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Harmful or Helpful Hypertension – Pathophysiological Basis

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1. Introduction

The analytic approach does not always give an unambiguous response to the question as to why the disorder has developed. Rather, it rather clarifies the mechanisms responsible for the disorder. There is a great difference between the two following questions:

1. How the disorder has appeared?
2. Why the disorder has appeared?

In order to understand complex mechanisms, both questions need to be considered.

By analyzing the individual parts of mechanisms, we assume them to have equal importance. But in reality, this is not true. Even in most difficult systems consisting of individual parts, their role, value, and participation are in hierarchy. Some elements may be superior to the others.

Usually not all the very difficult mechanisms lying very deep within cells are apparent. However, this can not excuse the assumption that none of phenomena can be determined only by intracellular processes. If we admit that we are the result of the huge evolution of life, our primeval substance is then represented by cells. The cells can be the hidden motor forcing the organism to fulfill the cellular needs. According to this view, blood pressure is not the only part of a functioning circulation.

Life has been formed in water which serves as the medium, procuring everything from the reception of energy to the elimination of unneeded substances. The changes in pressure might represent a simple mechanism allowing the functioning of cells. Even more simple are however the alterations in osmotic concentration of internal water environment. Is this not a phylogenetically conserved regulation? The increase in blood pressure in human organisms brings about an increase in the elimination of water together with natriuresis. Nevertheless, the question of regulation can be posed the other way round. So far, we used to say that blood pressure is influenced by defined factors. We usually suppose that blood pressure is regulated by known and lesser-known mechanisms. Might the order not be reversed? Could not the blood pressure serve as a cellular tool that optimizes the osmotic factors? Such

mechanisms can not be isolated, and are probably more complex. Subsequently the complexity raises the possibility that undesired anomalies will develop. This is the reason why many disorders can occur and they can not be easily included in a single scheme.

In the far past, at the beginning of evolution of difficult biological systems, water, osmotic factors, and pressure factors occurring in layers separating two interfaces represented the mechanisms that determined entirely everything. Perhaps we should see the phylogenetic residue in the fact that the activity of organism can be associated with a change in these values on the level of all cells. The optimization of osmotic and pressure factors can be achieved in various ways. These mechanisms can very effectively manage new situations in each cell, preferably in selected cells. The activation of organism that is associated with the activity of the sympathoadrenal system (SAS) triggers complex pathways. The long-lasting activation of these mechanisms may lead to their fixation, enabling the pressure to serve as a tool for increasing the natriuresis at general load.

Biological systems, which are considered to be our primeval predecessors, had to develop their own mechanisms to improve their ability to retain sodium. At the same time, they had to develop mechanisms that could basically help them to eliminate the excessive sodium. Moreover, a perfect system necessarily needs to develop mechanisms to gain sodium. In this aspect, we can operate with three facts. The first is the ability to save sodium, the second is to eliminate its excess, and the third is to gain sodium.

People living in warm geographical latitudes of the Earth needed to save sodium to retain water, and to procure its return. Later, when it got colder and people moved to territories with milder climate, a new situation had consequently emerged that did not require one to guard the stored sodium. The mechanisms used for its gaining became excessive. The fact that Afro- American people are more sensitive to salt-intake than Caucasians can be a 'message from our premedieval past'. This assumption is supported by the polymorphisms of the gene for angiotensinogen (ATG gene), beta₂ adrenergic receptors, and epithelial sodium channels in some African populations. Perspiration and infectious diarrhea were the reasons of permanent loss of sodium [1]. Therefore the long-lasting evolution preferred genotypes, which were better equipped to save sodium. This notion can be acceptable; however, it does not necessarily need to be correct.

There exists a negative correlation between the risk of hypertension and birth weight. Low weight at birth in babies of mothers living under dire social and economic conditions is a strong predisposition for the development of hypertension in adulthood of their offspring. The reason can also reside in the fact that during their intrauterine life, these individuals have not reached the full glomerular count, resulting in a smaller filtration area. Lower filtration rate is then compensated by increased pressure in order to achieve optimal natriuresis. If these facts were proved, it would be possible to eliminate the possible risks incurred by intrauterine development of kidneys by changing the system of nutrition in children with low birth weight.

The genetic determination applies when appropriate conditions or mechanisms playing the role of triggers are present. This gives the basis for the conception that hypertension can never originate from one single cause. Moreover, all biologic systems show great plasticity. The possible maladaptation of some mechanisms however, can function as the factor responsible for the consequences leading to hypertension.

Hypertension is an extraordinarily difficult pathophysiologic problem. It has very often devastating consequences; however many times it is only asymptomatic and remains such for a long time before an acute crisis occurs. Hypertension mainly leads to negative conditions as follows: disorder of coronary bed, renal failure, and changes in peripheral vessels in limbs. Hypertension is going to be the largest risk of premature deaths [2].

Nevertheless, the basic question of the origin of hypertension is to be raised, or rather the justness of our used conceptions should be called into question. We can question whether hypertension is actually caused solely by changes in mechanisms, molecules, or some structures. Could we not assume that hypertension is an inevitable adaptation to provide adequate oxygenation in tissues? In that case, reducing the blood pressure would protect one from catastrophic consequences; however at the same time it would particularly inconvenience oxygenation on the level of microcirculation. Does the decrease in pressure procure optimal oxygenation of brain in hypertensive patients? Can it not be assumed that successful treatment of hypertension on one hand eliminates the risks of catastrophe though at the same time, it accelerates chronic degenerative processes [3]? An increase in pressure to a certain limit might improve the oxygenation of tissues. A marked increase in pressure brings about a decrease in perfusion due to induced vasoconstriction. Therefore, there can be a positive correlation with neurodegenerative diseases [4].

In general, it is accepted that hypertension is a complex disorder determined by several factors. It is assumed that it occurs as a result of interactions between genetic factors predisposing to development of hypertension and external environment (diet habits, obesity, hyperlipidemia, smoking, stress).

2. Functional anatomy of the circulation

The circulation (Table 1) can perform its basic function in an optimal way only when the amount of blood flowing through the capillaries of each tissue, or organ per a time unit is fair enough to keep the homeostasis of that organ, so that it can perform its function adequately. The blood flow per minute via the capillaries of the given tissue or organ is the most important parameter of the blood flow (haemodynamics).

The vessels from the functional point of view can be divided into:

1. Compliance vessels, that form the large and intermediate arteries. Their function is to provide a continuous flow of blood. Ensure a fast transport of blood to the peripheries.
2. Resistant vessels are the major determinants of the general peripheral vascular resistance and by this even the regional blood flow. The whole peripheral vascular resistance is an important factor upon which the intermediate arterial blood pressure depends. It includes: The elastic resistance in the arterial system, the peripheral resistance of the resistant vessels, and the resistance which is imposed by the pre-capillary sphincter. We recognize two types of the resistant vessels:
 - a. pre-capillary resistant vessels - small arteries and arterioles - which form about one half of the value of the peripheral vascular resistance.
 - b. post-capillary resistant vessels - venules and small veins - that form a small part of the resistance. They participate in the changes of the potential volume of the capacity field.

- 3. pre-capillary sphincter is that part of the vessel that regulates blood flow into the capillaries and selectively distributes blood into those capillaries. By opening and closing these segments we can determine the number of transition capillaries in a given organ or tissue. The pre-capillary sphincter undergoes systemic and local effects. That determines the metabolism of the tissue or organ.
- 4. capacitance vessels (volume) are mainly the large systemic veins. They represent the reservoir for heart filling.
- 5. exchange vessels are the true blood capillaries. They mediate the contact between the blood field and the interstitial place.
- 6. shunt vessels of the arterio-venous shunts. These vessels provide a fast flow of blood from the arterial to the venous side without passing through the capillaries (bypassing the capillaries). They exist in certain tissues such as skin and lungs.

The primary function of the cardiovascular system is to provide adequate flow of blood through different tissues. The power that provides this is the mean arterial pressure. There is a physical relation between the mean arterial pressure, the minute volume of the heart, and the total peripheral resistance.

The mean arterial pressure = minute volume multiplied by the total peripheral resistance.

aorta	2.5 cm ²
small arteries	20.0 cm ²
arterioles	40.0 cm ²
capillaries	2500.0 cm ²
venules	250.0 cm ²
small veins	80.0 cm ²
vena cava	8.0 cm ²

Table 1. Area of the calibres of different vessels of the circulation.

3. Regulation of blood pressure to its optimal level

Under the headline the arterial (systemic) blood pressure we understand the lateral hydrostatic pressure that acts on the arterial wall during the ventricular systole. The perfusion of organs and tissues is dependent upon the mean arterial pressure. The value of which depend on:

- 1. The volume of blood pumped by the left ventricle in a time unit. The cardiac output.
- 2. The resistance to the blood flow laid down by the vessels in the peripheries of the vascular field.

The minute cardiac output is regulated by four factors:

- a. The end diastolic volume of the left ventricle (preload)
- b. The myocardial contractility
- c. The resistance against which the left ventricle pumps the blood (afterload)
- d. The frequency of the heart.

All these factors affecting the minute cardiac output are affected by the autonomic nervous system: that activates adrenergic receptors in the SA (sinoatrial) node, the myocardium, the smooth muscle in the arterial wall, venules, and veins.

Regulation of vascular tonus. The value of the tonus depends on the structural and functional characteristics of the individual vessels. This value is under the effect of many systemic and local factors.

Systemic factors regulating the vascular tonus are mainly nervous mechanisms, sympathoadrenal system, renin-angiotensin-aldosterone system, and the vasopressin system.

Local factors can be divided into three groups:

1. the vascular myogenic reaction to tension
 2. chemical factors having metabolic origin
 3. humoral factors
- i. The caliber of blood vessels is determined by two physical antagonizing factors. These are the transmural distending pressure and the tangentially acting tension on the vascular wall. In the state of equilibrium the relation between these two and the diameter of the vessel is defined by Laplace law. According to this law the smaller is the vascular diameter the lower is the pressure needed to close the vessel. This is why as soon as the pre-capillary sphincter starts to contract and its translucency is decreased (the wall thickness increases) the tendency of this sphincter to close the vessel is increasing. This magic circle tends to close the vessels completely.
 - ii. An increase in the tissue metabolism is accompanied by an increase in the regional blood flow, which is known as functional hyperemia. The regional vascular tonus is decreasing and the blood flow is increasing. Contraversly in non functioning organs or tissues the blood flow drops down. Functional hyperemia is related to the effects of local chemical factors, either by the accumulation of metabolic products or by the depletion of nutrients. Intensive hyperemia occurs during muscular exertion: there is a marked dilatation of the pre-capillary and post-capillary resistant vessels. According to the vasodilatatory theory the vascular tonus is regulated by factors that originate during the exertion in the contracted muscle fibers, released to the interstitium and can affect the vascular tone directly: CO₂, lactate, other carbohydrate metabolites, decrease in pH, acetylcholin, (ATP – adenosine triphosphate) that evoke active vasodilatation such as histamine and bradykinin, and eventually leading to an increase of capillary permeability. According to the oxygen theory - vascular vasodilatation in active tissues is caused by inadequate O₂ supply. Attention is given mainly to three factors: Hypoxia, regional increase of the extracellular concentration of potassium, and regional hyperosmolarity. Changes in the extracellular concentration of potassium and osmolarity probably influence the vascular tone via the Ca²⁺ influx into the muscle fiber.
 - iii. Humoral factors: a group of vasoactive substances - kinins that have the character of local hormones. Their main function is the regulation of microcirculation. These are mainly: acetylcholin, histamine, 5-hydroxytryptamine - serotonin, prostaglandin, endothelium derived relaxing factor - EDRF, endothelin.

Direct regulation of blood pressure is provided by three reflexes:

- baroreceptor reflex
- chemoreceptor reflex
- ischemic reaction CNS (central nervous system) – (Cushing reflex)
 - Baroreceptors are situated in the carotid sinus, aortic arch, pulmonary arteries and less frequently in other large arteries in the upper chest. Any increase in arterial blood pressure stimulate the baroreceptors, these will depress the activity of the vasomotor center that is followed by lowering the sympathetic tonus: resulting in peripheral vasodilatation lowering cardiac activity and normalization of blood pressure. An opposite effect could be achieved when there is an initial drop in blood pressure.
 - Chemoreceptors react to changes in pO_2 of blood flowing towards the aortic and carotid bodies and they exert their action on blood pressure that ranges between 40-100 mmHg. When there is decrease in the blood flow there is a consequent drop in oxygen supply and a resulting conduction of activity to the vasomotor center will aim to return the pressure back to its original level.
 - Reaction of CNS to ischemia is a defensive mechanism against the extreme drop of blood pressure. This is about a mechanism that ensures an adequate blood flow to the brain. When the blood pressure drops down or the brain is badly perfused due to other reason, the vasomotor centrum suffers and starts to be exclusively active. It starts to send sympathetic vasoconstricting impulses to the vessels and cardiac accelerating impulses to the heart. This mechanism is activated only when the arterial blood pressure drops below 60 mmHg.

The vasomotor center is mainly controlled by the hypothalamus, which posterolateral part increases the activity of the vasomotor center, the anterior part inhibits it.

The central and peripheral sympathetic nervous systems regulate the cardiovascular function via adrenoreceptors. The mediator is noradrenaline, which is produced by the nerve endings. Sympathetic vasoconstricting agents (eg. psycho-emotional stress) stimulate the chromaffin system of the adrenals as well, that leads to the production of adrenaline and low amounts of noradrenaline. Adrenaline leads to an increment in the cardiac output, evokes tachycardia, and increases the systolic blood pressure. The total peripheral resistance is basically not changed. Noradrenaline increases the systolic and diastolic blood pressure by increasing the peripheral vascular resistance. Catecholamins lead to a decrement of the vascular blood flow through the kidneys, and hence a decrement of sodium and water excretion by the kidneys. There is also activation of the renin-angiotensin system.

The renin-angiotensin system is composed of a multistep cascade of on each other dependent substances. The key substance and a limiting factor is the enzyme renin. This enzyme is produced in the juxtaglomerular apparatus of the kidneys. The renin-angiotensin system exists in other tissues too. This extrarenal system is subjected to an intensive study mainly in the vessels.

Angiotensin II binds to the cellular membrane receptors and stimulates Ca^{2+} influx, but do not activate adenylcyclase. Angiotensin as well stimulates the biosynthesis and proliferation of smooth muscle. It causes constriction of the systemic arterioles (by its direct effect on the pre-capillary resistant vessels). During physiological conditions there is a dynamic equilibrium between the pressor and the depressor mechanism, this equilibrium keeps the blood pressure in the optimal range. (Arterial hypertension can be the consequence of the

disorder of the mentioned equilibrium being either due to the relative or the absolute excess of the pressing factors or the inadequacy of the depressing factors).

Differing from the nervous regulatory mechanisms that can react within few seconds, other regulatory mechanisms need longer time for exerting their effect.

1. Transcapillary shift of fluids (the flow of fluid out of the capillaries or into the capillaries): With blood pressure change there will be a change in the capillary pressure. When the arterial blood pressure drops down there will be a consequent drop of fluid filtration through the capillary membrane into the interstitial space and hence increasing the amount of circulating blood. Contraversly, in cases of increased blood pressure there will be fluid escape into the interstitial space. This mechanism reacts slowly.
2. Mechanism of vascular adaptation: For example after a massive blood transfusion there will be an initial raise in blood pressure, yet after certain time – from 10 minutes to one hour - and due to vascular relaxation the blood pressure returns to normal range even though the blood volume increases by nearly 30% over the normal level. Contraversly after a massive bleeding this mechanism can lead to vasoconstriction enclosing the remaining blood volume and by this keeping normal haemodynamics. This mechanism has its restriction by which it can correct only changes ranging between +30% and -15% of the blood volume.

Long lasting regulation of blood pressure is obtained mainly by the kidneys as an organ. Aldosterone limits water and salt loss.

The renal mechanisms of sodium and water excretion have the greatest importance for long lasting regulation. With raising blood pressure there is a consequent raise of perfusion pressure in the kidneys and sodium and water excretion into urine. The raise in blood pressure that results from the raise of cardiac output (for e.g.: in cases of expansion of the body fluids) at normal renal function will evoke pressure diuresis and natriuresis and hence decrease in volume and blood pressure. In renal function disturbance e.g. in low blood flow through the kidneys, which results from the general drop of blood pressure, or from a loss of functional kidney parenchyma there will be sodium and water retention in the organism that will consequently lead to raise in the venous return, cardiac output, and blood pressure.

There will be an establishment of a new state of equilibrium (high blood pressure, high peripheral resistance, normal cardiac output, and normal volume of body fluids) that characterizes most of the hypertension cases. This condition modifies the function of baroreceptors, sympaticoadrenergic mechanisms, renin-angiotensin system, mineralocorticoids and other factors.

Blood pressure is a relative variable and a continuous physiologic value. The level of blood pressure deserves attention because it has been found that it almost directly increases the cardiovascular risk. As the increase is continuous, arbitrary values of arterial hypertension (hereinafter hypertension), at which we can consider the cardiovascular risk to be increased, have been assessed. These values are currently 90 mmHg for the diastolic and 140 mmHg for the systolic blood pressure. According to this criterion, approximately 25% of the world population suffers from hypertension. It seems that the risk of complications depends more on the increase in systolic pressure than diastolic pressure, and it is higher in some specific

groups, for example, in Afro-Americans. As opposed to the latter, a decrease in blood pressure in hypertensive patients markedly decreases the incidence of ischemic disease of the heart, heart failure, brain attack, and the incidence of lethal attacks.

It is necessary to understand the regulation of blood pressure and especially the molecular pathways of its regulation, to be able to treat it. Despite our persistent struggle, we still do not know the details of many of its mechanisms.

We are successful in assessing the etiology of hypertension only in 5%–15% of patients. Secondary hypertension most often develops on the basis of primary hyperaldosteronism, Cushing's syndrome, feochromocytoma, atherosclerotic narrowing of renal artery (renovascular hypertension) or other disorders.

In 80%-95% of patients, the cause of hypertension is unknown. So far, the efforts to find the factor that is responsible for the origin of this 'essential hypertension' have failed. Individual physiological components as cardiac output, volume of extracellular fluid, or plasmatic renin activity differs among patients, implying that essential hypertension is not a disease, but rather a syndrome that is common in several diseases based on variable etiology. The interconnection of difficult mechanisms regulating the blood pressure however leads to the fact that even if there is one factor primarily responsible for the origin of hypertension, others are responsible for its maintenance. It shows that environmental factors as stress, lack of exercise, smoking, alcohol, fat intake, and especially sodium intake in food have to find a sufficiently 'fertile' genetic substrate.

4. Analytical view of blood pressure regulation and factors leading to hypertension

The analytical view of any problem resides in the breakdown of the entire system right down to its individual parts. The latter can be further broken down until we achieve a simplification that can be easily understood. This approach is fully justified in the process of scientific research. However, it is necessary to note that after losing the associations of individual parts with the entire unit, this procedure can lead to a dead end.

Etiology and pathogenesis of essential hypertension is only partially understood. Due to a large number of factors and pathogenic mechanisms that participate in the development and progression of hypertension its pathogenesis is rather complicated. The heterogeneity of the factors which lead to the eventual effect - increasing the systemic arterial blood pressure - is the cause of the fact that has not been unified yet. It seems that it is not even possible, because according to the newest information essential hypertension is a common name for regulatory disturbances of blood pressure, which might have various causes of development and therefore different pathogenic mechanism. Most of the theories which try to explain the pathogenesis do agree on that there is a disorder in blood pressure regulation (this disturbance may probably affect any parts of the regulating chain), that is due to some internal (endogenous) or external (exogenous) factors.

The endogenic factors are multifactorial, including genetic ones. The exogenous factors are the realizers of the genetic propensity, and they include primarily a high salt intake, high energy provision and some psychogenic factors.

4.1 Genetic and familiar affects

It is known, that hypertension usually affects more than one member of the family. The blood pressure, similarly as other quantitative constitutional signs, is to a certain limit similar in all members of the same family.

The decisive factor yet is considered to be the inheritance of those factors that have some importance in the etiology and the pathogenesis of essential hypertension. It was proven that some biochemical and other markers, and even some reactions to different stimuli - that are present in people with essential hypertension - can be noticed also in still healthy normotensive members of hypertensive families:

- There might be some genetically conditioned changes of the metabolism and the release of catecholamines.
- Fast release of noradrenaline from the thrombocytes, can be one of the genetic markers (the place of noradrenaline storage are even the thrombocytes).
- Low contents of kallicrein (a depressor factor) were found in some children of hypertensive families.
- Apart from the discovered high systolic and diastolic blood pressure as well as the body weight in children of the hypertensive families, they also have a significantly low level of plasma aldosterone.
- There is also a genetically based high sensitivity to Na^+ expected in people with essential hypertension.
- There might be a genetic factor that is expressed even due to stress (e.g. normotensive people react differently to various psychogenic stimuli by increasing the blood pressure and a long lasting increment of the blood pressure).
- Meanwhile there is an intensive study about some enzyme transport systems, mainly for Na^+ , K^+ , Ca^{2+} (in the kidneys and the vascular wall, in erythrocytes, leukocytes, and lymphocytes). The genetic determinant of these transport abnormalities in patients suffering from essential hypertension was shown.

The question of genetic markers is very important for the practical field - mainly for the future. As markers blood and serum groups are being studied before all. Meanwhile it is the HLA system and other systems that influence the immunity. For hypertension they are important only for its familiar predilection and also for prognosis of atherosclerosis development and its complications. The hereditary factors basically participate in the variability of the blood pressure and in the genesis of essential hypertension. The type of inheritance is most probably polygenic, additive and it further more interacts with exogenic factors.

4.2 Factors of external environment

SALT: The relation between salt and hypertension development has been known since the beginning of this century. Its role in the pathogenesis is based partly on many epidemiological studies (from different regions of the world), from which it was clear that the prevalence of hypertension is directly related to the amount of salt intake. And partly due to some clinical studies, that refer to that that lowering the blood pressure is parallel with decreasing the extracellular fluid that may be accomplished by diet containing markedly low quantities of salt or by continuous diuretic therapy.

Increasing the salt intake will result in increased volume of extracellular fluid. This fact results in a larger venous return to the heart, that will consequently cause an increase of the cardiac output and due to autoregulation peripheral vessel resistance will be secondarily increased. According to Guyton the peripheral tissues protect themselves in this way from high perfusion, if they are not functioning. Another possibility is a primary increase of the peripheral resistance. During an abnormally high sodium intake there will be an increase of sodium concentration in the muscle cells of the vascular wall that will consequently result in the retention of more Ca^{2+} ions leading to higher vascular wall sensitivity to vasoconstricting agents.

According to the latest studies concerning the pathogenesis of essential hypertension the genetic defect of kidneys to excrete salt plays a very important role. Yet, the exact mechanism that results in increasing of the blood pressure is still not exactly understood or proven. One of the possible explanations that are accepted nowadays are the changes of the cation transport across the cellular membrane. To maintain a constant low Na^+ concentration of Na^+ intracellularly, the Na^+ has to be expelled out across the cellular membrane using these active transport mechanisms:

- $\text{Na}^+\text{-K}^+$ pump: actively expels Na^+ extracellularly against the concentration gradient. The needed energy for this active process is supplied from the hydrolysis of ATP with the aid of the Na^+ , K^+ dependent ATPase. The activity of the $\text{Na}^+\text{-K}^+$ ATPase is a measure of the sodium pump activity. From the quantitative point of view sodium pump is responsible for about 80 % of the active transport of sodium from the cell, the action of which is inhibited by ouabain or digoxin.
- $\text{Na}^+\text{-K}^+$ cotransport mediates a simultaneous unidirectional transport of Na^+ , and K^+ and may be also chlorides intra- or extracellularly.

In physiological conditions these and other transport systems form an optimal electrolyte composition of the intracellular fluid. A disorder of these transport mechanisms can decrease the active transport of sodium from the cell. This means that during an unchanged passive intracellular transport the content of intracellular Na^+ will rise. This rise of the intracellular Na^+ concentration causes rise of the concentration of free intracellular Ca^{2+} as well (due to the fact that there is close relation between the intracellular Ca^{2+} concentration and a transmembrane Na^+ gradient due to the presence of $\text{Ca}^{2+}\text{-Na}^+$ exchange mechanism. Even a slight rise of the intracellular sodium concentration leads to an increment of Ca^{2+} transport intracellularly.)

These transport systems do exist even in the formed blood elements such as erythrocytes, leukocytes, and lymphocytes. This provides us with the chance to study the activity of those transport systems for Na^+ also in human and not only in experimental animals. The activity of $\text{Na}^+\text{-K}^+$ ATPase was proven to be low in erythrocytes, leukocytes, and even lymphocytes of patients with essential hypertension.

Low $\text{Na}^+\text{-K}^+$ ATPase activity is more prominent in patients with high or normo renin essential hypertension (according to the plasma renin activity we classify hypertension as: low-, normo-, and high renin hypertension). Upon increasing the volume of extracellular fluid and hence increasing the extracellular Na^+ content the organism will compensate this by increasing the level of natriuretic substances, mainly, the atrial natriuretic peptide (ANP), which is formed in the cardiac atria and its function is realized in the kidneys where ANP

increases the excretion of Na^+ by increasing the glomerular filtration and inhibiting its tubular reabsorption. It also lowers the aldosterone production. Another of the natriuretic substances is a natriuretic hormone that inhibits $\text{Na}^+\text{-K}^+$ ATPase, which will consequently lead to a limited transport into cells or to expulsion of Na^+ outside the cells, and hence to an increase of the intracellular Na^+ content followed by an increase of intracellular Ca^{2+} content as well (as explained previously). It is not clear yet whether the natriuretic hormone and digitalis-like endogenous substances (digitalis-like compounds) are the same and the only $\text{Na}^+\text{-K}^+$ ATPase inhibitors.

As a consequence of all above mentioned is that there might be a congenital primary defect of the transmembranous Na^+ transport caused by a high level of humoral substance - that is supposed to be the natriuretic hormone.

What is more important here is that during the mentioned exchange mechanisms intracellular Ca^{2+} concentration increases, which is then a trigger mechanism for muscular contraction of vessels. By this mechanism the increased Na^+ concentration in the myocytes of the vascular wall could lead to an increased susceptibility for vasoconstriction stimuli, and by this to become an important pathogenic mechanism for the development of hypertension.

Potassium (K^+) There is a lot of evidence that a high K^+ intake is protective against hypertension and maybe even against other harmful effects of high sodium intake. High potassium intake results in drop of the blood pressure. (Individuals that consume mainly vegetarian food have low blood pressure). The combination of low Na^+ intake and higher K^+ intake is more effective than low Na^+ intake alone.

There are many possibilities of the hypotensive effect of potassium:

1. It causes diuresis and hence lowers the plasma volume.
2. In patients treated with K^+ there is a drop in the body weight and there is a decrease of Na^+ content in the organism.
3. It inhibits the plasma renin activity.
4. It can cause vasodilatation due to a direct effect on the arteriolar smooth muscle.

Magnesium (Mg^{2+}) It was found that adding Mg^{2+} (in the form of aspartate hydrochloride) increases the depressor effect of the diuretics. Any disturbance of Mg^{2+} metabolism may result in generalized muscular contraction and hence affecting the blood pressure. Mg^{2+} is a $\text{Na}^+\text{-K}^+$ ATPase activator and it is a Ca^{2+} antagonist. When the level of Mg^{2+} is low it causes an increase of the intracellular Ca^{2+} concentration and hence promotes vasoconstriction.

Obesity practically all the epidemiological studies point to that there is a direct relationship between the level of the blood pressure and the body weight. This relationship concerns the primitive as well as the developed populations, and also concerns both children and adults.

To explain the relationship between obesity and blood pressure we noticed that obese people who expend more energy need as well a higher expenditure of salt per day. In obese people there might be hyperinsulinemia and as well as insulin resistance. Insulin enhances the retention of sodium in the kidneys. Too much eating is also accompanied by an increase of the sympathetic tone and an increased noradrenaline turnover.

Psychoemotional stress In the interaction with other mechanisms the neurovegetative system also takes part in the regulation of blood pressure. Also its function arises from the basic circulatory functions - in any case to ensure the supply of oxygenated blood under the required blood pressure to all organs and tissues according to their actual needs.

The CNS reacts to exogenous stress factors (stressors of the outside environment) actually via a dual efferent stereotype which affects also the blood pressure:

1. Activating the sympathetic system that leads to the release of catecholamines from the adrenal medulla and this is characterized by some known reactions.
 - fight (associated with vasodilatation in all limbs)
 - flight (vasodilatation only in lower limbs)
2. Activating of the adenohypophysis and via the adrenocorticotrophic hormone the stimulation of the adrenal cortex.

In the initial phase of stress there will be an activation of antidiuretic hormone (ADH) that is formed in the hypothalamus. After its release from the neurohypophysis (where it is only stored) into the circulation, it acts on the distal and the collecting tubules of the kidneys. Its action lies in enhancing the reabsorption of water. Apart from this it shares the modulation of blood pressure. In the beginning of the stress situation and as a result of the peripheral vasoconstriction there will be a lowered renal perfusion that leads to the activation of the renin-angiotensin-aldosterone system.

Aldosterone increases the volume of body fluids by the reabsorption of Na^+ and hence water in the distal tubules. Angiotensin II is a pressor factor. It stimulates vasoconstriction via direct mechanism. It enhances the synthesis and the release of noradrenaline from the nerve endings and it also blocks its uptake by the nerve terminals. Apart from this it stimulates adrenaline and aldosterone release from the adrenals as well as the vasopressin from the neurohypophysis, what will consequently lead into an increased vascular susceptibility to vasoconstricting agents.

Along with the stimulation of the sympathetic nervous system and the adrenal medulla, there will also be release of hormones of the anterior lobe of the pituitary (adenohypophysis), from which the most important one in stressful situations is the adrenocorticotrophic hormone (ACTH).

The accepted fact meanwhile is that high blood pressure is associated with certain personality characters as well as with certain type of occupation. From this point of view there are some interesting studies that classify people according to their behavior and reactivity into two types: type A and type B. Type A people - who are predisposed to hypertension are characterized by high agility, ambition, psychological instability that might turn into aggressive and impulsive behaviour, the person is despotic and egocentric. People of type B are characterized as phlegmatic, psychologically stable, with no personal ambitions.

From the mechanistic point of view, blood pressure is proportionate to the cardiac output and peripheral resistance. Therefore, all factors involved in the development or maintenance of hypertension must be associated with changes in one or both of these two physiological values.

In a majority of patients with incipient essential hypertension, there is an increase in cardiac output, whereas the peripheral resistance and the extracellular fluid volume stay normal. Later, as blood pressure increases, the cardiac output decreases again to physiological or mildly increased values just as well as the volume of extracellular fluid (with the exception of the disorder in renin-angiotensin-aldosterone system), whereas the peripheral resistance increases. In advanced stages of the disease as a result of the damage incurred to target organs, the glomerular filtration decreases (the extracellular volume increases), and the perfusion of the brain and coronary vessels also decreases. In this phase, the maintenance of high blood pressure is inevitable in order to procure sufficient perfusion of brain and kidneys (to maintain the glomerular filtration at a decreased filtration surface). Hypertrophic heart muscle without the respective growth in coronary perfusion, however, is not able to provide sufficient perfusion pressure against the increased vascular resistance. The activation of renin-aldosterone system and the retention of fluids theoretically improve this state, yet eventually they bring about further fixation and progression of hypertension. As a result of progressive damage to nephrons, a decrease in glomerular filtration takes place in advanced stages of the disease and further contributes to the retention of sodium and extracellular fluid.

Consequent comprehension of the pathomechanism of hypertension needs to take into account all the possible disorders in regulation of individual physiological components, determining the development and maintenance of increased blood pressure, cardiac output, and peripheral resistance.

5. Factors determining the peripheral resistance and its role in blood pressure regulation

Haemodynamic changes in essential hypertension

During the initial stage of the essential hypertension the cardiac output is increased and tachycardia is present. The causes and the mechanism of an increased cardiac output in hypertensive patients with the initial stage of essential hypertension are due to an increased sympathetico-adrenal activity. It acts directly on the heart and the vascular structure, where there is an increased tension of the vascular wall in the resistant and the capacitive (venous) field. Narrowing the venous field will increase the preload and could be the primary cause of increased cardiac output.

But more marked haemodynamic changes can be seen in people with essential hypertension during physical activity. During the early stages of hypertension there will already be a drop in cardiac output due to the drop of systolic output. However, the resistance of arteries increases. In the late stages the signs of hypokinetic situation due to the subnormal systole become even more prominent.

In patients with long lasting hypertension high blood pressure is the result of high peripheral resistance in case of low functioning myocardium, or a marked cardiac insufficiency. The first change occurring in the vessels can be functional vasoconstriction or some structural changes in the vascular wall.

During vasoconstriction that is caused by high sympathetic tonus, concentration of Na^+ , Ca^{2+} and water content in the vascular wall also increase. Later on there will be some

structural changes in the wall of the vessels: Thickening of the wall due to the hypertrophy of the media and hyperplasia of the collagen fibers. That is the cause of the changes in the relation between the thickness of the vascular wall and its lumen. Narrowing of the lumen alone can increase peripheral resistance. In patients with developed hypertension the high peripheral resistance is caused by vasoconstriction and by structural changes in vascular walls.

The arteriolar vasoconstriction and the vascular resistance do not occur in all organs equally in essential hypertension. The most affected are the vessels of the skin and kidneys, whereas the skeletal muscles are perfused normally.

Peripheral resistance is determined especially by the lumen of resistant arterioles, and to a lesser extent, by the lumen of medium and large arteries. These can be changed either by active contraction of smooth muscles, or passively by remodeling. Both mechanisms are influenced by hemodynamic load and neurohumoral regulation (balance between vasoconstrictors and vasodilators), as well as by concentrations of sodium and potassium ions.

Further, it is necessary to note that on one hand the vascular bed perfusion is directly proportional to pressure difference; on the other hand however, it is inversely proportional to peripheral vascular resistance. In other words, the increased blood pressure under the condition of increased peripheral resistance does not necessarily have to improve the perfusion. On the contrary, increased peripheral resistance means that in order to maintain the same perfusion, it is necessary to increase the systemic pressure; thus greater cardiac work is needed. If the increase in blood pressure is inappropriate in relation to the increase in vascular resistance, then the microcirculation can even deteriorate by forming a further requirement to increase the blood pressure. In this way a vicious circle develops, leading to further fixation and progression of hypertension.

6. The role of microcirculation

A great problem resides in microcirculation. The perfusion of blood via capillary bed is regulated by physical laws. We can quantify neither the details of myogenic tonus of arterioles, nor the transmural pressure within capillaries [5-7].

It is very probable that the capillary bed functions as a modular system. The blood does not flow instantly through all capillaries. The fluctuation of perfusion and nonperfusion forms a complex system that has not yet been investigated. The diameter of capillaries ranges from 4 to 12 μm ; erythrocytes achieve the diameter of 7.2 μm . This fact implies that the perfusion of blood through capillaries has no analogy in the flow of water through an elastic system. Probably it would be very illusory to imagine that in the capillarized organism, the processes of filtration and reabsorption take place very near each other, and at the same time. The argument can be seen in the structure of kidneys. The arterial end of capillary with filtration is represented by capillaries within glomeruli and the venous end of capillaries is represented by peritubular capillaries.

When imagining the modular system of microcirculation the filtration takes place, with subsequent reabsorption in the same capillaries. The exchange of filtration and reabsorption is probably a complex system, the changes of which compel the inflow of blood to take place under higher pressure.

The increased heart rate represents another problem. The pulse waves crash into one another, possibly resulting in decreased perfusion. Each increase in heart rate causes an increase in the filling of the system; however not an increase in microcirculation via capillaries. In adrenergic situations, the increase in blood pressure with no increase in heart rate would be more advantageous for the organism. The entire process is however a matter of the complex system of regulation and participation of the sympathetic nerves, enabling the circulation to adapt to various stimuli.

7. Pathophysiologic outcome for the possible therapeutic benefit

The vessels supplying the tissues with blood and thus with oxygen can be regarded as an elastic system that is submerged within the elastic environment (e.g. myocardium). Two elastic systems are involved. A change in pressure within the tissue surrounding the vascular bed influences the blood perfusion [8, 9]. The impact of pressure on vessels and perfusion is in close relation to their diameter. An increase in outer pressure decreases the perfusion within arterioles and shifts the blood into the capillary bed [8]. It is very probable that Hook's law can also be applied in this situation. Despite the great progress achieved in medicine, and two centuries of investigation, the exchange of substances on the capillary level remains a problem for both physiologists and philosophers [10].

In their biomechanic studies, Wang et al. [11] applied the Hook's law to intravascular blood circulation. A decrease in compliance and elasticity (increased rigidity, or increased pressure) within the surrounding tissue can decrease the blood perfusion even in an entirely intact vascular bed. Current clinical studies as well as experimental investigations are focused on the vascular system, especially its distributing part. These measurements provide many valuable parameters. The changes in structures and tissues surrounding the capillary bed however still elude our understanding. We lack precise parameters and have only a mosaic notion of them. We can only assume that within these tissues plasticity and elasticity decrease with age.

Animal experiments prove our conception of the possible impact that changes occurring within the perivascular tissue pressure have on blood perfusion [12]. The latter authors however admit that in large vessels also the tunnel-in-gel concept is justified. In compliance with this conception, a change in elastic properties of tissues, namely a decrease in their elasticity decreases the blood perfusion within these tissues. This notion is in accord with experimental measurements of Golub et al. [13]. By using a special technique of phosphorescence quenching microscopy they found that the decrease in partial oxygen pressure in the course of arterioles is negligible. They found that there is a measurable difference between partial oxygen pressure present in small arterioles and that in venules. By means of the latter technique, they discovered local differences in tissue pO_2 and the dependence of O_2 consumption on local pressure changes. Wilson et al. [14] used this technique to measure the partial oxygen pressure and stated a hypothesis that the capillary wall had no impact on the diffusion of oxygen from plasma into pericellular space.

It is generally known that electrophysiological measurements of intracellular and pericellular values of oxygen pressure range from 0 mmHg to 5 mmHg, and within the mixed venous blood it ranges between 30 mmHg and 40 mmHg. The normal function of both isolated cells and cells within tissues requires pressure exceeding 2 mmHg [15]. The

most significant moment appears to be the difference between vascular and intracellular values of oxygen pressure. We assume that a decrease in diastolic pressure can bring about a decrease in intracellular and pericellular values of oxygen pressure. The mechanisms of processing this information within the body are still not known. A decrease in pericellular and intracellular oxygen can be a consequence of decreased diastolic and hydrostatic pressure (Fig. 1). This phenomenon is facilitated by the fact that pericellular and intracellular values of oxygen pressure are already under very low physiological conditions. This conception can possibly be an acceptable explanation of adverse effects that appear as a consequence of therapeutic decrease of blood pressure down to the level of 70 mmHg or lower [16, 17, 18].

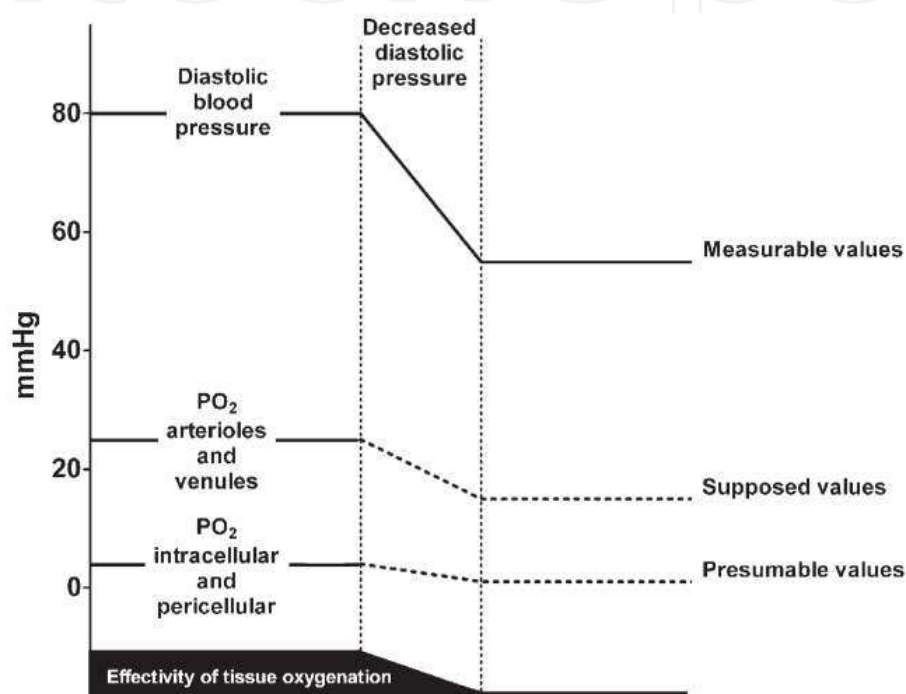


Fig. 1. Probable changes of oxygen pressure caused by decreased diastolic pressure.

8. Conclusions

Essential hypertension is a consequence of complex multifactorial disorders. In some cases it can be the mutation of one gene in a large population. Most probably essential hypertension is a result of a combination of mutations and polymorphisms of some genes influencing the blood pressure in interaction with various environmental factors.

Most probably, even in the future it will still not be possible to assess all polymorphisms and altered molecular mechanisms responsible for the origin of hypertension. However, a more detailed knowledge about the molecular pathways involved in blood pressure regulation would most probably help us to understand the development of hypertension in more details. We assume that the origin of hypertension can be inevitable to ensure sufficient oxygen delivery under higher pressure because it is necessary due to the hypertension-induced alteration in the structure of microcirculation. On the contrary, a therapeutic decrease in blood pressure can deteriorate tissues oxygenation at least, for a particular time until a new balance is formed and until new remodeling takes place (Fig. 2).

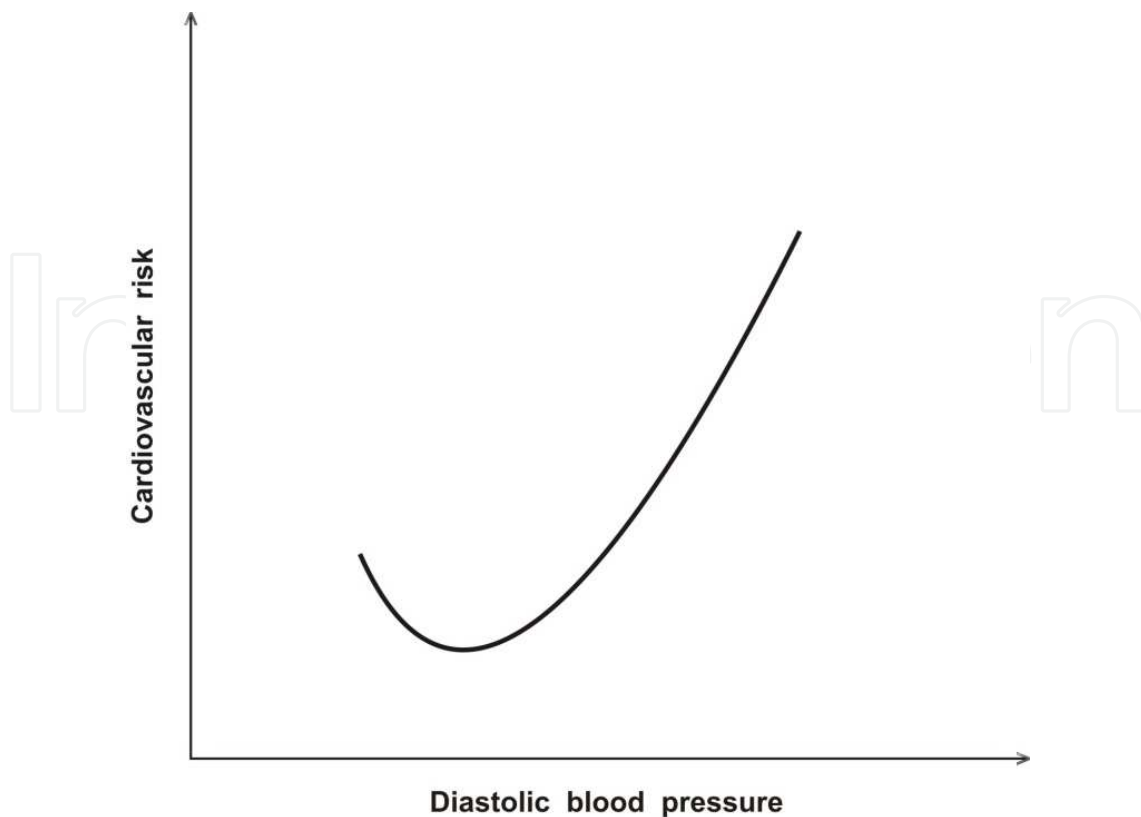


Fig. 2. J-curve as a possible consequence of insufficient tissues oxygenation.

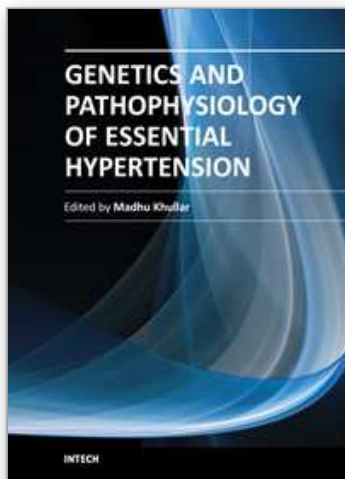
9. Learning points

- The cells can be the hidden motor forcing the organism to fulfill the cellular needs. In this view blood pressure is not only a part of a functioning circulation.
- The optimization of osmotic and pressure factors can be achieved in various ways. These mechanisms can very effectively manage new situations in each cell, preferably in selected cells. The long-lasting activation of these mechanisms may lead to their fixation enabling the pressure to serve as a tool for increasing natriuresis at general load.
- Essential hypertension is a consequence of complex multifactorial disorders. Most probably, essential hypertension is a result of a combination of mutations and polymorphisms of some genes influencing the blood pressure in interaction with various environmental factors.
- We assume that the origin of hypertension can be essential to ensure sufficient oxygen delivery under higher pressure because it is necessary due to hypertension-induced alteration in the structure of microcirculation.
- Therapeutic decrease in blood pressure can deteriorate tissue oxygenation, at least for a particular time until a new balance is formed and until new remodeling takes place. Does the decrease in pressure procure optimal oxygenation of brain in hypertensive patients?
- It is an established fact that about hypertension has accumulated a lot of information. Hypertension can be treated successfully. Drug therapy reaches approximately physiological blood pressure. Hypertensive patients with approximately normal blood pressure in spite of this fact die due to hypertension. Successfully treated patients

compared with untreated live a little longer. But they die on the same consequences as untreated patients with hypertension.

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This book, authored by renowned researchers in the field of Hypertension Research, details the state of the art knowledge in genetics, genomics and pathophysiology of Essential hypertension, specifically the genetic determinants of hypertension and role of gene variants in response to anti-hypertensive therapy. Two chapters describe mitochondrial mutations in Essential hypertension and in hypertension associated Left ventricular hypertrophy, one chapter reviews in detail the global gene expression in hypertension, and an up to date treatise on pathophysiology of resistant hypertension is detailed in another chapter. Other topics included in the book are end organ damage, baroreceptor sensitivity and role of music therapy in essential hypertension.

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