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

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Review Article

Blood Pressure Measurement in Clinical Practice Methods and Emerging Options

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Abstract

Accurate measurement of blood pressure (BP) is pre-requisite for diagnosis and therapy of hypertension (HTN). The standard clinical method of estimating BP in office, by inflatable rubber cuff, using Korotkoff sounds is obsolete and is used more often for standardization of other indirect methods. The oscillometric technique is the current standard for the measurement of BP. Alternative methods of indirect estimation of BP – applanation tonometry, vascular clamp method, and pulse transit time, are under evaluation and need refinement, before recommending for routine clinical application. Current clinical standard mandates, blood pressure measurement not only in office but also out of office for the diagnosis and therapy of HTN.

Key words: Blood pressure, measurement, mercury manometer, oscillometry, out of office measurement

Introduction

"*Whatever the measurement system is, it needs to be consistent, repeatable, and as unbiased as possible*"

Pearl Zhu[1]

William Harvey discovered circulation in 1628 and century elapsed before Reverend Stephen Hales performed his famous experiment in 1733, demonstrating the rise of blood to height of eight feet, three inches, in glass pipe placed in artery of Horse. It was not until non-invasive occluding arm cuff devised by Scipione Riva Rocci in 1896 that clinical measurement of blood pressure (BP) became reality. He inflated cuff, until it occluded pulse distal to cuff. This application of external counter pressure until the pulse disappeared by palpation corresponds to peak systolic BP (SBP). Quantification of counterpressure was done by connecting the inflatable bag to mercury manometer. In April 1905, Russian surgeon-Nikolai Sergeevich Korotkoff described the measurement of BP by auscultation-peak systolic pressure corresponding to onset of audible sounds by Stethoscope distal to occluding cuff and disappearance of sounds to end-diastolic pressure. Alternative methods of BP measurement, using oscillometry, applanation tonometry, volume clamp method, and analysis of various parameters of arterial pulse wave, have been utilized for non-invasive measurement of arterial BP.

The evolution of methods of BP measurement continues and the latest technique of non-invasive measurement of BP using Android smartphone, is commercially available but not yet approved by regulating organizations and professional societies.

Direct intra-arterial pressure measurement by cannulation of the vessel is gold standard, but it is not practical for routine clinical measurement of ambulatory patients, as it is invasive and requires technical skill and is associated, although rarely with potential major complications of occlusion of vessels and injury to adjacent structures.

Thus, indirect non-invasive measurement of BP is currently clinical standard. Most of these methods base the measurement of pressure, indirectly by applying counter pressure to blood vessels or analyzing various components of pulse wave recorded indirectly by device/sensors applied to blood vessels, transcutaneously.

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These Methods Include

- Conventional inflatable rubber bag method (RivaRocci-Korotkoff [RRK] - method)
- Oscillometry
- Vascular clamps method
- Applanation tonometry
- Pulse wave analysis including (pulse transit time [PTT]).

RRK Method

Till recently, this method has been the mainstay of clinical BP measurement and is gradually replaced by other automated techniques. In this auscultatory method the audible sounds (Korotkoff sounds), distal to the occluded artery, during slow deflation of inflated rubber cuff are produced by vibration of the vessel wall, consequent to the rapid flow of blood passing through the collapsed artery. In this auscultatory method of indirect measurement of BP, the onset of audible sounds (Phase I) during deflation is equal to peak SBP and disappearance of sounds (Phase V) as corresponding to end-diastolic pressure.

In situations where Korotkoff sounds are heard, even after complete deflation – such as AR (Aortic Regurgitation), the fourth phase (Muffling of sounds) may be used as diastolic BP (DBP). In some patients – especially in older patients the Korotkoff sounds may be inaudible between SBP and DBP (independent of respiration and cardiac arrhythmias), as the cuff deflation is continued, this is called auscultatory gap. It is commonly seen in patients with stiff arteries and is most likely to occur in subjects with target organ damage.

External brachial pulse recording during standard BP cuff deflation reveals three components, labeled as K1, K2, and K3.

Table 1: Cuff size measurement of blood pressure

Lean arms	Circumference in cm	Dimensions in cm	
		BHS	AHA
Adults and children	22–26	-	12×22
Adult arms	27–-34	12×18	16×30
Large	35–44	12×26	16×36
Thigh	45–52	-	20×42

BHS: British Hypertension Society, AHA: American Heart Association

The K2 component is high frequency triphasic component that coincides with audible Korotkoff sounds. In conditions characterized by stiff arteries, the K2 component either is blunted or disappears, resulting in loss of Korotkoff sounds and thus auscultation gap.[2] Thus, it is desirable to measure SBP by palpatory method and inflate cuff to 30 mmHg more than SBP (obtained by palpation) during auscultation. The auscultatory method has been validated in animal experiments and human beings, with intravascular pressure recordings. The SBP by auscultatory method is often underestimated (by about 5–10 mmHg), and DBP is overestimated with nearly equal mean arterial pressure (MAP).

Mercury manometers used in traditional auscultatory methods are gradually replaced due to possible environmental toxicities of mercury – by aneroid manometers and hybrid sphygmomanometers. Hybrid manometers have been developed to overcome the banning of mercury in measuring instruments, by replacing mercury with electronic pressure gauge. In aneroid devices, the pressure is registered by the mechanical system of metal bellows that expand as the cuff pressure increase and register the pressure on circular scale. Being mechanical systems may lose stability over time and need to be calibrated periodically by mercury manometers.

A common source of error in measuring BP by this technique is using of inappropriate size of cuff that encircles the upper arm. Ideal cuff should have bladder length that is 80% of circumference and width of at least 40% arm distance with length-width ratio of 2:1.

The Recommended Size of Cuff for Various Arm Sizes Table-1, after Home BP Moitor Table-2 are as Follows[3]

BP measurements are commonly made in the sitting position with feet flatly touching floor and with back support and upper arm at the level of heart, with support (to eliminate possible isometric exercise in trying to hold at level). It is also measured in supine position and standing position if needed (in Elderly and on drug therapy) but has to make sure that measuring arm should be at the level of the heart. Any variability of arm position in relation to heart level is due to hydrostatic pressure and may result in 2 mmHg change for every inch above or below heart level (Higher when arm is below and lower if arm is Higher).

Table 2: Home blood pressure technique, timing, and schedule

Technique	Timing	Schedule
Comfortable	5 min after resting–after emptying the bladder	7-day monitoring schedule
Distraction-free environment	2 h after meal	Duplicate measurements – each time
Sitting position	1 h after coffee or tobacco usage	Morning and evening (4 measurements per day)
Back supported	30 min after exercise	Not fewer than 12 readings, i.e., at least 3 days data
Feet flat on the floor	Before taking medicines	(for diagnostic purposes)
Legs–uncrossed		Long-term–1–2 duplicate measurements per week
Arm supported		initially (Long-term monitoring)
Middle of the cuff at heart level		
Arm bare with the lower edge of the		
cuff 3 cm above the elbow		
No conversation and no movement		

Interpretation: Discard 1st-day readings and take average of remaining readings. Normal values – <135/85 mmHg (Same as daytime readings of ABP)

BP should be measured in both arms at first examination, and when there is consistent arm difference between the two, the arm with higher BP values should be used for follow-up. Before investigation for possible obstructive artery disease – simultaneous measurement in two arms is mandatory. Any difference of BP by >15 mmHg between the arms (inter arms difference) is sign of obstructive arterial disease and demands further evaluation.

The BP should also be measured in lower limbs generally at the level of ankle, as it does not require special inflatable rubber cuff (as the size of ankle and arm are approximately same girth). The ankle SBP is generally expressed as a ratio in comparison to brachial SBP – ankle-brachial index (ABI). Normally, ABI is 0.9–1.1 any deviation from this value indicates peripheral vascular disease – lower value <0.9 indicating occlusive vascular disease and higher values >1.3 indicating stiffer vessel wall both these conditions indicate worse long-term clinical outcome.

Apart from technical details of the measurement of BP cuff size, position of patient and arm, the observer is the important component of accurate BP measurement and must fulfill all the following criteria.

He should be properly trained in the technique of BP measurement by selecting the appropriate size of cuff, instrument, and positions arm appropriately. The mercury columns should be deflated at 2–3 mmHg/s and listen to Korotkoff sounds noting the level at which first sound appears (phase-I SBP) and last sound disappears (Phase-V–DBP). The columns should be read to nearest 2 mmHg. The observer should recognize subject factors – anxiety, Nicotine, coffee use, etc., that would adversely affect the BP measurement. It is important to note that observer and patients should not converse during measurement. The BP should be measured after rest period of 5 min and not immediately after arrival to the examining room. The mercury manometer should be at the eye level of observers, to prevent parallax error. Observer error is a major limitation of auscultatory methods, just as terminal digit preference. It is recommended to read BP to nearest 2 mmHg.

Because observer error is a major limitation of auscultatory method, automated measurement by oscillometric method has become popular and currently the standard of clinical care.

Oscillometric Method

In this method, Riva-Rocci arm cuff is used to measure the BP by analyzing pressure oscillation by device in the cuff. When the cuff is inflated above SBP, there are no pressure oscillations. The maximum oscillations during the deflation of cuff correspond to the mean arterial BP and have been validated by invasive methods.[4] From the mean arterial BP, the SBP and DBP are derived using a variety of algorithms. Currently, the oscillometric method is popular, as it is independent of observer errors and ease of multiple recordings. Further oscillometric techniques tend to overestimate low pressure and underestimate when pressure is high. Finally, movement of the arm during measurement can give false reading, mistaking movement as oscillation.

The predictive power of multiple BP recordings is much greater than single office recording. Presently, it is recommended to measure BP readings automatically in quiet room without any health-care providers in the room after the rest of 5 min (Automatic Office BP [AOBP]). The major advantage of automatic devices is avoidance of observer errors, multiple readings and the ease of use even by layperson with elementary training. This has resulted in increasing use of oscillometric devices in office, home, and ambulatory monitoring of BP measurement.

The disadvantage of oscillometric techniques includes inherent error in oscillometric techniques and lack of long-term outcome data based on oscillometric techniques. For appropriate evaluation of patient with hypertension (HTN) it should not only be measured in office but also out of office environment (000 BP) either at home or by continuous ambulatory BP (ABP) recording measurement. Home/self-monitoring has several advantages, as it identifies white coat HTN (isolated office HTN) and masked HTN (isolated home HTN with normal office BP). It also provides a convenient way of monitoring BP over long periods of time and may improve, drugs compliance, and HTN control. For accurate reporting, devices that have memory or printout of readings should be recommended. The measurement of BP in office, like measurement at home, also demands same guidelines to be implemented.

Home BP Recording

It is generally done by oscillometric technique and should adhere to the following guidelines. The ideal requirement for appropriate measurements is as follows.

Utility

- Diagnostic – diagnosis of HTN-white coat or masked
- Prognostic – better than on base percentage recording
- Home BP variability
- Therapeutic – Effectiveness of drug treatment
- Drug duration of action
- Home BP ratio – Morning/Evening is similar to trough to peak ratio by ABP.

Limitations

- Usage of poor-quality devices
- Need for elementary training
- Misrepresenting of data – patients
- Self-adjustment of drug therapy
- Anxiety – due to "high" or low BP values
- Inability to monitor nocturnal BP.

ABP Measurement

ABP is automated technique of BP recording over an extended period of time, typically for 24 h. The equipment consists of cuff, connected to recorder by a tubing, which in turn is attached to

belt tied at waist. BP is measured by oscillometric technique. The frequency of measurement can be programmed – every 15 min, 30 min, or hourly. During typical ABP monitoring BP is measured every 15–30 min during awake and hourly during sleep hours preferably on working days. The number of readings usually vary 50–100 are analyzed offline and provides report giving mean values by hour and period – day time and night and 24 h – SBP and DBP mean during day and night time-24 h values are used in decision-making.

The inflatable rubber cuff should be attached to non-dominant arm and series of calibration readings taken with mercury manometer to ensure that device is giving readings within 5 mmHg of mercury manometer. ABP should be appropriately used in identifying patients with white coat HTN. Non-dipper at night by ABP (<10% decrease) super dipper (>20% decrease) has adverse prognosis. ABP can also be used for correlating patients' symptoms with BP as in (postural hypotension) and to know adequacy 24 h coverage of antihypertensive effects by drugs.

Normal ABP values are as follows:

- Average 24 h–130/80 mmHg
- Day time – 135/85
- Night time – 120/75
- Normal fall (Dipper) in SBP and DBP during night sleep 10–20%.

ABP record is recognized as a gold standard for evaluation of elevated office BP by US preventive service task force and National Clinical Guideline Centre in United Kingdom. Guidelines recommend at least 20 or more-day time recordings and at least seven or more-night time recordings for appropriate interpretation of ABP. Recommendations vary from obtaining at least 70% of programmable readings to 20 awake/daytime and seven asleep or night time readings. IDACO (International Database ABP in relation to cardiovascular [CV] outcome) studies applied fixed clock time intervals excluding transition period in morning and evening when BP rapidly changes.

BP Measurements in Special Situations

Elderly

Measurement of BP in the elderly should not only be in sitting position but also in standing position, with the upper arm at heart level, as postural hypotension related to disease or drug therapy will determine the dose and type of anti-HTN drugs.

Pseudo HTN

It is defined as elevated BP by the indirect method of estimation with normal invasive intra-arterial pressure is gold standard for diagnosis of pseudo HTN. It is presumably due to stiff vessel wall of brachial artery that makes the indirect measurement of BP unreliable when compared to intra-arterial pressure. The time tested Osler's maneuver of identifying thickened vessel wall after complete occlusion of blood flow by inflating the BP cuff to suprasystemic level is good clinical indicator of vessel wall pathology at bedside. Quantification of vessel wall thickness was done in one study by estimating PWV which was markedly increased in patients with pseudo HTN.

Systematic study of the prevalence of pseudohypertension is very low (1.7%), in non-selected elderly population. There was no correlation observed between pulse wave velocity (PWV) and difference between direct and indirect pressures.[6] The Osler's maneuver was misleading being positive in patients with no pseudohypertension and negative in some patients with pseudohypertension.

Diagnosis of pseudohypertension is suspected, when BP recording is very high over a long period of the time with no target organ damage and attempting to treat suspected HTN with drug therapy results in symptoms of low BP – dizziness, confusion, etc.

Measurement of intravascular pressure is gold standard for diagnosis. Alternative methods of estimating BP at finger level by vascular clamp method are useful in diagnosis of pseudohypertension.

Obesity

Diagnosis of HTN in obese patients by indirect BP measurement should be done after making sure that it is not due to an error in cuff sizing-smaller cuff leading to overestimation of BP.

Pregnancy

Measurement of BP during pregnancy should be in sitting position but supine BP should be measured in left lateral position is reasonable alternative during labor. Korotkoff Phase- V Should be the DBP while using auscultatory sphygmomanometer.

Children

Interpretation of BP values should take into consideration age, gender, and height. A BP value that is consistently higher than 95th percentile of distribution should lead to one to diagnose HTN. The table that provides SBP, DBP level at 95th percentile according to age, gender, and height should be consulted before labeling patients as HTN. The role of ABP in children is less clear in diagnosis of HTN.

Cardiac Arrhythmias

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, being present in 1–2% of general population, with increasing prevalence with age-approximately 5% of adults older than 65 years.

Assessment of BP in AF is challenging, due to significant variability in SBP, consequent to varying cardiac cycle lengths (varying stroke volume). The accuracy of the automated oscillometric technique is questionable and recommended repeated measurements using auscultatory method. Recently automated BP monitors with AF detection capability-

MICROLIFE – are available and are reliable in estimation of BP (in the setting of AF). National Institute for Health Care Excellence recommends MICROLIFE for BP Measurement in patients 65 years and older, in primary care, for detection and therapy of AF, leading to reduction of stroke in the community.

In patients with bradycardia, measurement of BP by auscultatory sphygmomanometry may be erroneous if the cuff deflation is fast and recommended slow deflation so as not missing the early onset and late offset of Korotkoff sounds.

Central Aortic Pressure

Some clinical trials and meta-analysis have shown that central aortic pressure predicts CV events better than brachial arterial BP. As of now, the incremental prognostic value of central aortic pressure remains unclear. Furthermore, the technique of derivation of central aortic pressure from brachial pressure is not standardized for routine clinical use; then, as of now central aortic pressure derivation is not recommended for clinical studies. The only exception may be isolated systolic HTN (ISH) in young, where the increased SBP at the brachial level may be due to high amplification of central pressure, while central aortic BP may be normal.[7]

Applanation Tonometry (Applanation-to Flatten, Tonometry-Measurement of Pressure)

Applanation tonometry is based on the work of Pressman and Newgard,[8] who showed that transducer strapped to artery transcutaneously can obtain arterial pulse wave, similar to intravascular pressure wave. This is based on Imbert–Fick Principle which states that thin-walled sphere inside pressure, is equal to force necessary to flatten surface, divided by area of flattening MAP obtained from pulse wave is used to derive SBP and DBP.

The superficial blood vessel in flattened by applying pressure over the artery against the underlying bone-classical radial artery. The arterial pressure in top of flattened artery equals the luminal pressure, allowing pressure waveform to be recorded. Comparative studies have shown that arterial pressure waveform recorded by transcutaneous tonometer corresponds to those recorded invasively with intra-arterial catheters. The major limitation of arterial tonometry is its inability to give absolute values of SBP and DBP as it has to calibrate tonometric pressure wave, with brachial artery pressure usually obtained by oscillometry. From these data obtained, central aortic pressure can also be determined either by direct method-analyzing carotid tonometric pressure wave or indirectly using radial artery tonometric pressure wave analysis. Central aortic BP has been shown to be better predictor of CV events in some of the clinical trials of HTN. The methodology of estimating central aortic pressure is not standardized, and its value over and above brachial arterial pressure is questioned.

Apart from measuring arterial BP, by pulse wave analysis, other parameters – augmentation index, BP amplification, and subendocardial viability ratio can be calculated. Commercially available, applanation tonometry includes – Pulse pen device – DiaTecna, Milan, Italy; Indirect-Sphygmocor (ATCOR Medical, Australia); OMRONHEM 9000A-OMRONHEM-Healthcare-Kyoto Japan.

One clinical study comparing arterial tonometry derived BP with invasive arterial pressure in post-operative patients[9] revealed poor agreement between two methods, well beyond the limits set by Association for Advancement of Medical Instruments. Thus, arterial tonometry may be useful in assessing the trend of BP during monitoring rather than absolute values.

Modification of transducer of tonometry by including another parameter – volume change in arterial lumen may yield additional physiologic data like compliance of vessel. Recent guidelines ESC and EHS advise recording of central aorta pressure – in patients with ISH and not in any other hypertensive conditions.

Volume Clamp Method (Arterial Unloading)

Volume clamp method is based on the work of Penaz, aCzech physiologist, who measured finger blood volume by photoplethysmography, which changes continuously throughout the cardiac cycle. The BP is measured at the finger, with transparent inflatable cuff, containing photodiode and photocell, which in turn is connected pressure controller. This technique measures the blood volume in finger by plethysmography.

The counter pressure that is required to keep finger blood volume constant is the arterial BP. By applying counter pressure from outside, the arterial wall is unloaded (i.e., not under stress of intraluminal pressure). The pressure controller adjusts the pressure (using servo mechanism) such that blood volume in finger is held constant. Thus, finger cuff pressure will represent arterial BP; it is calibrated to brachial arterial BP, measured by independent technique. (Usually by oscillometric method) and triggered automatically and periodically) (Once in 15–30 s). This method of non-invasive measurement of BP is commercially available for continuous beat to beat measurement of BP, in critical area of monitoring-during anesthesia, intraoperative, post-operative, and intensive care units.

Disadvantages

The pneumatic cuff on finger continuously causes discomfort and can compromise digital circulation. Peripheral vasomotor changes occurring spontaneously or in response to various drugs (Inotropes, vasopressors, vasodilators can cause error, and primarily affecting SBP). Improper application of finger cuff can also cause inaccurate pressure results. This method is also motion sensitive and cannot be used during normal physical activities, just as it cannot be used in patients which finger deformities either congenital or acquired like in rheumatoid disease.

Cuff less, Continuous BP Measurement

Since 1990 novel techniques-based on PWV principles have been developed. PWV is speed of movement of expansile

impulse of vessel wall (Not velocity of blood flow), which progressively increases from 4 M/s in central aorta to reach 8 M/s in iliac arteries. This PWV is proportional to magnitude of BP in addition to compliance of blood vessels.

PTT is the time delay for pressure wave to travel between two arterial sites and can be measured as the time interval between peak of "R" wave (of electrocardiogram [ECG]) and onset of blood flow. PTT is inversely related to the magnitude of mean arterial BP. Calibration of these PTT parameters is crucial component of accurate measurement of BP by this method. Recently, Food and Drug Administration (FDA) has cleared Visimobile – For continuous noninvasive cuffless BP measurement BP. Cuffless BP measurement device using PTT for beat to beat calculation of BP values has been validated over short period of time-Somnomedics (GmbH, Germany).

Recent study of cuffless, continuous noninvasive BP[11] measurement using PTT technology is compared to ABP oscillometric technique. (Ambulatory BP) monitoring using oscillometry technique) found a significant difference between the two systems-PTT system-showing consistently higher values ranging from 5 to 10 mmHg in both SBP and DBP. Thus, this system using PTT technique has to be refined for improving the accuracy before widespread use in clinical settings.

Measurement of BP using Smartphones

These devices – smartphones are used as processors by having BP App. The biological signals from ECG, Plethysmography or pressure transducers, are recorded by appropriate sensors and transmitted to the smartphone by blue tooth technology, or sensors are inbuilt in instrument. Analysis and calibration of signals are the crucial part of application.

The BP measurement from health App in one study[12] was highly inaccurate with 77.5% of individuals with HTN being shown in non-hypertensive range. As on today, in 2018, this technology is in its nascent stage and is not ready for prime time. The US-FDA, which regulates devices, has not approved any of the BP Apps. These instruments underestimated higher BP range and overestimated lower BP range giving false reassurance that their BP is under control.

Wearable Devices

Wearable technology is a broad term for electronics that are worn on body, either as a part of garment or as an accessory individual unit.

Wearable BP monitoring device is available that looks like a smartwatch and provides many of the measures-like walking speed and distance covered and heart rate in addition to BP measurement. This does not have an arm cuff but still has inflatable cuff built into wrist band and provides SBP and DBP.

Another wearable device technology-a bracelet, utilizes, combination of optical sensors, and smartphone app to measure and monitor BP.

These wearable BP measurement gadgets are available but are not validated for accuracy.

Transdermal Optical Imaging Technology

Facial video, using cameras, were analyzed for variations in skin color, caused by pulsatile blood volume changes in cutaneous arteries. These variations were converted to SBP and DBP using mathematical models. These values were comparable to BP recorded with arm cuff methods This study was conducted in East Asians in still subjects, using two light sources at fixed distances. In people with dark skin and variations in position of head, consequent to movement, it is difficult to extract skin color variation of skin principle of using skin color variation, for measurement of BP is a novel concept but has too many limitations, for routine clinical applications at the present time.

Assessment of BP

(Clinical methodology) Ambulatory Patients Clinical Methods

Four approaches can be used:

- AOBP
- Non-AOBP (Standard office measurements)
- ABP monitoring
- Home BP monitoring.

(Threshold for Diagnosis of HTN is Different for each of the above Methods)

- AOBP is the preferred method of performing in office measurement but is not practical in India
- Multiple BP recordings in non-AOBP is most frequently performed for evaluation of BP, but should always be combined with out of office measurements, especially in the absence of target organ damage or clinical CV disease
- In the absence of AOBP, the next preferable method of evaluation of BP is by ABP, usually recording for 24 h. Ideal if available, affordable and tolerable
- Home monitoring of BP has to be done as a part of out of office measurement in the absence of ABP monitoring
- Combination of office BP and out of office measurements is mandatory for the diagnosis of HTN.

Summary

Multiple methods of the measurement of BP by indirect methods are available.

- Standard inflatable rubber cuff using mercury manometer is outdated for clinical purpose but still has utility for calibration of other indirect methods
- Commonly used BP devices in clinical practice are by oscillometry, though less reliable in patients with cardiac arrhythmias
- Out of office (000-BP) BP measurement, either at home or by ABP record, in addition to office BP (AOBP), is the current standard for diagnosis of HTN and as substitute for multiple recordings in office
- Newer methods of measuring BP continuously on the beat to

beat are in evaluation using pulse wave analysis-like PTT and applanation tonometry
- They are being evaluated against the standard methods of measuring BP by oscillometry
- Measurement of BP by android smartphone is unreliable and currently not approved by any regulatory agencies or any professional organization.

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Review Article

Hypertension as a Cause of Dementia

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Abstract

Several observational studies have demonstrated a link between high blood pressure (BP) and memory decline. The association is more with midlife rather than late-life hypertension and with systolic rather than diastolic BP. Hypertension by causing vessel wall thickening, reduced luminal diameter and vascular obstruction can lead to vascular dementia. Brain infarcts by decreasing the brain reserve lower the threshold for neurofibrillary tangles and amyloid plaques to produce Alzheimer's disease. Longer and intensive lowering of systolic BP has been shown to reduce the prevalence of mild cognitive impairment and dementia.

Key words: Dementia, midlife, hypertension

Introduction

Much attention has been paid to kidneys and heart as targets of end-organ damage due to hypertension. However, both large and small artery brain vasculature are probably more vulnerable to this end-organ damage. Many prospective studies have addressed the relationship between high blood pressure (BP) and memory decline. The overall impression does suggest that midlife hypertension has a strong association with late-life dementia of both vascular dementia (VaD) and Alzheimer's disease (AD) type. The aim of this article is to review the available literature on the subject of hypertension as a cause of dementia.

Hypertension Dementia Studies

Many studies have examined the relationship between midlife hypertension and late-life dementia.[1-4] The Honolulu-Asia Aging Study (HAAS) studied this relationship in 3703 Japanese-American men aged 45–68 years who were followed prospectively for 26 years.[5] A strong association between midlife hypertension (>160/95) and dementia (both AD and VaD) was established. Other studies also found similar results[4] high systolic BP (SBP) combined with an elevated total cholesterol level, further increased the risk for AD or VaD.[6]

As opposed to midlife high BP, the association between late-life high BP and dementia is not very robust. Only two studies have identified an association between late-life hypertension and dementia.[7,8] The first among these was a community-based cohort of 1270 participants (aged >75 years) followed for 6 years, out of whom 339 subjects developed dementia.[7] Subjects with very high SBP (>180 mmHg) were at 1½ times at risk to develop dementia, whereas those with high diastolic BP (DBP) (>90 mmHg) were not associated with an increased risk. Surprisingly, low DBP (<65 mmHg) was associated with an increased risk of dementia. Second study comprising 382 subjects described an association of both elevated SBP and DBP with a subsequent diagnosis of AD and VaD.[8]

In another study comprising 2356 participants, the relationship between BP and the risk for dementia across a range of older ages (>65 years) was studied over 8 years.[9] The youngest age group showed a significant association between high SBP (>160 mmHg) and all-cause dementia. The risk estimates for dementia associated with SBP declined with advancing age. It, therefore, seems that longer exposure to systolic hypertension has the strongest association with dementia.

Mechanism of Hypertension-Dementia Connection

Persistently, high BP may cause vessel wall thickening, reduced luminal diameter, and occlusion of large as well as microvessels of the brain.[10] A single strategically located infarct can cause acute

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VaD. Accumulation of multiple relatively silent infarcts over the course of time can also eventually lead to VaD. The presence of cerebral infarcts also lowers the brain reserve and the threshold for neurofibrillary tangles and amyloid plaques to precipitate AD.[11-13] Hypertension has also been proposed to cause ischemic damage to the cornu ammonis 1 hippocampal sector, which is the prime site for AD-type neurofibrillary degeneration.[14] The autopsy follow-up of 243 participants demonstrated that elevated SBP in midlife was associated with vasculopathic changes, a lower brain weight, and greater number of neuritic (ß-amyloid) plaques in both the neocortex and the hippocampus.[15] A neuroimaging study has demonstrated an association between midlife untreated hypertension and hippocampal atrophy.[16] There is also evidence to suggest that hypoxia-induced factors may strengthen amyloidogenic mechanisms by inducing BACE (beta-site amyloid precursor protein cleaving enzyme) a protein associated with the production of ß-amyloid, resulting in expression of AD.[17,18] This evidence suggests that hypertension by causing cerebral ischemia may lead to the development of both VaD and AD. Of note, many studies have shown an association of AD with atherosclerosis, high cholesterol, diabetes mellitus, and obesity, all of which often coexist with hypertension.[19-22]

Dementia and Antihypertensive Therapy; Observational Studies

The data from observational studies are mixed, but in general there seems to be a trend in reduction of both VaD and AD prevalence with antihypertensive therapy. The Rotterdam Study, a community cohort of 6416 nondemented subjects followed up for 2.2 years, reported a significant association between antihypertensive therapy and reduction in VaD but not AD.[23] However, Baltimore Longitudinal Study of aging, and the cache county study found that the use of Antihypertensive (AH) therapy was associated with a reduced risk of developing AD.[24,25] A 5-year follow-up study on a community sample of 1617 African Americans demonstrated 40% reduction in risk of dementia by the use of medications that control vascular risk factors.[26]

The HAAS was conducted on a sample of Asian American men between 1965 and 1995.[5] The relationship between the use of AH drugs and hippocampal atrophy was analyzed in a random sample of 543 participants.[16] The risk of hippocampal atrophy was increased in patients who never received AH drugs compared to those who received AH therapy. A further report of 848 participants from the HAAS, who had a history of mid-life hypertension and were dementia-free in 1991 showed that longer duration of AH treatment was associated with a reduced risk of AD and VaD. Each year of AH therapy was associated with a 6% reduction in the risk for dementia, compared with those never treated.[27]

On the contrary, two population studies, which had enrolled patients >65 years of age, failed to show any association between AH therapy and dementia. The East Boston cohort (n = 634 subjects >65 years of age) and the Canadian study of health and aging (n = 3238 subjects, >65 years of age), with follow-up periods of 4 and 5 years respectively, demonstrated no benefit for AH treatment.[28,29]

Dementia and Antihypertensive Therapy; Randomized Controlled Trials

Several large trials on hypertension have evaluated the effects of antihypertensive drugs on cognition with mixed results. Most of these trials were primarily designed to study the effect of AH medication on cardiovascular and stroke outcomes. Cognitive outcomes were measured only as a secondary outcome.

Systolic Hypertension in the Elderly Program (SHEP)

This double-blind placebo-controlled trial (1991) included 4736 patients with a mean age of 72 years.[30] Active treatment consisted of the diuretic chlorthalidone, with the possible addition of atenolol or reserpine. SHEP failed to demonstrate a significant effect of antihypertensive treatment on the incidence of dementia, despite between-group BP differences of >10 mmHg SBP, and >4 mmHg DBP.

Medical Research Council (MRC) Treatment Trial of Hypertension Study

In this prospectively planned MRC trial of treatment in 2584 patients (age 65–74) with hypertension, subjects were randomized to a diuretic, ß-blocker, or placebo.[31] There was a mean fall in SBP following treatment of 33.5 mmHg in the diuretic group, 30.9 mmHg in the ß-blocker group, and 16.4 mmHg in the placebo group. Subjects were followed up for 54 months, and no significant difference in cognition was found between the two groups.

Systolic Hypertension in Europe Study (Syst-Eur)

The VaD project included in the Syst-Eur demonstrated for the 1st time a reduction in the incidence of dementia following AH treatment.[32] Participants with age above 60 years (n = 2418) with isolated systolic hypertension were randomized to placebo or a dihydropyridine-calcium channel blocker (DHP-CCB) nitrendipine with or without an angiotensin-converting enzyme (ACE) inhibitor (enalapril), or a diuretic (hydrochlorothiazide) or both drugs to achieve adequate BP control. The trial was stopped prematurely because active treatment resulted in a 42% reduction in the primary endpoint of fatal and nonfatal stroke. Nitrendipine was the only antihypertensive used in 60% of patients in the active treatment group. The incidence of dementia was reduced by 50% in the treatment group. All patients enrolled in this trial were invited to continue or commence the study medication for a further follow-up period of 2 years (Syst-Eur).[33] Follow-up showed that the long-term antihypertensive therapy reduced the incidence of dementia by 55% from 7.4

to 3.3 cases/1000 patient years. Both the incidence of AD and VaD were reduced. These results indicate that the treatment of 1000 patients for 5 years can prevent 20 cases of dementia.

SBP Intervention Trial (SPRINT)

A substudy of SPRINT MIND project showed that at 1 year, mean systolic BP was 121.4 mmHg in the intensive-treatment group and 136.2 mmHg in the standard group. There was a "significantly lower rate" of mild cognitive impairment (MCI) and a "non-significant reduction" in the primary outcome of probable dementia in the intensive treatment group. The secondary outcome of a combined outcome of MCI plus probable dementia was significantly lower in the intensive versus standard treatment group. The SPRINT MIND magnetic resonance imaging (MRI) trial found that treating with a systolic BP target <120 mmHg also reduced the rise in cerebral white matter lesion on MRI scans but found no significant change in total brain volume.[34]

Perindopril Protection against Recurrent Stroke Study (PROGRESS)

The PROGRESS study was a randomized, double-blind, and placebo-controlled clinical trial on 6105 patients from 19 countries (mean age 64 years).[35] The active treatment group received the ACE inhibitor perindopril with or without the diuretic indapamide. Following a mean follow-up period of 3.9 years, active treatment reduced the risk of cognitive decline in the whole population by 12% in the active treatment group. The effect was similar in hypertensive or non-hypertensive subjects. Combination therapy with perindopril and indapamide was more effective than monotherapy with perindopril alone in reducing the risk of dementia due to greater reduction of BP in former.

Study on Cognition and Prognosis in the Elderly (SCOPE)

The SCOPE study evaluated the effect of angiotensin receptor blocker candesartan, with or without diuretic, in 4964 non-demented (MMSE score >24) elderly (mean age 76 years), hypertensive patients. After 3.7 years of follow-up, there was no significant difference between the two groups for cognitive function and dementia.[36]

Hypertension in the Very Elderly Trial-cognitive Function Assessment (HYVET-COG)

The HYVET was designed to assess the risks and benefits of treatment of hypertension in the very elderly patients and included a cognitive assessment, the HYVET-COG.[37] Non-demented ($n = 3336$) patients with hypertension aged >80 years of age were randomly assigned to receive 1.5 mg slow release indapamide, with the option of 2–4 mg perindopril, or placebo. No statistical differences were found between treatment and placebo groups with regard to cognitive decline or dementia.

Do Antihypertensive Agents Vary in their Effect on Dementia?

CCB

A Cochrane review of the clinical efficacy of nimodipine in treating dementia, found benefit associated with nimodipine (90 mg/day at 12 weeks) compared with placebo on cognitive function, and this benefit was similar for AD and VaD.[38] Lipophilic CCBs cross the blood–brain barrier with ease enabling more local effects within the brain. It is hypothesized that DHP-CCBs exert these effects by correcting the cerebral hypoperfusion that can precede clinical symptoms of both AD and VaD. DHP-CCBs also appear to antagonize the ß-amyloid-induced vasoconstriction associated with AD.[39] The aging brain loses its ability to efficiently regulate intracellular calcium levels, leading to cell death[40] and contributing to the development of AD[41] It is hypothesized that DHP-CCBs may alter this disruption.[42]

ACE Inhibitors

Findings from the Syst-Eur, PROGRESS and HYVET trials suggest that ACE inhibitors with and without diuretics seem to reduce cognitive decline, especially in stroke-related dementia. Only lipophilic ACE inhibitors, capable of crossing the blood–brain barrier (e.g., captopril and perindopril) is associated with decreased rates of cognitive impairment and dementia.[43] Other postulated mechanisms to reduce the risk of cognitive decline include modulation of cerebral blood flow, pleiotropic effects on the musculoskeletal system and nervous system, or effects on inflammation and oxygen-free radicals.[44-46] The gradual increase of white matter intensities on MRI, which play a part in pathogenesis of both AD and VaD, is also believed to be modified by ACE inhibitors.[47]

Beta-blockers and Thiazides

A study of patients with cognitive impairment and dementia at baseline found that lipophilic central nervous system ß-blocker use was associated with poorer cognitive scores.[48] Studies have shown that adrenergic signaling plays a role in the retrieval of intermediate-term contextual memories because the hippocampus receives dense input from adrenergic terminals.[49] Theoretically, this process could be affected by the use of ß-blockers with adverse effects on cognition.

Thiazide and loop diuretics reduce potassium concentration in brain, which is associated with increased oxidative stress. Increased inflammation, platelet aggregation, and vasoconstriction, all of which are potential contributors to AD pathogenesis.[50-52] On the other hand, potassium-sparing diuretics do not adversely affect cognition and may, in fact, improve it.[25]

Summary

Midlife hypertension is a significant risk factor for the later development of both AD and VaD. There is less evidence for this connection with late-life hypertension. Accumulating evidence suggests that intensive treatment of high SBP with AH medications may lower the incidence of dementia in individuals at risk, particularly if treated for a long duration. One has to careful to avoid hypotension in elderly which in itself has been shown to be associated with dementia.

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Review Article

Hypertension and Cardiovascular Trends in India

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Abstract

HTN is found to have a high prevalence across various states in our country. Latest data have shown that 25–30% of population from urban areas and 10–20% of those in rural India are hypertensive. According to the 2011 census, there are around 95–100 million adults with HTN in India (of the total of 1.21 billion). Pre-HTN and Stage I HTN constitute a major chunk of the hypertensive population in India. There is a dearth of awareness, as well as very low rates of control and appropriate therapy in India, a fact with a rural preponderance. Lower socioeconomic status, living in rural areas and female gender are determinants of poor control and treatment.

Key words: Cardiovascular trends india, hypertension, hypertension trends

Introduction

Cardiovascular diseases (CVDs) cause most of the death worldwide. Hypertension (HTN) leads to 57% of cerebrovascular accidents and 24% of all coronary artery disease-deaths in India.[1] According to the World Health Organisation, HTN is one of the leading causes of premature deaths around the globe.[2] The prevalence of CVD is increasing in alarming proportion in India and it accounts for 30% of all deaths. Increasing incidence of CV risk factors such as hypertension (HTN), diabetes mellitus, tobacco use, and metabolic syndrome leads to increasing CVD in India.

Apart from tobacco cessation, control of HTN forms the most important of the various treatment strategies to reduce CV mortality. HTN control is poor in developing countries. The Prospective Urban Rural Epidemiology study reported that control of HTN is about 50% in high-income countries and 10% in low- and lower middle-income countries.[3] Studies have reported better control of HTN rates in the past 50 years from Western Europe and the USA.[4] The National Health and Nutrition Examination Surveys from 1988 to 2008 and 1999 to 2012 have reported that the prevalence of HTN remained static at 30–35% during this period, whereas increasing rates of HTN treatment (from 60% to 75%) and its control (from 53% to 69%) were observed.[5] There is a linear relationship between elevation of blood pressure (BP) and CV risk, as the BP rises above 115/75 mmHg.[6] The Global Burden of Diseases (GBD) 2015 analysis reveals that the estimated mortality rate per year associated with systolic BP (SBP) of at least 110–115 mmHg between 1990 and 2015 has risen from 135.6 to 145.2/100,000 persons.[7] Patel *et al*. have estimated that a decrease of 2 mmHg SBP in the population can prevent approximately 150,000 strokes and coronary artery disease (CAD) deaths in our country.[8] However, prospective data on HTN trends with respect to prevalence, awareness, and treatment from our country are scarce.

Prevalence of HTN in India

Several Indian studies over the years have shown increasing prevalence of HTN in both urban and rural areas.[1,9-13] In the mid-1950s, epidemiological studies had employed older World Health Organization diagnostic definitions (SBP ≥ 160 mmHg and/or diastolic BP [DBP] ≥95 mmHg) and reported an urban prevalence of 1.2–4%. The urban prevalence of HTN has been steadily rising from around 3–4% in the early 1960s to 11–15.5% in the mid-1900s. The prevalence in rural areas though low has also shown a significant rise from <1% in the early 1960s to 5–7% in the late 1990s.[11]

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Table 1: Prevalence studies in urban population[14]

Authors	Year	Place	Age group (years)	Sample size (*n*)	Prevalence (%)
Gupta *et al.*	1995	Jaipur	>20	2212	31
Anand *et al.*	2000	Mumbai	30–60	1662	34
Gupta *et al.*	2002	Jaipur	>20	1123	33
Shanthirani *et al.*	2003	Chennai	>20	1262	21
Gupta	2004	Mumbai	>35	88653	48
Prabhakaran	2005	Delhi	20–59	2935	30
Reddy *et al.*	2006	National	20–69	19973	27
Mohan *et al.*	2007	Chennai	>20	2350	20
Yadav *et al.*	2008	Lucknow	>30	1746	32
Gupta *et al.*	2012	National	>35	2616	48
Prince *et al.*	2012	Chennai	>60	1000	60
Joshi *et al.*	2012	National	49 (mean)	15662	46
Gupta *et al.*	2013	National	>20	6106	32
Bhansali	2014	National	>20	14059	26

Table 2: Prevalence studies in rural populations[14]

Authors	Place	Year reported	Age group (years)	Sample size (*n*)	Prevalence (%)
Gupta *et al.*	Rajasthan	1994	>20	3148	17
Kushima	Andhra	2004	>20	1316	21
Hazarika *et al.*	Assam	2004	>30	3180	33
Krishnan *et al.*	Haryana	2008	15–64	2828	9
Todkar *et al.*	Maharashtra	2009	>20	1297	7
Kinra *et al.*	All India	2010	20–69	1983	20
Gupta *et al.*	All India	2012	>35	4624	32
Prince *et al.*	Tamil Nadu	2012	>65	1000	29
Kalar *et al.*	Tamil Nadu	2012	25–64	10463	21
Borah *et al.*	Assam	2012	>30	916	55
Haddad *et al.*	Kerala	2012	18–96	1660	24
Meshram *et al.*	Kerala	2012	>20	4193	40
Bhagyalakshmi *et al.*	Gujarat	2013	15–64	1684	15

Later studies of prevalence employed the JNC-7 diagnostic criteria (known HTN or SBP ≥140 mmHg and/or DBP ≥90 mmHg).[12,13] There have been multiple studies (mostly regional) from urban [Table 1] and rural [Table 2] Indian populations.[14] These studies report varying prevalence rates of HTN, 20%–60% in urban areas and 7.2%–55.6% in rural areas. Among rural areas, Assam has a very high prevalence of HTN in tea plantation workers due to high salt intake, excess alcohol use, and Khaini use.

Anchala *et al.* in a review and meta-analysis reported the prevalence of awareness and control of HTN in urban/rural areas of different regions of India (North, East, South, and West).[12] HTN in India was prevalent in about 29.8% overall and about 33% of urban and 25% of rural population [Table 3].

Table 3: Prevalence of HTN region wise (rural vs. urban)[12]

Rural	Prevalence	Urban	Prevalence
North	16.7	North	33.5
East	33.17	East	33.28
West	18.22	West	34.89
South	28.27	South	33.12
Overall	27.61	Overall	33.81

HTN: Hypertension

Awareness, Treatment, and Control

Only few prospective cross-sectional studies on HTN prevalence, awareness, and control were reported (Jaipur Heart Watch [JHW] study in urban population and National

Table 4: JHW studies – trends in age- and sex-adjusted HTN prevalence and awareness[15]

Number	JHW 1	JHW 2	JHW 3	JHW 4	JHW 5	JHW 6
	2212	1123	458	1127	739	1781
Years of study	1992–94	1999–2001	2003–04	2006–07	2010–11	2012–14
Crude prevalence rate	30.9	36.9	51.3	53.3	34.4	38.9
Age-/sex-adjusted prevalence	29.9	35.3	35.8	39.4	34.4	36
HTN awareness (% of total HTN cases)	13.2	43.8	49.1	44	49.2	56.1
Treatment	9	22	38	34	41	36
Control	2	14	13	18	21	21

HTN: Hypertension, JHW: Jaipur Heart Watch

Capital Region (NCR) study in urban and rural population). The JHW study [Table 4] is the only prospective cross-sectional HTN and other CV risk factor epidemiological studies in India which looked at HTN awareness and treatment over 25 years.[15]

There has been a steady rise in awareness (13% in the 1990s to >56% in the 2010s) of HTN despite the overall prevalence of HTN being varied from 30% to 50% in JHW studies [Table 4]. Even though awareness in urban area has increased to 56%, there is still a great need to increase awareness further to 70–80% as in most developed countries by screening of people for HTN and public education.

There has also been a phenomenal rise in HTN treatment through the years among all participants in the JHW studies. The rates of treatment have risen from 9% in JHW-1 to 36% in JHW-6. HTN control, however, remained low among participants, but there was an overall increase in control rates from 2% in JHW-1 to 21% in JHW-6 over 25 years.

Ambuj *et al.* conducted two representative cross-sectional surveys (Survey-1 from 1991 to 1994 and Survey-2 from 2010 to 2012) in the NCR of India. HTN prevalence was found to have risen from 23% to 42% and 11% to 29% in urban NCR and rural NCR of India, respectively [Table 5].[16]

Overall awareness, treatment, and control rates of HTN between the two surveys, however, remained the same. There was a rise in HTN prevalence with a rise in body mass index (BMI) as well as educational status in both urban and rural areas. Diabetic and pre-diabetic populations had the highest prevalence of HTN. There was a higher prevalence of HTN associated with ethanol consumption. This study has reported the highest increased prevalence of HTN in the youngest age group (35–44 years).

In a recent meta-analysis, Anchala *et al.* reviewed HTN awareness, treatment, and control studies and found that overall awareness was 42% for urban and 25% for rural population. Approximately 35% of urban population were aware of HTN in almost all studies, a fact reflected in the treatment and control rates (37.6% and 20.2%, respectively), while in rural populations, the treatment rate was 25.1% and control rate was 10.7%. The control rates, however, in urban and rural populations have remained low (11.6%–28.7% for urban and 6.5%–15% for rural).[12] Our country has a high prevalence of HTN with low awareness, treatment, and control rates in both urban and rural populations. Poor control can be linked to myriad factors such as female gender, poverty, rural residence, and low educational status as well as obesity.[1]

Table 5: Awareness, Treatment and Control trends in Indian hypertensive patients in two separate surveys (Survey 1: 1991-1994; Survey 2: 2010-2012)[16]

Demographic characteristic	Awareness		Treatment		Control	
	Survey 1%	Survey 2%	Survey 1%	Survey 2%	Survey 1%	Survey 2%
Total	38	39	32	32	14	13
Men	33	27	28	21	13	7
Women	42	51	35	44	16	19
Urban						
Total	49	46	49	40	16	16
Men	44	35	38	29	11	11
Women	53	57	45	50	20	20
Rural						
Total	7	27	7	20	8	8
Men	6	17	5	11	3	3
Women	9	40	9	9	15	15

HTN: Hypertension, NCR: National Capital Region

Trends of CVD in India

The India State-Level Disease Burden Initiative has reported a varied epidemiological transition among the states of India from 1990 to 2016 as part of the GBD, injuries, and risk factors study 2016. The investigators analyzed the prevalence and disability-adjusted life-years (DALYs) due to CVDs and the major component causes in the states of India from 1990 to 2016. They categorized states into four groups based on epidemiological transition level (ETL), which was defined using the ratio of DALYs from communicable diseases to those from non-communicable diseases and injuries combined, with a low ratio denoting high ETL and vice versa [Table 6]. The investigators found that CVDs were

Table 6: Prevalence and DALY rates of cardiovascular diseases as per ETL group[17]

ETL group	Ischemic heart disease		Stroke		Rheumatic heart disease	
	Prevalence (%)	DALYs (%)	Prevalence (%)	DALYs (%)	Prevalence (%)	DALYs (%)
Low (ratio 0.56–0.75)	39	46.7	1.9	44.1	−28.8	−4.3
Bihar Jharkhand Uttar Pradesh Rajasthan Meghalaya Assam Chhattisgarh Madhya Pradesh Odisha						
Lower middle (ratio 0.41–0.55)	39.4	58.5	4.1	61.3	−38	1.2
Arunachal Pradesh Mizoram Nagaland Uttarakhand Gujarat Tripura Sikkim Manipur						
Higher middle (ratio 0.31–0.40)	34.8	57.3	3.5	61.3	−37	3.3
Haryana Delhi Telangana Andhra Pradesh Jammu and Kashmir Karnataka West Bengal Maharashtra Other Union territories						
High (ratio<0.31)	33.6	68.7	−15.9	67.7	−42.6	−1.0
Himachal Pradesh Punjab Tamil Nadu Goa Kerala						
India	33.8	53	0.2	53.6	−33.1	−1.1

DALYs: Disability-adjusted life-years, ETL: Epidemiological transition level

Table 7: Percentage of total deaths and DALYs due to each cause under cardiovascular diseases by sex in India, 2016[17]

Demographic characteristic	Percentage of total deaths (%)		Percentage of total DALYs (%)	
	Men	Women	Men	Women
Total cardiovascular disease	29.2	26.7	15.8	12.2
Ischemic heart disease	19.6	15.6	10.4	6.6
Stroke	6.9	7.3	3.6	3.4
Hypertensive heart disease	1.1	1.6	0.6	0.7
Rheumatic heart disease	0.8	1.5	0.7	1.0
Atrial fibrillation and flutter	0.17	0.25	0.13	0.15

DALYs: Disability-adjusted life-years

responsible for 28% of overall mortality and 14% of DALYs in India in 2016 when compared to 15% and 7% in 1990. Men had a higher mortality burden from CAD, whereas the burden from cerebrovascular accidents was similar between men and women [Table 7]. Dietary risk factors which contributed to around 56%, HTN (54%), air pollutants (30%), dyslipidemia (29%), tobacco (19%), diabetes (17%), and elevated BMI (15%) were the leading CV risk factors in India [Table 8].[17]

In general, from 1990 to 2016, the prevalence rates of high SBP, high total cholesterol, and high fasting blood glucose have increased in India and all ETL state groups while the prevalence of smoking has reduced.

Table 8: Percentage contribution of major risk factors to ischemic heart disease DALYs in India[17]

Risk factor	DALYs	
	Men (%)	Women (%)
Dietary risks	71.5	68.9
High systolic blood pressure	54	54.3
Air pollution	37.5	36.1
High total cholesterol	44.7	43.2
Tobacco	27.2	11.4
High fasting plasma glucose	20.7	18.2
High body mass index	14.5	14.3

DALYs: Disability-adjusted life-years

Conclusion

HTN is prevalent in about 30% of the urban and 25% of the rural populace of India. Only about 25% of the hypertensive population in rural areas are aware and receive therapy for HTN. In contrast, 42% of urban Indian hypertensive patients are aware and 38% receive therapy. However, probably, the point of major concern remains the disturbing fact that a significant minority of the urban (25%) as well as rural (10%) population have their BP at target, which exposes them to the associated morbidities and risk of mortality with uncontrolled HTN. The rising trends of CVD and the high prevalence of existing risk factors such as HTN, high BMI, smoking, as well as the emergence of new risk factors like air pollution, especially in the urban areas, are a sign of an impending epidemiological shift in the landscape of CVDs in India.

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Review Article

Hypertension in Elderly – Pathogenesis and Treatment

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Abstract

Hypertension is the leading cause of cardiovascular events in the elderly and its prevalence increases with age. Elderly patients have altered biological functions which coupled with multiple comorbidities presents a unique therapeutic challenge. Due to contrasting major society guidelines and data from large trials the optimum target blood pressure is less well defined in elderly. This confusion and the resulting dilemma between whom to label as hypertensive or normotensive may lead to delays in treatment. Hypertension in elderly has certain unique clinical situations like isolated systolic hypertension, "dippers", orthostatic hypotension and pseudohypertension. The presence of multiple comorbidities like CAD, CVA, gout, cognitive decline and diabetes, their complications and management only further complicate the therapeutic challenge. The management of hypertension in the elderly has to be individualized based on various factors.

Key words: Hypertension, elderly hypertensive, blood pressure

Introduction

"Old age is like a plane flying through a storm. Once you're aboard, there's nothing you can do."

-Golda Meir

Hypertension (HTN) is a leading risk factor in the aged for cardio/cerebrovascular events, the prevalence of which increases with age. Pathophysiologically, it differs from HTN of the young (altered structure and function of conduit arteries vis-a-vis resistance vessels of the young). Older hypertensives have altered or downregulated biological functions, have multiple comorbidities warranting polypharmacy with attendant drug interactions.

Elevated blood pressure (BP) is the most common cause of mortality over the globe, being responsible for about 13% of all deaths every year, accounting for about 57 million disability-adjusted life years.[1] The prevalence of elevated BP worldwide in 2008 was about 40%, being highest in the WHO African region (46%) and lowest in the Americas (35% in both sexes). The prevalence of uncontrolled HTN has increased by approximately 600 million compared to that in 1980.[2] The burden of HTN is rising globally due to the growth of the obese and aged population and is projected to affect around 70% of the global population by 2025.[3]

HTN continues to be one of the most common easily identified and important risk factors for coronary artery disease (CAD), atrial fibrillation, cerebrovascular disease/accidents, heart failure, peripheral arterial disease, aortic diseases (dissection/aneurysm), and cognitive decline.[4,5] The burden of HTN is maximum in the developing world, where poor BP control has contributed to the growing epidemic of cardiovascular disease (CVD). Elevated BP continues to be responsible for 67% of cerebrovascular accidents (CVA) and 50% of CAD globally.

Definition

HTN is defined as an office BP of 140/90 mmHg or higher. However, epidemiologic data have shown a positive linear relationship between the risk of death due to CAD and CVA with systolic or diastolic BP (DBP) down to values as low as 115 or 75 mmHg, respectively.[6] The dilemma and confusion between defining HTN and normotension in elderly population may delay medication management until there is an irreversible compromise of vascular health by elevated BP values that were previously considered normal.

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As a consequence of this data put together with the outcomes of landmark trials like Systolic Blood Pressure Intervention Trial (SPRINT), the ACC/AHA 2017 guidelines have recommended a cutoff 130/80 mmHg or higher to diagnose HTN. The SPRINT showed a significant benefit of lowering the BP even in patients >75 years of age, concluding that chronological age alone should not be a reason to deny treatment. Healthy people living independently should receive appropriate therapy for HTN. While most of the guidelines have defined elderly population as >60 years, the ESC 2018 guidelines define the elderly as those >65 years.

The ACC/AHA guidelines (2017) define HTN as systolic blood pressure (SBP) ≥130 mmHg and DBP ≥80 mmHg,[7] whereas the ESC 2018 guidelines define HTN as office SBP ≥140 mmHg and/or DBP ≥90 mmHg.[8] The ACC/AHA recommends out-of-office BP measurements to make a diagnosis of HTN and to initiate and titrate BP-lowering therapies (Class I). Table 1 shows the relationship for corresponding values between out-of-office BP and clinic measurements.

Table 1: Corresponding values of SBP/DBP for clinic, HBPM: Home BP monitoring, Daytime, nighttime, and 24 h ABPM (ambulatory BP monitoring) measurements

Clinic	HBPM	Daytime ABPM	Nighttime ABPM	24 h ABPM
120/80	120/80	120/80	100/65	115/75
130/80	130/80	130/80	110/65	125/75
140/90	135/85	135/85	120/70	130/80
160/100	145/90	145/90	140/85	145/90

ABPM indicates ambulatory blood pressure monitoring; BP: Blood pressure, DBP: Diastolic blood pressure, HBPM: Home blood pressure monitoring, SBP: Systolic blood pressure

HTN in the Elderly

HTN tends to be more prevalent with rising age. There is a prevalence of HTN of ~60% in individuals >60 years and ~75% in those >75 years. Elderly populace can be further classified as old elderly (60–79 years) and very old (≥80 years) of age. The elderly HTN differs in pathophysiology when compared to midlife HTN. Between age 50 and 69, DBP is high in 50%. At age 70, only 10% have high DBP.

After 55 years of age, isolated systolic HTN (ISH) defined as an SBP >140 mmHg and DBP <90 mmHg predominates. In developed countries, an increase in SBP is linear with age; while in contrast, DBP rises until about 55 years of age, then falls progressively. Figure 1 illustrates the variation of systolic and diastolic pressures with age and gender.[9] As a consequence of the increased stiffness of the arterial wall in the central aorta and a brisker return of the reflected peripheral pulse wave, the pulse pressure widens leading to a rise in SBP [Figure 2]. ISH may represent an exaggeration of this age-dependent stiffening process, although SBP and pulse pressure do not rise with age in the absence of urbanization. ISH is found to occur with a greater preponderance in females and those with prehypertension and is usually found in conjunction with a greater incidence of heart failure with preserved ejection fraction. The major differences between midlife and systolic HTN are mentioned in Table 2.

In the past two decades, a multitude of controlled trials and observational studies has demonstrated the importance and utility of the pulse pressure as a major risk factor for CVD, which was demonstrated by a study of the Multiple Risk Factor Intervention Trial data. The study found that patients who had an SBP >160 mmHg and a DBP <80 mmHg constituted the highest risk group.[10] In the Framingham Heart Study, a combination of mean arterial pressure (MAP) (a measure of resistance) and pulse pressure (a hitherto mentioned measure

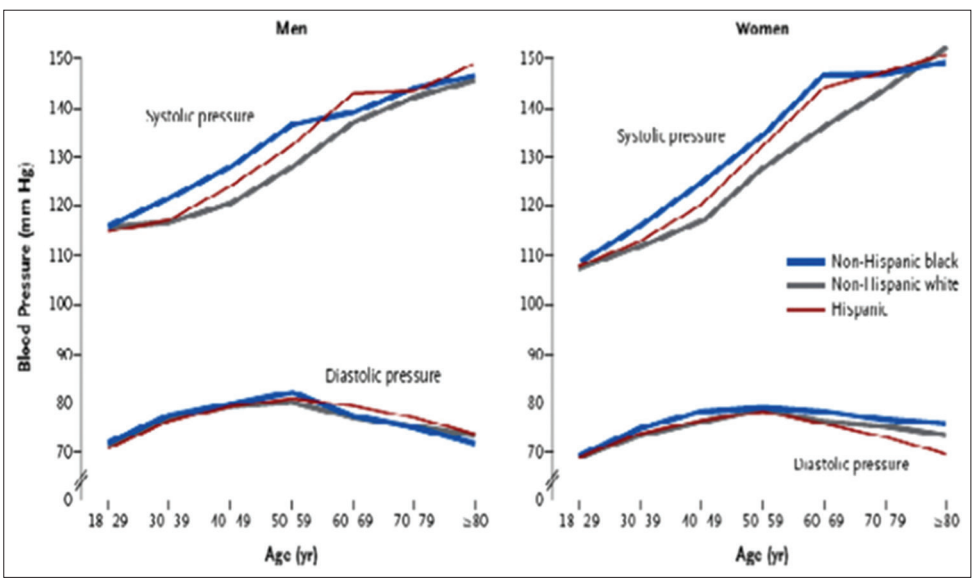

Figure 1: Behavior of systolic and diastolic blood pressure with age and gender[9]

of vascular stiffness) used together yielded a better chance of predicting CVD collectively or CAD, CVA, and heart failure independently, rather than any individual BP component on its own.[11] Combining the pulse pressure with the MAP, the two major physiologic components of hydraulic load could be related to the clinical outcomes.[2] In individuals with ISH and a normal or low DBP (<70 mmHg), there is a body of evidence-backed data to support the existence of a diastolic J-curve of increased cardiovascular risk, this was seen in about one-third of treatment-naive persons of at least 60 years of age in the National Health and Nutrition Examination Survey.[12] Widened pulse pressure and a low DBP were found with a greater prevalence in females, diabetics and those with advanced age.

There is a very real concern of an exaggerated nocturnal "dipping" of BP in elderly patients on antihypertensive therapy, a concern that only gains more mileage from the fact that most BP measurements at clinics are done during the daytime/waking hours. These nocturnal dippers have cerebral hypoperfusion during the dips and have been found to be at a greater risk for CV adverse events.

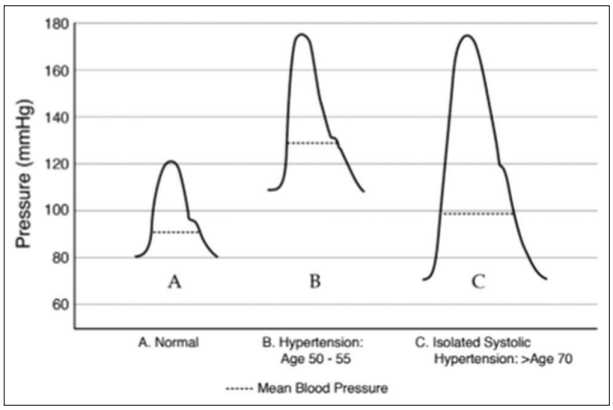

Figure 2: Diagrammatic representation of aortic pulses in normotension (a), midlife hypertension (HTN) (b), and systolic HTN (c)

Table 2: Major clinical differences between midlife and systolic hypertension

Clinical differences	Midlife	Systolic
Age (years)	<55 (midlife)	>55 (older)
Prevalence (%)	30–35	65
BP control	Relatively easy	Relatively difficult
SBP	Elevated	Elevated
DBP	High	Normal or low
PP	Mildly increased	Markedly increased
MBP	High	Slightly increased
Major mechanism	Hormonal	Mechanical
Hemodynamic cause	Increased TPR	Increased aortic stiffness
Sleep apnea	Yes	No
Atherosclerosis	Yes	No
Therapy	ACEI, ARB, CCB, etc.	Future regimens versus arteriosclerosis
SBP treatment target		
JNC 8	130–140 mmHg	150 mmHg
SPRINT	120 mmHg	120 mmHg

ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker, BP: Blood pressure, CCB: Calcium channel blocker, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, PP: Pulse pressure, TPR: Total peripheral resistance

Pathophysiology

With advanced age, there is a fragmentation and degradation of elastin (forms as a nidus for calcification), increase in collagen content, and cross-linking of collagen and elastin by advanced glycation end products which leads to a stiffening of the aorta [Figure 3]. Pulse wave velocity (PWV) indicates vascular age and aortic stiffness (arteriosclerosis). Carotid to femoral PWV >10 m/s correlates with increased pulse pressure and poor outcomes. Brain and kidney are high flow, low resistance organs which are more likely to be affected by SBP. Aortic stiffness is not affected by BP lowering drugs which leads to the therapeutic challenges in the management of HTN in the elderly. There is a variable response to change in posture in the elderly as a consequence of autonomic dysregulation which leads to orthostatic hypotension (risk of falls/CVA) as well as orthostatic HTN, leading to the left ventricular hypertrophy (LVH), and an increased risk of CVA and CAD.[13]

Comorbidities in the Elderly

Gout is 3 times more common in the elderly hypertensives and thiazide diuretics worsen it. Arthritis, common in the elderly, causes a chronic inflammatory burden. Nonsteroidal anti-inflammatory drug use leads to arterial stiffness and a consequent rise in BP. Pseudohypertension is due to non-compressible vessels due to arteriosclerosis.

Treatment

Choice of antihypertensive drugs for elderly patients should take into account that the beneficial clinical trials were based on either a diuretic[14,15] or calcium channel blocker (CCB)[6] as initial therapy. Angiotensin receptor blockers (ARBs) are more effective in stroke prevention compared to beta-blockers (losartan intervention for endpoint trial).[16] Furthermore, the increased potential for bradycardia and exacerbation of obstructive pulmonary disease has to be kept in mind with using a beta-blocker, and hence, beta-blockers are best reserved for used in patients with compelling cardiac indications (e.g., CAD and LV dysfunction). In elderly hypertensive patients, intensive

BP control (SBP <140 mmHg) leads to a decreased rate of major CV adverse events including mortality as evidenced by data from a 2017 meta-analysis of four major trials. There were limited data on adverse events, but an increased risk of renal failure was suggested with intensive therapy. The authors concluded that when an intensive BP lowering regimen is considered a careful balance of CV benefit versus potential risks including that of falls and renal failure is essential.[17]

It is prudent to initiate drug therapy using a single drug in lowest possible dose with uptitration. Issues of polypharmacy, non-adherence, and drug interactions are of concern in average elderly hypertensive patients, most of whom use around six drugs. HTN in the elderly is salt sensitive and is more prone to diuretic-related side effects. The various physiological changes that take place with aging affect the pharmacokinetics of BP lowering drugs [Table 3]. Unrelated to the class of drug used, it is important to monitor the patient carefully for adverse reactions [Table 4] that may affect the quality of life [Figure 4]. The risk of hyponatremia in the elderly is significant and is found to be much more common in women than men matched for age among the elderly [Figure 5].[18]

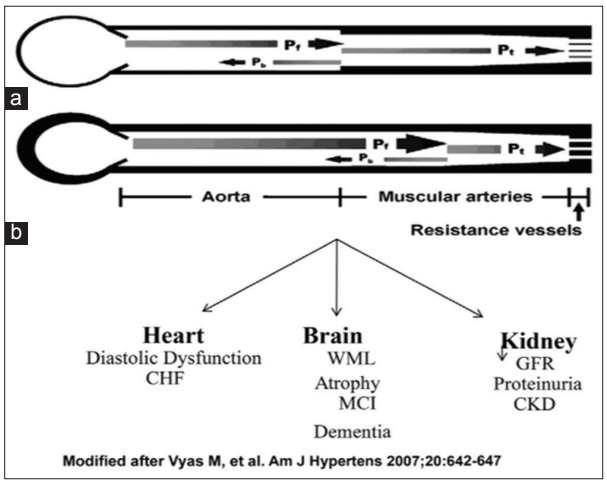

Figure 3: Model showing the effects of impedance matching on the forward (Pf), backward (Pb), and transmitted (Pt) pressure waves. (a) Youthful pattern where aortic stiffness (indicated by thin walls) is less than muscular artery stiffness. (b) The elderly pattern where aortic stiffness (indicated by thicker walls) equals muscular artery stiffness

BP lowering drug therapies reduce rather than eliminate the risks, not to mention the potential adverse drug effects/interactions and high costs of many antihypertensive medications. A multitude of experimental and observational studies has shown that there exists a string relationship between BP and nutrition. Due to these, there has been a recent renewal of interest in non-pharmacological approaches to prevent and treat HTN. The importance of weight loss and dietary sodium restriction in the treatment of HTN in middle-aged patients has been proven in clinical trials. Such non-pharmacological interventions are also central to the management of HTN in older individuals. In the Trial of Nonpharmacologic Interventions in the Elderly, sodium restriction alone as well as in combination with weight reduction was better than in those assigned to usual care in terms of rates of withdrawal of antihypertensive therapy (93% vs. 87%, respectively) and led the authors to conclude that sodium restriction and weight reduction constituted a safe, effective, and feasible non-pharmacological BP lowering therapy in elderly population with HTN.[19]

There is irrefutable proof from many placebo-controlled trials that any antihypertensive regimen reduces CV events in elderly patients with HTN, and this benefit is seen even in frail older individuals where BP lowering is associated with a reduction in mortality risk. In most trials, the mean age of the population was 70–76 years with the exception of the HTN in the Very Elderly Trial (HYVET). In the HYVET trial, all patients were ≥80 years.[20] The SPRINT found that in those >75 years of age, an intensive treatment goal of an SBP <120 mmHg was more

Table 3: Physiologic changes with aging potentially affecting the pharmacokinetics of antihypertensive drugs

Process	Physiological change	Result	Drugs affected
Absorption	↓ Gastric acid production ↓ Gastric emptying time ↓ GI motility, GI blood flow, and absorptive surface	↓ Tablet dissolution and ↓ solubility of basic drugs ↓ Absorption for acidic drugs ↓ Opportunity for drug absorption	
Distribution	↓ Total body mass, ↑ proportion of body fat ↓ Proportion of body water ↓ Plasma albumin, disease-related increased α1 acid glycoprotein, and altered relative tissue perfusion	↑ Vd of highly lipid-soluble drugs ↓ Vd of hydrophilic drugs Changed percent if free drug Vd and measured levels of bound drugs	BB/central α agonists ACEIs Propranolol
Metabolism	↓ Liver mass, liver blood flow, and hepatic metabolic capacity	Accumulation of metabolized drugs	Propranolol Diltiazem Labetalol Verapamil
Excretion	↓Glomerular filtration, renal tubular function, and renal blood flow	Accumulation of cleared drugs	ACEI Atenolol Sotalol Nadolol

ACEI: Angiotensin-converting enzyme inhibitor, GI: Gastrointestinal, Vd: Volume of distribution

effective when compared to those between 50 and 75 years of age.[21] However, many older patients are more likely to be less healthy that those enrolled in HYVET or SPRINT.

The presence of comorbid conditions such as CAD with or without heart failure, past CVA, cognitive dysfunction, and other chronic conditions affects optimal decisions for best outcomes. Treatment of ISH had myriad benefits which included fewer coronary events, strokes, HF events, and deaths. However, the intensity of BP lowering must be weighed against the increased risk of hypotension, which can precipitate falls and ischemic events.[22] Orthostatic hypotension may be asymptomatic until increased medication is given to achieve lower goals. Risk of falls and serious fractures may occur with intensive treatment of more frail elderly.

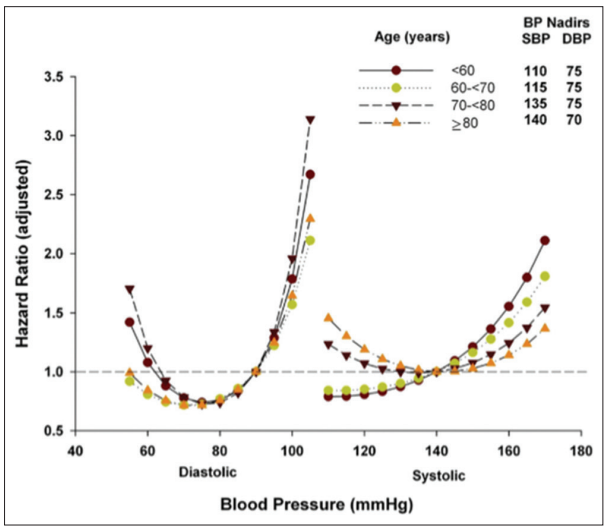

Figure 4: J wave response – aggressive treatment of blood pressure leads to a fall of diastolic blood pressure, leading to compromise of coronary perfusion and affecting outcomes

The 2017 ACC/AHA guidelines have placed renewed emphasis on home and ambulatory BP recordings for clinical decision-making which is in line with the data from IDACO International Database which laid emphasis on home and ambulatory BP recording as routine for elderly individuals, especially to detect masked and white coat HTN as well as to identify extreme dippers.[23]

The guideline recommendation of the ACC/AHA is to an SBP goal of <130 mmHg for non-institutionalized ambulatory adults ≥65 years of age with an average SBP of ≥130 mmHg (Class I).[7] On the contrary, the 2018 ESC guidelines recommend BP lowering with drugs and lifestyle intervention in fit older patients (>65 years but not >80 years) when SBP is in the range of 140–159 mmHg, provided that treatment is well tolerated (Class I). The BP targets for individuals <65 years are recommended to be 120–129 mmHg and in older patients (≥65 years), it is recommended to target a BP range of 130–139 mmHg.[8]

Pseudohypertension

A condition results as a consequence of the failure of densely sclerotic arteries to collapse during BP cuff inflation, leading to false high values, which can be confirmed by intra-arterial BP measurement. It has been reported to have an incidence of 1.75–70% of the elderly. The Osler maneuver has been recommended to identify this condition but with doubtful efficacy.

Orthostatic Hypotension

A reduction in SBP of at least 20 mm Hg or DBP of at least 10 mmHg within 3 min of quiet standing, or, a similar decline

Table 4: Adverse effects of antihypertensive therapy in the elderly

Drug class	Adverse effect
Thiazide and loop diuretics	Hypokalemia, hyponatremia, hypomagnesemia, volume depletion hypotension, renal impairment, hyperuricemia, gout, hyperglycemia
Potassium sparing diuretics	Hyperkalemia, hypotension
Beta-blockers	Sinus bradycardia, fatigue, AV nodal heart block, bronchospasm, intermittent claudication, confusion, aggravation of acute heart failure, hyperglycemia
Alpha-beta adrenergic blockers	Hypotension, hseart block, sinus bradycardia, bronchospasm
Alpha-1 adrenergic antagonists	Orthostatic hypotension
ACEIs	Cough, hyperkalemia (with eGFR <50 ml/min), angioneurotic edema, rash, altered taste sensation, renal impairment
Central-acting drugs	Sedation, constipation, dry mouth
CCB	
Non-dihydropyridines	Rash, exacerbation of GERD, sinus bradycardia, heart block, heart failure, constipation (verapamil), gingival hyperplasia
Dihydropyridines	Peripheral edema, heart failure, tachycardia, aggravation of angina (short-acting agents)
Direct vasodilators	Tachycardia, fluid retention, angina pectoris

AV: Atrioventricular, ACEI: Angiotensin-converting enzyme inhibitor, GERD: Gastroesophageal reflux disease

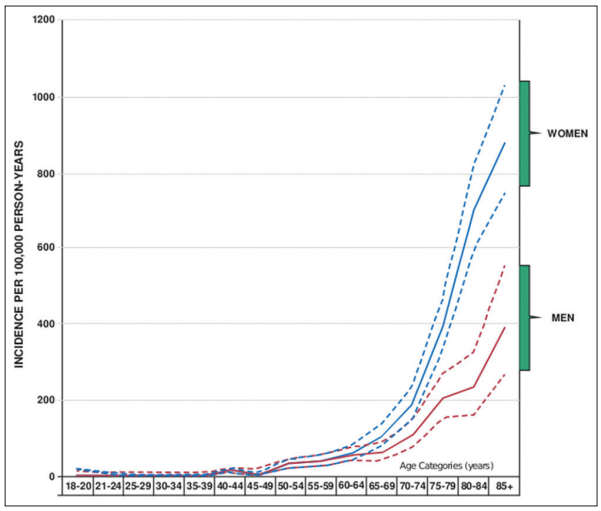

Figure 5: Age-specific incidence of hyponatremia per 100,000 person-years stratified by sex. Means (solid lines) and 95% confidence intervals (dashed lines) are shown. A total of 1033 cases of hyponatremia (serum sodium <130 mmol/L) from the Dutch Integrated Primary Care Information database between 1996 and 2011[18]

Table 5: Effects of intensive BP lowering in elderly individuals[17]

Beneficial effects
~29% reduction in MACE
~33% reduction in CV mortality
~37% reduction in heart failure
Drawbacks
Patients use an increased number of antihypertensive medications
Possible increase in renal failure
Possible increase in serious adverse events
Possible increase in hypotension, syncope, and other adverse events

CV: Cardiovascular

during head-up tilt testing at 60° is defined as orthostatic hypotension. The clinical presentation may be in an asymptomatic individual, where it is detected during a routine physical examination or it may be diagnosed in a patient who presents for the evaluation of giddiness, light-headedness, frequent falls, or syncope. The orthostatic drop in BP may be chronic as in diabetics or in those with pure autonomic failure. The clinical dilemma and therapeutic challenge are to control the BP in such patients with orthostatic hypotension and concomitant supine HTN. The supine hypertensive person is at risk of serious consequences, such as LVH and CVAs. In addition to orthostatic hypotension, the incidence of postprandial hypotension is also very common among elderly population.

CAD

The value of beta-blockers, diuretics, and angiotensin-converting enzyme inhibitors (ACEIs) for HTN with angina in patients with established CAD is strongly supported. The role of the dihydropyridine (DHP) CCBs is less clear, although these drugs can be effective for angina when added to beta-blockers.[25] Verapamil or diltiazem, the non-DHP CCBs, may be effective when beta-blockers cannot be given. ARBs may be helpful in patients who cannot tolerate ACEIs, either due to troublesome dry cough or angioneurotic edema.

Diabetes and HTN

HTN in persons with diabetes needs to be controlled to prevent micro- and macrovascular complications of the same; the predicted goals for such treatment had been <130/80 mmHg for office pressures. However, the results of the ACCORD trial combined with several large prospective surveys support a goal of about 135/85 mmHg for office pressures.[26,27] The value of ACEIs and ARBs may be additive to BP reduction for diabetics for the prevention of renal disease and reduction of microalbuminuria or proteinuria. Some authors have suggested that diabetic hypertensives are relatively resistant to antihypertensive drug treatment,[28] but the data from ACCORD indicate that currently available drugs in combination at appropriate doses can achieve treatment goals well below 140 mmHg systolic pressure.

Stroke/CVAs

Elevated BP *per se* is an important risk factor, leading to stroke/CVAs. Even after the development of stroke, appropriate antihypertensive therapy plays a central role in secondary prophylaxis. A combination of an ACEI and diuretic has been reported to be effective for preventing a second stroke.[29] Intervisit BP variability has been found to contribute to an increased risk of recurrent strokes.

Cognitive Impairment

HTN in the elderly has been associated with an increased risk of dementia and various other forms of cognitive impairment.[30] Cognitive decline has been linked to signs of cerebral microvascular pathology on imaging. Antihypertensive therapy does not appear to significantly increase the likelihood of dementia or cognitive impairment.[31] In the ONTARGET comparing an ACEI with an ARB, there was no difference between the two with regard to rates of cognitive impairment during the study.[32] Among the ACEIs, those that cross the blood–brain barrier (captopril, lisinopril, ramipril, perindopril, fosinopril, and trandolapril) may be more effective in preventing cognitive decline than those that do not.

Conclusion

HTN is a modern-day curse on the chronicle of human history. It is present with an alarming rate of prevalence among elderly

populace and accounts to a considerable rate of morbidity and mortality. Due to the effects of aging on the arterial wall, HTN in the elderly is characterized by an elevated systolic and pulse pressure with low DBP.

Definition of optimal BP goals in the elderly continues to be highly individualized and ultimately rests more on flexible targets based on prudent clinical judgment rather than targets set in stone. The pros and cons of BP lowering in the elderly are summarized in Table 5.

There is an ongoing trial, the ESH-CHL-SHOT (optimal BP and cholesterol targets for preventing recurrent strokes in hypertensives) which may shed some light regarding optimal targets for BP lowering in the elderly.[33]

It is important to keep in mind that in the very elderly population, too much becomes too bad as a low BP leads to a higher mortality, especially in those having multiple drugs as part of their BP lowering armoury. BP lowering therapies in the elderly generally have a favorable risk/benefit ratio with treatment to an SBP <150 mmHg. The SPRINT suggested that even in individuals >75 years, a lower SBP target could provide benefits, however, this trial notably excluded more frail individuals. In elderly individuals, we thus have to balance the benefits of BP lowering with the risks of renal injury, orthostatic HTN, and consequent falls and CVAs. Non-pharmacological therapies such as salt and weight reduction also play a major role in control of BP and may even enable the withdrawal of antihypertensive therapy in this population.

Thus, the management of HTN in the elderly is not a "one size fits all" approach but must rather be individualized based on various factors including but not limited to the age, comorbidities, and frailty of the individual.

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Review Article

Therapeutic Principles in Hypertension Management in Patients with Congestive Heart Failure and Coronary Artery Disease

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Abstract

Systemic hypertension (HTN) is the most common known risk factor for the development of cardiovascular disorders. Epidemiological studies have revealed strong association between elevated arterial blood pressure (BP) and the development of coronary artery disease (CAD), stroke, renal failure, aortic dissection, peripheral arterial disease, and heart failure. There is enough evidence to suggest that lowering BP has a significant impact on mortality and morbidity. Of all cardiovascular disorders, CAD and heart failure contribute to majority of deaths. Management guidelines are well established for heart failure with reduced ejection fraction, but less well established for HTN with preserved systolic function. Prevention, early detection, and control of HTN are of paramount importance. Antihypertensive drugs along with the management of comorbid conditions and adhering to lifestyle measures are considered the backbone of primary and secondary prevention strategies.

Key words: Coronary artery disease, heart failure, hypertension

Introduction

Systemic hypertension (HTN) is the most common identifiable risk factor for the development of cardiovascular diseases (CVD). Epidemiological studies have shown strong association between elevated arterial blood pressure (BP) and the development of coronary artery disease (CAD), stroke cerebrovascular accident, renal failure, aortic dissection, peripheral arterial disease (PAD), and heart failure (HF).[1] There is enough evidence to suggest that lowering BP has a significant impact on morbidity and mortality.[2] Out of all CV disorders, CAD and HF contribute to the majority of deaths. Thus, prevention, early detection, and control of HTN are of paramount importance. HTN is aptly classified as Stage A HF because of their strong association. Treatment of HTN in patients with HF must take into consideration the type of HF that is present: HF with reduced ejection fraction (HFrEF), in which systolic function is impaired; or HF with preserved ejection fraction (HFpEF), in which diastolic function is impaired but systolic function is preserved. Management guidelines are well established for HFrEF, but less certain for HFpEF. HF patients are nearly evenly divided between those with reduced left ventricular (LV) systolic function and those with preserved LV systolic function. Elderly hypertensives are more prone to HF. Any increase in BP above 120 mmHg systolic or 85 mmHg diastolic is associated with increased risk of developing CAD and eliminating this risk factor is a major concern of primary prevention.[3] Long-standing BP elevations promote endothelial injury, resulting in impaired nitric oxide (vasodilator) release and increased release of inflammatory mediators that promote the development of atherosclerosis and vascular occlusion. Uncontrolled HTN is also responsible for the occurrence of acute coronary events in patients with chronic stable angina.

Management of Hypertension in HF

Management of Hypertension in HF is Discussed Under the Following Situations

Management of HTN in patients at risk of HF

Control of both systolic and diastolic HTN reduces the risk of developing HF by 50%. Initial therapy should include a

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combination of an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), and calcium channel blocker (CCB), or diuretic.[4] If the target BP is not achieved, escalate to triple-drug combination comprising ACEI or ARB, CCB, and diuretic. If BP remains above target, add either mineralocorticoid antagonist or a beta-blocker or an alpha-blocker.

Management of hypertension in patients with reduced EF

HFrEF has been well studied, but little is known about the benefits of treating coexisting HTN because BP usually normalizes or decreases as cardiac function declines. BP target is <130/80 mmHg in these patients. The target can be lower than this as long as there is no vital organ hypoperfusion because these drugs have favorable mortality benefits in HF that is independent of their BP-lowering effects. In the very elderly, special care must be taken to avoid orthostatic hypotension. During every out-patient visit, one should seek symptoms and signs of orthostatic hypotension in the elderly. The goals of antihypertensive therapy in the setting of HFrEF are to reduce both preload to diminish congestive symptoms using diuretics and afterload to improve cardiac output using particularly antagonists of the renin–angiotensin–aldosterone system (RAAS). Heightened sympathetic activity is the hallmark of HF, beta-blockers (BB) would counter this. HFrEF should be treated, if BP permits, with ACEI or ARB, BB, diuretics, and aldosterone antagonists. In addition to mortality benefit, many patients will experience considerable improvement in their EF. To maximize clinical improvement, whenever possible, titrate the dose to attain the target doses of these drugs that were used in the clinical trials.

ACEI are considered first-line drugs in the management of hypertension in the presence of HFrEF.[5] Weekly up-titration of doses, if possible, is recommended. Monitoring of renal function, serum potassium, organ perfusion, and BP is mandatory while escalating the dose. Substitute ARBs in patients who are not tolerating ACEI.[6] Combining ACEI and ARB should be avoided as it is fraught with serious adverse events. In PARADIGM-HF trial, the combination of ARB and angiotensin receptor-neprilysin inhibitors (ARNI) proved superior to ACEI therapy for HF. Presently, only limited data is available for the treatment of hypertension with ARNI.

Beta-blockers including carvedilol, metoprolol succinate, bisoprolol, and nebivolol have been shown to improve overall survival in patients with mild to advanced HF.[7-9] Beta-blockers are considered first-line drugs along with ACEI or ARBs due to their favorable effects on survival and disease progression. Administration of BB should be started as soon as possible after the diagnosis of systolic dysfunction and up-titrated to the maximum dose while monitoring hemodynamics.

Mineralocorticoid receptor antagonists prevent myocardial fibrosis and LV remodeling which are attributed to hyperaldosteronism. Antagonizing negative effects of aldosterone can improve the survival of patients. Studies have shown, spironolactone (RALES) and eplerenone (EPHESUS), decrease both systolic and diastolic arterial pressures compared with placebo and can be of additional benefit in the management of HTN not responding to first-line drugs in these HF populations.[10,11] Monitoring of serum potassium and renal function is mandatory, especially when these drugs are combined with ACEI or ARBs or in the presence of renal dysfunction.

Hydralazine/nitrates are useful as add-on therapy when hypertension is not under control despite other drugs or when RAAS inhibitors are contraindicated because of intolerance, hyperkalemia, or renal failure. Although diuretics are the mainstay of therapy for acutely decompensated HF or volume overloaded state, none of the randomized clinical trials have shown mortality benefits in HF in the absence of congestion.

Loop diuretics are preferred in HFrEF and renal failure. Diuretics not only reduce congestion but also reduce BP. In hypertensive patients, diuretics may decrease systolic and diastolic BP (DBP) by as much as 15.8 mmHg and 8.2 mmHg, respectively.

Recent guidelines suggest initiation of therapy with ACEI or ARB, BB, and diuretic. Mineralocorticoid receptor antagonist is added if target BP is not reached. Long-acting dihydropyridine CCBs, amlodipine and felodipine, are useful in ACEI intolerance, renal dysfunction or when BP remains high despite other first-line drugs. CCBs have neutral effect on cardiac events and mortality.

Management of hypertension in patients with HFpEF

The optimal therapy of HFpEF is uncertain. In most of the cases, management of comorbid conditions helps relieve symptoms. HTN and LV hypertrophy (LVH) are frequently present and regression of LVH may improve diastolic dysfunction as well as symptoms. Most of the anti-hypertensive drugs promote regression of LVH with ARBs, ACEI, and CCBs causing more LVH regression than BB or diuretics.[12-14] The same BP threshold and target for drug treatment of HFrEF are applicable to HFpEF. No single agent has been identified as being effective in improving CV outcomes in these patients Table 1.

Summary and Recommendations

1. Hypertension is the most prevalent modifiable risk factor for the development of HF
2. Treatment of hypertension in patients with HF must take into account the type of HF that is present
3. In general, patients with HFrEF should be treated, if possible, with ACEI or ARB, a beta-blocker, and a diuretic
4. A mineralocorticoid receptor antagonist is added if BP is not adequately controlled
5. The optimal therapy of hypertension in patients with HFpEF is uncertain; most antihypertensive agents can reduce LVH and relieve symptoms.

Management of Hypertension in CAD

Long-standing uncontrolled BP accelerates endothelial injury, resulting in impaired vasodilator (e.g., nitric oxide) release and increased release of inflammatory mediators that promote the development of atherosclerosis and vascular occlusion. Oxygen

Table 1: Therapeutic strategies in hypertensive patients with heart failure

Recommendations	Class	Level
In hypertensive patients with heart failure (with reduced or preserved ejection fraction), BP-lowering treatment should be considered if BP is ≥140/90 mmHg	IIa	B
In patients with HFrEF, BP-lowering treatment comprises an ACEI or ARB, a beta-blocker, a diuretic and/or MRA if required	I	A
Dihydropyridine CCBs may be added if BP control is not achieved	IIb	C
In patients with HFpEF, BP treatment threshold, and target values should be the same as for HFrEF	IIa	B
Because no specific drug has proven its superiority in HFpEF, all major agents can be used		
In all patients with LVH It is recommended to treat with an RAAS blocker in combination with a CCB or diuretic Systolic BP should be lowered to a range of 120–130 mmHg	IIa	B

BP: Blood pressure, HFrEF: Heart failure with reduced ejection fraction, ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker, MRA: Mineralocorticoid receptor antagonist, CCB: Calcium channel blocker, HFpEF: Heart failure with preserved ejection fraction, LVH: Left ventricular hypertrophy, RAAS: Renin–angiotensin–aldosterone system

Table 2: Therapeutic strategies in hypertensive patients with CAD

Recommendations	Class	Level
To target SBP to ≤130 mmHg if tolerated, but not <120 mmHg	1	A
In older patients (aged ≥65 years), to target to an SBP range of 130–140 mmHg	1	A
To target DBP to <80 mmHg, but not <70 mmHg	1	C
In hypertensive patients with a history of myocardial infarction, beta-blockers and RAAS blockers are recommended as part of treatment.	1	A
In patients with symptomatic angina, beta-blockers and/or CCBs are recommended	1	A

SBP: Systolic blood pressure, CAD: Coronary artery disease, DBP: Diastolic blood pressure, RAAS: Renin–angiotensin–aldosterone system, CCB: Calcium channel blocker

demand can increase because of increased afterload and LVH in patients with uncontrolled hypertension. Therefore, patients with elevated BP are more likely to develop manifestations of CAD (angina, and myocardial infarction [MI]) and are at higher mortality risk following an event.[15] The INTERHEART study showed that 50% of the population-attributable risk of a MI can be accounted for by the lipids, with hypertension accounting for 25%. There is compelling evidence to show the beneficial effect of lowering of high BP on reducing the risk of MI. A recent meta-analysis of randomized controlled trials of antihypertensive therapy revealed that for every 10 mmHg reduction in systolic BP (SBP), CAD risk was reduced by 17%. Younger subjects with hypertension (i.e., aged <50 years) often have an increased DBP, whereas older subjects usually have increased SBP.[16,17] Accordingly, in younger individuals, DBP is more closely associated with CAD development, whereas SBP is more predictive in those aged 60 years or older. In elderly people, pulse pressure becomes a strong predictor of CAD risk. Importantly, the risk of CAD-related fatal events doubles for every 20 mmHg increase in SBP or 10 mmHg increase in DBP between a BP range of 115/75 and 185/115 mmHg. A target BP of approximately <130/80 mmHg in patients with CAD appears safe and can be recommended, however, achieving a BP <120/80 mmHg is not recommended.

Primary Prevention of CAD in Patients With Hypertension

Effective antihypertensive therapy substantially reduces all CV adverse outcomes. Therefore, sustained BP control is the primary goal. The optimal goal for reducing the risk of CAD development is not known. The current target for BP control is <140/90, though lower target <130/80 mmHg may be considered in high-risk population.

Management of HTN in Established CAD is Discussed Under the FollowHing Situations

Management of hypertension in stable angina

The immediate aim of antihypertensive treatment in patients with symptomatic CAD is preventing acute coronary syndrome (ACS) and death. In addition to BP control, management of concomitant risk factors such as smoking, diabetes, lipid abnormalities, and weight substantially improves outcomes.

A BP goal <140/90 mmHg is currently recommended in patients with stable angina, or, optionally, <130/80 mmHg in selected patients, including those with the previous stroke or transient ischemic attack, CAD, PAD, or abdominal aortic aneurysm. These guidelines are published before the completion of systolic blood pressure intervention trial (SPRINT), but as only about 20% of patients enrolled in SPRINT had clinical or subclinical CVD, it may be premature to extrapolate the SPRINT findings to those with stable angina or the broader ischemic heart disease (IHD) population. As discussed previously, excessive lowering of DBP, in particular, may reduce coronary perfusion, thus increasing myocardial ischemia and coronary events. In the hypertension optimal treatment trial, in which patients were randomly assigned to three different DBP goals (≤90 mmHg, ≤85 mmHg, or ≤80 mmHg), a J-curve relationship was noted between DBP and the cardiac events in the subgroup of 3080 patients with IHD at baseline, whereas no such relationship was observed in the much larger subgroup without IHD at baseline.[18]

BB, including metoprolol succinate and bisoprolol, are generally considered first-line agents in patients with symptomatic CAD and hypertension. These drugs relieve angina as well as control BP.[19,20]

ACEIs are considered first-line therapy in all pts with stable angina and hypertension, unless contraindications exist. In the heart outcomes prevention evaluation trial, treatment with

Table 3: Pharmacologic treatments for hypertension in patients with CAD

Drug/class	Stable angina	Acute coronary syndrome	Heart failure due to CAD
ACEI or ARB	1 (prior MI, LV dysfunction, diabetes, or proteinuric CKD)	1 (prior MI, LV dysfunction, diabetes, proteinuric CKD)	1
Diuretic (chlorthalidone preferred)	1	1 (chlorthalidone preferred)	1
Beta-blocker	1	1 (esmolol IV, metoprolol tartrate or bisoprolol orally)	1 (carvedilol, metoprolol succinate, bisoprolol)
Non-DHP CCB (verapamil, and diltiazem)	2	2 (without LV systolic dysfunction)	contraindicated
DHP CCB	2	2	Uncontrolled BP
Nitrates	1	2 (IV NTG for control of BP)	2
Aldosterone antagonist	2	2	1
Hydralazine/isosorbide dinitrate	-	-	2 (limited data are available in heart failure due to CAD)

1=First-line drug, 2=Second-line drug. CAD: Coronary artery disease, ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker, MI: Myocardial infarction, LV: Left ventricular, CKD: Chronic kidney disease, DHP: Dihydropyridine, CCB: Calcium channel blocker, BP: Blood pressure, IV: Intravenous

ramipril was associated with around 20% risk reduction in the primary outcome (MI, stroke, or death as a result of CV causes) among 80% of patients with baseline CAD. Similarly, in the European Trial on Reduction of Cardiac Events with Perindopril in Stable CAD (EUROPA),[21] the addition of perindopril to the BB therapy significantly reduced the risk of CV events and death, without any greater risk of adverse events, among patients with low-risk stable CAD. ARBs can be used in patients who are intolerant of ACEIs.

When contraindications to the use of BB exist, nondihydropyridine (verapamil and diltiazem) or long acting dihydropyridine (e.g., amlodipine, felodipine, or long-acting nifedipine), CCBs are appropriate alternatives for angina and HTN. Studies of CCBs have similar efficacy to BB on controlling angina and reducing major adverse events, including death. Nevertheless, CCBs generally are recommended as second-line therapy, either as an alternative for patients unable to tolerate a BB or as adjunctive therapy when BP remains elevated or when angina persists despite BB use.

Aldosterone antagonists should be prescribed for post-MI patients and patients with LV dysfunction without significant renal dysfunction (serum creatinine ≥2.5 mg/dl in men and ≥2.0 mg/dl in women) or hyperkalemia (serum potassium ≥5.0 mEq/L).

Management of hypertension in ACS

Hypertension is common in patients with ACS, affecting two-thirds of patients with ST-elevation myocardial infarction (STEMI) and between 70% and 80% of patients with non-STEMI. Uncontrolled BP can precipitate an ACS by triggering plaque rupture. Hypertension management in these patients can be challenging for the following reasons. First, the relationship between BP and outcome is complex, particularly in the first few hours following ACS. Second, BP may be spuriously elevated because of discomfort and restlessness. The initial focus should be on stabilizing the patient condition rather than hypertension. Finally, there are no outcome trials which assessed the impact of BP control in ACS. Incidence of hemorrhagic stroke is a major concern in patients with ACS who receive antiplatelet drugs, anticoagulants, and thrombolytic therapy. However, several studies have also observed that low BP, particularly SBP <90 mmHg is much more strongly associated with risk of death than having HTN or elevated SBP.[22,23]

The goals of therapy in patients with ACS and hypertension are to safely control BP, balance myocardial 2 supply and demand, and prevent acute coronary events, and death.[24] The anti-hypertensive agents with the most compelling evidence for use in patients with hypertension and ACS include IV nitrates and oral administration of beta-blockers, ACEI or ARBs, and aldosterone antagonists. Intravenous BB and ACEI should be avoided. Cardioselective BB should be initiated within 24 h of symptoms onset. The most recent ACC/AHA/ASH guidelines recommend continuing BB therapy for at least 3 years. These agents reduce infarct size and the occurrence of both sudden cardiac death and subsequent re-infarction. However, the maximum benefit is seen in the 1st year.[25]

Long-acting dihydropyridine CCBs have not been studied in AMI. Nevertheless, these agents are frequently used as add-on therapy in patients with an AMI when HTN is not adequately controlled by BBs, ACEIs/ARBs, and diuretics.[26,27] Short-acting nifedipine should be avoided in CAD patients.

An ACEI in combination with beta-blockers is reasonable in most patients with ACS, including any patient with hypertension, as well as in those with normal BP, if the patient has LVEF 40% or less, DM, or CKD. Evidence for the use of ACEI in NSTEMI or UA is largely extrapolated from the studies carried out in the STEMI population. Importantly, ACEI should be used cautiously in the acute phase of an MI, especially in those with low SBP (<120 mmHg) at presentation, in whom critical hypotension or acute kidney injury may be precipitated.

Aldosterone antagonists, which decrease ventricular remodeling and fibrosis, are appropriate in patients with AMI complicated by LV systolic dysfunction or HF (EPHESUS, and RALES). The role of new drug ARNI is not studied in the management of hypertension in ACS Tables 2 and 3.

Summary and Recommendations

1. Recent meta-analyses suggest that all major BP-lowering drug classes have a similar impact in primary prevention of CAD events and stroke and that the critical issue is smooth BP lowering, independent of drug class
2. Lowering of BP is known to benefit patients with CAD but to what extent BP should be lowered is not clear
3. In primary and secondary prevention of CAD in patients with arterial hypertension, BP lowering to at least <140/90 mmHg is critical
4. Care should be taken in lowering BP smoothly because sudden rapid fall is detrimental in patients with significant occlusive CAD
5. Nevertheless, it seems reasonable to recommend the use of an ACEI, usually with a thiazide diuretic, or an ACEI with CCB, as first-line drugs in the primary prevention of CAD in patients with hypertension
6. Treatment choices for the patient with hypertension and established CAD are more straight forward. Beta-blockers are effective in the management of hypertension, angina, and ACS
7. If both BBs and CCBs are required for angina and hypertension control, then a long-acting dihydropyridine along with BBs should be used.

Conclusions

Systemic arterial hypertension is the most prevalent major risk factor contributing to CV disorders such as CAD, HF, stroke, renal failure, PAD, and dissection of aorta. Ever-increasing morbidity and mortality due to CV disorders is unequivocally linked to the rising incidence of HF and CAD. There is abundant evidence to suggest that control of elevated arterial pressures results in a reduction in the incidence of CAD and HF. Antihypertensive therapy, management of comorbid conditions, and lifestyle measures are considered cornerstones of primary and secondary prevention strategies.[28] In primary and secondary prevention of CAD in patients with arterial hypertension, BP lowering to at least 140/90 mmHg is critical. Caution should be exercised while lowering BP as sudden changes in BP may precipitate acute coronary events with attendant morbidity and mortality. Beta-blockers, RAAS inhibitors and diuretics are considered first-line of therapy of hypertension in the presence of CAD and HF. Newer agents such as valsartan/sacubitril, now indicated for HF, may represent potent therapies to reduce the progression from hypertension to HF.

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Case Report

Isolated Unilateral Renal Artery Stenosis in Young Female with Takayasu Arteritis: Case Report

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Abstract

Vasculitis as a cause of renovascular hypertension is not uncommon. However, isolated involvement of the left renal artery without affection of other vascular beds is extremely rare in any vasculitis, including Takayasu arteritis. Here, we present a case of a young girl with resistant hypertension and recurrent flash pulmonary edema secondary to renal artery stenosis (RAS). The cause of the RAS was vasculitis probably Takayasu arteritis. She was managed with immunosuppression with endovascular intervention.

Key words: Secondary hypertension, Takayasu arteritis, renal artery stenosis

Introduction

Secondary hypertension affects a small but significant number of the hypertensive population and, unlike primary hypertension, is a potentially curable condition. About 5–15% of patients with hypertension have a secondary cause.[1] Hypertension in the young population is associated with increase adverse cardiovascular outcomes. Renal artery stenosis (RAS) is one of the most common causes of secondary hypertension. Recurrent flash pulmonary edema is a strong indication for the evaluation of the renovascular cause of hypertension.

Common causes of RAS are atherosclerotic, fibromuscular dysplasia (FMD), or Takayasu arteritis. Among, Takayasu arteritis and FMD are common culprit in a young female.

Here, we present a case of isolated involvement of renal artery in young female of Takayasu arteritis, who presented to us with recurrent flash pulmonary edema. She was managed with stenting of renal artery. Isolated involvement of renal artery in Takayasu arteritis is extremely rare. This is first case report of isolated involvement of Takayasu arteritis in young female to the best of our knowledge.

Case Report

A 21-year-old non-obese, girl with a no family history of hypertension, and no other risk factors for hypertension such as obstructive sleep apnea and obesity, caffiented drugs, or polycystic ovary syndrome was recently diagnosed with hypertension by primary care provider. She was on three antihypertensive drugs including diuretics. She presented to us with sudden onset of Class IV dyspnea. On examination, she was having tachycardia with heart rate of 142 bpm. Spo_2 was 86% on room air and blood pressure (BP) of 176/112 mm Hg. Respiratory system examination revealed tachypnea with bilateral crepitation. Electrocardiography was unremarkable except for sinus tachycardia. On 2D-echo her left ventricle (LV) function was 25% with global LV hypokinesia. She was stabilized with IV diuretics and non-invasive ventilator support. After stabilization, she had another episode of pulmonary edema on 3rd day of hospitalization. In view of young hypertension and recurrent flash pulmonary edema, we suspected renovascular etiology. On blood investigation, her Hb was 12.3, total count 12,300, platelets 3.2 lac, serum creatinine 0.7, serum potassium 4.2, and serum sodium 142. She had high plasma renin activity (>24) and high aldosterone level. Erythrocyte sedimentation rate (ESR) was 112 and C-reactive protein (CRP) was 98. Ultrasonography abdomen showed asymmetrical kidney size. Computerized tomography angiogram revealed diffuse thickening and enhancement of aortic wall and its major branches along with critical narrowing of ostium of left renal artery [Figure 1]. Atherosclerotic RAS is extremely unknown at this age. We put two differential diagnosis, one is unifocal FMD and other is

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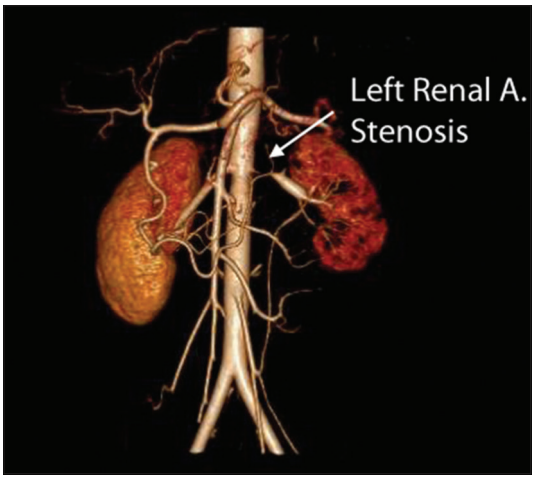

Figure 1: Computed tomography angiogram revealed diffuse thickening and enhancement of aortic wall and its major branches along with critical narrowing of the ostium of left renal artery

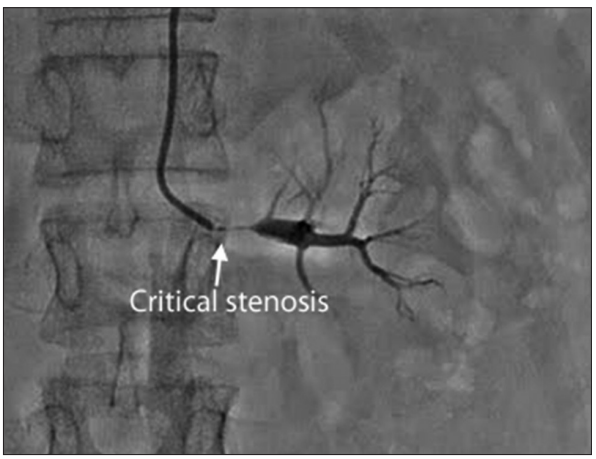

Figure 2: Selective angiography showed critical stenosis of the left renal artery

Takayasu arteritis. High inflammatory marker such as ESR and CRP and diffuse thickening and enhancement of aorta and its major branches on imaging were suggestive of inflammatory vasculitis. Other causes of vasculitis were ruled out. Hence, we put the diagnosis of Takayasu arteritis with isolated RAS. She was put on oral steroid after rheumatological consultation. Marker of inflammation became normal; we took patient for endovascular intervention. Selective angiography showed critical stenosis of left renal artery [Figure 2]. We did stenting for renal stenosis [Figure 3]. Post-procedure patient was stable. Her BP comes within normal range. She improved of her symptoms, and her LV function too improved 2 weeks after intervention. She was discharged from hospital in hemodynamic stable condition. On follow-up examination, after 6 weeks she was asymptomatic with normal BP on single antihypertensive medicine. This is extremely rare presentation of isolated RAS in a case of vasculitis probably Takayasu arteritis.

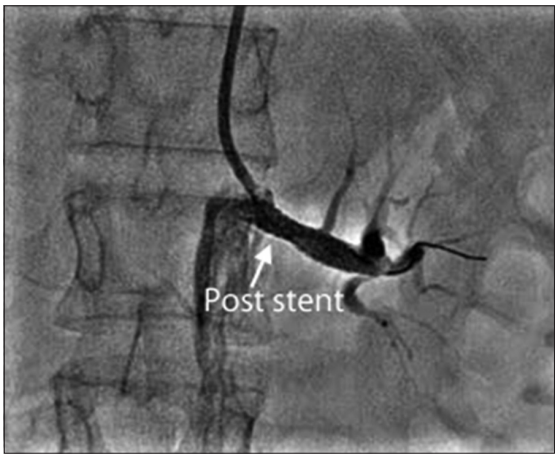

Figure 3: Post-endovascular intervention result in the left renal artery

Discussion

About 5–15% of patients with hypertension have a secondary cause, which may be treatable with a specific intervention.[1] RAS is one of the most important causes of secondary hypertension and affects 1–5% of all hypertensive patients.[2] Atherosclerosis and FMD are the most common etiologies; less frequent causes of RAS are Takayasu arteritis.[3] Diagnosis of Takayasu arteritis can be made in a patient with both suggestive clinical findings (e.g., constitutional symptoms, hypertension, diminished or absent pulses, and/or arterial bruits) and imaging showing narrowing of the aorta and its primary branches. While FMD dysplasia is diagnosed by classical beaded appearance on angiography, there are two subtypes of FMD, unifocal FMD and multifocal FMD.

Although renal involvement in Takayasu arteritis in not rare, isolated involvement of single renal artery without the involvement of other large vessels is extremely rare, here we have presented a case of isolated RAS with recurrent flash pulmonary edema due to vasculitis probable Takayasu arteritis. She was managed with anti-failure treatment, steroid, and endovascular intervention for RAS. She had improved her symptoms and doing well in follow-up.

Although secondary hypertension has number of causes, certain clinical clues help us to suspect renovascular etiology. Young age of onset, drug-resistant hypertension, recurrent flash pulmonary edema, asymmetrical kidney size on ultrasound, and high plasma renin activity, are important clues which help to suspect renovascular cause of hypertension.[4] Diagnosing the cause of secondary hypertension is extremely important as they can be potentially treated.

Conclusion

Renovascular hypertension is one of the very important treatable causes of hypertension. RAS should always be suspected when there are specific clues to that. Renal

artery involvement in Takayasu arteritis is not uncommon; however, isolated involvement of the unilateral renal artery is extremely rare in any vasculitis, including Takayasu arteritis. This case is unique in the sense that isolated left renal artery is critically affected in young woman with vasculitis probable Takayasu arteritis without the involvement of other vascular beds.

Clinical Significance

Secondary causes of hypertension should always be sought in young patient with hypertension. Among all causes of secondary hypertension renovascular hypertension are most common one. Recurrent flash pulmonary edema is strong clue for renovascular hypertension. In our case, young girl with vasculitis (Takayasu arteritis) has very unusual presentation of isolated unilateral RAS without any apparent involvement of other vascular beds. However, imaging evidence of affection of aorta and its major branches was there. High index of suspicion is the key to diagnose renovascular hypertension with vasculitis.

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