaries peripheral to the resistance arteries decreases.

Cilnidipine can provide synergistic effect with angiotensin II receptor blockers as it suppresses RAS through sympathetic N-type Ca channel blockade. Cilnidipine is beneficial for the suppression of pathological cardiac remodeling, at least partly, via a superior improving effect on ambulatory BP profile compared with control CCBs in hypertensive CKD patients.

Cilnidipine improves LV diastolic function in hypertensive heart disease by suppressing cardiac sympathetic over-activity. It exerts vasodilatory action without stimulating sympathetic nervous activity, thus improving insulin sensitivity. Antioxidant activity of cilnidipine and amlodipine was compared by measuring ionomycin-stimulated superoxide production in cultured human mesangial cells. Cilnidipine showed a significantly higher antioxidant activity than amlodipine.

Azelnidipine
It is a CCB with a half-life of about 8 hours. Dosage is 8–16 mg orally once daily. It blocks L- and T-type calcium channels Azelnidipine primarily undergoes first-pass hepatic metabolism and has no active metabolite product. It is highly lipid soluble so it is retained in the vascular wall after clearance from the blood and continues to elicit a hypotensive effect. So it causes a gradual and prolonged fall in blood pressure in hypertensive patients and no reflex tachycardia. It has a strong anti-atherosclerotic action in vessels and antioxidative activity due to its high affinity for vascular tissue. Azelnidipine reduces heart rate and proteinuria in hypertensive patients by inhibiting sympathetic nerve activity and also prevents insulin resistance.

CALVLOC trial studied effect of azelnidipine on diastolic function left ventricular filling pressure in patients with preserved ejection fraction and diastolic dysfunction. Results showed it is associated with improvements in LV diastolic function, a reduction in LV filling pressure, and a decrease in the brain natriuretic peptide level.

Benidipine
Benidipine blocks all the three L-, N- and T-type calcium channels. It has a strong and long effect due to its high affinity for the DHP binding site. There is slow binding and slow dissociation from the DHP binding site. This is known as "membrane approach" (approach to the cell membrane followed by long retention in the DHP binding site). This state contributes to the long-lasting antihypertensive effects of benidipine. Its cardio- and vasoprotective effects are due to vascular selectivity and enhanced nitric oxide (NO) production. It is absorbed rapidly and reaches maximum drug concentration within 2 hours. Dosing is 2–8 mg once daily.

Benidipine renoprotective effects are due to
- Dilation of the efferent arterioles due to inhibition of T-type Ca channels
- Marked increase in renal plasma flow rate
- Natriuretic effect by acting on both the upper segment of tubules and the distal tubules
- Increased NO formation in the renal parenchyma
- Suppression of increased expression of transforming growth factor (TGF)-β and α-smooth muscle actin in the glomeruli.

It has an anti-oxidant effect. In a study using cultured endothelial cells, benidipine suppressed endothelial damage induced by lysophosphatidylcholine [one of the lipids constituting oxidized low density lipoprotein (LDL)] more potently than nifedipine and amlodipine. Benidipine suppresses the progression of atherosclerosis by stimulating the formation of NO by its direct action on vascular endothelial cells.

Benidipine increases coronary blood flow as it increases NO production during ischemia. Vascular selectivity of various CCBs was evaluated using isolated coronary arteries and the right ventricular papillary muscles of dogs; the coronary artery selectivity of benidipine was 14.4 times higher than that of nifedipine and 19 times higher than that of amlodipine. These effects protect the myocardium, contributing to better prognosis for angina pectoris. It also stimulates the differentiation of osteoblasts, suppresses the proliferation of vascular smooth muscles, suppresses
the proliferation of mesangial cells, and protects the myocardium.

**Efonidipine**

Efonidipine blocks both, L- and T-type Ca^{2+} channels. It prolongs the late phase 4 depolarization of the sinoatrial node action potential through blockade of both L- and T-type Ca^{2+} channels, leading to its potent negative chronotropic effect. It has long lasting vasodilator actions and less reflex tachycardia.\(^{10}\) It increases adiponectin levels without a corresponding change in BMI. Increasing adiponectin levels are predicted to improve both insulin sensitivity and endothelial function by multiple mechanisms.\(^{11}\)

**Conclusion**

Thus, novel CCBs due to their action on N- and T-type calcium channels along with L-type calcium channels decrease norepinephrine release and lead to vasodilatation, decrease in heart rate, and increase in renal blood flow. They cause prolonged antihypertensive action, less reflex tachycardia, less pedal edema, better control of proteinuria, increase insulin sensitivity and, more antioxidation activities.

**References**

CHAPTER 23

Beta-adrenergic Receptor Blockers in Hypertension

Amit Kumar Das

Abstract
Hypertension remains one of the most important preventable causes of morbidity and mortality because of cardiovascular disease. Beta adrenergic receptor blockers are one of the most used and easily available antihypertensive agents. By blocking the beta receptors, they reduce the cardiac output and cause bradycardia. Selective beta 2 receptor agonism can lead to peripheral vasodilatation and reduce peripheral vascular resistance. All of these and decreased rennin all lead to effective lowering of blood pressure without decreasing cardiac output. Apart from that some drugs in this category lead to prolongation of phase 2 (repolarization) of action potential and give additional antiarrhythmic advantage. As antihypertensive agents, beta adrenoreceptors are particularly suitable in hypertensive patients with coexistent Ischemic Heart Disease. They are also valuable antihypertensive agents when used in combination with other agents like CCB, ARB, and diuretics. Certain contraindications like Bronchial Asthma, COPD, High Degree AV block, etc. need to be taken care of before prescribing these agents. Despite its share of controversies, beta blockers still remain useful antihypertensive agents.

Introduction
Despite its high prevalence, associated morbidity, and increased mortality, hypertension still remains inadequately treated in the majority of patients. From epidemiological perspective, several data have clarified the importance of blood pressure as a risk factor for CVD. In the largest and the most detailed analysis, information from one million adults with no known vascular disease at baseline, included in 61 prospective observational studies of the relationship between blood pressure and mortality, was observed.

Primary goal of treatment of hypertension is to prevent cardiovascular disease and death based on results of recent trials the choice of antihypertensive can be adjusted according to the presence or absence of associated conditions.

Beta (β)-adrenergic receptor blockers are among the most widely used agents in clinical medicine. Since 1976 after availability of propranolol for treatment of hypertension, quite a few β-blockers have been introduced.

In this article I will deal with the role of β-blockers in the management of hypertension.

Types and Mode of Action
These drugs act as competitive inhibitors of the binding of epinephrine and norepinephrine to β-adrenergic receptor sites. Two subtypes of β-adrenergic receptors exist: the β₁ subtype (predominates in the heart) and the β₂ subtype (predominates in the peripheral vasculature and bronchial smooth muscle). Most β-adrenergic receptor blockers exist as pairs of optical isomers. Almost all clinical activities are due to the levorotatory (negative) stereoisomer.

By reducing systemic vascular resistance β-blockers decrease blood pressure while maintaining cardiac output.
and cardiac afterload and preload reduced due peripheral vasodilation. Compensatory peripheral vasoconstriction due to reduced cardiac output abets increased peripheral resistance (Table 1).

### β-blockers in the Treatment of Hypertension

Effects of various β-blockers on outcomes in hypertensive patients have already evaluated in many trials. When β-blockers were compared with diuretics it has observed that there was no statistically significant differences between the two treatments and three-fourths of patients achieved their DBP goals receiving either drug class. Recent clinical data suggest that although brachial (arm) blood pressure effectively reduced by traditional β-blockers but compared with other antihypertensive classes they may have less effect on reducing central aortic pressure.

There were several trials which confirm the potency of labetolal to rapidly lowers of blood pressure. Carvedilol in a placebo-controlled, double-blind trial in 338 patients with essential hypertension shows statistical significant reduction in mean 24-hour systolic blood pressure (SBP) and diastolic blood pressure (DBP) assessed by ambulatory blood pressure monitoring compared with placebo (p ≤0.001 for all). In an open-label, 6-week trial significantly lowered mean systolic blood pressure and diastolic blood pressure from baseline (~24 and ~13 mm Hg, respectively, p <0.001 for both) by nebivolol (5–10 mg/ day) in 6,356 patients with mild hypertension (defined as DBP of 90–115 mm Hg) and mean baseline SBP of 162 mm Hg. In 2,838 patients with type 2 diabetes mellitus for ≥3 months and hypertension nebivolol (2.5–10 mg/day) was also assessed as monotherapy or as add-on therapy and lowered SBP and DBP from baseline by 21 and 11 mm Hg, respectively. Nebivolol has already documented to exhibit safe and well tolerated profile and higher achievement of blood pressure targets or goal reductions than that of ACE inhibitors (odds ratio 1.92, p = 0.001) and similar to that of other β-blockers, CCBs, and losartan.

### Combination Therapy with β-blockers

Single drug therapy remains the preferred way to begin treatment of hypertension although in many patients this is unable to bring blood pressure to goal levels. It is increasingly being seen that the elusive goal of a "Normal BP" is achieved only if multidrug therapy is employed. β-blockers and calcium channel blockers combination offers a potential therapeutic benefits for uncontrolled hypertensive patients. These two interacted by complementary hemodynamic mechanisms with the calcium channel antagonists reducing α-adrenergic reflex vasoconstriction induced by β-blockers and the β-blockers acting through a reduction in cardiac output. Combination products do not employ non-dihydropyridine calcium channel blockers due to concern for excessive effects on sinus and AV nodal junction.

The commonly employed combinations contain the CCB amlodipine and metoprolol for which the response rate is good and which preserves the normal diurnal BP rhythm. Adverse effects like β-blockers related cold extremities are less common.

β-blockers blunt RAA axis activation produced by diuretics while the latter curb any Na+ retention provided by β-blockers. β-blockers and diuretics reduce BP additively not synergistically. Dose dependent adverse effects occur less frequently with low dose combinations and less so with β selective antagonists.

---

**TABLE 1** β-blockers pharmacology

<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selectivity</td>
<td>Greater β, affinity at common therapeutic ranges (selectivity is dose dependent: at high doses even selective drugs interact with β₂-receptors)</td>
<td>Acebutolol, atenolol, bisoprolol, betaxolol, esmolol, metaprolol</td>
</tr>
<tr>
<td>Intrinsic symptomatic activity</td>
<td>Partial β-adrenergic agonist activity in the absence of catecholamines (milder rest bradycardia)</td>
<td>Acebutolol, oxprenolol, pindolol</td>
</tr>
<tr>
<td>β₁-Receptor inhibition</td>
<td>β₁-blocked; vasodilation is due to β-blockade</td>
<td>Carvedilol, labetalol, nebivolol</td>
</tr>
<tr>
<td>Additional antiarrhythmic</td>
<td>Prolongation of phase 2 (repolarization) of action potential (class III)</td>
<td>Sotalol</td>
</tr>
<tr>
<td>properties</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hypertension

SECTION 2

Why β-blockers Recommended in Hypertension with Ischemic Heart Disease

A combination of effects accounts for the efficacy of β-blockers in ischemic heart disease (IHD). β-blockers are competitive antagonists of β-adrenergic receptors. β-receptors inhibition slows the heart and atrioventricular conduction and lowers blood pressure and contractility, thus decreasing myocardial oxygen demand. The slower heart rate also enhances diastolic perfusion time.

β-blockers are also effective antihypertensive agents and antiarrhythmics. They reduce the risk of death and major cardiovascular events after myocardial infarction (MI). They also relieve symptoms at rest, increase exercise tolerance and prolong survival in many groups of patients. For these reasons they are a first-line choice in IHD.

A few small randomized studies have tested β-blockers in patients with stable angina, normal blood pressure and no history of MI. The Total Ischemic Burden European Trial (TIBET) reported nonsignificant reduction of the risk of death and MI with the combination of atenolol and nifedipine. The results did not differ from those with either drug in monotherapy. The Angina Prognosis Study In Stockholm (APSIS) found no difference between metaprolol and verapamil in terms of death, major cardiovascular events, or quality of life. The Atenolol Silent Ischemia Study (ASIST) versus placebo showed that atenolol decreased cardiovascular events and the frequency and duration of ischemic episodes and increased event free survival. The Total Ischemic Burden Bisoprolol Study (TIBBS) showed bisoprolol to be more effective than nifedipine in reducing the frequency and duration of ischemic episodes. The International Multicentre Angina Exercise (IMAGE) study showed that both nifedipine and metoprolol increased time to ischemia during exercise. The combination of the two drugs was more effective than either as monotherapy.

Controversy

Few recently published data have argued that use of β-blockers is not beneficial for treating hypertensive patients as a first-line treatment mainly because there is no significant reduction in mortality or coronary heart disease as well as due to their modest effect on stroke as compared to placebo or other antihypertensive agents.

As compare to traditional β-blockers (atenolol, metoprolol, and propranolol), vasodilatory β-blockers (carvedilol, nebivolol) lower blood pressure to a similar degree as other antihypertensive drugs and are associated with neutral or favorable metabolic effects. In most of the metaanalysis and even guidelines consider mainly these traditional β-blockers in which data are not favoring the use of β-blockers in uncomplicated hypertension as a first-line agent.

High dose of β-blockers may worsen diabetic control, by increasing insulin resistance. β-blockers, by blunting the catecholamine response, mask hypoglycemic symptoms so that hypoglycemia manifests only when severe. Poorly controlled diabetes mellitus, particularly if treated with insulin: β-blocked can interfere with receptor sensitivity to insulin, causing hypo- or hyperglycemia; in addition, its sympathetic effect may conceal symptoms of endogenous hypoglycemia, preventing correction, and thus endangering the patient. With pooled data of 94,492 patients with hypertension, the traditional β-blockers atenolol and propranolol compared with placebo (n = 16,372, p = 0.33), reported a 44% increased new-onset diabetes risk. β-blocker–based therapies (atenolol, metoprolol, and any β-blocker and diuretic together) increase the new-onset diabetes risk by 21% as compared with CCBs (p <0.0001) and 23% as compared with ACE inhibitors or ARBs (p = 0.007). In contrast, GEMINI (Glycemic Effect in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives) trial conducted on 1,235 patients confirms that with same BP control the discontinuation rate because of poor glycemic control was only 0.6% with carvedilol (p = 0.04) and no adverse effect on glycosylated hemoglobin values as compare to traditional β-blockers like metaprolol. In another study with nebivolol arm there is statistical significant reduction in glycated hemoglobin (HbA1c%) and fasting blood glucose (p <0.001).

β-blockers exacerbate asthma and should not be used in patients with asthma. Severe chronic obstructive pulmonary disease (COPD) due to broncho stenosis and increasing hypoxia and hypercapnia: selective β1-blockers can be used at very low doses if there is a strong indication of β-blocked, but they not tolerate; β-blockers may worsen symptoms even in mild COPD and have to be withdrawn. β-blockers should be administrated with caution in first degree atrioventricular block. Well recognized
side effects include asthenia, fatigue, insomnia, and nightmares. Some erectile dysfunction is relatively common (in up to 25% of patients), but persistent impotence is rare (1%). Lipid effects are mild and not a reason for treatment withdrawal. Though most β-blockers increase triglyceride and decrease HDL-cholesterol levels, they certainly reduce the incidence of sudden death, overall mortality and recurrent MI. In summary, the vast majority of patients are eligible for β-blockers therapy, provided the drug is carefully chosen and titrated.

**Conclusion**

More than 45 years in various other clinical situations along with the treatment of hypertension β-adrenergic receptor blockers have been used extensively. From 1973 to till date numerous clinical trials and meta-analysis were performed to evaluate the functional role of β-blockers in the management of hypertension and it has established their efficacy in the reduction of cardiovascular morbidity and mortality associated with hypertension. In modern clinical practice, clinicians require combination of two or multiple drugs to control hypertension and require more aggressive goal especially with comorbidities. To achieve target goal in hypertension patients with comorbidities like high coronary artery disease risk or even with diabetes β-blockers are a beneficial, guideline-recommended treatment option. Thus, in conclusion, the vast majority of patients are eligible for β-blockers therapy, provided the drug is carefully chosen and titrated.

**References**

Abstract

Centrally-acting antihypertensive is usually used as add on therapy in a patient who requires multiple drugs to control the hypertension.

Various available drugs (Clonidine, α-Methyldopa, Guanfacine, Guanabenz, Moxonidine, and Rilmenidine) though belong to same group, act with subtle different mechanism and thus one drug has advantage over other for its use in specific condition.

Clonidine being the non selective (acting on α-2 Adrenoceptors and imidazoline-1 receptors) has more adverse effect and sometimes intolerant for the patients (causing sedation, postural hypotension). Methyldopa can be used safely in pregnancy as it maintains the uterine blood flow. Guanfacine and guanabenz can be used and better tolerated in cases where patient is intolerant to clonidine.

The moxonidine and rilmenidine due to their mechanism of action (selective for imidazoline receptor) cause less adverse effects thus better tolerated. However, both drugs are cautiously given in advanced renal failure and moxonidine is avoided in advanced heart failure.

Mechanism of Action

The centrally-acting antihypertensive (clonidine, α-methyldopa, guanfacine, guanabenz, moxonidine, and rilmenidine) have different antihypertensive actions, which result in sodium excretion and decrease in cardiac output, heart rate, total peripheral resistance, and renin release (Flowchart 1).

These centrally acting antihypertensive agents cross the blood brain barrier and stimulate imidazolin-1 (I₁) receptor and/or central postsynaptic α₂ adrenoceptor in the brain stem's sympathetic nervous control centers, the rostral ventrolateral medulla (RVLM) and the nucleus tractus solitarii.

Clonidine non selectively stimulates both α₂ adrenoceptors and I₁ imidazolin receptors as compared to methyldopa, guanabenz, and guanfacine, which
TABLE 1  Centrally-acting antihypertensive agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Preparation</th>
<th>Pharmacodynamics</th>
<th>Daily dose</th>
<th>Adverse effect</th>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Onset—0.5–1 hour</td>
<td>Initial—0.1 mg</td>
<td>Sedation drowsiness, dry mouth</td>
<td>Sick sinus syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peak 3–5 hours</td>
<td>Range 0.2–1.2 mg</td>
<td>Withdrawal syndrome</td>
<td>2nd and 3rd degree AV block</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma half-life, 12–16 hours</td>
<td>Max 1.2 mg</td>
<td>Rebound hypertnesion (Uncommon with dose &lt;1.2 mg daily)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metabolism—Liver</td>
<td>Usually BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transdermal</td>
<td></td>
<td>Duration of BP lowering 1 week</td>
<td>1, 2, 3, once weekly</td>
<td>Headache, bradycardia, orthostatic hypotension</td>
<td>Active hepatic disease</td>
</tr>
<tr>
<td>Methyldopa</td>
<td></td>
<td></td>
<td></td>
<td>Sedation, Drowsiness, Dry mouth</td>
<td>Active hepatic disease</td>
</tr>
<tr>
<td></td>
<td>125 mg</td>
<td>Onset—2–3 hours</td>
<td>Average: 250–300 mg</td>
<td>Positive Coomb's test and anemia, Lupus like syndrome withdraw syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>250 mg</td>
<td>Peak—5 hours</td>
<td>BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>500 mg</td>
<td>Plasma half-life—6 hours</td>
<td>Max 3000 mg</td>
<td>Rebound hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metabolism—Renal</td>
<td></td>
<td>Impotence</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 mg</td>
<td>Onse—1 hour</td>
<td>1 mg at bed time</td>
<td>Sedation, Drowsiness, Dry mouth withdrawal syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 mg</td>
<td>Peak—4 hour</td>
<td>Max 3 mg</td>
<td>Rebound hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma half-life—12 hours</td>
<td>Same as clonidine</td>
<td>Impotence</td>
<td></td>
</tr>
<tr>
<td>Guanabenz</td>
<td>1 mg</td>
<td>Onset—1 hour</td>
<td>Excretion: Renal 80%</td>
<td>Sedation, Drowsiness, Dry mouth withdrawal syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 mg</td>
<td>Peak—4 hour</td>
<td>1 mg at bed time</td>
<td>Rebound hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma half-life—12 hours</td>
<td>Max 3 mg</td>
<td>Impotence</td>
<td></td>
</tr>
<tr>
<td>Guanfacine</td>
<td>1 mg</td>
<td>Onset—1 hour</td>
<td>Excretion: Renal</td>
<td>Sedation, Drowsiness, Dry mouth withdrawal syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 mg</td>
<td>Peak—1 hour</td>
<td>1 mg at bed time</td>
<td>Rebound hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma half-life—12 hours</td>
<td>Same as clonidine</td>
<td>Impotence</td>
<td></td>
</tr>
<tr>
<td>Moxonidine</td>
<td>0.2 mg</td>
<td>Peak—0.5–3 hours</td>
<td>Average 0.2 mg</td>
<td>Several renal impairment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.3 mg</td>
<td>Plasma half-life—2–3 hours</td>
<td>once daily</td>
<td>GFR &lt;30 mL/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excretion: Renal 57–75%</td>
<td>Max 0.6 mg</td>
<td>Advanced heart failure</td>
<td></td>
</tr>
<tr>
<td>Rilmenidine</td>
<td>1 mg</td>
<td>Peak—1.7 hour</td>
<td>1–2 mg/day</td>
<td>Advanced stage of CKD (relatively contraindicated)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma half-life—8.5 hours</td>
<td></td>
<td>1 mg alternate day if, GFR &lt;15mL/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excretion: Renal 52–93%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Individually, these agents work by stimulating alpha-2 adrenoceptors, which are activated by drugs that selectively stimulate them.

**Clonidine:**
- This drug has a 30–60 minutes onset of action.
- It is useful in hypertensive emergencies, but requires frequent dosing due to its shorter duration of action.

**Methyldopa:**
- This drug has a 30–60 minutes onset of action.
- It is useful in hypertensive emergencies, but requires frequent dosing due to its shorter duration of action.

**Guanabenz:**
- This drug has a 30–60 minutes onset of action.
- It is useful in hypertensive emergencies, but requires frequent dosing due to its shorter duration of action.

**Moxonidine:**
- This drug has a 30–60 minutes onset of action.
- It is useful in hypertensive emergencies, but requires frequent dosing due to its shorter duration of action.

**Rilmenidine:**
- This drug has a 30–60 minutes onset of action.
- It is useful in hypertensive emergencies, but requires frequent dosing due to its shorter duration of action.
Hypertension with restless leg syndrome
Clonidine is also available as Transdermal patch and is of particular utility for management of:
- The labile hypertension which require multiple medication,
- The hospitalized patient unable to take oral medication, and
- The patient with prominent early morning blood pressure surge.

Transdermal clonidine patch is best absorbed from the chest or upper arm and it causes more dose dependent salt and water retention as compare to oral clonidine. Transdermal patch delivers drug daily for 7 days, but it starts its action at least 1 day later after its application; hence oral clonidine is given for 1–2 days after application of clonidine transdermal patch. Even when transdermal patch is removed drug present in the skin continue its antihypertensive effect.

Clonidine has its suppressing effect on sinus as well as atrioventricular nodal function sometimes causing significant bradycardia. Hence, this drug should be best avoided in patients with sinus node dysfunction and those suffering from CKD who are at risk of developing significant bradycardia.

When clonidine is suddenly stopped it causes rebound hypertension, which may be quite significant if patient is also receiving beta-blocker but not in the presence α/β adrenergic antagonist like labetalol or carvedilol. This rebound hypertension has not been observed with moxonidine and rilmenidine.

Methyldopa: Indications of using this drug are—
- In patient who are intolerant to clonidine
- Pregnancy induced hypertension
- In hypertensive emergencies—used intravenously dose 20–40 mg/kg/day 6 hourly

However, intravenous use of methyldopa is infrequent due to availability of other effective drugs.

As it is excreted through kidneys, reduced doses are desirable in renal failure; however, methyldopa is dialyzable.

Methyldopa, besides its common side effect somnolence and depression, causes hypersensitivity reactions leading to hepatitis and coombs positive hemolytic anemia. It occurs only 10–20% patients receiving...
methyl dopa. If patient has coombs test positive but no hemolytic anemia, it is not wise to stop methyl dopa.

Flu like symptoms, lupus like syndromes and enhanced prolactin release (pseudo lactation) have also been observed.

Guanabenz: This drug acts similarly as that of clonidine, but its duration of action is prolonged. It is less frequently associated with rebound hypertension, salt, and water retention and/or significant postural hypotension. Guanabenz is broadly biotransformed and does not accumulate in the patient with significant reduction in renal function. Guanabenz reduces total cholesterol level 10–20%. Sedation with this drug is dose-dependent decreases over the period of time.

This drug has been found to reduce left ventricular hypertrophy in hypertensive patients and also reducing morning hypertension when given at night time.

Guanfacine: This drug has longer duration of action (24 hours) hence given once daily. Guanfacine has its antihypertensive effect longer than guanabenz. It is preferably given in the evening so as to suppress early morning surge of catecholamines and blood pressure. Its blood pressure effect is enhanced when given with diuretic. This drug can be used instead of clonidine when excessive sedation is the problem.

Moxonidine: This drug when used alone or in combination with other antihypertensive agents, it significantly reduces the blood pressure. It does not decrease heart rate like clonidine. This drug is mainly excreted through kidneys. Its dose adjustment according to the glomerular filtration rate (GFR) is mandatory.

This drug should not be used when GFR falls 30 Ml/min or less and also in advanced heart failure.

Rilmenidine: This drug is used in the treatment of mild to moderate hypertension. Rilmenidine can be used alone (1–2 mg/day) or in combination with other antihypertensive and has been well tolerated and effective in studies. This drug does not affect heart rate while reducing blood pressure as it increases parasympathetic tone.

Treatment withdrawal rebound hypertension does not appear to occur with rilmenidine. It is much less frequently associated with sedation and dry mouth. The low rate of orthostatic hypotension with rilmenidine may be related to an enhancement in baroreflex sensitivity. Rilmenidine is relatively contraindicated in advance stage chronic kidney disease.

Usefulness of Centrally-acting Antihypertensive in Other Clinical Conditions

Clonidine has been used:
- In migraine prophylaxis.
- Post-traumatic stress syndrome.
- To reduce postmenopausal flushes.
- In moderate alcohol and opioid withdrawal syndrome.
- To secondarily reduce aqueous humor production in open angle glaucoma.
- In short gut syndrome and/or high output proximal ileojejunostomies for effectively reducing fecal output.
- In diagnosis of pheochromocytoma: After administration of 0.1 mg clonidine per hour for 3 hours, plasma, nor-epinephrine levels decreases in patient with essential hypertension but remained unaffected in patient with pheochromocytoma.
- In new onset of atrial fibrillation can control the ventricular rate.

Similarly guanfacine can be used in:
- Attention deficit order
- The fragile X-syndrome

Drug Interactions

Certain catecholamine assay can be disturbed by methyl dopa and its metabolites. This also interferes with levodopa, bromocriptine, and monoamino oxidase inhibitors. Therapeutic effect of methyl dopa is reduced with coingestion of iron.

Guanabenz may increase the absorption of hydrochlorothiazide when given concomitantly.

The antihypertensive effect of clonidine and guanfacine is reduced by tricyclic antidepressents (imipramine, amitriptyline, etc.) because they are antagonist to central α receptors.

The moxonidine and rilmenidine should not be given with monoamino oxidase inhibitors.
Conclusion

In the present context centrally acting antihypertensive agents can be used as add on therapy in the treatment of hypertension, especially resistant hypertension. However, in sympathetically mediated hypertension they can be used with preference.

Though due to dose dependent side effects, the use of clonidine and methyldopa is now less; however, methyldopa is an agent that can be used safely in pregnancy induced hypertension. Guanfacine and Guanabenz can be used and better tolerated in cases where patient is intolerant to clonidine.

The moxonidine and rilmenidine due to their mechanism of action (selectively for imidazoline receptors), causeless sedation, dryness of mouth, and postural hypotension, thus better tolerated.

References

Abstract
Hypertension in the young is commonly essential hypertension and is on the rise because of rapid urbanization, increasing stress, addictions (tobacco and alcohol), and changing lifestyles. However, secondary hypertension also needs to be ruled out as it is remediable and appropriate management can obviate the need for lifelong treatment. It is imperative that a judicious approach is adopted while evaluating the young hypertensive and pharmacological as well as non-pharmacological measures are adopted while managing these patients. Anxiety levels are high in young patients, and renin-angiotensin system (RAS) activity also is heightened. Drug usage should therefore be chosen to inhibit the RAS, have long-term control, and minimize side-effects.

Introduction
Cardiovascular disorders are the leading cause of morbidity and mortality worldwide. Nearly 30% of global deaths are attributable to cardiovascular disease (CVD). Systemic hypertension is the leading root cause of premature mortality and morbidity among the patients of CVD. Prevalence of hypertension is rapidly increasing in the community and it is estimated that the world will have about 1.5 billion adult hypertensives by end of this decade.

In India, the situation is alarming as its prevalence is about 33% in urban part and about 27% in rural area. The overall prevalence of hypertension is about 29% suggesting urban rural convergence due to rapidly changing lifestyle. The current BP control rates of less than 10% in the rural and less than 20% in the urban areas is itself a big challenge. India has wide variations in race, ethnicity, socioeconomic status, and cultural practices. The lifestyle is rapidly changing becoming more sedentary due to rapid urbanization. Thus, the incidence of chronic illness like diabetes, hypertension, and CVD are increasing.

Weight gain, obesity, and physical inactivity are important risk factors for development of hypertension in young adults. These patients are more likely to respond to lifestyle changes and weight management but they are less likely to believe that they have disease. In Indians, hypertension develops relatively early in life. In individuals aged between 15 and 49 years, the prevalence is about 18% with variations between rural/urban and amongst different regions of country. Moreover, only about 44% of young hypertensives are aware of their diagnosis and only 14% are receiving treatment.

Definition and Classification
Definition of "Young adults" for hypertension is not defined, but age between 20 and 49 years may be taken as in Framingham Offspring Study.

There is a continuous relationship between the level of blood pressure and the risk of complications starting at BP of 115/75 mm Hg. As Asian, Indians are more prone to CVDs, the risk for cardiovascular events is higher and
Hypertension

The ACC/AHA guidelines changed the definition of hypertension at 130/80, but European guidelines and recently published Indian guidelines for hypertension IV continue with the previous definition of 140/90 mm Hg. The same definition of hypertension applies in young adults. Classification is for adults more than 18 years of age, who are not on antihypertensive medication and have no acute illness. It is based on the average of two or more office blood pressure readings taken at least on two occasions (Table 1).

In addition to classifying stages of hypertension on the basis of average blood pressure levels, clinicians should specify presence or absence of target organ disease and additional risk factors.

The screening for hypertension in all adults is recommended. All adults (18 years or older) should have their office BP measured at every point of contact with health professionals or allied health staff. This will include all points and levels of care—the village/multipurpose health worker, trained non-physician staff at sub-centers, primary health center, community health center, and referral hospital (District hospital, Medical College). This screening will enable people with high normal BP to be identified, so that they can be prevented from developing hypertension by use of appropriate lifestyle modifications.

Risk Factors of Hypertension in Young Adults

Incidence of hypertension is higher among young men than women, increasing threefold from second to fifth decade in men and eightfold in women. Under age 40, men were twice as likely as women to develop hypertension, but after age 40, 8-year incidence rates were similar in men (14.2%) and women (12.9%). The proposed ominous octet of “S,” a constellation of risk factors starting with the letter “S,” leading to development of non-communicable diseases are sex, salt, sugar, sleep, smoking, stress, sunlight, and sedentary behavior. These become more prominent in today’s tech savvy young adults. Consumption of saturated fat and prolonged sitting may be added to complete the list. Risk factors like physical inactivity, weight gain, obesity, metabolic syndrome, and obstructive sleep apnea are more common in these patients. Smoking, alcohol, illicit drug intake, and psychosocial stress are becoming more common in this age group. High sodium intake, low potassium and calcium in diet are the other factors responsible.

Psychosocial stress is a major contributor to development of hypertension in young. This group has enormous work, travel related, and domestic pressure leading to busy and erratic schedule. This must be considered in planning treatment strategies.

Causes of Hypertension in Young Adults

Most of the hypertension in young adults are essential hypertension having no identifiable cause. Secondary cause of hypertension should be ruled out if blood pressure is very high at first presentation, episodic rise in blood pressure, non-responding hypertension, or poorly responding hypertension despite good adherence and resistant hypertension. Some endocrine disorders causing hypertension have their obvious signs and symptoms at presentation. Special enquiry of illicit drug use, oral contraceptive pills, and other medications must be made in this group of patients. The important etiologies of hypertension are enumerated in Table 2.

Approach to the Patient

The key elements of evaluation of a patient of hypertension are accurate measurement of blood pressure, focused medical history and physical examination, and laboratory investigations. These are aimed to determine presence of end-organ disease, possible causes of hypertension, cardiovascular risk factors, and to get baseline values for starting and judging biochemical effects of therapy.
Baseline investigations are urine dipstick, blood urea and electrolytes +/- eGFR, 12 lead ECG, fundoscopy, blood glucose, and serum lipid profile.

A judicious search for secondary causes warrants in this age group. A secondary etiology may be suggested by symptoms like flushing and sweating in pheochromocytoma, by clinical findings; a renal bruit in renal artery stenosis, or laboratory abnormalities, for example, hypokalemia suggestive of aldosteronism. In the absence of clinical signs to suggest possible secondary hypertension, indications for further evaluation are if blood pressure having early onset, rapid onset, or resistant hypertension. In young women, renal artery stenosis caused by fibromuscular dysplasia is one of the most common secondary etiologies. It can be detected by abdominal magnetic resonance imaging or computed tomography. For aldosteronism, the recommended initial diagnostic test is an aldosterone/renin ratio. Obstructive sleep apnea can be a secondary cause of or contribute to hypertension. The standard diagnostic test is polysomnography, but clinical assessment tools (e.g., Epworth Sleepiness Scale, Sleep Apnea Clinical Score) with nighttime pulse oximetry may be used to get initial clue particularly in places of limited availability.

Counseling of patients for lifestyle changes and modification and/or treatment of contributory risk factors should start once the blood pressure crosses 130/80 mm Hg. In absence of comorbid conditions in patients with stage 1 hypertension at first visit lifestyle modifications should be started and blood pressure reading should be repeated within 2–3 weeks. Drug treatment may need to be started after 1 month. For stage II hypertension shorter repeat interval is desirable. And in stage III hypertension BP should be repeated after few hours to start pharmacological management. The target blood pressure should be 130/80 mm Hg.

Young patients with secondary causes may have first presentation with hypertensive crisis. A wise clinical examination is needed to rule out hypertensive emergency and target organ damage.

Management of Hypertension in Young Patients

Non-Pharmacological Therapy

The young hypertensives are better responders to non-pharmacological measures. Regular physical activity, weight loss, avoidance of tobacco, excessive alcohol, and stress management are important component of such therapy. Daily brisk walking for 30 minutes and outdoor games have proven to reduce blood pressure. Just adding few habits in daily routine may amount for few miles of activity as listed in Box 1.

The patient who is having raised blood pressure either in high normal or hypertension range is encouraged to adopt dietary approaches to stop hypertension (DASH)-type dietary plan which is rich in fruits, vegetables, and low-fat dairy products with reduced content of saturated and total fat. The total salt intake is to be restricted to less than 6 gm/day (Box 2). Young working persons are relatively more habituated to outside food. Avoidance of fast food, excessive tea, coffee, and aerated drinks are key components of dietary advice. Adequate sleep, yoga, and meditation have proven to be beneficial in stress management. Young adults should be advised to spend some quality time in these activities.
Pharmacological Management

Unwillingness to take medicines and not believing the seriousness of raised blood pressure are more common in young adults. Besides these, inadequate counseling of patients and physician’s inertia to start medicines are factors responsible for not getting desired blood pressure control. A patient centered approach should be followed while choosing drug for blood pressure management. As per current guidelines, the choice of medicines is similar in young adults and relatively older individuals but emphasis must be laid upon tolerability. Various classes of medicine may be associated with side effects like increased micturition, fatigue, sexual dysfunction, and peripheral edema. Many young working patients may find these inconvenient and troublesome. Side effects must not reduce the work capability of these young achievers. All these should be discussed prior to prescription and drug should be tailored accordingly. This will increase acceptability and adherence of medicines. Any of the first line medicines, viz. diuretics, calcium channel blockers, and renin angiotensin system (RAS) blockers, ACE inhibitors/ARBs may be used first. Young persons are having higher sympathetic tone and renin secretion, so ACEIs and ARBs are the preferred agents in young if not having any contraindication of its use. However, in young females who may be planning conception, due counseling to discontinue ACEIs and shift to alternative antihypertensive agent needs to be provided. A long half-life medicine with once daily dosing is preferred. Combination therapy in single pill is encouraged for better compliance.

Comprehensive Approach

Significant numbers of young patients having hypertension have other components of metabolic syndrome like diabetes/pre-diabetes, dyslipidemia, and obesity. Targeting other components of metabolic syndrome is an opportunity in these patients. Lifestyle changes like diet control and physical activity should be targeted to achieve good control of other components. Even modest weight loss may lead to reduction of blood pressure. The selected medicines should help control other metabolic risk factors or at least must be neutral. Thus, the beta blockers and diuretics should be avoided in patients with dyslipidemia and glucose intolerance.

Young and Technology

On an average a young patient is more technology savvy than their older counterparts. There are gadgets and mobile applications available in market, which monitor diet, physical activity, and act as reminder to support adherence to the treatment. Online counseling, telehealth projects, and related services are easily accessible and offer help in management of hypertension. However, they have their own limitations. Many awareness programs and activity are conducted by various national and international societies of hypertension and social organizations are now focusing on primary prevention to educate the masses.

Conclusion

Hypertension in the young needs to be carefully considered and evaluated, as it is a significant cause of morbidity and mortality. Young individuals have a variable lifestyle, and are difficult to convince that they have the disease. Therefore treatment needs to be individualised. Lifestyle management, salt restriction, ACE-inhibitors/ARBs (unless contraindicated) need to be initiated and reinforced for compliance on each visit.

References


BOX 2 Measures to limit salt intake

- Avoid processed food, cheese, sandwiches, pizza, and salty snacks
- Avoid red meat, tinned food products, and aerated drinks
- Use olive oil and avoid salted butter
- Use vinegar and lemon juice instead of the salt where possible
Abstract

Hypertension is recognized as one of the leading risk factors for human morbidity and mortality. It puts an individual at the risk of myocardial infarction, heart failure, cerebrovascular accident, and end stage renal disease. These diseases can thus be prevented and controlled early by screening and timely diagnosis of hypertension. Both the Korotkoff sound and oscillometric method of blood pressure (BP) measurement require cuff. Also, BP changes can occur according to operator and prevailing conditions, for example, White coat hypertension. Hence new technologies which allow BP monitoring without the use of cuff are being developed. This chapter describes the fundamentals of current technology in cuffless blood pressure measurement using nanosensors or photoplethysmography (PPG) to monitor blood pressure frequently and accurately for outpatient care and general health monitoring.

Introduction

Hypertension (HTN) is an epidemic affecting around one billion people. Globally 29.2% of males and 24.8% of females have HTN. It has been ranked on the top as a cause of disability-adjusted life years. However, awareness, treatment, and control rate for HTN are low. Approximately half of the total hypertensives are aware of having HTN and 50% of known hypertensives are not on any treatment. Moreover, adequate control of BP is present only in 50% of patients taking treatment. Hypertensives patients are precariously to develop heart attack, stroke, coronary artery disease, chronic kidney disease, and congestive heart failure and thus are at increased risk of premature death. Early detection and timely initiation of treatment regime for adequate BP control is a major step toward reducing complications and deaths due to HTN. Conventional blood pressure measurement techniques change according to conditions and are operator dependent. Ambulatory monitoring was introduced to overcome the problems associated with current manual office blood pressure measurement. A 24-hour ambulatory monitoring can help identify “white-coat” HTN, masked HTN, nocturnal HTN, labile HTN as well as postural hypotension, thus providing improved estimates of true blood pressure to guide decisions about treatment. Ambulatory blood pressure monitoring (ABPM) is done with a portable version of conventional oscillometer, the cuff of which fits around upper arm and inflates periodically as programmed while the person continues regular daily activities. However, patient is required to keep the arm static while the cuff inflates, which interferes with sleep and other activities of person. Also, in rare cases, continuous BP monitoring via cuff has been reported to cause hematomas, bursitis, phlebitis, and acute neuralgia. Hence, a wearable cuffless BP technology that offers continuous and noninvasive measurements has gained more attention. Handheld and wearable apparatus, which are small, comfortable, and less expensive, are now being used to measure other physiological vitals as well like oxygen saturation, body temperature and respiratory rate.
Biosensors

Biosensors are devices that convert a biological response into an electrical signal. These estimate the level of biological markers or any chemical reaction by producing the signals that are associated with the concentration of an analyte in that reaction. Biosensors consist of a biocatalyst that can detect a biological element/analyte and a transducer which converts the combination event of the biocatalyst and the analyte into discernible parameters (Fig. 1). An ideal biosensor should be specific, sensitive, stable, and reproducible to detect a specific analyte in very small concentrations without being affected in and around the biosensing system with the ability to program identical output after replenishment of experiment. Linearity, which is defined as a considerable change in the signal with little change in concentration of an analyte, is considered an important component of the biosensor.

Types of Biosensors

Depending on the method of signal transduction, biosensors are classified into different groups. These are as follows:

- Optical/visual biosensors which detect changes in properties of light such as refraction index, fluorescence, or light scattering resulting from the interaction between an analyte and receptor. Photoplethysmography (PPG) sensor is an optical biosensor that measures the blood volumetric changes and can be used in wearable devices to monitor blood pressure.

- Electrochemical biosensors consist of electrodes that translate the chemical signal into an electrical signal.

- Calorimetric biosensors measure the heat released or absorbed by the reaction.

Wearable biosensors (WBS) have gained attention recently with the use of technology for health monitoring, especially cardiovascular monitoring. These devices measure BP while person is performing routine daily activities, without creating any disturbance. By sensing elevated blood pressure, they can predict a missed dose of medication. Some of these devices are fitted with an alarm that is triggered by change in BP and serve as a reminder for patients to take medicine. WBS can be used in triage in waiting lobby of emergency rooms of hospital. In the era of COVID pandemic where telemedicine has become the “new normal,” WBS fitted with alarm can allow increased surveillance by cardiovascular monitoring for patients at home and this data can be digitally shared with treating physician for the ease of teleconsultation and further reference.

Photoplethysmography

PPG is an optical biosensor used for measuring the amount of light that is absorbed or reflected by blood vessels in animate flesh, which depends on the amount of blood that is present in the optical path. It is a high-fusion signal that covers the activity of the heart’s systolic and diastolic periods, the hemodynamics and network information of the peripheral microcirculation system. Thus, it is the external manifestation of various physiological processes in the cardiovascular system like heart rate, BP, cardiac output, and microcirculatory blood flow. PPG is a
convenient and inexpensive technique and its principles can be utilized for development of wearable cuffless BP monitoring devices.

**PPG Signal Formation, Preprocessing, Feature Extraction**

WBS is fitted with a LED (light emitting diode) transmitter, which either transmits or reflects red/infrared light to read PPG signal (Fig. 2).

The raw PPG is corrupted, of poor quality and is difficult to access. This signal undergoes preprocessing via normalization and denoising/filtering with the help of median and notch filter. This uncorrupted PPG waveform contains the systolic phase and diastolic phase separated by dicrotic notch as shown in Figure 3. It is used to extract useful features like peak to peak interval, systolic peak, stiffness index, crest time, and pulse area.

The systolic peak defined by the amplitude of PPG waveform is used to calculate heart rate. Systolic amplitude gives an indication of the pulsatile changes in blood volume. Stiffness index is a measure of arterial stiffness and depends on the height and age of person. It is obtained as the time interval between systolic peak and diastolic peak. Crest time is defined as duration of time from the base of PPG waveform to its peak. These parameters of PPG signal are used in various time-domain processing methods like peak detection, transition point calculation, etc.

**PPG in Hypertension**

Methods used for the continuous and cuffless measurement of BP via PPG are as follows:

- PTT based methods
- Non PTT based methods
- PTT based methods combined with non PTT based methods
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Biosensors in Hypertension

PTT-based Methods

BP can be estimated by measuring pulse transit time (PTT), which is defined as the time taken by the pressure wave to travel from one point to another in the arterial tree within a particular cardiac cycle. The velocity of this pressure wave is termed as pulse wave velocity (PWV). PTT can be used to estimate PWV. The speed of transmission of pulse wave depends on the rigidity and resistance of the vessel wall. HTN causes an increase in thickness in the arterial media that leads to the rise in wall tension. Thus, PWV is influenced by BP. BP can therefore be estimated by measuring PTT and PWV.6 PTT can be obtained by following methods.6

PPG Combined with Other Cardiovascular Signals

PTT can be calculated from PPG when it is combined with other cardiovascular signals, for example, electrocardiogram (ECG), ballistocardiogram (BCG), and phonocardiogram (PCG). PTT is measured as the temporal distance from one distinct point of the other signal to a specific point in the PPG waveform.

- Electrocardiogram (ECG): When PPG is combined with ECG, PTT is measured by calculating pulse arrival time (PAT). PAT can be measured as the distance between R wave of ECG and systolic peak of the PPG waveform. PAT = PTT + PET (Pre-ejection time). PET is the time elapsed between the electrical depolarization of the left ventricle (QRS on the ECG) and the beginning of mechanical ventricular ejection. PET is variable and gives different reading of BP. To avoid this variability, efforts are being done to establish PTT directly from multiple PPG signals instead of PPG-ECG combination (Fig. 4).

- Phonocardiogram (PCG): It records the sounds produced by the movement of cardiac valves. When PPG is combined with PCG, PTT is measured by calculating vascular transit time (VTT). VTT can be measured as the distance between S1 (first heart sound produced by closure of atrioventricular valves) of a PCG and systolic peak of corresponding PPG.5,6,7

- Ballistocardiography (BCG): It records the movements of the body caused by contraction of the heart. When PPG signal is combined with BCG, PTT is measured by calculating time difference (TD). Mainly three waves (I,J,K) are defined in BCG. J wave peak corresponds approximately to the foot of the BP waveform at the outlet of the descending aorta. Time difference is measured as the time between J peak and systolic peak in PPG waveform (Fig. 5).

Dual-Channel PPG

In this, PTT is measured at different peripheral sites, as the distance between the corresponding characteristic points of two PPG signals.

Single-Channel PPG

In this, PTT is measured as the distance between the forward and reflected wave of the second derivative of the PPG waveform.

Once PTT, PAT, and PWV parameters are estimated, mathematical models are used to derive BP. These models require two measurements from two sensors, for example, PPG and ECG signals. These sensors might have different sampling rates in real time, plus their operability depends on complicated arterial wave propagation models. Also, the extraction of feature points of each heartbeat correctly is a cumbersome method. It is very difficult to continuously monitor different physiological parameters in different point in time. This huge data can be well managed by artificial intelligence (AI). AI is a computer system that simulates human intelligence and performs tasks like speech recognition, decision-making, and visual perception. Machine learning (ML), a subset of AI, is a set of algorithms that analyzes data, learns from it and then applies what it has learned to make intelligent decisions. Machine learning requires various algorithms known as neural networks. Neural networks are built on the idea of human brain neural networks and consist of multiple layers, for example, input, output, and hidden layers to process, understand and produce result in a large data in continuous fashion, keeping in view the knowledge from previous result and modifying new results accordingly. Common pre-trained neural networks methods include GoogleNet, VGGNet, and AlexNet, which are trained based on ImageNet Large Scale Visual Recognition Challenge (ILSVRC).8 PPG equipped with NN (Neural network) can deduce data from PPG signals which can be used to identify and classify HTN. This can provide real-time data and thus reduce morbidity and mortality. A mobile app named HeartSense was developed using a neural network to produce BP readings.4
Non-PTT-based Method

In this method, morphological features of PPG such as pulse amplitude, signal steepness, peak to onset interval, signal amplitude, and many other time domain and frequency domain features have been used to estimate blood pressure.6

PTT-based Methods Combined with Non-PTT-based Methods

This method improves accuracy.

Implementation of PPG in Mobile and Wearable Health Devices

Out of hospital and continuous BP monitoring using handy and inexpensive instruments have become an
area of growing interest. Many companies have tried incorporating PPG in mobiles and wearable devices like wristband, armband, wristwatch, finger probe, eyeglass frame, chest belt.9,10

**Wearable Rings**

Wearable ring fitted with biosensor is an optimal device for measuring BP as the finger vasculature lies in proximity to the skin surface. It works on the concept of measuring arterial blood flow using PPG by optical biosensor that consist of LED, which illuminates the vessel of finger and photodetector that detects the amount of light transmitted/reflected.11 This device can be worn by persons at all times for 24-hour BP measurement without the fear of finger necrosis, as the cuff is not used.

**BP Monitoring Watch**

Proximal timing (blood ejected from left ventricle into aorta) is obtained by an accelerometer, which measures the thoracic vibrations when user places the face of watch on his sternum for about 15 seconds. Distal timing (arrival of pulse wave at the radial artery on wrist) is obtained by PPG signal on the watch. The delay between these proximal and distal timing provides PTT, which is used to estimate BP. This device cannot be used for continuous measurement as one fiducial point is user dependent, but it can serve as a handy cuffless BP measurement technique where person can monitor BP as and when required by placing arm near chest wall.12

**Eyeglasses**

Especially designed eyeglasses are fitted with small-sized PPG sensors that sample pulse waveform at bridge of the nose (for angular artery pulsations), on side of the head (for temporal artery pulsations) and behind the ear (for occipital artery). The time delay between pulse time from one artery to the other provides PTT.13 However, no clinical setting has validated this product to date.

**Biosensor in Phone**

By using the oscillometric mechanism, mobile phones can also be used as a tool for BP monitoring. The pressure of finger’s vessel is increased when person presses his finger against the rear camera of phone. Pulsatile blood volume oscillations within the artery are measured via PPG and transducer, embedded in the phone. The amplitude of these oscillations is used to compute BP. Both android and iPhone have mobile applications based on this method to measure BP (Fig. 6).

Smartphone devices can also measure BP using PPG signals by measuring PTT and VTT.14 Phone cameras provide the proximal timing of PPG signal from person’s finger. Another fiducial distal point is derived from heart sounds collected by microphone instilled in mobile phones. VTT is calculated between two points to estimate BP. Mobile applications like instant blood pressure (IBP) and wello, released by Auralife (Newport Beach, CA) and iPhone respectively, estimate BP using the above mentioned method of wave propagation.

**Electrochemical Biosensors**

Electrochemical sensors can be used for the quantification of various biological compounds that indirectly serve as markers of HTN. Cortisol, increased nitric oxide, galectin-3, ghrelin in saliva and inflammatory markers like C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), interleukins, etc. are a few examples of such biological compounds.15 Sodium-sensitive electrode is employed for the potentiometric detection of sodium from sweat samples based on the fact that high levels of sodium increase the stiffness of the endothelial cells leading to HTN. Kidneys control total sodium content through epithelial sodium channel (ENAC) and its deregulation is associated with HTN. Fabricated anti ENAC conjugates were detected by optical sensors. The fluorescence intensity enables discriminating between normotensives and hypertensives. Thus, represents a useful diagnostic tool for HTN.16 Development of nanosensors for point of care diagnostics has led electrochemical sensors to display superior sensitivity, response time, precision time, and wider range for specific and reproducible detection of key markers that aid in diagnosing HTN. Although there are many hand-held or field biosensors available, most of these technologies have not been fully utilized for the detection of HTN and is used for research purpose only. The direction is yet to be explored as it holds immense promise for clinical applications but their specificity and cost efficiency are a major issue.
Fig. 6: Topmost figure shows conventional oscillometer. In second figure person places his finger on phone’s camera, and phone embedded with photoplethysmography (PPG) and force transducers serves as the sensor to measure the blood volume oscillations and applied pressure.
Conclusion

The principle of PPG is widely used for measuring oxygen saturation. However, its use in clinical setting for BP is relatively new. Major phone companies like iPhone and Samsung have developed mobile applications that measure BP using PPG waveform that is obtained by pressing finger against phone camera. The widespread use of portable and wearable health devices allow timely BP measurement and monitoring, guides the health-care personnel of fluctuations patterns of person’s BP, for example, nocturnal HTN and in some cases also reminds the person of missed dose by ringing an alarm. This prevents the complications related to HTN, prolongs customer’s expected life span and also improves quality of life. In addition, these will bring down health costs in long run. However, high initial cost, less selectivity and a limited number of physiological parameter monitoring limit their use. A comprehensive understanding of PPG is required so that researchers can successfully develop advanced technologies for better care of hypertensive patients.

References
