Hypertension (High Blood Pressure, HBP) — Classification and Clinical Signs

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With a prevalence of approximately 50 %, arterial hypertension is a very common disease. Blood pressure is a risk factor of secondary diseases such as stroke, CHD and cardiac insufficiency. Social connections as well as a relationship between hypertension, body weight and age are apparent. Many individuals with hypertension are not treated at all or receive insufficient therapy and, in many cases, are not aware they have the disease.

Definition of Hypertension

Hypertension relates to a blood pressure which is higher than the following limits:

- Systolic > 130 mm Hg
- Diastolic > 80 mm Hg

If the patients’ blood pressure is above these levels, they will benefit from blood pressure lowering therapy.

Epidemiology of Hypertension

Widespread hypertension

Approximately one-fourth of the world's population suffers from arterial hypertension, and about a half of them are not aware of the fact that they have this condition.
In more than 50% of the patients who know of their hypertension, the disease is not adjusted at all or only to an insufficient degree.

The prevalence of arterial hypertension increases with age and body weight. The disease affects men more frequently than women; post-menopausal women, however, are commonly affected as well.

Etiology of Hypertension

With regard to the causes of this disease, arterial hypertension must be divided into primary and secondary hypertension.

Primary hypertension

The majority of individuals with hypertension (> 90%) suffer from primary hypertension, which is defined by the fact that it is idiopathic in nature without any secondary causes. This means that the diagnosis is made by the principle of exclusion.

There are some risk factors associated with this form of hypertension that usually occur in individuals over the age of 30. These include, in particular:

- Nutritional factors such as excess weight, alcohol consumption and a diet high in sodium
- Stress factors
- Smoking
- Advanced age
- Lower social status

Secondary hypertension

Secondary hypertension develops because of other diseases, such as sleep apnea syndrome, aortic isthmus stenosis or atherosclerosis. Neurogenic, psychogenic and iatrogenic forms of the disease are also known. The latter includes, among others, ovulation inhibitors and NSAR drugs. Drugs and toxic substances, such as excessive licorice consumption, may also cause secondary hypertension.

Renal hypertension caused by renal parenchymal diseases or renal artery stenosis as
well as endocrine hypertension, i.e., in cases of primary and secondary hyperaldosteronism, pheochromocytoma, Cushing syndrome or thyrotoxicosis, are also among the secondary forms of hypertension.

Another type of arterial hypertension is hypertensive disease of pregnancy. Among the risk factors are increasing maternal age and multi-fetal pregnancies.

Hypertensive disorders of pregnancy include a variety of diseases which can occur in pregnancy, such as:

- Gestational hypertension (Hypertension not associated with proteinuria)
- Pre-eclampsia (Hypertension associated with proteinuria)
- Eclampsia (pre-eclampsia with at least one convulsion episode)

Classification of Hypertension

Hypertension can be divided into several stages. An increase in blood pressure as a result of physical exertion does not count as hypertension.

A disproportional increase in blood pressure with little exertion is referred to as unstable hypertension.

A life-threatening form of arterial hypertension is accompanied by diastolic blood pressure above 120 mmHg that drops less than 10 % overnight and is referred to as malignant hypertension.

The following table will give you an overview of the different stages of hypertension according to the WHO classification:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Systolic pressure in mmHg</th>
<th>Diastolic Pressure in mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt; 120</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>Normal</td>
<td>120 – 129</td>
<td>80 – 84</td>
</tr>
<tr>
<td>Pre-hypertension</td>
<td>130 – 139</td>
<td>85 – 89</td>
</tr>
<tr>
<td>Stage 1: Mild hypertension</td>
<td>140 – 159</td>
<td>90 – 99</td>
</tr>
<tr>
<td>Stage 2: Moderate hypertension</td>
<td>160 – 179</td>
<td>100 – 109</td>
</tr>
<tr>
<td>Stage 3: Severe hypertension</td>
<td>≥ 180</td>
<td>≥ 110</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>≥ 140</td>
<td>&lt; 90</td>
</tr>
</tbody>
</table>

Pathophysiology of Hypertension

Development of hypertension

Arterial hypertension develops due to a disturbance of the regulatory mechanism that usually keeps blood pressure constant. This includes increased peripheral resistance, an increase in cardiac output or a combination of both.

During the progression of the disease, several compensatory mechanisms take place, consistently keeping the blood pressure at an elevated level. In order to maintain cardiac output, cardiac hypertrophy occurs which helps to permanently withstand the increased pressure. The resistant vessels hypertrophy as well. The baroreceptor reflex that usually registers increased blood pressure values is shifted, allowing higher blood pressure values to be considered normal.
The kidneys play a role in this compensatory process as well. Even though renal blood flow and glomerular filtration rate are kept constant for the most part, an increase in sodium excretion (pressure natriuresis) accompanies the increase in blood pressure in order to counteract hypertension. The influences of the release of renin as well as the changes in renal sodium reabsorption, for instance, on pressure natriuresis, are the topic of this discussion.

Clinical Signs of Hypertension

Symptoms of hypertension

Symptoms of arterial hypertension frequently manifest themselves rather late. Typical symptoms include:

- Early morning headache
- Sleep disorders, dizziness
- Nosebleeds
- Ringing in the ears
- Non-specific cardiac symptoms
- Palpitations

In cases of secondary hypertension, symptoms of the individual underlying disease will accompany those of hypertension.

Progression and Special Forms of Hypertension

Special forms of arterial hypertension are isolated office hypertension and isolated ambulatory hypertension.

Isolated office hypertension

Isolated office hypertension, also referred to as "white-coat hypertension", is characterized by measurements \( \geq 130/80 \text{ mm Hg} \) in the physician's office, while measurements were taken at home and during blood pressure monitoring is normal.

Isolated ambulatory hypertension

Isolated ambulatory hypertension is also referred to as masked hypertension. In these cases, blood pressure readings at the office are normal, readings at home or during blood pressure monitoring, however, are elevated \( \geq 130/80 \text{ mm Hg} \). This special form can be linked to factors such as male gender, younger patients as well as smoking, alcohol consumption, and stress. In cases where the individual is already being treated for hypertension, this is referred to as masked uncontrolled hypertension (MUCH).

Diagnosis of Hypertension

Medical history and physical examination

Gathering a patient's medical history is essential—it helps in figuring out possible symptoms and reveals previously measured blood pressure values as well as possible risk factors. It is also necessary to inquire about any medications the patient is or has been
taking as NSAR drugs, ovulation inhibitors and corticosteroids, for instance, may raise blood pressure. Previous illnesses must also be inquired about as well as the patient’s family history.

The patient’s physical examination will include, aside from measuring blood pressure, taking radial and femoral pulse as well as performing an abdominal auscultation as this may be an indication of renal artery stenosis.

Furthermore, it is essential to look for signs of cardiac insufficiency and renal failure. The fundus of the eye should be examined as well.

**Measuring blood pressure**

The focal point of diagnosing arterial hypertension is the non-invasive measurement of blood pressure according to Riva Rocci. Here, it is necessary to make sure that elevated blood pressure must be established by taking at least three readings on two different days. It is also a fact that the first readings are frequently 10 % higher than subsequent readings.

In order to diagnose forms of white-coat hypertension—or to rule this form out—and to establish permanently elevated blood pressure, ambulatory blood pressure monitoring (ABPM) over a period of 24 hours is appropriate. The average daytime measurement should be below 135/85 mm Hg, the average nighttime measurement below 120/70 mmHg. The average 24-hour measurement should be below 130/80 mm Hg.

**Laboratory diagnostics**

**Hb** and **HcT** are the blood parameters that may indicate anemia due to underlying renal disease. Renal function may be tested by measuring creatinine and eGFR levels. **Potassium levels** will provide more information if Conn’s syndrome is suspected. Furthermore, other parameters such as cholesterol, triglycerides, and glucose should be measured in order to determine the risk for atherosclerosis.

In order to evaluate the presence of endocrine hypertension, parameters such as **T3**, **T4**, **TSH**, **aldosterone**, and **renin** may be measured.

Urinalysis may be another test option because microalbuminuria may be an early indicator of renal damage, especially in diabetic patients. Determining glucose levels is necessary to rule out potential diabetes mellitus. Nitrite levels may reveal urinary tract infections, and catecholamine in combination with severely high diastolic blood pressure (> 110 mm Hg) are indicators of pheochromocytoma.

**Instrument-based diagnostics**

Instrument-based diagnostics is primarily used for diagnosing secondary hypertension. This includes ECG screening to rule out left ventricular damage or coronary heart disease. Chest x-rays may be reasonable as well, in order to determine the presence of any dilatation.

Echocardiography is used to determine ventricular circumference and to rule out any impairment of the pump function of the heart. Carotid Doppler sonography, renal sonographies or color duplex sonographies of the renal arteries may also be an option in specific situations.
Therapy of Hypertension

Non-pharmacological measures

Blood pressure lowering therapy may begin with non-pharmacological measures, unless in cases of hypertensive crisis or a hypertensive emergency. This type of therapy includes:

- Weight reduction until a BMI of approximately 25 kg/m² has been achieved.
- Diet low in sodium, with no more than 5-6 g NaCl per day.
- Switching to a Mediterranean diet.
- Adjusting one’s lifestyle to reduce hypertension—smoking, alcohol and coffee intake should be reconsidered.

Medications that may cause hypertension may no longer be taken, either. In addition, dynamic conditioning training to include sports such as swimming, jogging or bicycling should be pursued three to four times per week.

Aside from these general measures, diseases that may cause secondary hypertension must be treated. According to the European Society of Hypertension (ESH), the target blood pressure values in individuals under the age of 60 years (source: JNC 8) are below 130/80 mm Hg, in patients older than that, the target values are below 150/90 mm Hg.

Pharmacological therapy

Pharmacological therapy may begin as monotherapy first. However, if blood pressure values strongly deviate from normal blood pressure values (> 140/80 mm Hg), or in cases of comorbidities, primary combination therapy should be initiated.

First-line medications include:

- Diuretics
- Beta-blockers
- ACE inhibitors
- AT1 receptor blockers
- Long-acting calcium channel blockers

Diuretics

Primary sites of action
**Thiazide Diuretics**

- Excellent first line therapy alone and in combination with other agents
- Generic and therefore inexpensive
- Shown to reduce cardiovascular event, for example, stroke, in patients with hypertension
- Chlorothiazide, Chlorthalidone, HCTZ, Indapamide, Metolazone

**Adverse effects (AEs) of thiazide diuretics**

- Hypokalemia — low blood potassium level — particularly a problem with chlorthalidone (dose-related, may affect the clinical outcome)
- Glucose intolerance = diabetic tendency
- Gout
- Kidney damage

**Antihypertensive drugs: hemodynamic mechanism of BP reduction**
Renin-angiotensin-aldosterone system

The kidney is central to blood pressure control through the juxtaglomerular apparatus. Baroreceptors in the arterial system inform the central nervous system concerning the level of blood pressure. The signals from baroreceptors lead to changes in autonomic nervous system activity. Renin initiates a biochemical sequence that eventually converts angiotensinogen produced in the liver into angiotensin, a strong vasoconstrictor. Angiotensin stimulates the release of aldosterone from the adrenal gland which causes the kidney to retain salt (NaCl) and water. Angiotensin stimulated the release of antidiuretic hormone from the pituitary gland which causes the kidney to retain water.

This system is part of the body’s defense against dehydration and/or blood loss. The idea is to restore blood volume to normal as quickly as possible.

Angiotensin-converting enzyme blockers (ACEI) and angiotensin receptor blockers (ARB)

- Captopril — ACEI
- Enalapril — ACEI
- Lisinopril — ACEI
- Ramipril — ACEI
- Losartan — ARB
- Candesartan — ARB
- Valsartan — ARB

AE’s with ACEI and ARB — 1st line Rx

Aldosterone antagonists: Mechanism of action
- Block aldosterone binding at receptors in kidneys, heart blood vessels, and brain
- Blockade of aldosterone in renal tubule → increased Na⁺Cl⁻ and water excretion and potassium retention

**Aldosterone inhibitors: Spironolactone**

![Diagram showing the effects of aldosterone inhibitors](image)

- **< Retention Na⁺** → < Edema
- **< Retention H₂O**
- **< Excretion K⁺** → < Arrhythmias
- **< Excretion Mg²⁺**
- **Collagen deposition** → Fibrosis
- **Myocardium vessels**

**Beta-blockers**

Beta blockers slow the heart rate and block the sympathetic nerve stimulation to the kidney (< renin release) and the peripheral nerves (< vascular resistance). They are second-line agents for hypertension.

- Propranolol
- Metoprolol
- Atenolol
- Carvedilol
- Bisoprolol
- Labetalol

**Adverse events**

The fluid retention worsening heart failure—more likely to occur during initiation and the first several months; later, the heart failure improves. Other adverse events are daily weights and careful adjustments of diuretics. Hypotension is more likely with carvedilol. The risk of bradycardia and heart block is of 5—10 % as the dose is increased. Fatigue and weakness may resolve with time or reduction in dose. Asthma will worsen or will develop.

**Calcium channel blockers**

Calcium channel blockers are first-line medications in patients with abnormal kidney function. They dilate arterioles (resistance vessels) and thereby decrease vascular resistance.

At the doses used in humans, these agents only dilate arterioles. There is no effect on the
electrical system of the heart (the conduction system). Dilate arterioles and also decrease the rate of passage of electrical impulses in heart muscle. Because of their effect on the electrical activity of the heart, they are often used to control arrhythmias.

Other forms of pharmacological therapy

**Other drugs occasionally used in the treatment of hypertension**

- Minoxidil — very potent blood vessel dilator; also used to grow hair
- Clonidine — blocks sympathetic nerve activity in the brain and leads to less sympathetic nervous system increase in vascular resistance
- Peripheral sympathetic receptor blockers in vascular smooth muscle — alpha blockers

Average number of antihypertensive agents used to achieve target blood pressure

<table>
<thead>
<tr>
<th>Trial</th>
<th>Target BP (mm Hg)</th>
<th>1 of Antihypertensive Agents</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS&lt;sup&gt;1&lt;/sup&gt;</td>
<td>DBP &lt;85</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCD&lt;sup&gt;2&lt;/sup&gt;</td>
<td>DBP &lt;75</td>
<td></td>
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<tr>
<td>MDRD&lt;sup&gt;3&lt;/sup&gt;</td>
<td>MAP ≤92</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOT&lt;sup&gt;4&lt;/sup&gt;</td>
<td>DBP ≤80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AASK&lt;sup&gt;5&lt;/sup&gt;</td>
<td>MAP ≤92</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDNT&lt;sup&gt;6&lt;/sup&gt;</td>
<td>SBP ≤135/DBP ≤85</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALLHAT&lt;sup&gt;7&lt;/sup&gt;</td>
<td>SBP ≤140/DBP ≤90</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7. ALLHAT. JAMA. 2002;288:2998-3007

Possible drug combination

Double combination options consist of, for instance, administering a diuretic in combination with a beta blocker, a long-acting calcium channel blocker, ACE inhibitors or AT1 receptor blockers.

An alternative is the combination of a calcium channel blocker with a beta blocker, ACE inhibitors or AT1 receptor blockers.
Note: Calcium channel blockers of the non-dihydropyridine variety must **not** be administered in combination with beta-blockers as they may promote bradycardia or an atrioventricular block (AV block)!

Depending on the individual comorbidities, the respective medications may either gain or lose significance. **A popular question in exams pertains to the following combinations:** In cases of hypertension combined with cardiac insufficiency, diuretics are an option. ACE inhibitors may also be used in cases of cardiac insufficiency but also with diabetic nephropathy. In cases of existing cardiac insufficiency, beta blockers are indicated as well.

With regard to the use of individual medications, factors such as side effects, individual tolerability, and interactions with other medications the patient is taking have to be considered. Triple combinations are another option as well, should the double combination not have the desired efficacy.

Isolated systolic hypertension may be treated the same way as systolic and diastolic hypertension is treated.

**Complications of Hypertension**
Dangers of hypertension

The problem with arterial hypertension is that, in many cases, it is not diagnosed for a long time and is not treated at all or only to an insufficient degree. In addition, lack of patient compliance caused by the patient not feeling ill may hinder therapy as well. This leads to secondary diseases, frequently affecting the heart, the kidneys, the brain and the eyes or that manifest themselves in the vessels of the lower extremities. These diseases are frequently the result of atherosclerosis in the affected sections of vessels.

Important secondary cardiac diseases, in the context of hypertensive heart disease, are left ventricular hypertrophy and left ventricular insufficiency as well as coronary heart disease. Cardiac hypertrophy occurs in order to withstand the increased pressure. The critical heart weight is at 500 g. If this weight is exceeded, the heart muscle can no longer be supplied sufficiently, finally resulting in left ventricular insufficiency.

As a result of atherosclerotic changes in the coronary blood vessels, the coronary reserve is impaired to the point that in individuals with hypertension, the increase in cardiac output on effort may not be sufficiently ensured. Therefore, this may more frequently result in angina pectoris, myocardial infarction or sudden cardiac arrest.

Hypertensive nephropathy is accompanied by damage to the kidneys, which may lead to microalbuminuria associated with endothelial damage, similar to what happens with diabetic patients. Years of arterial hypertension may lead to pronounced
nephrosclerosis with terminal kidney failure.

Arterial hypertension may result in transient ischemic attacks (TIAs) as well as cerebral infarction, hypertensive hemorrhaging or acute hypertensive encephalopathy. The risk of suffering a stroke can significantly be lowered with antihypertensive therapy.

**Hypertensive retinopathy** is usually the result of broadening atherosclerosis in the vessels of the retina. Vascular diseases caused by hypertension include peripheral arterial disease, abdominal aortic aneurysm as well as aortic dissection.

Prevention of Hypertension

Preventative approaches include the elimination of risk factors or their reduction.

Review Questions

The answers are below the references.

1. How is isolated systolic hypertension treated?
   A. Not at all.
   B. It is treated the same way as systolic and diastolic hypertension is treated.
   C. With beta blockers only.
   D. With ACE inhibitors only.
   E. With diuretics only.

2. What is not among the antihypertensive first-line medications?
   A. Beta-blockers
   B. ACE inhibitors
   C. α-1 receptor blockers
   D. AT1 receptor blockers
   E. Diuretics

3. Which of the following laboratory parameters must be determined first when diagnosing hypertension?
   A. GOT
   B. CRP
   C. TSH
   D. ESR
   E. GPT

References


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**Correct answers:** 1B, 2C, 3C

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