

# Scientific Reports in Medicine

## Hypertension Measurement Methods and Differential Diagnosis

### Hypertension and differential diagnosis

Bülent Kaya<sup>1</sup>

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**Abstract:** Hypertension, a prevalent global health concern, significantly contributes to cardiovascular morbidity and mortality. Accurate diagnosis and management are essential to mitigate its complications. This review highlights the importance of various blood pressure (BP) measurement methods, including office BP (OBP), ambulatory BP monitoring (ABPM), and home BP monitoring (HBPM), emphasizing their roles in identifying conditions such as white coat hypertension (WCH) and masked hypertension (MH). ABPM and HBPM are preferred for their superior predictive value for target organ damage and cardiovascular risk compared to OBP. Central aortic BP (cBP) and arterial stiffness, assessed via pulse wave velocity (PWV), provide additional insights into vascular aging and cardiovascular risk. The review also explores subtypes of hypertension, including WCH, MH, nocturnal hypertension, and secondary hypertension, discussing their pathophysiology, clinical implications, and management strategies. Lifestyle modifications, such as dietary changes and exercise, remain pivotal in hypertension management, with the DASH diet and sodium restriction being particularly effective. Pharmacological interventions, including renin-angiotensin-aldosterone system inhibitors and SGLT2 inhibitors, demonstrate efficacy in BP control and cardiovascular risk reduction. Additionally, the impact of comorbid conditions like obstructive sleep apnea (OSA) and the role of antihypertensive therapies during COVID-19 are discussed. Emerging evidence underscores the need for individualized treatment approaches, incorporating advanced diagnostic tools and addressing modifiable risk factors. This comprehensive review aims to enhance understanding of hypertension's complexities, guiding clinicians toward improved diagnostic accuracy and therapeutic outcomes.

**Keywords:** Hypertension, Blood pressure measurement, Central aortic blood pressure

<sup>1</sup> Çukurova University Faculty of Medicine Department of Nephrology, 01330, Sarıçam, Adana, Turkey.  
E-mail: bulentkaya32@gmail.com  
ORCID iD: 0000-0003-4697-4815

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## Introduction

Hypertension, commonly known as high blood pressure (BP), is a significant public health concern that can lead to serious complications if left untreated. Understanding the differential diagnosis is crucial for identifying underlying causes and ensuring appropriate management of the condition. Hypertension is most commonly defined as systolic arterial BP  $\geq 140$  mmHg or diastolic BP  $\geq 90$  mmHg; however, these definitions may vary depending on professional societies and cardiovascular risk profiles (1, 2). Hypertension is also a major risk factor for cardiovascular diseases and mortality (3).

The diagnosis of hypertension can vary depending on the measurement method (4). The 2018 European Hypertension Management Guidelines recommend that the diagnosis of hypertension should not rely solely on office BP (OBP) but also include “out-of-office” measurements, such as ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) (5). This approach provides a more accurate diagnosis, especially in cases of WCH and masked hypertension (MH). This review aims to discuss the clinical conditions that must be considered in the differential diagnosis and management of hypertension.

## A. The Importance of Arterial Blood Pressure Measurement Methods

### 1. Office Blood Pressure Measurement (OBP)

OBP is typically performed as a single measurement in a clinical setting and can be influenced by external factors such as stress and white coat hypertension (WCH). Some guidelines define hypertension as an OBP of  $\geq 140/90$  mmHg, while others set the threshold at  $\geq 130/80$  mmHg (5, 6). OBP is affected by several limitations, including its inability to accurately diagnose WCH and MH, the use of faulty devices, methodological errors, and the lack of standardization in measurement conditions. Due to these and other shortcomings, current guidelines now recommend OBP as a screening method only, while ABPM or HBPM are preferred as diagnostic methods for hypertension (7). Additionally, the

correlation between OBP and target organ damage is weaker compared to other measurement methods (8). This diminished correlation suggests that relying solely on OBP could lead to an incomplete understanding of a patient's cardiovascular health. Consequently, more reliable methods like ABPM or HBPM are advocated to ensure accurate diagnosis and effective management of hypertension.

### 2. Ambulatory Blood Pressure Monitoring (ABPM)

The ABPM is a type of out-of-office BP monitoring, typically assessed using the oscillometric method. Studies have shown that elevated BP measured via ABPM is a stronger predictor of target organ damage and cardiovascular events compared to OBP (9).

In clinical practice, ABPM is used to identify various conditions, including WCH, MH, white coat effect, masked uncontrolled hypertension, nocturnal hypertension, and BP dipping patterns (e.g., dipper, non-dipper, extreme dipper, and reverse dipper) (10). Additionally, ABPM can monitor the effectiveness of antihypertensive drug therapy and evaluate conditions such as orthostatic, postprandial, and drug-induced hypotension, as well as hypotension caused by autonomic dysfunction (10, 11).

The thresholds for elevated BP in ABPM are generally defined as follows:

- Daytime BP  $\geq 135/85$  mmHg
- 24-hour BP  $\geq 130/80$  mmHg
- Nighttime BP  $\geq 120/70$  mmHg (11).

These ABPM thresholds correspond to an OBP of  $\geq 140/90$  mmHg and are consistent with the thresholds recommended in international guidelines (5, 12). While some studies suggest that ABPM may be superior to HBPM in terms of prognostic value, the overall data remain insufficient to definitively conclude whether ABPM or HBPM is superior for assessing cardiovascular risk (13, 14).

### 3. Home Blood Pressure Monitoring

The HBPM involves measurements taken by individuals in their homes. However, as it usually

reflects only a single time point measurement, it may not accurately represent the dynamic variability of BP. On the other hand, the primary advantage of out-of-office BP measurement lies in its ability to perform multiple readings with reduced white coat effects and observer bias, providing a more reliable assessment of true BP (15). The preferred duration for HBPM is 7 days, with measurements taken in the morning and afternoon each day (16). Once BP is controlled, 1–3 days of monitoring is considered sufficient (17). In the literature, HBPM has been reported to predict subclinical target organ damage as effectively as ABPM in untreated hypertensive patients (18). Furthermore, several studies have indicated that HBPM is more closely associated with target organ damage compared to OBP and even ABPM (19, 20).

#### Key Considerations for HBPM

1. The patient's arm should be supported, such as resting on a table.
2. The cuff should be placed directly over the antecubital fossa.
3. The center of the bladder should align with the artery of the upper arm (16).

### B. Central Aortic Blood Pressure Measurement and Arterial Stiffness

Central Aortic BP (cBP) Arterial Stiffness and BP levels change with aging, characterized by a typical increase in systolic BP and pulse pressure (systolic-diastolic BP), while diastolic BP decreases. Aging and hypertension collectively result in progressive structural and functional alterations of the large arteries, involving inflammatory processes and remodeling. In large arteries, such as the aorta, the thinning of elastin fibers combined with the relative increase in collagen content results in changes to arterial wall architecture, leading to vascular stiffness. Inflammatory processes and vascular calcification make these changes and the loss of elasticity and compliance in the arteries even worse (21–23). Endothelial dysfunction is another hallmark of vascular degeneration associated with aging and hypertension (24). Age-associated structural and functional alterations accelerate and intensify in hypertensive patients, resulting in a phenomenon

known as “early vascular aging” in hypertension (25). Reliable techniques are being developed to evaluate vascular aging in clinical practice. Pulse wave velocity (PWV) and cBP, which measure how stiff a large artery is, give a more accurate picture of vascular aging and may be better at predicting cardiovascular risk (26).

In elastic arteries, reflected waves typically reach the central aorta in late systole or predominantly during diastole, minimizing their impact on central aortic systolic BP. However, with reduced elasticity in stiffer arteries, reflected waves move more quickly and arrive in the ascending aorta during early systole. Consequently, central aortic systolic pressure increases, diastolic pressure decreases, and this leads to increased central pulsatility (i.e., higher pulse pressure) and elevated PWV (27).

This rise in left ventricular afterload contributes to left ventricular hypertrophy and diastolic dysfunction. Simultaneously, a reduction in central diastolic pressure can compromise coronary perfusion and predispose to myocardial ischemia (28). Arterial hypertension accelerates these changes earlier in life (29). When the central elastic arteries get stiffer, pressure waves travel outwards. This puts stress on the brain and kidneys' microcirculation, which normally widens the blood vessels. This process can lead to complications like cerebral lacunar infarcts and albuminuria. Moreover, aortic stiffness increases the risk of ischemic and hemorrhagic strokes due to vessel dissection and ruptured intracranial aneurysms. Similarly, kidneys, being high-flow, low-resistance organs, experience increased pressure in the glomerular capillary network, leading to glomerular damage and proteinuria, eventually progressing to kidney failure (30, 31).

**Measuring Vascular Stiffness and cBP:** The PWV is calculated as the distance between two points in the arterial tree divided by the travel time of the pulse wave over that distance (32). The PWV is influenced by the stiffness of the vessels it traverses; stiffer arteries propagate the wave faster. With aging, central arteries stiffen earlier than peripheral

arteries. Carotid-femoral PWV is used to assess central arterial stiffness, while carotid-brachial PWV is utilized for peripheral stiffness evaluation (23). PWV remains the most accurate and valuable index for assessing arterial stiffness. Despite the widespread use of brachial cuff measurements for diagnosing hypertension, cBP more accurately reflects the hemodynamic load on the heart and large arteries. Among individuals with similar brachial pressures, significant variations in central pressure exist. Pharmacological interventions may also exert differential effects.

Most of the time, non-invasive methods are used to measure cBP because invasive cardiac catheterization with specialized catheters to record pressures in the ascending aorta is not practical in clinical practice (31). For example, oscillometric signals that show intra-arterial pressure waveforms have been used in cuff-based techniques to estimate cBP (67, 68). The cBP values that are normalized for age and sex can help doctors evaluate and treat patients.

Interventions for Arterial Stiffness: Exercise, weight loss, low-sodium diets, moderate alcohol consumption, and non-pharmacological strategies such as garlic powder, alpha-linolenic acid, dark chocolate, and fish oil may reduce arterial stiffness (34, 35).

While most antihypertensive therapies effectively lower brachial BP, only certain treatments demonstrate greater efficacy in reducing cBP. For example, beta blockers lack significant effects on cBP compared to renin-angiotensin-aldosterone system inhibitors. However, beta blockers with alpha-blockade activity (e.g., carvedilol) or nitric oxide-releasing properties (e.g., nebivolol) may show beneficial effects, though clinical evidence is inconclusive. Calcium channel blockers (CCBs) and diuretics reduce both brachial and cBP proportionally, showing parallel decreases in systolic and diastolic pressures. Notably, olmesartan/CCB regimens are more effective than olmesartan/diuretic combinations in lowering cBP (36).

Current guidelines for high BP say that people should start with a combination of ACEi/ARBs, CCBs, or thiazides to stop any organ damage caused by high BP(5). About 70% of people with high-normal brachial systolic BP also have cBP levels that are the same as those with stage I hypertension. Also, 30% of men and 10% of women with normal brachial BP also have cBP levels that are the same as those with stage I hypertension. These results suggest that patients with high cBP may not be getting enough treatment if only looking at brachial BP thresholds. More research is needed to see if making clinical decisions based on cBP is good for patients in the long term.

Lastly, sacubitril/valsartan, which was just approved to treat heart failure with low ejection fraction, looks like it could be useful for changing central parameters in people with high BP. It reduces vascular wall stress through diuresis, natriuresis, and increased levels of natriuretic peptides (31). Targeting cardiovascular risk factors, including diabetes, dyslipidemia, and smoking, may delay arterial aging. Statins have also demonstrated improvements in arterial stiffness, further supporting their role in cardiovascular prevention (38).

## C. Types of Hypertension

### 1. White Coat Hypertension (WCH)

WCH, also referred to as isolated office or isolated clinical hypertension, describes a condition where BP is elevated in a clinical or office setting but remains within normal limits (<140/90 mmHg) outside of the office. Its prevalence is estimated to be 10–20%. Although the exact etiology remains unclear, anxiety may play a role. Patients with WCH are at risk of developing sustained hypertension over time. WCH is associated with increased cardiovascular morbidity and mortality compared to normotensive individuals. Lifestyle modifications and periodic BP monitoring are recommended to reduce cardiovascular risk. Routine pharmacological treatment is not necessary. However, treatment may be considered for patients with evidence of target organ damage or very high cardiovascular risk (5).



## 2. Masked Hypertension

MH refers to a condition where OBP measurements are  $<140/90$  mmHg, but elevated BP is detected during home or ABPM. Its prevalence in the general population ranges from 8.5% to 16.6% (39, 40). MH is associated with an increased risk of cardiovascular morbidity and mortality, similar to that observed in patients with sustained hypertension (40).

### Types and Causes of Masked Hypertension:

- **Morning Hypertension:** The most common form of MH, often caused by natural circadian rhythms, evening alcohol consumption, or the use of short-acting antihypertensive medications.

- **Daytime Hypertension:** May result from lifestyle factors such as habitual smoking, mental or physical stress.

- **Nighttime Hypertension:** Commonly associated with high salt intake, kidney disease, obesity, sleep apnea, and autonomic dysfunction (41).

**Management of Masked Hypertension:** Management should focus on aggressively addressing modifiable risk factors associated with MH, such as obesity, diabetes, sleep apnea, smoking, and alcohol consumption. A treatment approach for MH involves using antihypertensive medications to lower out-of-office BP, even in the absence of elevated OBP. Periodic ABPM is recommended during treatment to assess out-of-office BP levels and guide therapy adjustments (40).

## 3. Physiological Causes of Hypertension (Pain and Anxiety)

Anxiety and pain are among the physiological causes of hypertension (42). For instance, some individuals find visiting a doctor to be an anxiety-inducing situation, potentially leading to WCH. Conversely, individuals with MH with WCH might have previously undergone unpleasant experiences, such as undesired medical diagnoses and painful medical procedures in a doctor's office, which could lead to transient anxiety and a concurrent rise in BP (45). Monitoring BP at home or using an automatic device to measure BP while the patient is alone in

the physician's office can help reduce errors that may lead to inaccurate results (42).

In normal physiology, acute pain signals triggered by tissue trauma and hypersensitivity evoke protective responses to minimize risk and promote tissue healing. Acute pain generates increased sympathetic nervous system activity. This process leads to heightened peripheral resistance, heart rate, and stroke volume. Additionally, the response involves activation of the neuroendocrine system, particularly the hypothalamic-pituitary-adrenal axis, as well as further activation of the sympathetic system by the adrenal glands (46). Therefore, painful conditions can elevate BP.

## 4. Labile Hypertension

Even in normotensive individuals, it is normal for BP to vary and fluctuate daily due to numerous factors, such as physical activity, emotions, body position, respiratory cycle, diet, salt intake, alcohol consumption, sleep deprivation, and others. However, there is no clear definition or quantitative criterion distinguishing normal from abnormal lability. Although most physicians are familiar with the term labile hypertension, it is more of a clinical impression than a specific diagnosis. Most cases attribute it to emotional stress, despite the lack of a clear and universally accepted definition. Patients may report being symptomatic or asymptomatic during episodes. Emotional stress-triggered sympathetic nervous system activation may link the etiology to increases in BP. Both genetic and environmental factors may contribute to exaggerated BP responses in patients with labile hypertension. Because the sympathetic nervous system may play a part in labile hypertension, it has been suggested that combined alpha and beta blockers and central alpha agonists be used to treat the condition (47). It remains uncertain whether the variable component of BP impacts cardiovascular outcomes, whether different medications have varying effects on BP variability, and whether reducing BP variability affects cardiovascular outcomes.

## 5. Paroxysmal Hypertension (Pseudopheochromocytoma)

Although the terms paroxysmal hypertension and labile hypertension are sometimes used interchangeably, they are considered distinct concepts due to differences in their clinical presentation and management. Unlike patients with labile hypertension, those with paroxysmal hypertension (pseudopheochromocytoma) typically experience hypertensive episodes that occur without evident emotional distress. Patients often describe these episodes as sudden and abrupt. The attacks typically begin unexpectedly and may last for minutes, hours, or even days. The abrupt increases in BP are accompanied by prominent and distressing physical symptoms such as headaches, palpitations, flushing, weakness, or dyspnea. The episodes often trigger fears of death or stroke; however, such fears usually occur after the onset of physical symptoms, not before. The fear of recurrent symptomatic episodes can lead to restrictions in lifestyle and functionality (48, 49). Biochemical screening for pheochromocytoma is mandatory; however, such a tumor is found in fewer than 2% of patients with paroxysmal hypertension (50). Catecholamine studies are generally normal but may exhibit mild abnormalities during or between paroxysmal episodes, possibly reflecting activation of the sympathetic nervous system (49). The differential diagnosis should include pheochromocytoma, labile hypertension, and panic disorder (47).

For patients with severe increases in BP, intravenous antihypertensives such as labetalol or nitroprusside may be considered. For those without extreme BP elevations, the use of an anxiolytic agent like alprazolam may be considered. The efficacy of any daily antihypertensive regimen in preventing, reducing the severity, or decreasing the frequency of paroxysmal episodes has not been adequately studied. Furthermore, the use of such regimens is limited by the risk of hypotension in patients whose BP returns to normal between paroxysmal episodes (47).

Due to the syndrome's similarity to panic disorder, experts have suggested using antidepressant

medications to prevent attacks. Importantly, most patients report that antidepressants, when used at recommended dosages for treating panic disorder, prevent recurrent paroxysmal conditions. There is no evidence indicating that one class of antidepressants is more effective than another. Additionally, an approach incorporating psychotherapeutic interventions should also be considered (47).

## 6. Nocturnal Hypertension

A 10-20% reduction in systolic BP during the night is considered a physiological dip (dipper). Nocturnal hypertension refers to high BP that occurs during sleep. It is defined as an average nighttime systolic BP of  $\geq 120$  mm Hg and/or an average diastolic BP of  $\geq 70$  mm Hg, as detected by ABPM (51). Nocturnal hypertension increases the risk of cardiovascular events and all-cause mortality, independent of daytime BP (52-54).

Nighttime BP reduction, compared to daytime BP, is categorized into four patterns: extreme dipper ( $>20\%$  reduction), dipper ( $10\text{--}20\%$  reduction), nondipper ( $<10\%$  reduction), and reverse dipper (nighttime BP is higher than daytime BP) (51). Isolated systolic nocturnal hypertension is another type of nocturnal hypertension. This type of hypertension is marked by an average BP of  $\geq 120/70$  mm Hg at night, as measured by ABPM without the use of antihypertensive drugs, while daytime BP does not meet the diagnostic threshold for hypertension (55).

Orthostatic hypotension and supine nocturnal hypertension can happen in some older patients. These conditions are often linked to stiffer arteries, less sensitive baroreflexes, and problems with the autonomic nervous system (56). These patients have autonomic nervous system disorders characterized by systemic vasoconstriction and insufficient compensatory increases in heart rate to maintain BP (56).

The principles of treatment include:

1. Identify and aim to eliminate causal factors, if possible.

2. Implement lifestyle modifications alongside medications and other treatment measures.
3. Use long-acting antihypertensive agents at full doses or combination therapy to control nighttime hypertension.
4. Select an individually effective nighttime BP-lowering treatment strategy.

For example, in patients consuming high-salt diets, salt intake should be strictly restricted. Patients with uncontrolled nighttime hypertension caused by inappropriate use of short- or medium-acting antihypertensive medications should switch to long-acting antihypertensives. Recommendations for other hypertensive patients are also applicable here, such as adopting a healthy diet, quitting smoking, moderating alcohol consumption, engaging in regular physical exercise, controlling weight, improving sleep patterns, and reducing mental stress.

## 7. Pseudohypertension

Pseudohypertension is a condition in which BP measured indirectly using a cuff overestimates the actual intra-arterial BP (57). It is defined as a cuff-measured diastolic BP that is at least 15 mmHg higher than simultaneous intra-arterial BP measurements (58). This condition is observed in elderly patients with calcified and stiff arteries who exhibit very high BP readings but minimal or no target organ damage. In such patients, an excessively high cuff pressure is required to compress the artery, leading to an erroneously elevated BP measurement. In summary, it occurs due to medial sclerosis and/or calcification of the arteries, which significantly diminish the arteries' ability to collapse.

A particularly high BP reading without significant target organ damage is an important clue and can be detected using a simple diagnostic method called the "Osler maneuver." Definitive diagnosis is made by comparing directly measured intra-arterial BP with indirectly measured BP (59, 60). When the cuff is inflated to a level that stops brachial arterial sounds, the Osler maneuver is considered positive as long as the radial artery can still be felt (60). While this

maneuver can serve as a cost-effective screening tool in resource-limited settings, it has low sensitivity and specificity (57). Additionally, calcification of small- and medium-sized arteries in these patients may appear as a "railroad track sign" on X-ray imaging (57).

Elderly hypertensive patients are particularly susceptible to the side effects of antihypertensive medications. Part of this susceptibility may stem from overtreatment due to overestimation of arterial BP caused by pseudohypertension in this age group. This overtreatment can lead to excessive reductions in arterial BP, resulting in inadequate blood flow to various vital organs such as the brain, heart, and kidneys (61).

## 8. Secondary Hypertension

Secondary hypertension refers to arterial hypertension caused by identifiable underlying conditions and affects approximately 5-10% of the general hypertensive population. The reported prevalence of the most common causes of secondary hypertension in hypertensive patients is as follows (58, 62):

- Obstructive sleep apnea (OSA): 5-15%
- Renal parenchymal disease: 1.6-8%
- Renal artery stenosis (RAS): 1-8%
- Primary hyperaldosteronism (PHA): 1.4-10%
- Thyroid diseases: 1-2%
- Cushing's syndrome: 0.5%
- Pheochromocytoma: 0.2-0.5%
- Coarctation of the aorta: <1%

Due to their rarity, secondary forms of hypertension should only be screened in patients with clinical suspicion, as the diagnostic workup can be time-consuming and costly. Finding general clinical clues that suggest secondary hypertension during the initial evaluation of hypertensive patients is one way to diagnose it (58, 62):

- Early-onset hypertension (e.g., before the age of 30) in patients without other risk factors (e.g., family

history, obesity) or elevated BP in prepubescent children

- Resistant hypertension
- Severe hypertension (>180/110 mmHg) or hypertensive emergencies
- Sudden increases in BP in previously stable patients
- Non-dipper or reverse-dipper patterns observed during 24-hour ABPM
- Presence of target organ damage (e.g., left ventricular hypertrophy, hypertensive retinopathy)

**Age:** Young adults (<30 years) without a family history of hypertension or other risk factors should be screened for secondary forms. In older adults with known atherosclerosis, severe hypertension or acute increases in BP may suggest a secondary form (58, 62).

**Body Mass Index (BMI):** Overweight patients with resistant hypertension should be screened for OSA and endocrine causes of hypertension (e.g., Cushing's syndrome, hypothyroidism) (58).

**Blood Pressure Level:** Patients with resistant hypertension despite adequate treatment, severe hypertension at baseline (>180/110 mmHg), or hypertensive emergencies should undergo screening for secondary forms of hypertension (58). Non-dipping during ABPM (i.e., <10% nocturnal reduction in BP compared to daytime values) is associated with secondary forms of hypertension (e.g., OSA, RAS); non-dipper or reverse-dipper patients should therefore be screened (63, 64).

**Prevalence of Atherosclerosis:** Among hypertensive patients with widespread atherosclerosis (e.g., coronary artery disease, peripheral vascular disease, and cerebrovascular disease), approximately 15–30% have significant RAS ( $\geq 50\%$  stenosis) (65).

**Resistant Hypertension:** Resistant hypertension is defined as uncontrolled BP (>140/90 mmHg) despite concurrent use of three classes of antihypertensive medications (e.g., a long-acting CCB, a renin-angiotensin system blocker, and a diuretic) prescribed at their maximum or maximum tolerable

doses. Screening for secondary forms should be conducted in these patients. However, before initiating screening, medication adherence should be confirmed and the white coat effect excluded (66).

Certain situations during antihypertensive treatment can also suggest the presence of secondary hypertension (58, 62):

- Excessive decline in glomerular filtration rate (GFR) with ACE inhibitor treatment (suggestive of RAS, particularly in bilateral cases)
- Hypokalemia with diuretic therapy (suggesting PHA or other endogenous/exogenous mineralocorticoid excess)
- Resistant hypertension
- Fluctuating BP that remains uncontrolled despite treatment

**Drug-Induced Hypertension:** Several medications can cause hypertension associated with treatment resistance. The most well-known are NSAIDs and corticosteroids, potentially due to sodium and fluid retention. Some medicines, like stimulants (like cocaine and amphetamines) and decongestants (like phenylephrine hydrochloride and naphazoline hydrochloride), can raise BP by activating the sympathetic nervous system. Licorice elevates BP by stimulating the mineralocorticoid receptor and inhibiting cortisol metabolism (58, 67). Oral contraceptives (estrogen + progestin) cause hypertension in about 5% of women. Antidepressants (e.g., venlafaxine, monoamine oxidase inhibitors) may increase BP dose-dependently, likely through noradrenergic stimulation. Immunosuppressive agents, especially cyclosporine A, raise BP through sympathetic activation and direct vasoconstriction (68). Lastly, vascular endothelial growth factor inhibitors (e.g., bevacizumab) and tyrosine kinase inhibitors (e.g., sunitinib, sorafenib) can also elevate BP (69).

**Renal Artery Stenosis (RAS):** RAS is a significant cause of secondary hypertension. In younger patients, fibromuscular dysplasia is the most common cause, while in adults, atherosclerosis is



the leading etiology. The prevalence of RAS in the general hypertensive population ranges from 1% to 8%, but it can be as high as 25%–35% in patients with widespread atherosclerosis (70). Hemodynamically significant atherosclerotic RAS (>70%) is found in approximately 10% of resistant hypertension cases in patients over the age of 65 (71). Clinical clues indicating RAS in adult patients include an abdominal bruit, deterioration in renal function with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, severe or sudden worsening of hypertension in smokers or diabetic patients, the presence of widespread atherosclerosis, and recurrent episodes of flash pulmonary edema (5).

**Primary Hyperaldosteronism (PHA):** PHA is a form of endocrine hypertension characterized by low renin, hypokalemia, and metabolic alkalosis resulting from excessive aldosterone production by one or both adrenal glands. The most common etiological causes are bilateral adrenal hyperplasia or aldosterone-producing adenomas. Excessive aldosterone production can lead to sodium retention, hypokalemia, and cardiovascular complications such as heart failure and atrial fibrillation. However, frequent observations also indicate normocalemic hypertension (72, 73).

Which patients should we suspect of having PHA (74)?

1. The patient has a history of hypertension and hypokalemia, which can be either spontaneous or induced by diuretics.
2. Resistant hypertension.
3. Coexisting adrenal incidentaloma with hypertension or hypokalemia.
4. Hypertension associated with sleep apnea.
5. Early-onset hypertension (under 40 years of age) or a history of cerebrovascular events.
6. Persistently elevated BP of  $\geq 150/100$  mmHg on three separate readings on different days.
7. History of hypertension in a first-degree relative diagnosed with PHA

Aldosterone-to-Renin Ratio (ARR)  $> 30$  ng/dL is the most reliable screening test for PHA. Ideally, if hypokalemia is present, it should be corrected with oral potassium supplements before testing. Hypokalemia inhibits aldosterone secretion, potentially leading to a false-negative screening result. Prior to testing, medications such as ACE inhibitors, ARBs, beta blockers, diuretics, direct renin inhibitors, and aldosterone antagonists should be discontinued 2–4 weeks before the test, if possible. Amlodipine and alpha blockers are considered safe for use. Some tests, like the oral sodium loading test, saline infusion test, captopril test, or fludrocortisone suppression test, must be used to confirm biochemically that the PHA level is higher than 30 ng/dL.

The next step after biochemical confirmation of hyperaldosteronism is to perform computed tomography imaging of the adrenal glands. Finally, adrenal venous sampling to determine the lateralization of excessive aldosterone secretion helps guide the decision between surgical and medical treatment (74).

**D. Hypertension and COVID-19:** It is known that angiotensin-converting enzyme-2 (ACE2) expression can be upregulated by ACEI and ARB (75). Since ACE2 facilitates cellular entry of SARS-CoV-2, concerns were raised during the pandemic that treatment with these drugs might increase the risk of severe COVID-19 (5, 75, 76).

In March 2020, the European Society of Cardiology recommended continuing regular antihypertensive treatment with ACEI or ARB, as there was no conclusive evidence that treatment with these agents was harmful during SARS-CoV-2 infection. Subsequent studies have confirmed that ACEI and ARB are not associated with an increased risk of severe COVID-19 progression (77, 78). It can be hypothesized that the long-term use of these medications may also have beneficial effects during COVID-19 through their favorable cardiovascular effects.

**E. Sleep Apnea and Hypertension:** OSA is considered one of the most common causes of secondary hypertension. It is characterized by recurrent obstructive apneas and hypopneas caused by the collapse of the upper airways during sleep. The severity of OSA is classified based on the apnea-hypopnea index (AHI), which represents the number of apneas and hypopneas per hour of sleep: mild (AHI 5-15), moderate (AHI 16-30), and severe (AHI >30).

Most patients with OSA complain of excessive daytime sleepiness, snoring, morning headaches, difficulty concentrating, and irritability. Typical clinical findings include obesity, a thick neck, and macroglossia. Both nighttime (non-dipping) and daytime BP levels are elevated in OSA patients (79).

Proposed mechanisms for increased BP in OSA include elevated sympathetic nerve activity and changes in the renin-angiotensin-aldosterone system resulting from recurrent nighttime hypoxemia (80, 81). Furthermore, hypoxemia is associated with endothelial dysfunction caused by oxidative stress (82). Additionally, studies have shown a reduction in both nighttime and daytime BP following successful treatment with continuous positive airway pressure (CPAP) therapy for OSA (83).

## F. Hypertension Treatment: Dietary Approaches

Effective lifestyle modifications can be sufficient to delay or even prevent the initiation of medication in patients with stage 1 hypertension (5). While lifestyle changes can enhance the efficacy of antihypertensive therapy, medication should not be delayed in hypertensive patients with high cardiovascular risk. Therefore, hypertension management guidelines emphasize lifestyle modifications, such as limiting salt intake, reducing alcohol consumption, increasing vegetable and fruit intake, and adopting a healthy diet (5).

The role of sodium in BP regulation is well-established. To lower high BP and improve cardiovascular outcomes, a daily salt intake of less than 5 grams is recommended (5).

One of the most significant dietary approaches in hypertension management is the Dietary Approaches to Stop Hypertension (DASH) (84). This diet emphasizes the consumption of fruits, vegetables, whole grains, lean proteins, and low-fat dairy products while reducing saturated fats, cholesterol, and sodium. Thus, salt restriction and lifestyle modifications remain effective options in the treatment of hypertensive patients with low cardiovascular risk. These approaches not only help manage BP but also contribute to overall cardiovascular health.

## G. Hypertension and SGLT-2 Inhibitors

Sodium-glucose cotransporter 2 (SGLT2) is a glucose transporter located in the proximal tubules of the nephrons in the kidney. In the kidney, SGLT2 facilitates glucose reabsorption from the tubular filtrate back into the bloodstream (85). SGLT2 inhibitors are a class of drugs that block the function of SGLT2, thereby preventing glucose reabsorption and promoting its excretion through urine (86). Beyond their glucose-lowering effects, SGLT2 inhibitors have been shown to have secondary effects, such as lowering BP independently of blood glucose levels (87, 88).

Therefore, the 2019 European Diabetes Management Guidelines recommend considering the BP-lowering effects of SGLT2 inhibitors during treatment (89). These medications appear advantageous in the treatment of cardiovascular disease, particularly heart failure, regardless of the presence of diabetes (90).

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