

Министерство здравоохранения республики Беларусь
Учреждение образования
«Гомельский государственный медицинский университет»

Кафедра патологической физиологии
Обсуждено на заседании кафедры
Протокол №7 от 30.08.2017

МЕТОДИЧЕСКАЯ РАЗРАБОТКА
Для проведения занятия со студентами
3 курса ФПСЗС, обучающихся на английском языке
по патологической физиологии

Тема: Расстройства кровообращения, связанные с нарушением функции сосудов

Theme: Circulatory disorders with vessels dysfunction

Время 3 ак. часа

1.Actuality of the theme. The disorders of the vascular tone arise for action of the various factors of the external and internal environment. It is distinguished two main groups of such disorders: arterial hypertension and arterial hypotension. Hypertensive disease as one example of arterial hypertension is the important problem of modern medicine. It is necessary to take into account that fact, that in 50 % of the men and in 75 % of the women, which suffer by hypertension the decrease of duration of life for 10 years is revealed fast progress atherosclerosis, symptom of heart ischemic disease. At the sometime many physicians frequently has deal with the patients in which the parameters of arterial pressure are sharply reduced (shock, collapse). The number of such patients in 4 times exceeds frequency of heart-vessels and malignant diseases, and in connection with acceleration of scientific and technical progress the tendency to growth of this kind pathology is observed.

Learning goals of the lesson: to study etiology and pathogenesis of vascular insufficiency.

Educational goals of the lesson: formation of scientific outlook and theoretical basis of future specialists on the basis of fundamental knowledge and the latest achievements of pathological physiology.

Objectives of the lesson:

1. To know definition, classifications, etiology and pathogenesis of hypertension.
2. Characterize forms and stages of hypertension development.
3. To know the causes, mechanisms of development of atherosclerosis and to be able to explain relationship of hypertension and atherosclerosis.
4. To study main pathology of cerebral circulation.

To repeat the following questions from related disciplines to ensure absolute mastery of the material:

1. Histological structure of vessels wall (histology, cytology, embryology disciplines).
2. Regulation of vascular tone and blood pressure (normal physiology discipline).

Control questions of the lesson:

1. Hypertension, definition. Principles of classification.
2. Primary (essential) hypertension: factors of stabilization of increased arterial pressure.
3. Secondary ("symptomatic") hypertension: types, causes and mechanisms of development.
4. Hemodynamics in various types of hypertension. Complications and consequences of hypertension. Principles of hypertension therapy.
5. Experimental models of hypertension.
6. Arterial hypotension: types, causes and mechanisms of development.
7. Atherosclerosis: causes, mechanisms of development, role in pathology of cardiovascular system. Interrelation of hypertension and atherosclerosis.
8. Pathology of cerebral circulation: general etiology and pathogenesis. Main forms of disorders, compensation mechanisms. Principles of therapy.

Calculation of study time

Total study time 3 ac.hours

№ п/п	Contents	Calculation of study time
1.	Introduction. Motivational characteristic of the theme	3 minutes
2.	Written control of students on the topic of the lesson	15 minutes
3.	Interviews with students about the topic of the lesson	60 minutes
4.	Self-managed student work	15 minutes
5.	Summing up the results of the lesson	5 minutes
6.	Decision of situational tasks	20 minutes
7.	Task for the next lesson	2 minutes

Additional material:

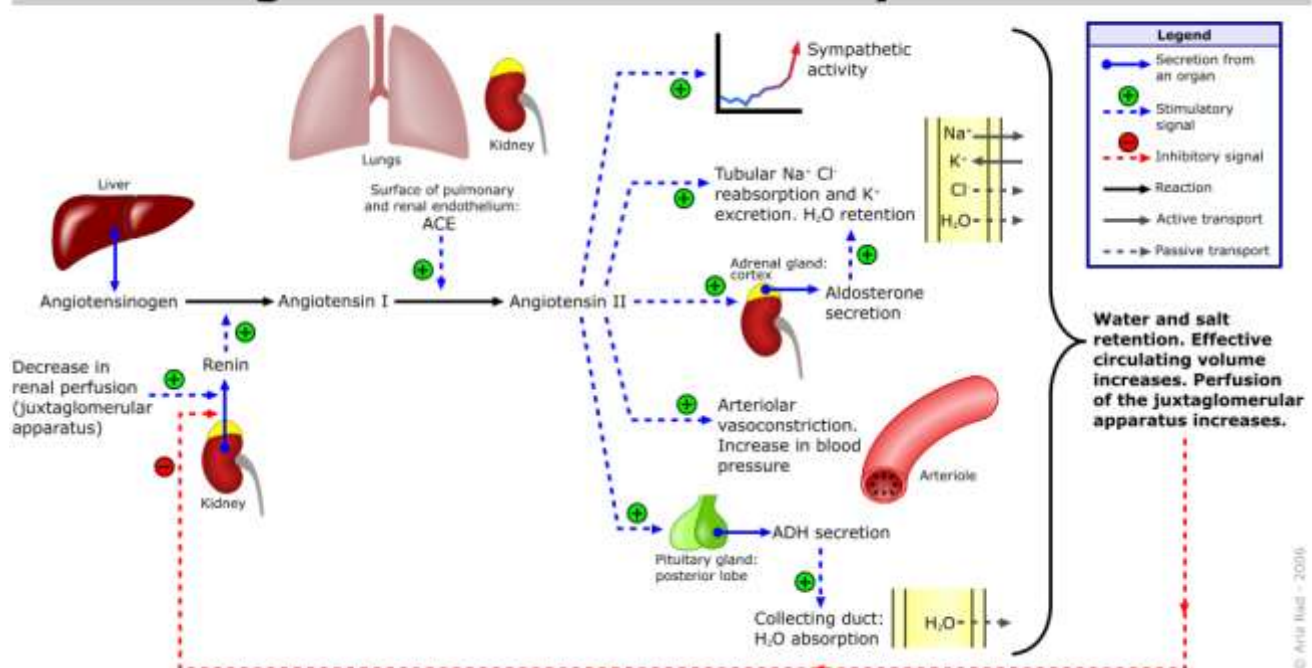
ARTERIAL HYPERTENSION

Regulation of blood pressure

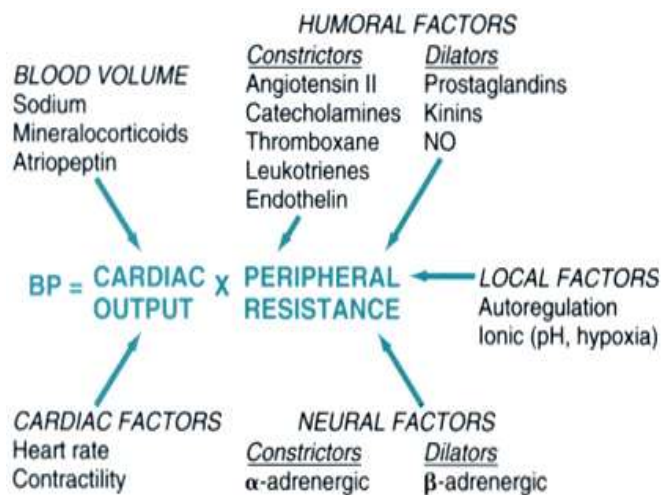
BP is the force exerted by the blood against the walls of the blood vessel. It must be adequate to maintain tissue perfusion during activity and rest. BP regulated by changes in cardiac output, total circulatory blood volume and total peripheral vascular resistance and elasticity of vessels. Provide by nervous, humoral, local regulation:

- Sympathetic nervous system (SNS) activation increases heart rate (HR) and cardiac contractility, produces widespread vasoconstriction in the peripheral arterioles, and promotes the release of renin from the kidneys.
- Baroreceptors, located in the carotid artery and the arch of the aorta, sense changes in BP. When BP is increased, these receptors send inhibitory impulses to the sympathetic vasomotor center in the brainstem resulting in decreased HR, decreased force of contraction, and vasodilation in peripheral arterioles.
- A decrease in BP leads to activation of the SNS resulting in constriction of the peripheral arterioles, increased HR, and increased contractility of the heart.
- In the presence of long-standing hypertension, the baroreceptors become adjusted to elevated levels of BP and recognize this level as “normal.”
- Norepinephrine (NE), released from SNS nerve endings, activates receptors located in the sinoatrial node, myocardium, and vascular smooth muscle.
- Vascular endothelium produces vasoactive substances and growth factors.
 - Nitric oxide, an endothelium-derived relaxing factor (EDRF), helps maintain low arterial tone at rest, inhibits growth of the smooth muscle layer, and inhibits platelet aggregation.
 - Endothelin (ET), produced by the endothelial cells, is an extremely potent vasoconstrictor.
- Kidneys contribute to BP regulation by controlling sodium excretion and extracellular fluid (ECF) volume.
 - Sodium retention results in water retention, which causes an increased ECF volume. This increases the venous return to the heart, increasing the stroke volume, which elevates the BP through an increase in CO.

Renin-angiotensin-aldosterone system



- Endocrine system:
 - The adrenal medulla releases epinephrine in response to SNS stimulation. Epinephrine activates β -adrenergic receptors causing vasodilation. In peripheral arterioles with only α -adrenergic receptors (skin and kidneys), epinephrine causes vasoconstriction.



- The adrenal cortex is stimulated by angiotensin II to release aldosterone. Aldosterone stimulates the kidneys to retain sodium and water. This increases BP by increasing CO.
- ADH is released from the posterior pituitary gland in response to an increased blood sodium and osmolarity level. ADH increases the ECF volume by promoting the reabsorption of water in the distal and collecting tubules of the kidneys resulting in an increase in blood volume and BP

Table 1 Classification of blood pressure levels of the British Hypertension Society 2003 year

Category	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Blood Pressure		
Optimal	<120	<80
Normal	<130	<85
High normal	130-139	85-89
Hypertension		
Grade 1 (mild)	140-159	90-99
Grade 2 (moderate)	160-179	100-109
Grade 3 (severe)	≥ 180	≥ 110
Isolated systolic hypertension		
Grade 1	140-159	<90
Grade 2	≥ 160	<90

By heart minute volume:

- hyperkinetic
- eukinetic
- hypokinetic

By the change in total peripheral resistance (TPR):

- with a high TPR
- with normal TPR
- with reduced TPR

By the blood circulating volume (BCV):

- hypervolemic
- normovolemic

According to the type of elevating BP:

- systolic
- diastolic
- mixed

On the content of renin in the blood and its effects:

- hyperrenin
- normorenin
- hyporenin

By the clinical course:

- benign
- malignant

By origin:

- Primary (essential) hypertension
- Secondary (symptomatic) hypertension

Etiology of hypertension

Primary (essential or idiopathic) hypertension: elevated BP without an identified cause; accounts for 90% to 95% of all cases of hypertension.

Secondary hypertension: elevated BP with a specific cause; accounts for 5% to 10% of hypertension in adults.

PRIMARY ARTERIAL HYPERTENSION

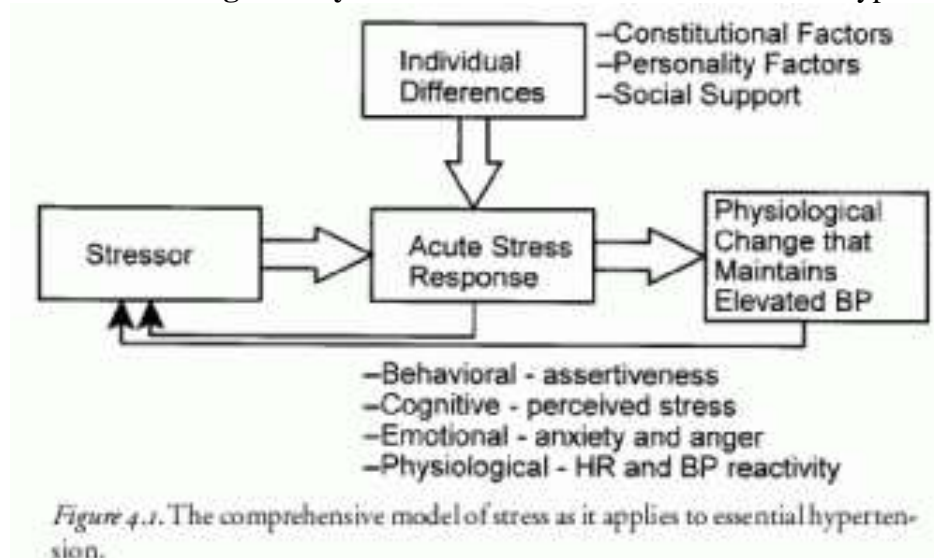
Pathophysiology of primary hypertension

- The hemodynamic features of hypertension is persistently increased systemic vascular resistance.
- Water and sodium retention: A high-sodium intake may activate a number of pressor mechanisms and cause water retention.
- Altered renin-angiotensin mechanism: High plasma renin activity (PRA) results in the increased conversion of angiotensinogen to angiotensin I causing arteriolar constriction, vascular hypertrophy, and aldosterone secretion.
- Stress and increased SNS activity: Arterial pressure is influenced by factors such as anger, fear, and pain. Physiologic responses to stress, which are normally protective, may persist to a pathologic degree, resulting in prolonged increase in SNS activity. Increased SNS stimulation produces increased vasoconstriction, increased HR, and increased renin release.
- Insulin resistance and hyperinsulinemia: Abnormalities of glucose, insulin, and lipoprotein metabolism are common in primary hypertension. High insulin concentration in the blood stimulates SNS activity and impairs nitric oxide-mediated vasodilation. Additional pressor effects of insulin include vascular hypertrophy and increased renal sodium reabsorption.
- Endothelial cell dysfunction: Some hypertensive people have a reduced vasodilator response to nitric oxide. Endothelin produces pronounced and prolonged vasoconstriction.

Theories of cause essential hypertension:

1. **Gull and Sutton**, was that the arteriolar injury was primary, and that this raised the vascular resistance, leading to strain on the heart (cardiac hypertrophy) and kidneys. This hypothesis was later adapted by Folkow, who argued that systemic vascular changes resulting in a reduction in the luminal diameter of small vessels could be a primary cause of the elevation in peripheral vascular resistance that is characteristic of most cases of essential hypertension.
2. **Sir George Johnson**, was that the kidney was the culprit, and that intrarenal disease slowed blood flow and raised systemic pressures that led to secondary vascular and cardiac involvement. This hypothesis was fuelled by earlier observations made by Bright and others that hypertension not only accompanied chronic renal disease but was also one of its earliest manifestations.
3. **Mahomed** from Guy's Hospital, who had suggested that hypertension was caused by a 'blood poison', such as lead or uric acid, and that this led to a rise in blood pressure that then had secondary effects on the kidney, blood vessels and heart.
4. The hypothesis of **Platt** that there was a single gene locus was quickly dispelled by the concept that there was probably the cumulative effect of multiple genes ('polygenic').
5. **Pickering** to suggest that hypertension might simply reflect the right end of a normal Gaussian curve for blood pressure in the population, and thus might not be a true 'disease'.
6. **Guyton's theory** makes a case for the renal origin of all hypertension. Guyton thought that this was due to salt overload when renal dysfunction limited salt excretion. The authors further proposed that both salt-resistant and salt-sensitive hypertension were renal dependent, but that they resulted in different types of pressure natriuresis curves. Salt-resistant hypertension would result in a parallel shift in the pressure natriuresis curve such that sodium handling would be similar to that observed in normal individuals except that it occurs at a higher baseline blood pressure; in contrast, salt-sensitive hypertension would be associated with an exaggerated increase or decrease in blood pressure with an increased or decreased intake in sodium, respectively.
7. **Dickinson** theory of cerebral ischemia: increased cerebrovascular resistance might come first and actually cause hypertension. Each 35 - 45 mmHg elevation of intracranial pressure consistently produced corresponding blood pressure elevations going from about 90 to about 130 mmHg some 20 s later

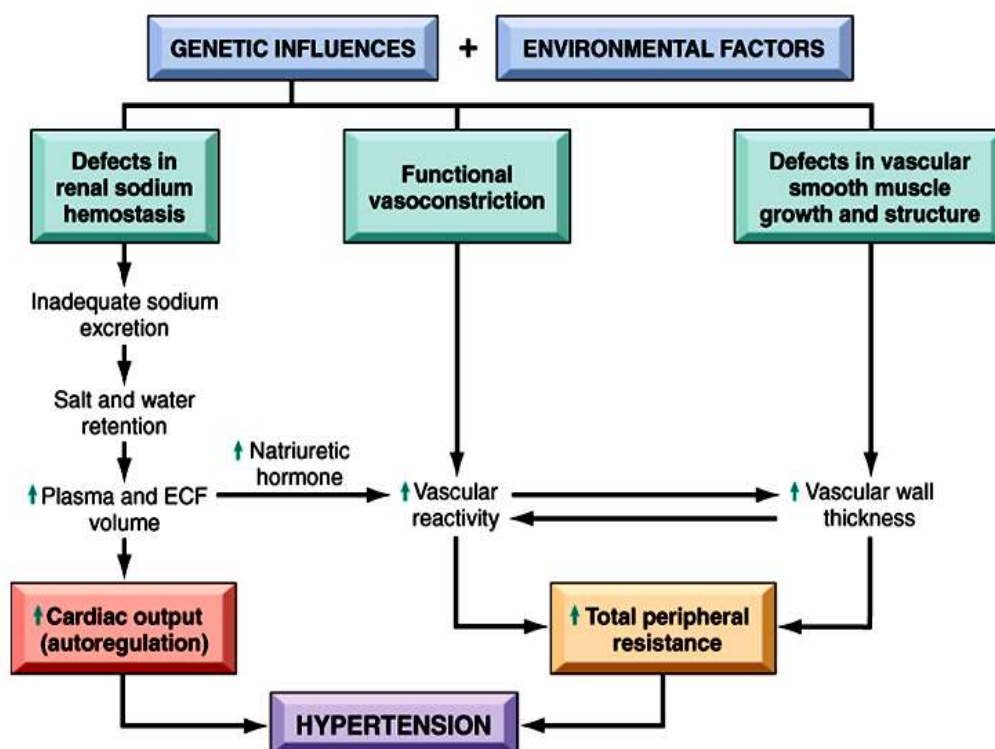
8. **The James-Lange theory:** relation between stress and essential hypertension



9. Theory **Y.V. Postnov S.N. Orlov**. The reason for the development of essential hypertension is a pathology of cell membranes. Acceleration of the $\text{Na}^+ - \text{H}^+$ exchange in the cytoplasmic membrane leads to increased Na^+ flow in cells and excretion of H^+ out of the cell, and alkalization of the intracellular medium. Simultaneously impaired outflow of Na^+ out of the cell as a result of excessive secretion of and mineralocorticoid natriuretic factor.

10. Neurogenic theory **Lange and Myasnicov**: decreasing inhibitory influence of cortex on subcortical structures \rightarrow focus of static excitation \rightarrow \uparrow tone SNA \rightarrow generalized arteriolar spasm \rightarrow \uparrow BP

11. Modern mosaics (multifactorial) theory **Paget** one etiological factor does not cause essential hypertension, sum of factors influences leading to the activation of SAS, RAAS.



Stages of hypertension

1. transitory
2. stable
3. organ changes

Clinical manifestations of hypertension

- Often called the "silent killer" because it is frequently asymptomatic until it becomes severe and target organ disease occurs.
- Target organ diseases occur in the heart (hypertensive heart disease),

brain(cerebrovascular disease), peripheral vasculature (peripheral vascular disease), kidney (nephrosclerosis), and eyes (retinal damage).

- Hypertension is a major risk factor for coronary artery disease (CAD).
- Sustained high BP increases the cardiac workload and produces left ventricular hypertrophy (LVH). Progressive LVH, especially in association with CAD, is associated with the development of heart failure.

- Hypertension is a major risk factor for cerebral atherosclerosis and stroke.
- Hypertension speeds up the process of atherosclerosis in the peripheral bloodvessels, leading to the development of peripheral vascular disease, aorticaneurysm, and aortic dissection.
- Intermittent claudication (ischemic muscle pain precipitated by activity andrelieved with rest) is a classic symptom of peripheral vascular disease involvingthe arteries.
- Hypertension is one of the leading causes of end-stage renal disease, especiallyamong African Americans. The earliest manifestation of renal dysfunction isusually nocturia.
- The retina provides important information about the severity and duration of hypertension. Damage to retinal vessels provides an indication of concurrentvessel damage in the heart, brain, and kidney. Manifestations of severe retinaldamage include blurring of vision, retinal hemorrhage, and loss of vision.

SECONDARY ARTERIAL HYPERTENSION

Secondary hypertension

1. Cardiovascular (hemodynamic)
2. Renal
3. Endocrine
4. Neurogenic hypertension due to diseases and organic CNS lesions.
5. Hypertension caused by exogenous (chemical factors)
6. Hypertension in gravidity (pregnancy)

- **RENAL HYPERTENSION:**

- *nephrogenic hypertension* – occurs as a result of the primary injury of the functional renal parenchyma;
- *renovascular (vasorenal) hypretension* – due to some anomalies and changes of the renal vasculature;
- *renoprive hypretension* – occurs as a result of surgical removing both kidney.

- **Injury of the renal parenchyma**

Hypertension during parenchyma injury is one of the most common types of the secondary hypertension. An increased blood pressure is mostly the first sign of the original renal disease.

One of the pathogenic factors to which is related the cause of the occurrence and the maintenance of the hypertension is a drop in the Na^+ excretion. The increased volume of the circulating blood will lead to an increased venous return into the heart. That is why the central venous pressure is increasing and the ventricular filling is increased as well. As a result of these changes there will be an increment of the cardiac output and the systemic arterial blood pressure - this is known as a volume hypertension.

The volume hypertension occurs in acute glomerulonephritis. It is usually transient - and after the acute stage the blood pressure returns to normal values. But hypertension may manifest later, after several years when additionally to the glomerular lesions some changes in the arteries and the arterioles arrive. In such cases there is already a combination of the volume and the resistance hypertension.

In patients with the tubulointerstitial diseases of the kidneys, the hypertension is less common as that in the glomerulonephritis. The cause lies in the lower ability of the reabsorption of water based on the primary injury of the tubules.

Another mechanism, by which the renal disease can result in an increased blood pressure is the resistance mechanism. The mechanism of the resistance hypertension is explained as the result of the effect of the pressor and depressor substances that are formed in the kidneys. One of the pressor substances that is incorporated in the regulation of the blood pressure in the physiological but mainly in the pathological conditions is the renin-angiotensin-aldosterone system.

The decisive role of the renin-angiotensin system (RAS) in the pathogenesis of hypertension is assumed in renal infarction, and in unilateral renal affection, and it is absolute and very aggressive in cases of renal tumor that secretes rennin. In cases of bilateral parenchymal diseases of the kidneys, the level of the plasma rennin activity (PRA) is only slightly increased, or it might even be normal, what on the other hand does not exclude the role of this factor in the pathogenesis, mainly when we are dealing with a consequent increase of the plasma volume. In 5-10 % patients with chronic renal failure that are treated by dialysis the hypertension does not subside after the normalization of the content of Na^+ and fluids in the organism. The finding increased PRA as well as the normalization of blood pressure after

nephrectomy prove that the RAS is the determining factor in the pathogenesis of hypertension (known as renin-dependent hypertension). RAS also plays an important role in the maintenance of vasoconstriction and of a high blood pressure in malignant hypertension. A certain role in the pathogenesis of some types of the renal hypertension can play the substances with vasopressor effect and natrium uretic effect, i.e. prostaglandins and kalikrein-kinin system.

Lowering the vasopressory function of the kidney explains the hypertension that accompanies renal diseases, which are presented with prominent destruction of the renal medulla, which produces the depressor substances (prostaglandins): chronic interstitial nephritis, pyelonephritis, obstructive uropathies, and polycystic kidneys.

➤ **Renovascular hypertension (vasorenal hypertension)**

Renovascular hypertension results from a narrowing of the renal artery. The cause of its narrowing lays in many pathological processes, most commonly they are atherosclerosis and fibromuscular hyperplasia.

As a result of the classical experiments with hypertension in animals it was considered sure till recent time that the cause of hypertension in those animals was due to renin - angiotensin system, that is activated by renal ischemia (i.e. by the lower pressure amplitude in the renal vascular area) caused by the drop in the kidneys perfusion. However, later on there appeared many pieces of evidence which deny a direct relationship between this system and a chronic clinical or experimental hypertension.

The course of renovascular hypertension is similar to the course of the essential hypertension, however it is usually more serious and a malignant deterioration is frequent. What is specific for this type of hypertension is a progressive ischemic post stenosis renal atrophy. From the mentioned above it is clear that two mechanisms share the pathogenesis of the renal hypertension.

The volume (hyporenin) mechanism and the resistance (hyperrenin) mechanism. According to the type of renal disease, the anatomical and functional renal injury, and the stage of this disease both those mechanisms can alternate with each other or interact with each other. In certain cases one of them has the primary role, that will promote the whole mechanism, in other cases it is the factor that maintains the hypertension.

Apart from the mentioned factors the haemodynamic changes caused by anemia play an important role in the pathogenesis of renal hypertension that accompanies chronic renal insufficiency.

For maintaining of hypertension an important role is played by the adapting mechanisms of neural regulation of the circulation and also by the secondary morphological changes of the cardiovascular apparatus (atherosclerosis and mainly its renal form-nephroangiosclerosis).

• **ENDOCRINAL HYPERTENSION**

It is a hypertension caused by an absolute or a relative abundance of hormones with pressor effect or by an abnormality of the hormonal balance, that affects some components of the regulatory mechanisms which influence the blood pressure.

Pheochromocytoma. It is a disease caused by an autonomic overproduction of catecholamines by the chromaphin cells tumor of the sympatoadrenal system. These are usually benign tumors.

Most of the pheochromocytomas produce noradrenalin and adrenaline. In nearly 90 % of cases the tumor is situated in the adrenal medulla; in the remaining 10 % it is situated in the area of the abdominal aorta, and less common in other places. Adrenaline stimulates mostly the beta-receptors and increases the minute cardiac output. Noradrenalin via the alpha receptors increases the peripheral vascular resistance.

With regards to the fact that in most patients with pheochromocytoma the overproduction of both hormones is mixed in various quantitative relations, the circulatory changes are markedly variable. Hypertension can be manifested in three different forms:

1. permanent hypertension (in nearly half the patients)
2. permanent hypertension with paroxysms of increasing values of the blood pressure
3. paroxysmal hypertension (with otherwise normal blood pressure).

The course of permanent hypertension is very much similar to the course of essential hypertension. The paroxysmal forms of the disease threaten the patients with the cerebrovascular accidents, myocardial infarction, and heart failure.

Adrenocortical dysfunction. It is a case of hypertension with an absolute or a relative overproduction (or inversely - an insufficiency) of some hormones of the adrenal cortex.

There are three types of hypertension that are caused by an adrenocortical dysfunction:

1. **Primary hyperaldosteronism.** It is a disease caused by an primary overproduction of aldosterone in the adrenal gland (benign adenoma, malignant tumors, bilateral hyperplasia), which differs from the secondary hyperaldosteronism, that occurs as a result of an over-stimulation of the renal cortex by the system renin - angiotensin and by other primary diseases (e.g. nephrotic syndrome, liver cirrhosis, cardiac insufficiency, an advanced essential and renal hypertension). An overproduction of aldosterone in primary hyperaldosteronism is responsible for all the clinical and the laboratory characteristics of the disease, which become normal after its removal. A long lasting overproduction of aldosterone can be manifested by:

- Arterial hypertension, and by increase of the extracellular Na⁺ content with a predisposition for hyponatremia

- Hypokalemia with alkalosis (a result of long lasting potassium depletion are some neuromuscular changes such as spasm, and the development of hypokalemic nephropathy). The raise of Na⁺ content and of the extracellular volume leads to (by a feed back mechanism) the lowering of the plasma renin activity, however not to a point that causes a clinically manifested edema. And so in arterial hypertension caused by the primary aldosteronism there are:

- increased of Na⁺ content and of the extracellular volume
- high level of aldosterone in the plasma and urine
- suppression of the plasma renin activity

Since the description of primary hyperaldosteronism in 1955 by Conn, it was shown that it is not a unified syndrome, but this disease has at least three subtypes:

- The classical Conn's syndrome, when the aldosterone overproduction is caused by an aldosterone producing adenoma, less common by a carcinoma affecting one adrenal gland.

- Idiopathic hyperaldosteronism - in cases of micro- or macronodular hyperplasia of both adrenals.

- Dexamethazone - suppressible hyperaldosteronism (Murlow's). It is a rare overproduction of aldosterone by hyperplastic or normal adrenals in children. Hypertension in this case can be stabilized only by supplementation of dexamethazone, which will inhibit the overproduction of aldosterone by a feed back mechanism.

2. **Cushing syndrome.** Hypertension results from the overproduction of glucocorticoids and sometimes also the mineralocorticoids. They could be produced by tumors or hyperplasia of the adrenal cortex, and also by adenoma of the adenohypophysis. The clinical and the laboratory picture are given by the ratio of overproduction of the glucocorticoids and mineralocorticoids. In other words the hypertension is a result of the overproduction of glucocorticoids, that increase the sensitivity of the vascular wall to endogenous pressor factors and most probably they also change the contractility of the myocardium and so increase of the cardiac output.

Cortisol also stimulates the formation of angiotensinogen in the liver and that is the reason why there is an increase of the plasma angiotensin concentration. Apart from this it increase the vascular wall sensitive to the pressor substances. The overproduction of mineralocorticoids promotes its effect via the Na⁺ retention.

3. **Adrenogenital syndrome with hypertension.**

They are rare congenital abnormalities that occur as a result of a disturbed formation and hence production of steroids. Hypertension is accompanied by hypokalemic alkalosis, by a suppressed plasma renin activity and by a disturbed sexual maturation and development. The inborn insufficiency of the enzymes needed for normal steroidogenesis causes stimulation of the formation of deoxycorticosterone (DOC) and hence deoxycortisol and androgens. That is why a mineralocorticoids hypertension is accompanied by the increased virilization. In case of a disturbed biosynthesis of cortisol, but also androgens and estrogens, the mineralocorticoid hypertension is usually accompanied by hypogonadism.

Primary hyperreninism. It is a rare disease, caused by renin overproduction by renal or extrarenal tumors. These are most commonly originating from the juxtaglomerular apparatus of the kidneys. Hypertension is caused by renin overproduction, which leads to the formation of large quantities of angiotensin II and so to a secondary hyperaldosteronism.

Hypertension that accompanies other endocrinopathies

1. Acromegaly. It is due to the overproduction of growth hormone most commonly in cases of adenoma of the adenohypophysis. Apart from the morphological and biochemical changes which are

characteristic for the acromegaly, this disease is accompanied by the hypertension which does not differ from the essential hypertension. The cardiomegally corresponds with the level of hypertension.

2. Hyperparathyroidism. An increased production of parathormone can be most commonly seen in cases of the parathyroid glands adenoma. The early renal complications that occur in hyperparathyroidism can play an important role in the development of hypertension.

3. Hyperthyroidism. An overfunction of the thyroid gland can also be accompanied by hypertension. In cases of hyperthyroidism it is usually a systolic hypertension with a high cardiac output (volume hypertension). Hypertension as well as other common cardiac complications is caused by the direct effect of the thyroid hormones on the myocardium.

4. Diabetes mellitus. The relation between hypertension and diabetes is well known for over 60 years. The presence of hypertension is more common in cases of non insulin dependent diabetes (type II) where it correlates with age, obesity, and with the drop in the renal function. Pathogenesis of this hypertension is quite. Many factors play a role here: e.g. renal factors, macro- and microangiopathy, renin- angiotensin-aldosterone system and catecholamines.

• **HYPERTENSION IN CARDIOVASCULAR DISEASES**

1. Coarctation of aorta. It is an inborn narrowing of the aortic isthmus, i.e. of the section between the ostia of the subclavian artery and the attachment of the ductus arteriosus. In broader sense of the coarctation of aorta its stenosis might be localized along the whole aorta, proximal and distal from the isthmus itself. In aortic coarctation the adequate blood flow and pressure in the lower half of the body is obtained via three mechanisms:

- by increasing the systolic blood pressure in the proximal segment of the aorta
- by arteriolar vasoconstriction that maintains a high diastolic blood pressure
- by a collateral circulation and possibly by the opening of ductus arteriosus.

The blood pressure measured in the upper limbs shows an increased systolic, diastolic, and mean arterial blood pressure, while the systolic blood pressure is measured in the lower limbs it is in all cases low, and the diastolic pressure is increased. The mean arterial blood pressure in the lower limbs is always low, however it is kept at the value around 50 mmHg (6,6 kPa), what is the minimal pressure needed for adequate function of the kidneys.

2. Aortic valve insufficiency. It will cause a raise in the systolic blood pressure, by the fact that a part of the systolic cardiac output flows back into the left ventricle at the beginning of the systole and hence increases its diastolic filling. The left ventricular systolic volume gets larger as the regurgitation volume increases. The diastolic blood pressure becomes lower due to the faster blood flow from the aorta. The total peripheral resistance is lower as a result of the adaptation to the increased cardiac output.

3. Large arteriovenous fistulae (congenital or acquired). They cause the increase of the systolic blood pressure what is the result of the increased cardiac output. The blood flow passes by the arterioles and the capillaries and that is why the diastolic blood pressure decreases. As an example of this is the systolic hypertension in cases of multiple arterio-venous aneurysms in the skeleton as it is in Pagets disease (chronic osteitis deformans - processes of new formation as well as bone resorption are faster and the blood supply is increased).

4. Increase of the minute cardiac output and tachycardia at hyperkinetic syndrome. It occurs at disfunction of the vegetative nervous system which is due to an increased sensitivity of the cardiac or blood vessels beta adrenoreceptors. The positive effect of beta blockers strengthens this hypothesis. We consider a hyperkinetic circulation also states with an increased cardiac output at rest and they are accompanied by a normal blood pressure (e.g. anemia). In cases of juvenile hypertension and also in early stages of the essential hypertension the peripheral vascular resistance is not able to adapt itself to this high blood flow and so the blood pressure increases. So the hypertension here does not start as a generalized vasoconstriction, rather as an inadequate ability of the peripheral vascular bed produce effective dilatation. This is considered to be so called relatively increased peripheral vascular resistance.

5. Decrease of elasticity of the large arteries with a restriction of aortic elasticity. It is usually an accompanying feature of a generalized atherosclerosis. The systolic blood pressure is usually slightly increased. The rigid arteries do not expand during systole. The diastolic blood pressure is normal or lower than normal, because the impedance strength which pushes the blood to the periphery during diastole cannot be applied. This type of hypertension is called elasticity hypertension.

• **HYPERTENSION IN DISEASES OF NERVOUS SYSTEM**

The hypertension might occur in patients with brain tumors, cerebral hemorrhage, encephalitis, or meningitis and also after cerebral accidents. Its occurrence is explained by:

- increase of the intracranial pressure
- cerebral ischemia
- lesion of the vasomotor centers.

In cases of acute cerebral ischemia (e.g.: stenosis of the carotid artery) the blood pressure is promptly increasing by so called Cushing's reflex. The brain ischemia is an enormously strong stimulus for the activation of the central components of the sympathetic nervous system and hence a factor leading to the raise of the systemic arterial blood pressure. The reaction of the cerebral blood vessels to this increment of systemic blood pressure is vasoconstriction, which will lead to the closure of a vicious circle. Hypertension often accompanies the atherosclerosis of main vessels of the brain.

Another mechanism that can play a role in the occurrence of the hypertension is the disinhibition of higher centers of the brain as a result of a mechanic, inflammatory, degenerative or toxic affection of the peripheral neurons in polyneuropathies (e.g.: alcoholic neuropathy), in diphtheria, porphyria, thallium intoxication, lead intoxication, phosphorus intoxication, etc. . Hypoxia and hypercapnia have a share in the pathogenesis of hypertension.

Low sensitivity of baroreceptors can be the cause of the systemic blood hypertension when there is a low pressure in the bulbus caroticus and the aorta which is characteristic for Takayasa disease (syndrome of the aortic arch known as an inversed stenosis of the aortic isthmus). What predisposes to hypertension here is also brain hypoxia and a lower aortic elasticity.

• **HYPERTENSION IN GRAVIDITY**

Hypertension together with edema and proteinuria form the basic trias of the late pregnancy eclampsia. During the gravidity the blood pressure is slightly lower than normal and this is why its increase by 30/15 mmHg (4/2 kPa) or over 140/90 mmHg (19/12 kPa) is considered as hypertension. Vasodi-lation in pregnancy is caused most probably by the higher secretion of progesterone and prostaglandins. During the first months of gravidity the renal blood flow increases by about 50% and also increases glomerular filtration. When approaching the end of the gravidity both those values return to normal.

Pathogenesis of the hypertension in gravidity is complicated. It is most probable that its pathogenesis is shared between the volume and resistant factors. One of the hypothesis provides us with the following explanation: During pregnancy the total body fluid volume is increased by at least 8,5 l. From this total volume the plasma volume during the gravidity increases by nearly 1,5 l above the normal. By this the appropriate conditions for the congestive circulation and for the occurrence of volume hypertension are created. Apart from this the postural characteristics of the pregnant women also have a certain role in the pathogenesis of this hypertension. In the late stages of pregnancy the pressure of the gravid uterus on the inferior vena cava in the horizontal position decreases the venous return from the lower limbs, what leads to a marked drop of the cardiac filling during diastole. As a result of this lowering of the cardiac filling the cardiac output decreases what is compensated by vasoconstriction in the splanchnic vascular bed and in the skin blood vessels. The lower blood flow via the kidneys is a very important factor which leads to the activation of the renin-angiotensin-aldosteron system.

Recently many hypothesis which tried to explain the pathogenesis of hypertension in gravidity come out of the fact that in some gravid women the renin-angiotensin-aldosteron system is activated. In the first gravidity preeclampsia state usually occurs after 20th week of the gravidity. It is characterized by a rapid gain of weight, the formation of edema, proteinuria and by the hypertension. The ophthalmoscopic examination of the retina reveals vascular spasms and sometimes papillary edema. The renal blood flow as well as the glomerular filtration is being worsened. In the inadequately perfused uterus renin is formed. Angiotensin then causes vasodilatation in the placenta by its effect on prostaglandin E release, but in other places of vascular bed angiotensin causes vasoconstriction. The glomerular filtration decreases and the natrium retention and the extracellular fluid volume increase. Those changes together with vasoconstriction lead to the increase of the systemic blood pressure.

• **HYPERTENSION CAUSED BY DRUGS AND TOXIC SUBSTANCES**

The arterial systemic hypertension can occur as an unwanted side effect that accompanies treatment with some drugs. From the etiopathogenic point of view drugs may lead to hypertension via three mechanisms:

- due to their natrium retention effect - similar to mineralocorticoids

- due to their effect on the biosynthesis, secretion or metabolism of the pressoric humoral substances
- by their direct vasoconstrictive effect

1. Hypertension resulted from the use of steroid peroral contraception. The steroid peroral contraceptive agents increase blood pressure in long term use even in otherwise healthy women. Yet chronic hypertension develops only in some women. We usually find hypertension in those females with a positive family history of hypertension in gravidity, in obese women, and in woman with a higher predisposition for Na⁺ retention and the formation of edema, as well as in women with chronic pyelonephritis.

The mechanism of the peroral contraceptive agents that leads to hypertension is complex and depends on estrogen content. Estrogens have a direct natrium retention effect and they activate renin - angiotensin - aldosterone system via a higher angiotensinogen synthesis in the liver.

The result of all this will be:

- a higher plasma renin activity till three folds more than normal
- more angiotensin II that via
- the stimulation of aldosterone leads into a secondary hyperaldosteronism and hence into
- an increased Na⁺ retention

The synthetic progesterones in contrast with the natural progesterones have also a mineralocorticoid natrium retention effect.

2. Other substances with estrogen and progesterone activity A relatively common occurrence of hypertension was described in those patients who were on a long lasting treatment with conjugated and synthetic estrogens, or synthetic gestagens. Natural progesterones inversely have an antihypertensive effect.

The mechanism of the development of hypertension here is similar to that occurring post the use of oral steroid contraceptive agents. There will be retention of Na⁺ via either direct natrium retention mechanism (estrogens or synthetic progesterones) or via the activation of rennin - angiotensin - aldosterone system (estrogens).

3. Glucocorticoids and mineralocorticoids. During the therapy with adrenocortical steroids previously some coarse extracts of the adrenal cortex were used and so hypertension was a common side effect of the treatment with corticosteroids. Today it is a rare complication during the substitution therapy of hypofunction syndromes.

During the use of mineralocorticoid substances, hypertension is accompanied by hypokalemia, alkalosis, and a suppressed plasma renin activity

4. Monoaminooxidase inhibitors. The treatment of depressive states by the use of monoaminooxidase inhibitors (MAOI) leads into often hypertensive crises in these patients after the uses of fermented drinks and food. MAOI causes hypertension via two mechanisms:

- by inhibiting the intracellular MAO and hence an increase in the level of monoamines due to their low turnover (break down)
- by interfering with tyramine deamination. In normal cases tyramine is quickly oxidized, yet with the presence of MAOI it cumulates in the tissues. Tyramine then releases adrenaline and noradrenalin from their reservoir in the nerve endings. Apart from this it has a direct pressor effect. A higher release of catecholamines and their lower break down is observed after meals which contain the tyramine (some cheese, alcohol drink, meat extract from cans, chocolate. In patients treated with MAOI (or *a* methyl dopa) these meals causes a progressive increase in the plasma concentration of catecholamines and a prominent hypertensive crises.

5. Licorice - Na carbenoxolon. A chronic use of licorice (like in some expectorants or sweets) can cause hypertension that is combined with hypokaliemia, alkalosis, and suppressed renin. This is caused by a natrium retention effect of the ammonia salts of the glycyrrhinic acid, contained in the licorice extracts. In other words they act similarly to mineralocorticoids.

6. From the toxic effects hypertension can be caused by acute porphyria, lead, thallium, carbon monoxide, mercury poisoning, and experimentally cadmium poisoning. The pathogenic mechanism is probably a centrally conditioned stimulation of adrenergic activity.

7. Postradiation hypertension. Occur in those patients treated by radiotherapy. Those are patients with abdominal tumors probably due to the occurrence of so known radiation nephritis. This hypertension might inquire a malignant character.

Stratification of hypertension risk

A simple approach to stratifying for total cardiovascular risk is suggested in Table 2. The terms low, moderate, high and very high added risk are calibrated to indicate an absolute 10-year risk of cardiovascular disease of , 15%, 15–20%, 20–30% and . 30%, respectively (Framingham criteria), or a 10-year risk of fatal cardiovascular disease of , 4%, 4–5%, 5–8% and . 8% (SCORE criteria). These categories can also be used as indicators of relative risk, the risk increasing by about 1.5 times going from a category to the next one.

Table 2. Stratification of risk

ESH-ESC					
BP (mmHg)	Normal	High normal	Grade 1	Grade 2	Grade 3
	SBP 120–129 or DBP 80–84	SBP 130–139 or DBP 85–89	SBP 140–159 or DBP 90–99	SBP 160–179 or DBP 100–109	SBP ≥ 180 or DBP ≥ 110
Other risk factors and disease history					
No other risk factors	Average	Average	Low	Moderate	High
1–2 risk factors	Low	Low	Moderate	Moderate	Very high
3 or more or TOD or diabetes	Moderate	High	High	High	Very high
ACC	High	Very high	Very high	Very high	Very high

Abbreviations: ACC, associated clinical conditions; DBP, diastolic blood pressure; SBP, systolic blood pressure; TOD, target organ damage.

Factors influencing prognosis:

1. Risk factors for cardiovascular disease used for stratification

- Levels of systolic and diastolic BP
- Men > 55 years
- Women > 65 years
- Smoking
- Dyslipidaemia (total cholesterol > 6.5 mmol/l, > 250 mg/dl* or LDL-cholesterol > 4.0 mmol/l, > 155 mg/dl*, or HDL-cholesterol M < 1.0, W < 1.2 mmol/l, M < 40, W < 48 mg/dl)
- Family history of premature cardiovascular disease (at age < 55 years M, < 65 years W)
- Abdominal obesity (abdominal circumference M ≥ 102 cm, W > 88 cm)
- C-reactive protein ≥ 1 mg/dl
- Diabetes mellitus
- Fasting plasma glucose > 7.0 mmol/l (> 126 mg/dl)
- Postprandial plasma glucose > 11.0 mmol/l (> 198 mg/dl)

2. Target organ damage (TOD)

- Left ventricular hypertrophy (electrocardiogram: Sokolow-Lyons > 38 mm; Cornell > 2440 mm/ms; echocardiogram: LVMI M > 125, W > 110g/m²)
- Ultrasound evidence of arterial wall thickening (carotid IMT ≥ 0.9 mm) or atherosclerotic plaque
- Slight increase in serum creatinine (M 115–133, W 107–124 μmol/l; M 1.3–1.5, W 1.2–1.4 mg/dl)
- Microalbuminuria (30–300 mg/24 h; albumin-creatinine ratio M > 22, W > 31 mg/g; M > 2.5, W ≥ 3.5 mg/mmol)

3. Associated clinical conditions (ACC)

- Cerebrovascular disease: ischaemic stroke; cerebral haemorrhage; transient ischaemic attack
- Heart disease: myocardial infarction; angina; coronary revascularization; congestive heart failure
- Renal disease: diabetic nephropathy; renal impairment (serum creatinine M > 133, W > 124 μmol/l; M > 1.5, W > 1.4 mg/dl) proteinuria (> 300 mg/24 h)
- Peripheral vascular disease
- Advanced retinopathy: haemorrhages or exudates, papilledema

M, men; W, women; LDL, low-density lipoprotein; HDL, high density lipoprotein; LVMI, left ventricular mass index; IMT, intima-media thickness. * Lower levels of total and LDL-cholesterol are known to delineate increased risk, but they were not used in the stratification.

Diagnostic evaluation:

I. Family and clinical history

II. Physical examination

- Signs suggesting secondary hypertension
- Signs of organ damage (brain, retina, heart, peripheral arteries,

III. Laboratory investigations:

1. Routine tests

- Plasma glucose (preferably fasting)
- Serum total and high-density lipoprotein (HDL) cholesterol; fasting serum triglycerides
- Serum creatinine
- Serum uric acid
- Serum potassium
- Haemoglobin and haematocrit
- Urinalysis (dipstick test and urinary sediment)
- Electrocardiogram

2. Recommended tests

- Echocardiogram
- Carotid (and femoral) ultrasound
- Postprandial plasma glucose (when fasting value ≥ 6.1 mmol/l or 110 mg/l)
- C-reactive protein (high sensitivity)
- Microalbuminuria (essential test in diabetics)
- Quantitative proteinuria (if dipstick test positive)
- Funduscopy (in severe hypertension)

3. Extended evaluation (domain of the specialist)

- Complicated hypertension
- Suspicion of secondary hypertension

Searching for target organ damage

- Target organ damage is important in determining the overall cardiovascular risk of the hypertensive patient (Table 2)
- Search carefully for organ involvement
- When treatment decisions are uncertain, cardiac and carotid ultrasound examinations and microalbuminuria measurement may help in more precisely classifying the overall risk of the hypertensive patient and in directing therapy

Initiation of antihypertensive treatment is based on two criteria:

- Total level of cardiovascular risk
- Level of systolic and diastolic BP

Goals of treatment

- Achieve the maximum reduction in the total cardiovascular risk
- Treat all reversible risk factors (smoking, dyslipidaemia, diabetes, etc.) and the associated clinical conditions in addition to treating the raised BP
- Reduce both systolic and diastolic BP to below 140/ 90 mmHg and to lower values if tolerated
- Aim at values below 130/80 mmHg in diabetics
- Achieving systolic BP values below 140 mmHg may be difficult in the elderly

Benefits of antihypertensive treatment

Numerous trials of active antihypertensive treatment compared with placebo (Fig. 1) have shown that BP lowering reduces:

- Cardiovascular and total mortality
 - Stroke
 - Coronary events
- Benefits have been proven:

- In patients with systolic-diastolic hypertension
- In elderly patients with isolated systolic hypertension

Benefits have been shown in placebo-controlled trials that have used all major antihypertensive drug classes:

- Diuretics
- Beta-blockers
- Calcium antagonists
- Angiotensin-converting enzyme (ACE)-inhibitors
- Angiotensin receptor antagonists

Lifestyle changes

• Lifestyle measures should be instituted wherever appropriate in all patients, including subjects with normal and high normal BP with additional risk factors, and in patients who require drug treatment. The purpose is to lower BP and to control other risk factors.

• The lifestyle measures lowering BP or cardiovascular risk are:

- smoking cessation
- weight reduction
- reduction of excessive alcohol intake
- physical exercise
- reduction of salt intake
- increase in fruit and vegetable intake
- decrease in saturated and total fat intake

Table 4 Initiation of antihypertensive treatment

Other risk factors and disease history	Blood pressure (mmHg)				
	Normal: SBP 120-129 or DBP 80-84	High normal: SBP 130-139 or DBP 85-89	Grade 1: SBP 140-159 or DBP 90-99	Grade 2: SBP 160-179 or DBP 100-109	Grade 3: SBP \geq 180 or DBP \geq 110
No other risk factors	No BP intervention	No BP intervention	Lifestyle changes for several months, then drug treatment if preferred by the patient and resources available	Lifestyle changes for several months, then drug treatment	Immediate drug treatment and lifestyle changes
1 -2 risk factors	Lifestyle changes	Lifestyle changes	Lifestyle changes for several months, then drug treatment	Lifestyle changes for several months, then drug treatment	Immediate drug treatment and lifestyle changes
3 or more risk factors or TOD or diabetes	Lifestyle changes	Drug treatment and lifestyle changes	Drug treatment and lifestyle changes	Drug treatment and lifestyle changes	Immediate drug treatment and lifestyle changes
ACC	Drug treatment and lifestyle changes	Immediate drug treatment and lifestyle changes	Immediate drug treatment and lifestyle changes	Immediate drug treatment and lifestyle changes	Immediate drug treatment and lifestyle changes

ACC, associated clinical conditions; DBP, diastolic blood pressure; SBP, systolic blood pressure; TOD, target organ damage.

Table 5 Indications and contraindications for the major classes of antihypertensive drugs

Class	Conditions favouring the use	Contraindications	
		Compelling	Possible
Diuretics (thiazides)	Congestive heart failure; elderly hypertensives; isolated systolic hypertension; hypertensives of African origin	Gout	Pregnancy
Diuretics (loop)	Renal insufficiency; congestive heart failure		

Diuretics (anti-aldosterone)	Congestive heart failure; post-myocardial infarction	Renal failure; hyperkalemia	
p-Blockers	Angina pectoris; post-myocardial infarction; congestive heart failure (up-titration); pregnancy; tachyarrhythmias	Asthma; chronic obstructive pulmonary disease; A-V block (grade 2 or 3)	Peripheral vascular disease; glucose intolerance; athletes and physically active patients
Calcium antagonists (dihydropyridines)	Elderly patients; isolated systolic hypertension; angina pectoris; peripheral vascular disease; carotid atherosclerosis; pregnancy		Tachyarrhythmias; congestive heart failure
Calcium antagonists (verapamil, diltiazem)	Angina pectoris; carotid atherosclerosis; supraventricular tachycardia	A-V block (grade 2 or 3); congestive heart failure	
Angiotensin-converting enzyme (ACE) inhibitors	Congestive heart failure; LV dysfunction; post-myocardial infarction; non-diabetic nephropathy; type 1 diabetic nephropathy; proteinuria	Pregnancy; hyperkalaemia; bilateral renal artery stenosis	
Angiotensin II receptor Antagonists (ATt -blockers)	Type 2 diabetic nephropathy; diabetic microalbuminuria; proteinuria; LV hypertrophy; ACE-inhibitor cough	Pregnancy; hyperkalaemia; bilateral renal artery stenosis	
a-Blockers	Prostatic hyperplasia (BPH); hyperlipidaemia	Orthostatic hypotension	Congestive heart failure

A-V, atrioventricular; LV, left ventricular.

Experimental models of hypertension

- Irritation of hypothalamus nucleuses (due to of peripheral resistance increase).
- Double-side damage nucleus tractus solitarius to medulla oblongata (location of primary synapsis of sinuaortic baroreceptors due to sharp increase of peripheral resistance)
- Reflexogenic hypertension after section depressor nerve Ludvig-Cion or sinus nerves Hering
- Renal :
 - Vasorenal hypertension, by narrowing renal arteries (partially; double-side; narrowing arteries of one kidney plus removal of the other kidney)
 - Renoprival hypertension (remove both kidneys)
- Confirming a role of adrenal glands:
 - Long-term introduction of aldosterone and solution NaCl instead of water (mineral-corticoids hypertension)
 - Salty hypertension

SYSTEMIC ARTERIAL HYPOTENSION

Hypotension — condition in which the pressure below 100 mm Hg.

Mechanisms:

- decreased cardiac output
- decreased peripheral resistance
- combination of both factors.

Classification of hypotensions:

- Physiological hypotension:
 1. Hypotension as individual variant of norm
 2. Hypotension of increased fitness (in sportsmen)
 3. Adaptive hypotension (compensated) (residents highland tropics and subtropics)
- **Classification of hypotensions:**
 - Pathological hypotension:
 1. neurocirculatory (primary or essential):
 - a) labile reversible course
 - b) expressed stable form (hypotension disease)
 2. idiopathic (orthostatic)
 3. symptomatic (secondary)

- a) acute (in shock, collapse)
- b) long-lasting (adrenal insufficiency, hypothyroidism, tetraethyl lead poisoning, etc.);
- c) with severe orthostatic syndrome (e. Shy-Drager syndrome)

A permanently low systolic blood pressure below 13,3 kPa (100 mmHg) and a diastolic blood pressure below 8,0 kPa (60 mmHg) in different positions (lying, sitting, standing) is marked as chronic arterial hypotension. It is not considered as a disease condition, the hypotensive patients usually reach older ages than the normotronics. The cause of the continuously low blood pressure is not exactly understood. From the theoretical point of view the hypotonics are on the opposite side than the hypertonics in the curve that determines the role of hereditary factors on a level of blood pressure. It might be a sign of a generalized asthenia in vagotonics. Its course is usually asymptomatic with the exception of the frequent sleeping or an increased tiredness. Cases of a transient hypotension (syncope and shock) are described elsewhere.

Arterial hypotension might occur in many diseases. It is the accompanying sign of inadequate adrenal function (Addison's syndrome), malabsorption syndrome, heart failure, aortic stenosis and constrictive pericarditis.

Orthostatic (postural) hypotension

The blood vessels are relatively elastic and permeable pipes. Upon taking the upright position, and due to the effect of gravity there is a tendency for the blood to cumulate in the distensible veins below the heart level and also to the escape of plasma into the interstitium. This transient blood distribution would be the cause of a sudden drop of the venous return, leading to a decrease of the arterial blood pressure with the consequent lower cerebral perfusion. In normal conditions when taking the upright posture there are reflex compensatory mechanisms keeping the arterial blood pressure within a certain limit of range. In the human organism the most important are the baroreceptor areas mainly those situated in the vessels above the heart level. Upon standing up the blood pressure above the heart level drops. This change is registered by the baroreceptors where the final effect is the reflexly increased sympathetic tonus of the vasomotor fibers that will provide vasoconstriction in the resistant vessels (a compensation of the lower systolic output) and even in the capacitance blood vessels (lower blood accumulation and hence a larger venous return). Despite the narrowing of the resistant vessels, the hydrostatic pressure in the lower limb capillaries in orthostasis would be over 13 kPa (100 mmHg), what considerably exceeds the colloidal osmotic pressure of blood protein. There would be a prompt plasma diffusion into the interstitium. The protective mechanism here is represented by the contraction of the precapillary sphincters. An abnormal vessel dilatation will, at the same time, be prevented by the muscular contractions that push the venous blood towards the heart.

The muscle contraction and muscle massage of the vessels in the lower limbs can be out of function in case of the passive tilting. During this examination the patient's position is changing on a mobile bed, to which the patient is tightened. According to the level of blood pressure during the passive changing of the patient's position, we might evaluate the activity of the sympathetic vasomotor reflexes without any side effects. Changes of the blood pressure during the passive tilting in healthy people do not exceed 1,3 kPa (10 mmHg). Orthostatic hypotension (orthos - upright, statio - standing, being orthostaticus means occurring while upright standing) is a condition, that is characterized by a drop in the systolic and even the diastolic pressure by 2,6 kPa (20 mmHg) when taking the upright standing position. In complicated situations the sitting alone may cause an evident drop of the blood pressure.

Since hypotension might occur in positions other than the upright position, we might use a wider term - postural hypotension. Apart from the usual picture we might include here some rare situations such as hypotension in the late trimester of gravidity, where the heavy gravid uterus will press in the veins upon laying on the back and causes hypotension that might lead to syncope.

Another rare condition might arise from the presence of atrial myxoma or a pendulous intraatrial thrombus during which hypotension might result upon sitting due to the low ventricular filling in this position.

Idiopathic orthostatic hypotension

Idiopathic orthostatic hypotension affects men more often than women. It is characterized by clear signs and symptoms caused by a disturbed or inadequate activity of the autonomic nervous system - postural hypotension, low sweating and fixed (unchanged) heart rate. Bradbury and Eggleston were the first who described this syndrome as a triad of a gradually progressing postural hypotension, anhidrosis that affects the whole body surface and impotence. The exact cause of this condition is yet unknown,

some hypothesis suggest a disturbance of biosynthesis of catecholamines in the sympathetic ganglia and neurons. The level of catecholamines in plasma and urine is often lower than normal. During the passive tilting there won't be normal reaction (a higher elimination of catecholamines by the urine). In some patients there is a lower reactivity effect of renin - angiotensin - aldosterone system. Hypovolemia is found quite frequently. In cases of lower sympathetic activity, the pumping function of the heart depends mostly on the venous return. As long as the veno-constriction is inadequate and a compensatory tachycardia doesn't occur, the cardiac output during the orthostasis will drop by one fourth. In this position a patient is unable to keep the normal values of the systolic and diastolic blood pressure. The lowering of blood pressure might be so serious that an inadequate cerebral blood flow leads to syncope and even loss of consciousness. Putting the patient to a horizontal position will improve his condition very quickly.

Secondary orthostatic hypotension

An inadequate response to gravitation might be an accompanying sign of many diseases. The most common cause is again a disturbance of a sympathoadrenal system at any level - it occurs in patients with neurological diseases (multiple sclerosis, diabetic and alcoholic neuropathy, peripheral neuropathies), after administration of sympatholytic or following surgical sympathectomy. After a long lying down, and in the cosmonauts after the long lasting loss of gravitation there is a developing orthostatic hypotension, that signalizes a slower or inadequately responding sympathetic nervous system to the effect of gravity to which the patient was not exposed for a long time. A short lasting training is enough to make the symptoms of orthostatic hypotension fade out. Another cause of orthostatic hypotension might commonly be the varicose syndrome. The failure of valves to close in the wider veins can be so serious, that an adequate venous return cannot be maintained upon standing upright even with the maximal activation of the SAS.

The signs of postural hypotension are also not uncommon in patients with cerebrovascular diseases, in whom syncope might occur upon coughing, a tiring defecation, most probably due to the failure of the reflex vasoconstriction with a low venous return (Valsalva maneuver).

Inversely a sudden drop of the arterial systemic blood pressure can cause focal neurological injury in patients suffering from atherosclerosis, intracranial vessel occlusion, carotid occlusion, or the vertebral artery occlusion.

PATHOPHYSIOLOGY OF THE BRAIN CIRCULATION

Anatomy of the Brain

3 Major Areas: Cerebrum-consists of two hemispheres (thalamus and hypothalamus) that are incompletely separated by the great longitudinal fissure

4 Lobes: Frontal-major functions are concentration, abstract thought, information storage or memory, and motor function. It also contains Broca's area, critical for motor control of speech

Parietal-analyzes sensory information and relays the interpretation of the info to the thalamus. It is essential for orientation in space and spatial relations.

Temporal-provides integration of somatization, visual and auditory areas and plays the most dominant role of any area of the cortex in thinking.

Occipital-responsible for visual interpretation

Thalamus-relay station for all sensation except smell.

Hypothalamus-works with pituitary gland to maintain fluid balance and maintains temp. regulation by promoting vasoconstriction or vasodilation. It is also the site of the hunger center and contains the center that regulate the sleep-wake cycle, blood pressure, aggressive and sexual behavior, and emotional response.

Brain Stem-consists of:

Midbrain-serves as the center for auditory and visual reflexes. CN nerves III and IV originate here.

Pons-contains motor and sensory pathways. CN nerves V through VIII connect to the brain in the pons.

Medulla Oblongata-contains motor fibers from the brain to the spinal cord and sensory fibers from the spinal cord to the brain. CN nerves IX through XII connect to the brain in the medulla.

Cerebellum-largely responsible for coordination of movement. It also controls fine movement, balance, position (postural) sense or proprioception (awareness of where each part of the body is), and integration of sensory output.

The normal blood flow through the brain is about 50-60 ml/100 g tissue/min. When this is lowered to 20 ml/100 g tissue/min, the functional activity of the neurons decreases and this is presented very fast in the cerebral cortex. **The structural changes in the brain neurons take place after few minutes when the blood flow level is decreased to 10 ml/100 g tissue/min.** The most sensitive are the neurons, then the glial cells and finally the endothelial cells of the brain vessels.

During the passive changes in the systemic arterial pressure the brain circulation is not affected due to the **autoregulatory compensatory mechanisms.**

Carbon dioxide can affect the brain vessels in 3 manners:

- through the pCO₂ level in the arterial blood
- indirectly acting on the vasomotor center in the medulla oblongata
- through pH changes in the tissue which may have an influence on contractile elements in vascular wall

Hypercapnia leads to vasodilatation of the brain vessels, acidosis in the perivascular space and in the smooth muscle cells in the vascular wall leads to vasodilatation as well.

The metabolic results of **hypoxia** (decrease in the hydrogen ions concentration, increase K⁺ and Ca²⁺ concentration, increase the level of catecholamins, and adenosin level increase in the tissues surrounding the arterioles) may lead to vasodilatation.

On the other hand hypocapnia, alkalosis, and hyperoxia have a blocking effect on the vasodilatation and have vasoconstrictory effect. Some other substances with vasoconstrictory effect are acetylcholine, norepinephrine, dopamin, serotonin, histamine, thromboxan A₂, haemoglobin, prostaglandin E₂ etc.

The neurogenic regulation is less prominent than the chemical regulation in the brain circulation and it has an adjusting action. The outcome of this regulation comes from the baroreceptors in the aortic arch and the carotic sinus. These are stimulated by any change in the diameter of the vessel where they are located. The role of the sympathetic nerves lies in protecting the brain against any sudden increase in the blood pressure. The stimulation of the sympathetic fibers leads usually to vasoconstriction similarly to the stimulation of the α -adrenergic receptors, on the contrary the stimulation of the β -adrenergic receptors leads to vasodilatation.

Cerebrovascular circulation

The brain consumes most of the body's glucose supply; however, it does not have a means of storing its own supply >> ***a constant flow of blood should be maintained***

Violation of cerebral circulation

- Interruption in cerebral blood flow resulting to a decrease or increase in blood supply
- Factors affecting cerebral blood flow:
 - Extracranial – systemic BP, CV function, blood viscosity
 - Intracranial – cerebral autoregulation, cerebral blood vessels, intracranial/CSF pressure
- Disruption (breakdown) in the blood-brain barrier resulting to cerebral edema

Focus on stroke. Stroke is the term used for the onset of acute neurologic deficit persisting for more than 24 hours caused by the interruption of blood flow to the brain

Types:

1. Ischemic stroke

Description – type of stroke which usually results from low cerebral blood flow due to occlusion of a blood vessel usually of the thrombotic or embolic type

Etiology

–thrombotic strokes are a consequence of the accumulation of atherosclerotic plaque in the vessel lumen

–embolic strokes occur when an embolus from the heart or lower circulation travels distally and lodges in a small vessel, resulting in a loss of blood supply

Pathophysiology

–ischemic stroke >> cerebral hemodynamic insult

–reduction in cerebral blood flow >> decreased perfusion >> formation of ischemic penumbra >> sustained anoxia initiates a chain of events >> brain infarction >> irreversible neuronal injury

–warning signs of ischemic stroke: episodes of transient ischemic attacks (TIA), neurologic symptoms, reversible ischemic neurologic defect lasting less than 24 hours

2. Subarachnoid hemorrhage

Description

–characterized by bleeding into the subarachnoid space usually caused by a cerebral aneurysm or arteriovenous malformation (AVM)

Etiology

- cerebral aneurysm
- AVMs
- hypertensive intracerebral hemorrhages
- bleeding from a cerebral tumor

Pathophysiology

- cerebral aneurysm
 - maturity of aneurysm >> increase in blood pressure >> increase pressure added onto the weak vessel (thinning due to aneurysm) >> vessel “balloons out” >> vessel walls thin out further >> rupture
- arteriovascular malformations
 - pathophysiology related to the size and location of the malformation
 - feeders (enlarged cerebral arteries) >> blood volume shunted to the malformation increases OR dilatation and tortuosity of vessel resulting from increased volume delivered at a higher than normal pressure

3. Intracerebral hemorrhage

Description

–characterized by bleeding into cerebral tissue >> destruction of cerebral tissue >> cerebral edema + IICP

Etiology

- most often caused by hypertensive rupture of a cerebral vessel
- other causes of spontaneous ICH: anticoagulation/thrombolytic therapy; coagulation disorders; hemorrhage into cerebral infarct or brain tumors

Pathophysiology

–continued elevated blood pressure >> increased force exerted against smaller blood vessels damaged from arteriosclerotic changes >> vessel rupture >> blood seeps into surrounding cerebral tissue >> hematoma formation + IICP in response to the increase in overall intracranial volume

4. Aneurysms

Description

– Intracranial aneurysm is an abnormally located dilatation of a cerebral artery which usually develops in a weakened area of the vessel wall.

Etiology

- congenital
- traumatic
- arteriosclerotic
- inflammatory.

Pathophysiology

– Congenital and traumatic aneurysms are the commonest causes of the subarachnoid haemorrhage. Besides the congenital aneurysms there are also the acquired ones usually due to mycotic embolisation. Some aneurysms have elastic wall and their rupture occur very rarely. So they are manifested by their pressure on the brain tissue or the cranial nerves.

5. Generalized arteriosclerosis of the small cerebral arteries

Description

– The pathologic anatomical finding of the cerebral arteriosclerosis is the picture **status verminosus** of the cerebral cortex (being the extinction of the ganglion cells due to ischaemia), **status cribrosus** of the basal ganglia being a widening of the perivascular spaces, and status lacunaris (being small cavities or post malacia pseudocysts).

Etiology

- In the elderly the brain tissue is subjected to a **diffuse slowly progressing arteriosclerosis**.

Pathophysiology

– The arteriosclerotic changes seems to develop gradually reaching the small vessels. During life a gradual hyalinization of the vessels takes place, particularly in hypertensive individuals, which is followed by fibrosis and necrosis. Thus the vessels loose their elasticity and the ability of dilatation. The illness **usually starts as pseudoneurosthenia being** (tiredness, irritability, apathic behavior). We can notice some memory problems, emotional liability, and some sleep disturbance.

6. Thrombosis and thrombophlebitis of the cerebral veins and sinuses

Venous obliteration can result from **inflammation** of the venous wall and **disturbances of the haemodynamics** with venous stasis.

Thrombophlebitis results from a generalized or a localized inflammation such as sinusitis, otitis media etc.

Questions for self-control of knowledge:

1. What are the signs by which differentiate arterial hypertension.
2. What are the differences between primary and secondary hypertension?
3. What are the risk factors, causes and mechanisms of arterial hypertension development?
4. What hormones increase blood pressure?
5. Describe the renal and extrarenal effects of aldosterone.
6. What are the mechanisms of endocrine arterial hypertension?
7. What are the mechanisms of the fall in blood pressure during hypertensive states?
8. What is the role of hereditary factors in the development of atherosclerosis?
9. What are the possible consequences of atherosclerotic vascular walls of arterioles?
10. What is the mechanism of regulation of cerebral blood flow?
11. What are the causes and consequences of bleeding in the brain?
12. What phenomenon is called "excess perfusion of the brain?" Why does it occur?
13. What are the principles of diagnostic the cerebral circulation pathology?

Tasks for self-managed student work:

1. Modern ideas about etiology and pathogenesis of essential hypertension.
2. Role of kidneys in onset and development of hypertension.
3. Excessive perfusion of brain, causes and mechanisms of development.

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K.A. Kidun