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UNIVERSITY COURSE

PATHOPHYSIOLOGY OF ARTERIAL HYPERTENSION

(mechanisms, consequences and predictors)

For medical students, residents and postgraduate mastership and doctoral searchers

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1. Abbreviations

AHT - arterial hypertension

Ang II – angiotensin II

BH4 – tetrahydrobiopterin

BP – blood pressure

COX – cyclooxygenase

CRP - C reactive protein

ECE – endothelin converting enzyme

ECM – extracellular matrix

EDHF - endothelium derived hyperpolarizing factor

EPCs – endothelial progenitor cells

ET-1 – endothelin 1

FOR – free oxygen radicals

IL- interleukines

LV – left ventricle

NE – norepinephrine

NF-kB – nuclear factor kappa B

NO – nitric oxide

NOSe – endothelial nitric synthase

NOSi – inducible nitric synthases

MMP – metalloproteinases

ONOO – peroxynitrite

PAI-1 – inhibitor of activator of plasminogen

PGI_2 – prostaglandin I_2

RAAS – renin-angiotensin-aldosterone system

RAGE – receptor of advanced glycation end products

TGF-1β – transforming growth factor

TNF-α – tumor necrosis factor

TLR – Toll-like receptor

VCAM – vascular cellular adhesion molecule

VEGF - vascular endothelial growth factor

CONTENTS

2. Preface

Essential or primary arterial hypertension (AHT) represents a pathology of cardiovascular homeostasis manifested by elevated levels of the blood pressure in any age and gender whose real etiology remain still unknown. When blood pressure increases in relation to the presence of an evident causing factor (e.g. kidney, endocrine, nervous disorders) capable conspicuously to contribute to blood pressure (BP) raising arterial hypertension is identified as secondary and follows namely as renal, endocrine, cerebral hypertension.

Among of the all cases of arterial hypertension HPT occupies around 90%, and in contrast to secondary arterial hypertension it is linked tightly to disorders of the vegetative system, vascular endothelium and metabolic abnormalities.

According to the recent approaches of AHT management the opportune diagnostical criteria eligible for persons with age >18 years are represented by systolic blood pressure >140 mm Hg and diastolic blood pressure >90 mm Hg. These criteria are stipulated in the guides of European Society of Cardiology and American Heart Association as well.

The main aspect of HPT is that the abnormal control of blood pressure for a certain time is not associated with any clinical symptoms. Allegorically HPT is defined as a mute "silent enemy" or "mute killer", and asymptomatic evolution in this regard delays the time of the person addressing to doctor. Therefore, the therapeutic strategy starts too late often when already there are deep morpho-functional disorders in the target vital organs, such as kidneys, brain, heart and eyes.

Raised levels of the blood pressure being associated with increased peripheral resistance lead to afterload increase provoking subsequently the phenomenon of remodeling of myocardium and small resistive arteries (cerebral, renal, coronary and ocular). Taken together, all patterns with cardiovascular remodeling triggered by AHT represent a precondition for heart failure development, cardiac arrhythmias and sudden death. Moreover, HPT is considered as a predictor of heart failure, renal failure, stroke, and a factor accelerating the atherosclerosis evolution as well.

Medical-social impact of AHT is determined by high incidence of vascular accidents like acute myocardial infarction and ischemic or hemorrhagic stroke frequently leading to premature death of patients or invalidation.

In this regard 4 crucial tasks are underlined by contemporary medicine regarding management of AHT:

1. Early diagnosis of elevated blood pressure.
2. Applying the algorithm of risk factors for AHT to design a useful strategy of prevention based on attenuation and mitigation of modifiable hazards as soon as

possible, employing in this context educational programs and population learning as well. Although conceptually AHT is accepted as a pathology progressing with ageing a worldwide tendency is accented - rejuvenation of hypertension. More and more cases of AHT are attested among children, an event that comprises a high probability of a serious circulatory dyshomeostasis developing in the adult period of life span like hypertensive heart and chronic heart failure, stroke, acute myocardial infarction etc.

3. In order to monitorize the risk of hypertension induced vital organ damaging is needed a feasible panel of circulatory multi-markers with a significant prediction value. This multi-marker strategy should be useful in both AHT diagnosis and prognosis. Likewise, it might emphasize the efficiency of applied antihypertensive treatment. Elucidation of markers with predictive power regarding diverse components of circulatory homeostasis is also an important tool of understanding and debunking of key pathogenic mechanisms triggering and sustaining hypertension.
4. Achieving the close controlled hypotensive effects of antihypertensive therapy based on modulation of main pathogenic mechanisms. Pathogenic treatment of AHT can be defined as an adequate extrapolation of known disease pathophysiological aspects in pharmacological field. Pathogenic treatment of AHT is referred not only on intrinsic blood pressure controlling systems, but also on prevention and attenuation of severe sequelae of prolonged arterial hypertension.

Most difficult supports of AHT pathophysiology are due to presence of an intricate complex of diverse intrinsic systems involved in blood pressure control, including priority vascular endothelium, neuroendocrine and vegetative systems, hemostasis, intercellular signaling molecules and growing factors, circulating vasoconstricting and vasorelaxing factors, and sure genetic traits.

Searching of the pathogenic mechanisms of AHT is precipitated on ostial conceptual bases of the blood pressure control. It emphasizes 3 main pylons:

1. Left ventricle (LV) pumping power and accordingly the blood jet spill force to press the vascular wall leading to elevation of systolic BP (>140 mm Hg). This kind of AHT is depicted as isolated systolic hypertension because usually the diastolic BP remains normal (<90 mm Hg). Isolated systolic hypertension is characteristic for young healthy persons and is due to boosted cardiac contraction. In around of 15% of the older population (>60 years old) isolated systolic hypertension is attributed to other causes, such as hyperthyroidism, artery stiffness, aortic valve insufficiency, and respectively is considered as secondary hypertension.

2. Blood viscosity. Its increase is a determinant factor of the vascular resistance, and it is expected to contribute to blood pressure elevation when the control mechanisms counteracting

increased blood viscosity (>4 c.u.) impact on especially small and resistive arterioles. This pathophysiological pattern of AHT is not tangible tackled because it is masked or embraced in the entity of other mechanisms.

3. Vegetative control, neuroendocrine regulation and vascular endothelium are principle actors orchestrating homeostasis endeavors for normal BP maintenance in the field of action of different extrinsic and intrinsic factors. The failure of their integrated functional capacity results in blood pressure raise and AHT evolution. Namely these arrangements will be analyzed beneath in context of known pathophysiological entities and mechanisms.

Likewise, a special glance will be assigned to other two aspects of the approached problem: (i) disclosure the traits of the AHT impact on the vital organs, so called target organs damage and (ii) unraveling the inherent markers having predictive value regarding AHT evolution and prognosis, as well as plausible involved mechanisms and pathophysiological interfaces.

3. Notion of risk factors of arterial hypertension

Although the real pathogenesis of AHT remains undeciphered a set of factors capable to provoke blood pressure elevation have been underlined. These factors are linked to life style and likewise are represented by harmful factors concerning cardiovascular homeostasis. Because they might trigger the BP raising are considered as risk factors for AHT. The most important risk factors of HPT are: smoking, alimentary disorder manifested by increased fats intake, hypodynamia, psychoemotional stress, narcotics, alcohol etc. Because these factors can be changed (i.e. improved) they are named as modifiable risk factors of HPT.

Another group of risk factors, contributing to susceptibility of the body to suffer from the BP elevation are not modificable. This group of nonmodifiable risk factors of AHT mostly includes genetical polymorphism, hyperhomocisteinemia, enzymopathy, gender and age. Generally, ageing is considered as a strong and independent risk factor for cardiovascular pathology. Ageing in this context is a crucial factor and precondition of worn vascular endothelium, who’s appearing is tightly linked to inflammation activation.

Many pathophysiologic factors implicated in the genesis and sustainable support of essential hypertension can be important scaffold elements for AHT pathogenesis building:

• Increased sympathetic nervous system activity, perhaps related to heightened exposure or response to psychosocial stress. The activation of sympathetic system is viewed also in regard to activity of parasympathetic, hence, contrary system.

• Increased activity of the renin-angiotensin-aldosterone system (RAAS) which is activated mostly by catecholamines and hypoperfusion of renin secreting cells of the kidney. Activated RAAS is manifested by elevated circulating levels of angiotensin II (Ang II), a vasoconstricting octapeptide, and aldosterone as well.

Sympathetic and RAAS activation is corroborated as neuroendocrine system activation, manifested in partly also by overproduction of sodium-retaining hormones and vasoconstrictors.

• Long-term high sodium intake. Inadequate dietary intake of potassium, magnesium and calcium.

• Disorders in lipid profile manifested by increased blood cholesterol level, and primary LDL-cholesterol (cholesterol transported by low density lipoproteins).

• Increased or inappropriate renin secretion with resultant increased production of Ang II and aldosterone.

• Deficiencies of vasodilators, such as prostacyclin, nitric oxide (NO), and the natriuretic peptides.

• Alterations in expression of the kallikrein– kinin system that affect vascular tone and renal salt handling.

• Abnormalities of resistance vessels, including selective lesions in the renal microvasculature.

• Diabetes mellitus, insulin resistance, and obesity.

• Increased activity of vascular growth factors leading to vascular remodeling.

• Alterations in adrenergic receptors that influence heart rate, inotropic properties of the heart, and vascular tone.

• Genetics, viewed as a pattern of genetical polymorphisms resulting in increased expression of most important actors playing a key role in the cardiovascular homeostasis control.

The novel concept that structural and functional abnormalities in the vasculature, including endothelial dysfunction, increased oxidative stress, vascular remodeling, and

decreased compliance, may antedate hypertension and contribute to its pathogenesis has gained support in recent years.

Synoptically, pathogenesis of AHT encompassing all most important factors and events able to influence detrimentally the vascular wall are exposed in the fig. 1.

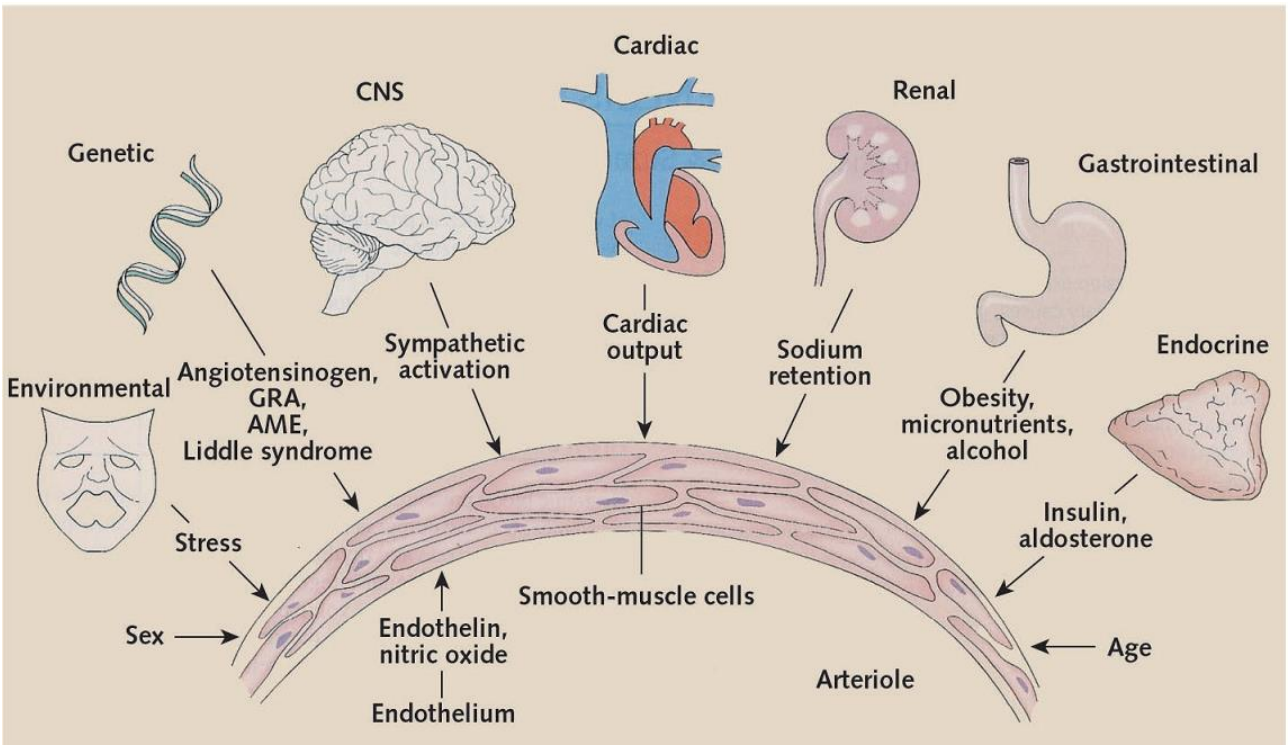

Figure 1. Factors consolidating pathogenesis scheme of AHT (S.Oparil et al. Pathogenesis of hypertension. Annals of Internal Medicine, 2003, vol.139, p. 761-776).

The central puzzle element of AHT pathogenesis is endothelial dysfunction and vascular remodeling because here are projected practically all factors making either vasodilatation or vasoconstriction. Vascular endothelium functioning intelligible becomes a target of AHT diagnosis and forecast estimation, as well as a target for antihypertensive treatment consolidation.

Nowadays this scheme is completed by other few pathophysiological factors of AHT such as hyperuricemia (increased circulating level of uric acid), vitamin D lack, arginase elevation, tetrahydrobiopterin deficiency, activated oxidative stress etc.

The markers of endothelial dysfunction and vascular remodeling, inflammation, oxidative stress and neuroendocrine activation, electrolyte disbalance, diabetic and lipid disorders became relevant circulatory predictors of arterial hypertension.

4. Role of autonomic system in AHT evolution

Abnormal increases in circulating plasma levels of the adrenergic neurotransmitters norepinephrine (NE) and epinephrine have repeatedly been demonstrated in individuals with a state of AHT mostly during the tests boosting psychoemotional activity. Pressor responses to a variety of laboratory stressors have also been examined and found to predict the subsequent development of arterial hypertension. A big number of young persons, sharing AHT demonstrate signs of overactivated sympathetic system.

It has been found that the increase in NE is not due to its reduced tissue disposal but rather to an enhanced spillover rate from neuroeffective junctions and thus to augmented norepinephrine secretion from sympathetic nerve terminals. White coat induced blood pressure elevation is tightly linked to excessive activation of sympathetic efferent stimuli. Remarkably, the sympathetic hyperactivity is likely to be accompanied by a decreased vagal influence on the vessels and heart. Thus, the both divisions of the autonomic nervous system may be altered in individuals who have a greater risk of developing hypertension, even when an overt blood pressure abnormality is not yet detectable. Noteworthy, in young patients with isolated systolic hypertension or so-called hyperkinetic syndrome associated with increase of cardiac output the ratio sympathetic/parasympathetic activity is increased. The reduction in glandular secretions under parasympathetic control, such as salivary flow in borderline hypertensive individuals suggest that in early hypertension, parasympathetic impairment is not confined to the heart or to the cardiovascular system, rather, it is generalized to all parasympathetically dependent functions. Conceptually is important that sympathetic activation is accompanied with increased expression of the both beta- and alpha-adrenergic receptors on both vessel and heart levels. A such positive feed-back regulatory mechanism underlines that sympathetic activation triggers a boosted reactivity of small resistive arteries and heart as well manifested by alpha-1-receptor provided vasoconstrictor effect of NE and positive chronotropic and inotropic cardiac effects of both NE and epinephrine.

Sympathetic activation is often detected in persons with body weight gain, hypodynamic statement, metabolic syndrome and insulin resistance syndrome accompanied with increased circulating levels of insulin and leptin. Nowadays is proven that both insulin and leptin could increase postganglionic sympathetic driving.

Adrenergic overdrive that characterizes hypertension might follow the blood pressure increase and the progression from uncomplicated to complicated stages that may occur in the course of the disease. The level of sympathetic activation has been shown to be more pronounced in hypertensive patients with left ventricular hypertrophy, impaired left

ventricular diastolic function and systolic heart failure, a fact which extends the sympathetic system contribution in the circulatory pathophysiology. This point emphasizes the pathogenic therapeutic approach based on sympatho-adrenergic antagonists aiming mitigation the sympathetic influences in cardiovascular system.

The sympathetic overactivity associated with the established hypertensive state is not uniformly distributed throughout the body. Rather, regional differences are such that it is marked in some districts and modest or even absent in others. For example, radiolabeling studies have shown that in established hypertension, there is increased norepinephrine spillover into the cerebral, coronary, and renal circulation but not at the level of the splanchnic and pulmonary vascular bed.

Pathophysiologic role of the sympathetic system in the arterial hypertension evolution is not confined only to blood pressure raising genesis, but refers also to vascular and cardiac morpho-functional changes appreciated as cardiovascular remodeling. Hypercatecholaminemia has been demonstrated to be a factor stimulating vascular smooth myocyte hypertrophy which results in arterial wall thickening and increased capacity of resistive arteries for a vasospasm. Additionally, metabolization of the catecholamine excess by either monoamine oxidase or catechol-o-methyltransferase leads to release of the free oxygen radicals (FOR) which compromise the natural mechanism of endothelial dependent blood pressure control thereby alteration of both endotheliocyte and nitric oxide (NO). Hypercatecholaminemia also actively leads to myocardium hypertrophy resulting consequently in increased cardiac systole and pulsatile pressure.

Finally, disbalance between sympathetic/parasympathetic activity in AHT explains why in these patients the blood pressure elevation is not so closely linked with baro-reflex induced vagal influence on heart. Therefore, increased BP does not induce heart rate diminution, and even a tendency of heart rate increase may occur. Hypercatecholaminemia, arterial hypertension and tachycardia are collectively a cluster of factors impairing circulatory homeostasis and evolution of the cardiovascular diseases, being also a strong risk factor for vascular accidents and mortality.

5. Endothelin 1 contribution in the AHT evolution

Endothelin1 (ET-1) is considered as the strongest natural vasoconstrictor agent. Remarkably, the circulating level of ET-1 is notably elevated in patients with diverse patterns of circulatory dyshomeostasis, such as AHT, heart failure, cardiac arrhythmias, atherosclerosis. It represents an oligopeptide from 21 aminoacids released mostly by endothelial cells in different stressogenic conditions, such as boosted hemodynamic stress,

hypoxia, oxidative stress, inflammatory response etc. Produced by the proteolytic cleavage of big endothelin-1 by endothelin converting enzyme (ECE), endothelial endothelin-1 is predominantly (>80%) released abluminally toward the vascular smooth muscle. Indeed, local endothelin-1 concentrations within the vascular wall are more than 100-fold greater than circulating plasma levels. This abluminal ET-1 action is considered as a pattern of paracrine action of oligopeptide, providing vascular smooth myocyte growing, an inherent sign of the vascular remodeling.

By activation of ETA and ETB receptors expressed on vascular smooth myocytes, ET-1 increases calcium entering in the cell leading to a durable vasoconstriction (L-type calcium channel blockers decrease the vasoconstrictor effect of endothelin-1 on the vasculature). Type ETB is also expressed on endothelial cells and its activation by ET-1 provokes release of NO having a well-known effect of cGMP stimulation and calcium entering mitigation. Endothelial ETB receptor activation can lead also to release of prostacyclin which reduces ET-1 induced prothrombotic state.

Likewise, vasoconstricting effect of ET-1 is due to its capacity to inhibit activity of the NOSe and subsequently to NO release diminution. This action is sustained also because ET-1 markedly stimulates evolution of atherosclerosis thereby of following mechanisms:

- Expression of intercellular adhesion molecules (selectins, integrins, VCAM).
- Expression of proinflammatory cytokines, such as NF-kB, IL-6 and TNF-α.
- Platelet aggregation and boosting of prothrombotic state.
- Excessive formation of FOR.

Increase for a long time of the ET-1 release leads to vascular remodeling which sustains elevated blood pressure, because it is manifested by hypertrophy of vascular media and vascular lumen diminution. Vascular wall thickening level is correlated with the arterial hypertension severity and peripheral resistance as well.

Important data are obtained in clinical and fundamental studies by using of the blockers of ETA and ETB receptors. It has been shown that both selective ETA and non-selective ETA/ETB receptor blocking improved acetylcholine mediated endothelium dependent vasorelaxation. So, ET-1 dysregulates the local vasomotor controlling system, and markedly tangles the action of the natural vasorelaxant agents.

Due to atherosclerosis progression the endothelial ETB expression is reduced, a phenomenon which augments the ET-1 abluminal action on muscular media of small arteries and arterioles (fig.2). Hence, in atherosclerosis and older people the ETA/ETB ration increases, and this event augment paracrine effects of ET-1 on smooth vascular myocytes

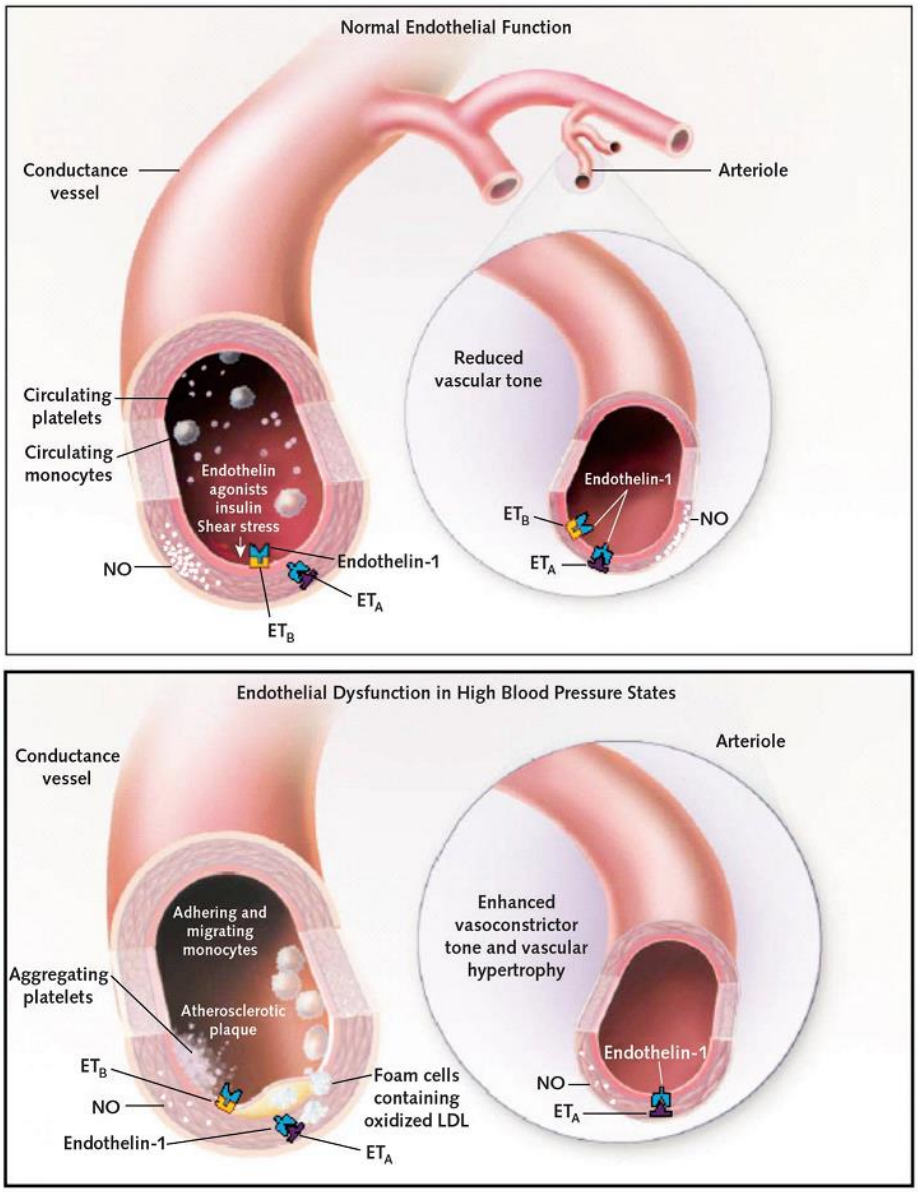

Figure 2. ETA/ETB receptor ration increases in atherosclerosis and endothelial dysfunction (S.Oparil et al. Pathogenesis of hypertension. Annals of Internal Medicine, 2003, vol.139, p. 761-776).

Noteworthy, the ET-1 induced blood pressure elevation is inversely correlated with taurine level expression in the vasculature, especially in the bed of resistive arteries. Taurine, a non-protein synthesis amino-acid, is known as a natural regulator of the calcium intracellular entering tool ("trigger of the calcium revolver") and it can blunt the vasoconstricting effect of ET-1. Furthermore, taurine can also confine the ET-1 induced muscular media hypertrophy and, respectively, vascular remodeling.

Between ET-1 and sympathetic system is found a certain relation. It has been demonstrated that beta-1-adrenergic stimulation boosts the ET-1 action on vessels and heart:

vasoconstriction and myocardium hypertrophy. Thus, beta-adrenergic blockers use in the treatment of AHT provides antihypertensive effect thereby ET-1 mitigation.

Importantly to note that physical activity decreases the ET-1 activity and limits its pathological action on cardiovascular system. Exercise-induced reductions in ET-1 system activation may contribute significantly to the known beneficial effects of exercise in preventing and treating hypertension and reducing the risk of atherosclerosis.

ET-1 is a predictor of vasomotor dysfunction and atherosclerosis, and a therapeutic target of arterial hypertension, especially in older persons. In this regard to underline the large searching of pharmacological possibilities to inhibit in hypertensive humans the either ECE expression or ECE activity.

6. Renin-angiotensin-aldosterone system and AHT evolution

Renin-angiotensin-aldosterone system (RAAS) plays a crucial role in the arterial hypertension triggering and evolution. Its activity primary depends on renin (also called as angiotensinogenase) released as exocytosis mostly by juxta-glomerular cells (localized between afferent and efferent renal arteries) of kidney under the action of renal ischemia and hypoxia, sympathetic efferents (NE activates via beta-1-adrenergic receptor these cells), hypovolemia and hypotension.

Renin cleaves a big protein synthesized by liver, angiotensinogen, resulting in the release of a non-active vascular decapeptide, angiotensin I. The last is shorted by 2 right amino-acids under the action of a special enzyme, ACE (angiotensin converting enzyme) and is transformed in the octapeptide, angiotensin II (Ang II) (fig.3).

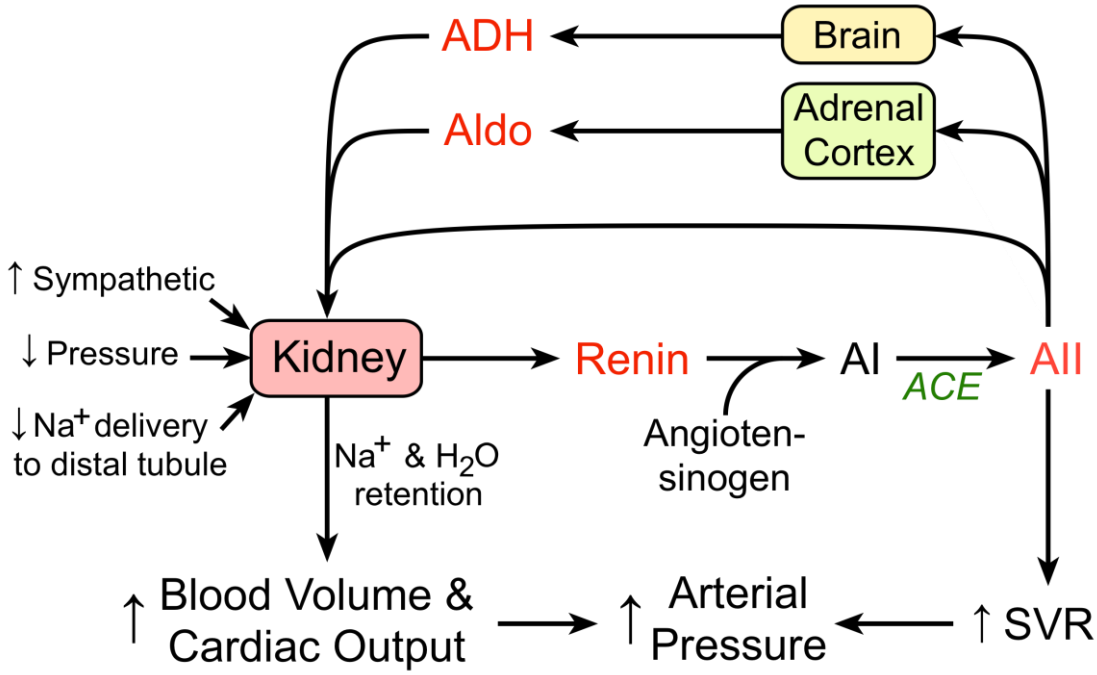

Figure 3. Factors involved in the angiotensin II (AII) formation (ADH – antidiuretic hormone)

Ang II is a very active vascular factor capable to induce a lot of phenomena, such as:

1. Vasoconstriction.
2. Hypertrophy of muscular media and vascular remodeling.
3. Activation of the prothrombotic state.
4. Activation of the fibroblasts and subsequently of extracellular matrix (EXM) growing due to increased synthesis of collagen and fibrosis. Stimulation the fibroblast transformation into myofibroblasts.
5. Activation of the EXM metalloproteinases (MMP) resulting in the degradation of reticular collagen type IV from elastic layers separating media from intima and adventice from media.
6. Cell migration, cell proliferation and neointima formation.
7. Expression of the proinflammatory cytokines.

All these effects are mediated by AT_1 receptor, whose expression is fond on smooth vascular myocyte, cardiomyocyte, interstitial fibroblasts etc. Another subtype of Ang II receptor is AT_2, which is expressed mostly on endothelial cell. Its activation leads to NO and prostacyclin release.

A special Ang II action is due to its capacity to activate oxidative stress, that results in endothelial damage triggering and exacerbation based mostly on NO diminution (fig. 4).

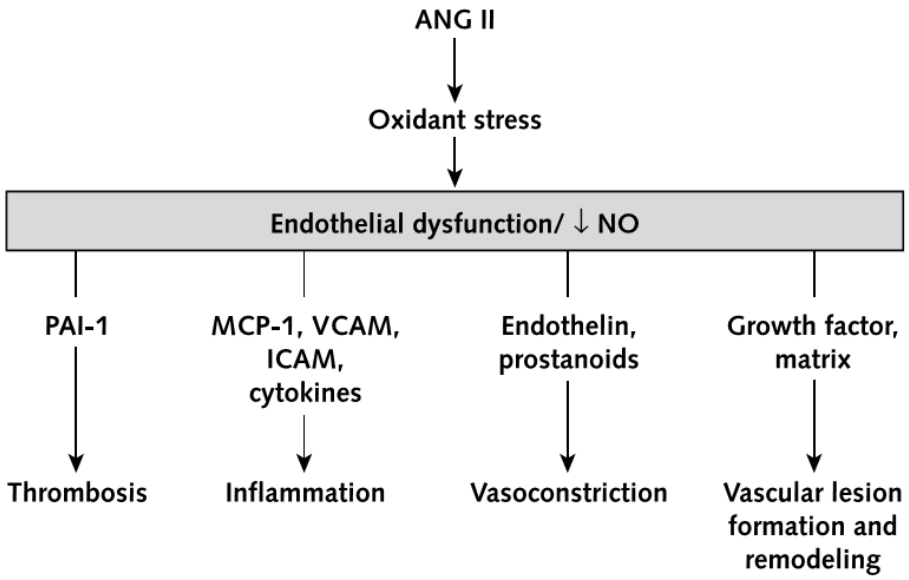

Figure 4. Pathological vascular events induced by Ang II thereby oxidative stress activation

Ang II is capable also alone to decrease the NOSe expression. So, one of the pivotal Ang II excess effects is the endothelial disorders, and especially NO reduction, that plays a crucial role in the Ang II induced vasoconstriction and vascular remodeling.

Besides vasoconstriction and vascular remodeling, the Ang II role in AHT evolution is based on octapeptide capacity to stimulate NE release from sympathetic nerve endings and to inhibit the NE re-uptake, that taken together results in increased sympathetic activity facilitating hence, maintenance of high levels of the peripheral vascular resistance.

Resistance to blood flow within a vascular network is determined by the size of individual vessels (length and diameter), the organization of the vascular network (series and parallel arrangements), physical characteristics of the blood (viscosity, laminar flow versus turbulent flow), and extravascular mechanical forces acting upon the vasculature. Of the above factors, changes in vessel diameter are most important quantitatively for regulating blood flow within an organ, as well as for regulating arterial pressure. Changes in vessel diameter, particularly in small arteries and arterioles, enable organs to adjust their own blood flow to meet the metabolic requirements of the tissue. Therefore, if an organ needs to adjust its blood flow (and therefore, oxygen delivery), cells surrounding these blood vessels release vasoactive substances that can either constrict or dilate the resistance vessels.

Ang II formation embraces 2 ways: (i) blood and (ii) tissue, because now is demonstrated that the ACE (dipeptidylcarboxypeptidase, family of kininase II) could by expressed not only by vascular endotheliocytes (especially pulmonary), but also by epiteliocytes, fibroblasts, cardiomyocytes, myocytes, astrocytes etc. Therefore 2 pools of Ang II are recognized: circulatory and tissular. So, Ang II can act in both manners: endocrine and paracrine. In the brain the local Ang II formation is proven because ACE is expressed mostly by choroid plexus and cerebral vascular endothelial layer, and in general, all compounds of RAAS are present in the brain, including the local renin and angiotensinogen. ACE activity is found in the areas of brain that lacks BBB (blood brain barrier), such as the subfornical organ and pineal gland. To note, the brain ACE expression diminution resulting in Ang II lack is associated with cognitive disorders.

The RAAS cascade is not ended by Ang II formation. A special branch of metabolic way is exhibited by formation of a heptapeptide, Ang 1-7, which is a product of right amino-acid cutting from Ang II chain under the action of ACE2, a monopeptidase (a zinc containing metalloenzyme) expressed abundantly by endotheliocytes and other cells, such as epiteliocytes, smooth vascular myocytes, hypothalamus, glial cell etc.

Recent studies show that Ang 1-7 being omnipresent is actively involved in the vascular biology control and regulation of the blood pressure. Its renowned effects are

stemmed from physiological properties to counteract the detrimental effects of the Ang II due to activation of a distinct class of receptors named as Mas receptors (fig. 5).

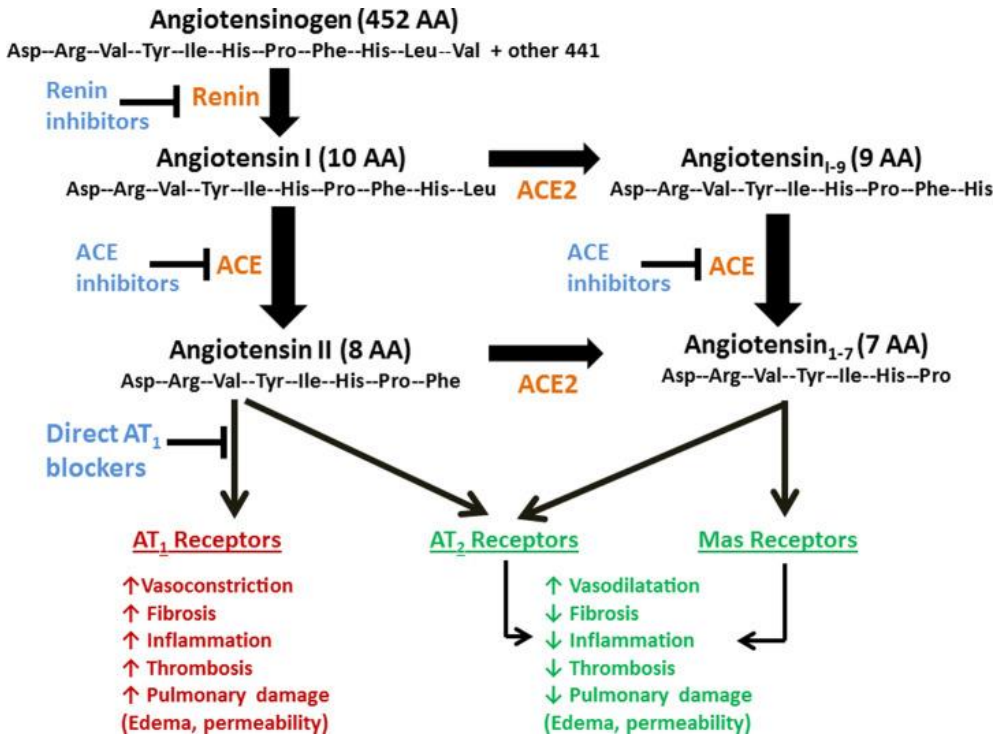

Figure 5. Formation and effects of Ang II and Ang 1-7 (P.Verdecchia et al. Eur. J. Intern. Med. 2020; doi:10.1016/j.ejim.2020.04.037)

Predominantly, Mas receptors are expressed by vascular endothelial cells. Mas receptor activation results primary in lowered activity of the AT_1 receptors, that confines the following actions of Ang II: vasoconstriction, fibrosis, thrombosis, oxidative stress and inflammatory response. Ang 1–7 also improves glucose and lipid homeostasis facilitating thus, vascular biology orchestration. Inhibitory action of Ang 1-7 regarding the Ang II effects is especially emphasized in hypertensive persons with obesity, metabolic syndrome and insulin resistant syndrome. Ang 1-7 reduces expression of leptin and proinflammatory cytokines, and decreases activity of the oxidative stress. Collectively these vascular protective benefits explain why an administration of exogenous Ang 1-7 significantly improved endothelium dependent vasodilation and vascular remodeling and reduced oxidative stress activity due to increased expression of superoxide-dismutase and catalase.

Ang 1-7 is metabolized by ACE, therefore dipeptidylcarboxypeptidase inhibition or ACE2 activation preserves higher amounts of Ang 1-7 with good repercussions for the circulatory homeostasis. They are detected in the heart and brain among the dynamics of blood pressure decline. A special benefit of Ang 1-7 is explained by its capacity to blunt the

muscular media hypertrophy and neointima formation as two paramount signs of the vascular remodeling. This effect is considered to be in partly dependent on increased susceptibility of AT_2 to Ang II action under the Ang 1-7 action mediated by Mas receptor.

In the patients with AHT, heart failure and diabetes mellitus type II the production of Ang 1-7 is reduced due to lowered expression of ACE2. Nowadays, Ang 1-7 represent an intriguing target of treatment of the AHT and other cardiovascular disorders. Several small studies already showed a promising therapeutic perspective of Ang 1-7.

7. Endothelial dysfunction – an ostial tool of AHT pathogenesis

Conceptually vascular endothelium occupies a key position in the control of blood pressure, as well as in regulation of inherent to vascular remodeling events, such as cell hypertrophy, cell proliferation and cell migration. Being an active endocrine tissue, the vascular endothelium secrets a lot of biologically active substances having remarkable benefits, such as antiplatelet, antiapoptotic, anti-inflammatory etc. Altogether, the majority of vascular endothelium benefits are based on nitric oxide a gas formed in the metabolic reaction regarding L-arginine and endothelial enzyme – NOS_3 (nitric-oxide-synthase type 3 or endothelial type, NOSe).

Today, NO is considered as the strongest vasorelaxant factor which cooperates with another endothelium derived factor, prostaglandin I_2 (PGI2) or prostacyclin, synthesized from arachidonic acid under the action of calcium and phospholipases.

Besides NO and prostaglandin, the capacity of vascular endothelium to provide vasodilation is relied on EDHF (endothelium derived hyperpolarizing factor) – fig. 6.

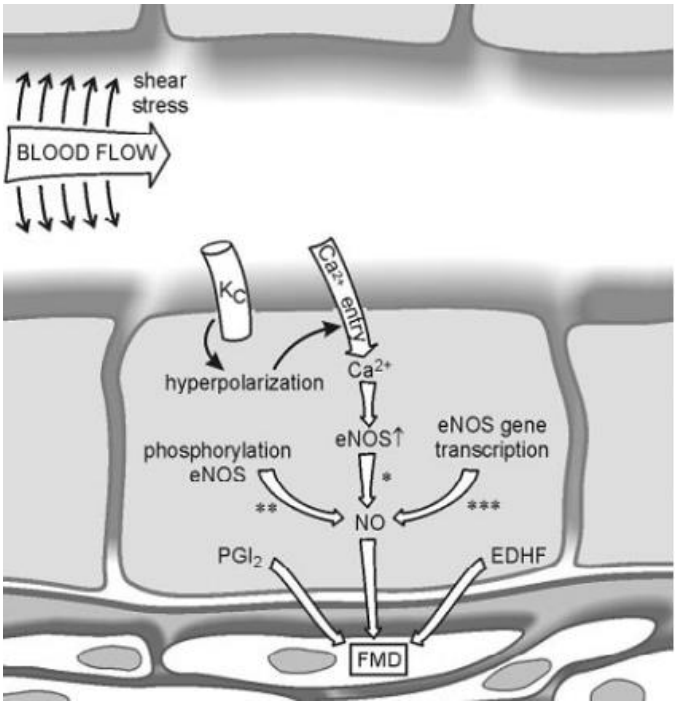

Figure 6. Factors of endothelium (NO, PGI_2 and EDHF) in the vascular tone control

The vasodilating effect of EDHF is due to its ability to provoke hyperpolarization of the both endotheliocyte and smooth vascular myocyte. The last phenomenon is associated with activation of potassium channels resulting in the inability of calcium entering the smooth vascular myocyte. As consequence smooth myocyte is relaxed and blood pressure is prone to decrease.

If both PGI_2 and EDHF are factors entirely involved in the vascular tone control, then NO is recognized as a factor controlling all phenomena happening in the vascular wall regarding vascular remodeling.

Endothelial dysfunction referred initially to structural changes in endothelium, such as those seen in atherosclerosis, but nowadays this term is used to describe the loss of the endothelium's ability to regulate vascular resistance.

Almost every stimulus evoking to a systemic inflammatory response i.e. severe infection, trauma, excessive tissue breakdown, solid tumors, leukaemia, pregnancy associated complications such as hypertensive disorders and liver failure, and toxicological or immunological responses and activation of the coagulation system can be associated with endothelial damage. Inflammatory processes that are involved in arteriosclerosis. Low-density lipoprotein (LDL) infiltrates the artery wall and undergoes modification by oxidation. The modified LDL particles then induce the expression of adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1). Monocytes migrate into the vessel wall and differentiate into macrophages. After migration through the endothelial layer, the monocytes differentiate into macrophages and scavenge the oxidized low-density lipoprotein (oxiLDL) from the vessel wall, resulting in foam cell formation. Stimulation of toll-like receptors (TLRs) of macrophages results in the release of several proinflammatory cytokines, such as TNF-α, IL-1β and IL-6. T cells become activated during this time and produce other mediators such as interferon (INF-γ), which further amplifies the inflammatory response and contributes to atherogenesis. The activation of TLRs also induces expression of matrix-degrading matrix metalloproteinases (MMPs), which probably play a role in weakening the fibrous cap and promoting plaque vulnerability.

Cardiovascular risk factors, such as smoking, hypercholesterolemia, and elevated blood pressure give rise to a variety of noxious stimuli that elicit secretion of both leukocyte soluble adhesion molecules, which facilitate the attachment of monocytes to endothelial cells, and chemotactic factors, which encourage the migration of monocytes into the subintimal space. The transformation of monocytes into macrophages and the uptake of cholesterol

lipoproteins are thought to initiate the fatty streak. Further injurious stimuli may continue the attraction and accumulation of macrophages, mast cells, and activated T lymphocytes within the growing atherosclerotic lesion, and secretion of metalloproteinases and other connective tissue enzymes by activated macrophages may break down collagen, weakening the cap and making it prone to rupture. Thus, virtually every step in atherogenesis is believed to involve cytokines, FOR, other bioactive molecules, and cells that are characteristically associated with inflammation.

An association between endothelial dysfunction and arterial hypertension is well established. The main link between AHT endothelial dysfunction is represented by incapacity of endothelium to produce adequate amounts of NO. Endothelium mediated vascular relaxation following acetylcholine infusion is reduced in essential hypertension compared to normotensive controls. The pathophysiology of hypertension involves a complex interaction of multiple vascular effectors including the activation of the sympathetic nervous system, of the renin–angiotensin–aldosterone system and of the inflammatory mediators. Subsequently vasoconstriction and inflammation ensue, leading to vessel wall remodeling and finally, to the formation of atherosclerotic lesions as the hallmark of advanced disease. Oxidative stress and endothelial dysfunction are consistently observed in hypertensive subjects, but emerging evidence suggests that they also have a causal role in the molecular processes leading to hypertension. The discovery of vascular receptors that control vessel tone and neurohumoral mediators in hypertension has led to the development of modern antihypertensive drugs such as beta-blockers, angiotensin converting enzyme inhibitors, AT-1 receptor blockers or calcium channel blockers. Although the pathophysiology of hypertension is extremely complex and multifactorial, and the role of factors such as endothelin, cyclooxygenase-dependent vasoconstrictors and endothelium-derived hyperpolarizing factor needs to be acknowledged, numerous experimental animal studies indicate that this condition is associated with an increased formation of oxygen radicals from all layers of the vascular wall.

Action of FOR on vascular endothelium is manifested mostly by alteration of protein and lipid structures (process defined as peroxidation). Has been demonstrated that oxidative stress activation associated by excess of FOR is accompanied by NOSe expression reducing, and this process is going in a robust correlation. More than that, FOR are able to reduce NO availability because superoxide anion (O_2^-), an aggressive free radical interacts with NO leading to formation of peroxynitrite ($ONOO^-$): $O_2^- + NO = ONOO^-$.

Peroxynitrite not only reduces NO life span, but it also markedly ensures worsening of arterial hypertension evolution because possesses itself vasoconstricting effect. Likewise, peroxynitrite sustains endothelial dysfunction, because it is able to trigger the endotheliocyte

apoptosis and irreversible injury as well. Peroxynitrite is considered to play a certain role in the NOSe expression diminution because it alters the structure of the caveolin and clathrin proteins, resulting in NOSe expression lowering.

A direct tool connecting of endothelial dysfunction and ageing is determined by oxidative stress. Aging impairs blood vessel function and leads to cardiovascular disease. The mechanisms underlying the age-related endothelial, smooth muscle and extracellular matrix vascular dysfunction are discussed in the field of acceptance of age as an independent cardiovascular risk factor. The aging process in vascular smooth muscle is characterized by changes in cellular phenotype and responsiveness to contracting and relaxing mediators. Contractile phenotype is controlled by a complex intrinsic system, whose main tool is micro-RNA-143 and micro-RNA-145. Their expression diminution leads to loss of contractile phenotype and appearance of the secretory phenotype. The vascular myocytes with secretory phenotype obtain impropriate traits, such as migration and proliferation viewed as 2 pieces of vascular remodeling triggered and sustained even by low-grade inflammation (or subclinical inflammation). The latest together with oxidative stress accelerate endothelial cell senescence.

The premature endothelial cell senescence is hallmark of AHT especially in persons exposed to cardiovascular risk factors like obesity and metabolic syndrome, insulin resistance syndrome and hyperglycemia, hyperhomocysteinemia and hyperuricemia, smoking and hypodynamic state and is exhibited by:

- increased production of free oxygen radicals;
- increased expression of proinflammatory cytokines;
- increased expression of arginase;
- increased expression of RAGE receptors;
- decreased expression of NOSe;
- decreased expression of Sirtuin-1.

So, impact of the many risk factors on vascular biology and system controlling blood pressure levels is manifested by early developed endothelial dysfunction.

Noteworthy, that the oxidative stress induced NO life span reducing can be improved by glucagon-like peptide 1 (GLP-1), a proglucagon-derived hormone secreted by intestinal endocrine L-type cells, which is rapidly inactivated by an enzyme dipeptidyl peptidase 4 in circulation. On one hand, GLP-1 analogues or dipeptidyl peptidase 4 inhibitors upregulate endothelial nitric oxide synthase expression and increase endothelial nitric oxide synthase phosphorylation, resulting in improved production of NO and thus endothelium-dependent relaxations. On the other hand, GLP-1 and related agents attenuate endothelium-dependent contractions by reducing reactive oxygen species generation and cyclooxygenase-2 expression.

GLP-1 elevating agents and GLP-1 receptor agonists improve endothelial function in hypertension, suggesting that GLP-1 signaling could be a therapeutic target in hypertension-related vascular events. So, each possibility for free oxygen radicals production decrease or antioxidant system augmenting is a candidate of therapeutic treatment of patients with AHT.

One of the mechanisms linking diabetes, endothelial dysfunction and arterial hypertension is arginase expression. Excessive arginase activity in hyperglycemia drives L-arginine metabolism towards the production of ornithine, polyamines, and proline, resulting hence in the NO production diminution in the NOSe triggering citrulline circle and proliferation of vascular smooth muscle cells and collagen formation, events which facilitate vascular remodeling. Remarkably, the arginase expression correlates with increased expression of the RAGE receptors, whose activation provokes a lot of phenomena altering vascular biology and vasomotor functions control, such as release of FOR, expression of proinflammatory cytokines and MMP, decreased expression of NOSe and increased expression of NOSi. Taken together these effects lead to vascular remodeling, progressing of atherosclerosis and arterial hypertension evolution as well.

Inflammatory status in obese hypertensive persons is augmented by adipokines, one of them having versatile functions on cardiovascular system is leptin. Leptin increases FOR synthesis, decreases NOSe expression, increases RAGE expression, elevates circulating levels of homocysteine and diminishes circulating pool of the endothelial progenitor cells (EPCs).

Then the serum level of homocysteine exceeds the value of 15 μmol/L is considered as hyperhomocysteinemia. It diminishes the vasodilation by nitric oxide, increases oxidative stress, stimulates the proliferation of vascular smooth muscle cells, and alters the elastic properties of the vascular wall resulting in the blood pressure raise. To note that the hyperhomocysteinemia is correlated with preclinical inflammation and premature atherosclerosis. The correction of elevated homocysteinemia by administration of vitamins B12, B6 and folic acid (vitamin B9), could be a useful adjuvant therapy of standard antihypertensive treatment.

Circulating endothelial progenitor cells, derived from myeloid pluripotent stem cells that also give rise to mature mononuclear cells, also play significant roles in maintaining endothelial homeostasis through their regenerative and repair mechanisms. Reduced levels of EPCs correlate with impaired vascular endothelial function and severity of the arterial hypertension. The regenerative and repair capacity of endothelial progenitor cells in newly diagnosed prehypertensive and hypertensive humans is impaired relative to healthy controls. Further, the level of circulating EPCs is negatively influenced by activated complement fragment C3a in hypertensive humans. Impairment of vascular endothelial function and

vascular injury related to C-reactive protein depends on the presence of C3. Overall, these newer data suggest that hypertension-associated vascular endothelial dysfunction relates to local vascular inflammation as well as to systemic inflammation.

A true endothelial target of action of the many risk factors in the field of blood pressure control is tetrahydrobiopterin (BH4). BH4 is a cofactor that regulates NOSe activity in part by stabilizing the NOSe dimer and promoting NOSe coupling. Notably, the NOSe dimer is destabilized, and eNOS becomes uncoupled when BH4 levels are depleted. BH_4 plays a crucial role in donating an electron that leads to scission of the O–O bond, leading to formation of an iron–oxy complex that participates in the hydroxylation of L-arginine, leading to formation of NO. In the absence of BH_4, the Fe2+ O–O complex dissociates to release superoxide ($O_2^{\bullet-}$). During conditions of oxidative stress tetrahydrobiopterin is decreased, because oxidation of BH4 to dihydrobiopterin which can not ensure the normal functioning of NOSe and respectively synthesis of the adequate quantities of NO. Tetrahydrobiopterin decline is closely proven in cases of augmented inflammatory state, hyperhomocysteinemia and decreased EPCs level. Nowadays, BH4 is used as a medicine (oral doses as 1, 5 or 10 mg/kg/day) for improvement of endothelial dysfunction associated with elevated blood pressure and a risk of AHT induced severe repercussion (target organs damage). Blood pressure fall is documented within first week of BH4 treatment.

Sirtuin or SIRT (Silent information regulator), as an intracellular family of proteins controlling cell survival due to its antiapoptotic (linked to control of protein 53), antioxidant and anti-inflammatory effects, appears to be an important interface focusing the action of many risk factors. In regard to the crucial role of the endothelial cell dysfunction in the AHT pathogenesis the SIRT-1 expression was found lowered, especially in patients with insulin resistant syndrome. SIRT-1 diminution is associated with decreased circulatory levels of EPCs and neointima formation due to proliferation of the migrated smooth vascular myocytes. Thus, SIRT-1 appears to be a significant predictor of the vascular remodeling and, respectively, of arterial hypertension. Furthermore, SIRT-1 is now recognized as an important therapeutic target of severe atherosclerosis induced vascular accidents. By ageing, SIRT-1 expression decreases and is hallmark of the endothelial cell senescence. Importantly, markedly lowered SIRT-1 is omnipresent in hyperglycemia, and this fact truly is emphasized as a mechanism of diabetes induced endothelial injury, vasomotor control failure and blood pressure elevation. Hyperglycemia induced endothelial cell apoptosis is plausible mediated by decreased SIRT-1 expression and dysregulation of the protein 53, an intracellular tool controlling the activity of pro- and apoptotic events. More than that, decreased SIRT-1

expression could be a causing factor of the asymmetric dimethylarginine enhancement, that intelligible leads to lowered production of NO.

8. Hyperuricemia and arterial hypertension

The plausible role of uric acid in AHT pathogenesis is coming from a body of evidences showing that in patients with elevated blood pressure increased circulating level of uric acid is often above normal value. Uric acid is a product of purinic bases degradation under the action of 2 main enzymes: xanthine- and hypoxanthine-oxidases. Gout is known in this regard as a disease induced by long-term of hyperuricemia. With respect to the human condition, the early appearance of hyperuricemia is a reliable predictor of later development of hypertension, and in adults with AHT the comorbidity of hyperuricemia is very common. In 90% of adolescents the hypertension is associated with hyperuricemia and that the threshold for the effect of serum urate in these children is between 5.0 and 5.5 mg/dL.

In ischemic and inflammatory vascular tissue, as is often associated with hypertension, the observation that there is a major upregulation of the production of endothelial-associated xanthine oxidase is of relevance. The latter xanthine oxidase is bound to the luminal surface of the endothelial cells, and recent studies have confirmed that endothelial dysfunction, mediated by xanthine oxidase, is an important component of vascular disease, such as arterial hypertension and coronary artery disease. In patients with cardiovascular pathology and endothelial dysfunction inhibition of xanthine oxidase by allopurinol results in significant symptomatic alleviation, associated with improvement of circulating and functional markers of vascular endothelium.

Hyperuricemia often accompanies metabolic syndrome, hypertension, diabetes, dyslipidemia, chronic renal disease, and obesity, and the serum uric acid level is known to vary significantly depending on meals, lifestyle, gender, and previous use of diuretics.

The first assumed mechanism of hyperuricemia linked AHT is determined by increase of the FOR production and oxidative stress activation respectively. In patients with gout the circulating levels of intermediate and final products of lipid peroxidation are significantly elevated. The same relation is detected in patients with AHT associated with hyperuricemia. Activated oxidative stress leads to NO life span reduction and excessive formation of peroxinitrite.

The second putative mechanism of hyperuricemia link to arterial hypertension is underlined by capacity of uric acid to stimulate the vascular inflammation.

Noteworthy, human vascular smooth muscle and endothelial cells contain the urate transporters URAT1 (SLC22A12) and URATv1/GLUT9 (SLC2A9). Uric acid enters the cells via these transporters, activates COX-2 via redox reaction, increases the MCP-1, involved in the inflammation of blood vessels and cellular proliferation, and triggers arteriosclerosis.

When the serum uric acid level exceeds 7.0 mg/dl, uric acid that does not stay dissolved in the blood vessel precipitates as monosodium urate crystals. The monosodium urate crystals are deposited on the vascular wall and affect blood coagulation, which likely leads to arteriosclerosis. In blood vessels, the monosodium urate crystal easily precipitates as a result of mechanical stimuli caused by blood pressure. This is the main reason why hyperuricemia is defined as serum uric acid levels that exceed 7.0 mg/dl in the treatment guidelines for hyperuricemia and gout. Monosodium urate crystals bind to plasma IgG, are recognized by the Fc receptors on blood platelets, and stimulate the platelets to induce coagulation; cytokines and thrombi that are produced during this process are involved in the progression of arteriosclerosis. Monosodium urate crystals also activate polynuclear leukocytes, monocytes, and lymphocytes, and generate a variety of inflammatory substances. When polymorphonuclear leukocytes engulf the monosodium urate crystals, this results in the release of superoxides, LDL oxidation, and disorders of endothelial cells and blood platelets - all of which facilitate arteriosclerosis.

Drugs with URAT1 inhibitory activity, such as benzbromarone, probenecid, fenofibrate (antidyslipidemia drug), losartan, and irbesartan (angiotensin receptor blockers/antihypertensive drugs) are well known.

The third mechanism of HPT dependence on hyperuricemia is linked to monosodium urate crystals formation. They are accumulated in the endothelial cells and challenge the inflammasome. Inflammasome activation results commonly in two opportune repercussions:

1. Triggering of cell apoptosis.
2. Activation of nuclear factor kappaB and stimulation of expression of pro-inflammatory cytokines. Thus, by this way hyperuricemia markedly alters endothelium and augments endothelial dysfunction due to atherosclerosis progression.

The fourth mechanism attributed to pathophysiology of AHT relation to hyperuricemia is designed by the fact that the last notable increases arterial stiffness and reduces vascular compliance respectively.

Increased arterial stiffness is associated with vascular wall ageing and atherosclerosis and entirely is linked to endothelial dysfunction. The basis of arterial wall stiffening consists on excessive synthesis of collagen and its deposition in extracellular matrix and neointima. On the other hand, activated oxidative stress activates extracellular matrix metalloproteinases resulting in excessive collagen break down. Accumulation of degraded collagen in neointima zone also contributes to thickening of vascular wall and compliance reducing. In addition to these structural abnormalities, endothelial dysfunction, which develops over time from both aging and hypertension, contributes functionally to increased arterial rigidity in elderly persons with isolated systolic hypertension. Reduced NO synthesis or release in this setting, perhaps related to the loss of endothelial function and reduction in endothelial NO synthase, contributes to increased wall thickness of conduit vessels, such as the common carotid artery. The functional importance of NO deficiency in isolated systolic hypertension is supported by the ability of NO donors, such as nitrates or derivatives, to increase arterial compliance and distensibility and reduce systolic blood pressure without decreasing diastolic blood pressure.

Other factors that decrease central arterial compliance include estrogen deficiency, high dietary salt intake, tobacco use, elevated homocysteine levels, and diabetes. These factors may damage the endothelium.

The fifth mechanism ensuring influence of hyperuricemia on blood pressure is determined by activation of rennin-angiotensin-aldosterone activity and increased Ang II.

The sixth mechanism of connection between hyperuricemia and endothelial dysfunction is prothrombotic pattern evoking atherosclerosis progression and worsening of endothelial dysfunction. Likewise, uric acid was disclosed as a potent factor to stimulate expression of intercellular adhesion molecules resulting in increased platelet adhesion and transendothelial passing of neutrophils and monocytes. The increased monocyte passing through endothelium is also supported by uric acid induced expression of MCP-1. Altogether, these events boost endothelium inflammation and atherosclerotic plaque growing.

9. The role of vitamin D lack in arterial hypertension evolution

Vitamin D lack associates a lot of somatic diseases. Among them arterial hypertension is demonstrated regardless of gender and age. More than that, vitamin D supplementation showed in many studies benefits regarding endothelial functioning and blood pressure control. Vitamin D is produced endogenously in the skin after exposure to the ultraviolet B spectrum of sunlight. Importantly, only few foods are natural sources of a consistent amount of vitamin D. Consequently, vitamin D insufficiency and deficiency are widespread among humans due

to limited sun exposure and insufficient consumption of foods or beverages containing vitamin D. The primary physiological role of vitamin D in regulating calcium homeostasis is well established: hypovitaminosis D is known to contribute to osteoporosis through a decline in calcium absorption, subsequent secondary hyperparathyroidism, and increased bone resorption. For this reason, decreased vitamin D levels are usually associated with increased parath-hormone levels, and vitamin D supplementation significantly reduces PTH plasma levels. Importantly, vitamin D receptors are expressed by virtually all tissues, including endothelial cells, vascular smooth muscle cells and cardiomyocytes. Therefore, the attention of researchers has recently shifted towards finding a link between hypovitaminosis D and cardiovascular diseases.

At least 4 major mechanisms are involved in the vitamin D lack induced blood pressure elevation.

Active form of vitamin D is 1,25(OH)2D, named as calcitriol that is obtained from circulating form, 25(OH)D under action of specialized enzyme, 1α-hidroxylase. Cell activation is realized by calcitriol acting on nuclear receptor type 1. Remarkable, calcitriol level is correlated with blood concentration of Ang II, NO and markers of inflammation and oxidative stress indicating hence the pathophysiological significance of a common interface concerning main mechanisms of endothelial dysfunction. Contemporary medicine suggests the close relation of vitamin D level and Klotho gene which controls also the expression of nuclear receptor. Decreasing of Klotho circulating protein is associated with calcitriol deficiency and notable endothelial dysfunction.

The first mechanism of vitamin D deficiency induced arterial hypertension is linked to increased activity of RAAS due to stimulation of rennin release. The last phenomenon is due to suppressing of renin gene by vitamin D. As a result, lowered levels of Ang II are formed, and vasoconstriction power of RAAS decreases. In addition, reduced Ang II level is a notable benefit regarding the vascular remodeling and arterial hypertension corroboration.

The second mechanism of vitamin D lack induced HPT is linked to calcium deficiency because calcitriol stimulates calcium intestinal absorption and proximal renal tube reabsorption. When serum calcium is low, $1,25(OH)_2D_3$ and parathyroid hormone (PTH) act to maintain calcium homeostasis. $1,25(OH)_2D_3$—the active form of vitamin D and the ligand for the vitamin D receptor (VDR)—acts to increase calcium absorption from the intestine. If normal calcium is unable to be maintained by intestinal calcium absorption, then

$1,25(OH)_2D_3$ and PTH, together acting via their receptors, release calcium from the bone stores and increase reabsorption of calcium from the distal tubule of the kidney.

Developed hypocalcemia by aging due to vitamin D loss is a cause of arterial wall stiffening and arterial hypertension in elderly]. Hypocalcemia leads to hyponatremia, and the last results in vascular tone increase due to boosting of alpha-adrenergic receptor affinity against norepinephrine. Additionally, hypocalcemia induces hypersecretion of EHT, which negatively influences the vascular wall remodeling because stimulates cell migration and cell proliferation.

The third mechanism underlying the link between vitamin D lack and arterial hypertension means the role of decreased expression and activity of endothelial NOS resulting in NO decline. As consequence vascular tone and blood pressure elevate. Beyond associations of vitamin D deficiency with arterial hypertension and the relationships to kidney dysfunction and inflammation, there is compelling evidence that low vitamin D levels are also associated with other classic cardiovascular risk factors.

10. Circulatory predictors of endothelial dysfunction and arterial hypertension

Today, medicine holds a large arsenal of functional and circulatory markers indicating the presence of endothelial dysfunction and its direct repercussion – blood pressure elevation.

Endothelial function is readily measured using both invasive and noninvasive modalities that have been subject of recent thorough reviews. These methods are designed to assess vasodilation to pharmacologic stimuli (e.g. acetylcholine or bradykinin), mechanical stimuli (shear), or both. Further, the vasodilator responses to these stimuli are primarily related to nitric oxide production capacity. Key research over the past several decades has identified NO as a central regulator of vascular endothelial function, with a loss of NO bioavailability identified as a central phenotypic characteristic of endothelial dysfunction.

Early studies measuring endothelial function were invasive, being performed in the coronary arteries using acetylcholine or pharmacologic flow manipulation. The cost and invasiveness of these methods now limits their use, and endothelial function is currently more widely measured using validated methods employing venous plethysmography, high-resolution ultrasound in the peripheral circulation, or, more recently, digital pulse arterial tonometry. Brachial artery reactivity testing using high-resolution ultrasound to measure vasodilation of the brachial artery to hyperemic shear has emerged as one of the most common methods of assessing endothelial function, based on both its noninvasive nature and

its proven validity. Endothelium-dependent vasodilation of the brachial artery is NO dependent, correlates with endothelial function in the coronary artery, and independently predicts future cardiovascular risk in patients with and without established atherosclerotic disease. The severity of hypertension correlates with increasing impairment of endothelial function as measured by brachial artery reactivity testing, and antihypertensive therapy that concomitantly reverses brachial artery endothelial dysfunction reduces cardiovascular risk. Thus, endothelial function is readily measurable in a reproducible, valid, and noninvasive manner in hypertensive patients.

Among circulatory markers a special predictive value regarding diagnosis and prognosis of HPT is attributed to:

- markers of inflammation
- markers of oxidative stress
- markers of collagen turnover
- markers of NOSe – NO system.

The multi-marker panel for inflammation assay consists basically from followings:

- High sensitivity C reactive protein (hsCRP) accepted as a general marker of cardiovascular risk. The Guidelines of European Society of Cardiology and American Heart Society point three levels of hsCRP concerning this cardiovascular risk: (i)<1,0 mg/L – minimal risk; (ii) 1-3 mg/L – moderate risk; (iii) >3,0 mg/L – high risk.
- Pro-inflammatory cytokines: IL-1, IL-2, IL-6, IL-8, IL-17, IL-18, SDF (stromal derived factor), TNF-alpha, phospholipase A_2 associated with circulatory lipoproteins, TC_2, resistin etc. Their serum elevation indicates the boosting of systemic or chronic inflammation.
- Anti-inflammatory cytokines: IL-4, IL-10, IL-13, IL-33, heregulin-1beta, antagonist of IL-beta receptor. Their serum elevation designs the mitigation of systemic or chronic inflammation and is a good predictor.
- Four groups of chemokines (C, CL, CCL, CxCL) whose main effect is circulatory cell transendothelial passing stimulation. A special predictive value among them is attributed to MCP-1 (monocyte chemoattractant protein). Likewise, the increased expression of selectins and integrins is considered as a hazard for inflammation induced endothelial dysfunction.

The main markers of oxidative stress used in patients with HPT are following:

- Total antioxidant activity;
- Malonic dialdehyde and advanced oxidant proteins;
- Catalase, superoxide-dismutase and glutathione-redox system as basic antioxidant factors.

Markers of collagen turnover include:

- Circulatory levels of extracellular matrix metalloproteinases, such as MMP-2, MMP-8 and MMP-9.
- Markers of fibrillar collagen synthesis. For collagen type I: PINP and PICP (N and C terminal propeptides of collagen I). For collagen type III: PIIINP and PIIICP (N and C terminal propeptides of collagen III).
- Markers of fibrillar collagen degradation. For collagen type I: NITP and CITP (N and C terminal telopeptides of collagen I). For collagen type III: NIIITP and CIIITP (N and C terminal telopeptides of collagen III).

Markers of NOSe – NO system include:

- NO blood concentration.
- Serum L-arginine level.
- Serum arginase activity. Its rise indicates the risk of deficient formed NO.
- Serum tetrahydrobiopterine level. Its diminution indicates decreased NOSe expression and decline of NO respectively.
- Asymmetric dimethylarginine level. Its rise predicts the alteration of NOSe-NO system and risk of increased vascular tone.

11. Arterial hypertension and the target organs damage

AHT is a "silent killer" because consistently and progressively leads to disorders of the vital organs, such as kidneys, eyes, heart, blood vessels and brain. In some clinical cases the symptoms of renal failure or vision disorders are signs helping diagnosis of AHT. On the other hand, the management of any hypertensive patient should be guided obligatory in concern to survey of the target organs functioning by use of specific markers and predictors.

● Arterial hypertension and kidney. Kidney damage and renal disorders begin even in uncomplicated hypertension whose evolution is slow and is associated with not so high levels of blood pressure. The relative risk of serious renal damage in patients with uncomplicated essential hypertension is low as compared with other cardiovascular complications. Nevertheless, given the huge prevalence of hypertension in the general population, it still remains the second leading cause of end-stage renal disease. More than that, AHT is able to exacerbate the evolution of the primary kidney diseases.

In the conceptual field hypertension-induced renal damage has been depicted into the 2 distinct clinical and histological patterns of "benign" and "malignant" nephrosclerosis.

Benign nephrosclerosis is the pattern developed in the majority of patients with AHT. The somewhat nonspecific vascular lesions of hyaline arteriosclerosis develop slowly without overt proteinuria. Although focal ischemic glomerular impact and nephron loss occur over time, renal function is not seriously. By contrast, "malignant" nephrosclerosis is observed with severe hypertension (malignant phase of essential hypertension) and has a characteristic

renal phenotype of acute disruptive vascular and glomerular injury with prominent fibrinoid necrosis and thrombosis. Ischemic glomeruli are frequent because of vascular injury. Renal failure can develop rapidly and subsequently developed the sodium and water retention will aggravate the clinical evolution of AHT.

Vascular pathology and glomerulosclerosis are most important pathogenic tools of AHT induced kidney disorders.

Vascular mechanism is based on several tools.

The first, blood pressure in the renal artery is quite high (>70 mm Hg) because it is a short vessel and is stemmed directly from abdominal aorta (i.e. descending aorta). Due to this hue the hemodynamic stress is conclusive and correlates with the levels of blood pressure. Increased hemodynamic stress is a robust factor triggering producing of more and more NO, that finally induces the exhaustion of endothelial cells in regard to use L-arginine for NO synthesis in citrulline circle even NOSe expression is not for a certain time significantly reduced. Resulted depletion of NO becomes a factor leading to renal arteries remodeling manifested by thickening of intima-media complex and losing of the renal artery vasodilatory response to vasorelaxant circulating and local factors. Lastly, a such renal artery remodeling is a precondition for renal tissue ischemia, nephron dysfunction and nephrosclerosis. Noteworthy, the vascular bed with a lowered hemodynamic stress is not so intensively exposed to exhaustion of the endothelial systems responsible for NO synthesis.

The second, AHT being induced or linked to endothelial disorders becomes a factor capable to augment endothelial injury due to increased inflammatory response and activated oxidative stress. It is considered that atherosclerosis evolution and endothelial ageing are many times faster in patients with arterial hypertension. Accordingly, even a slowly developing AHT harms glomerular endothelial barrier producing a diminution of glomerular filtration rate, which is an early and informative predictor of renal failure. Deterioration of the endothelial layer in AHT leads to increased filtration of albumins and to microalbuminuria - another early marker of renal failure, which in many cases appears earlier than inherent clinical symptoms of hypertensive status.

The third, elevated blood pressure and increased vascular tone in AHT will trigger the local glomerular system for maintenance of normal and adequate perfusion of the glomerular apparatus. Physiologically, increases in systemic BP, episodic or sustained, are prevented from fully reaching the renal microvasculature by proportionate autoregulatory vasoconstriction of the preglomerular vasculature such that renal blood flow and glomerular hydrostatic pressures are maintained relatively constant. These autoregulatory responses therefore provide the primary protection against hypertensive renal damage. As long as blood

pressure remains below a certain limit (within the autoregulatory range), only benign nephrosclerosis is observed; however, if this threshold is exceeded, acute disruptive injury (malignant nephrosclerosis) is expected to result despite normal functioning of autoregulation system. However, once vascular injury develops, autoregulatory responses can be secondarily compromised and results in the amplification of renal damage. When autoregulatory mechanism is failed the blood pressure in glomerular arterioles and capillaries increase that can lead to vascular media hypertrophy and vascular remodeling. Likewise, increased glomerular pressure might be a factor producing barotrauma of glomerular barrier and nephrons. It has been proposed that the glomerular capillary epithelial cell (podocyte) through its interdigitating foot processes provides structural support against pressures that are substantially higher than in systemic capillaries (≈45 mm Hg versus ≈20 mm Hg). The triggering of several downstream deleterious cellular and molecular pathways is postulated to lead to oxidative stress and the activation of growth factors and fibrogenic mediators such as TGF-1β (transforming growth factor-1β) and PAI (plasminogen activator inhibitor-1).

The entity of blood pressure load impact on kidney is mostly linked to the level of pulsatile pressure rather than mean systolic or diastolic pressure. Moreover, the frequency of BP fluctuation is a proved pathogenic mechanism of the arterial hypertension induced kidney disorders. BP fluctuation facilitates transmission of the increased glomerular pressure to susceptible structures of nephron and renal microvasculature, resulting in a real risk of nephrosclerosis.

The detection in time the transition of the renal afferent vasoconstriction in afferent vasodilation due to failure of the autocontrol system is very difficult. The presence of the renal afferent vasoconstriction can be documented using the test of protein or aminoacid infusion which shows reduced renal clearance. If the glomerular hyperperfusion and respectively renal hyperfiltration starts the proteinuria enhances and it is augmented during progression of endothelial glomerular barrier alteration.

Glomerular hypertension leads to glomerular capillary stretching and podocytes injury which overall result in glomerulosclerosis, a serious tool of kidney disorders as target organ alteration in arterial hypertension (fig.33).

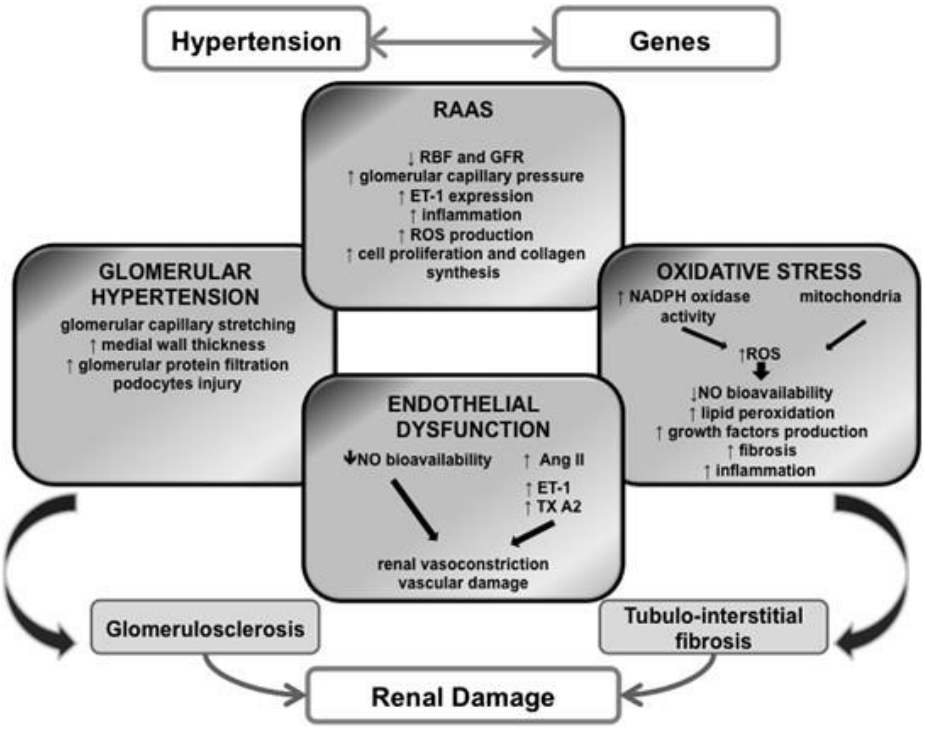

Figure 7. Pathogenic synoptic scheme of renal damage in AHT

An early predictor of glomerulosclerosis is increased circulating level of uric acid. Hyperuricemia progresses when nephrosclerosis associates glomerulosclerosis and becomes an independent risk factor of hypertension induced vascular damage. In general hyperuricemia is considered as an independent cardiovascular risk factor especially in patients with metabolic syndrome and diabetes mellitus type II.

Arterial hypertension impact on kidney is mediated also by boosted process of lipid peroxidation due to activated oxidative stress which together with inflammation mediators (e.g. TNF-α, FGF-2, FGF-23 and TGF-1β) activate interstitial fibroblasts conducing to tubulo-interstitial fibrosis and impairment of nephron functioning. These processes are supported by renal ischemia and hypoxia due to in partly to decreased production of local vasodilating factors (prostaglandins as metabolites of arachidonic acid) and renal artery reactivity disorders to action of either vasodilating or vasoconstricting agents. Even the effects of natriuretic peptides regarding water homeostasis control could be compromised.

As a summarized note. Arterial hypertension may cause renal vascular lesions and glomerular damage, constituting hypertensive nephrosclerosis a precondition of end-stage renal failure. The pressure induced glomerular damage is limited by an autoregulation based on vasoconstriction of the afferent arteriole. The efficiency of this autoregulation is largely under genetic influence. A deficient autoregulation with vasodilated afferent arterioles leads to more early and severe glomerular damage.

●Arterial hypertension has profound effects on various parts of the eye. Classically, elevated blood pressure results in a series of retinal microvascular changes called

hypertensive retinopathy, comprising of generalized and focal retinal arteriolar narrowing, arteriovenous nicking, retinal hemorrhages, microaneurysms and, in severe cases, optic disc and macular edema. Even in the non-diabetic persons suffering by mild AHT the hypertensive retinopathy occurs in 10% of cases. Hypertensive retinopathy signs are associated with other indicators of end-organ damage (for example, left ventricular hypertrophy, renal impairment) and may be a risk marker of future clinical events, such as stroke, congestive heart failure and cardiovascular mortality. Furthermore, hypertension is one of the major risk factors for development and progression of diabetic retinopathy, and control of blood pressure has been shown in large clinical trials to prevent visual loss from diabetic retinopathy. In addition, several retinal diseases such as retinal vascular occlusion (artery and vein occlusion), retinal arteriolar emboli, macro-aneurysms, ischemic optic neuropathy and age-related macular degeneration may also be related to AHT. In management of patients with hypertension, physicians should be aware of the full spectrum of the relationship of blood pressure and the eye.

The detection of hypertensive retinopathy is a part of the standard evaluation of persons with hypertension. More than that, the presence of retinopathy may be an indication for initiating antihypertensive treatment, even in people with stage 1 hypertension (blood pressure, 140 to 159/90 to 99 mm Hg) who have no other evidence of target-organ damage.

The retinal circulation undergoes a series of pathophysiological changes in response to elevated blood pressure. In the initial, vasoconstrictive stage, there is vasospasm and an increase in retinal arteriolar tone owing to local autoregulatory mechanisms. This stage is seen clinically as a generalized narrowing of the retinal arterioles. Persistently elevated blood pressure leads to intimal thickening, hyperplasia of the media wall, and hyaline degeneration in the subsequent, sclerotic, stage. This stage corresponds to more severe generalized and focal areas of arteriolar narrowing, changes in the arteriolar and venular junctions (i.e. arteriovenous nicking or nipping), and alterations in the arteriolar light reflex (i.e. widening and accentuation of the central light reflex). This is followed by an exudative stage, in which there is disruption of the blood–retina barrier, necrosis of the smooth muscles and endothelial cells, exudation of blood and lipids, and retinal ischemia. These changes are manifested in the retina as micro-aneurysms, hemorrhages, hard exudates, and cotton-wool spots. Swelling of the optic disk may occur at this time and usually indicates severely elevated blood pressure (i.e. severe or malignant hypertension). Because better methods for the control of blood pressure are now available in the general population, malignant hypertension is rarely seen. In contrast, other retinal vascular complications of hypertension, such as macro-aneurysms and branch-vein occlusions, are not uncommon in patients with chronically elevated blood

pressure. Signs of retinopathy that reflect the exudative stage, such as retinal hemorrhage or micro-aneurysm, may be seen in eyes that do not have features of the sclerotic stage (e.g. arteriovenous nicking). The exudative signs are nonspecific, since they are seen in diabetes and other conditions.

Remarkably, the generalized and focal narrowing of the retinal arterioles has been shown to predict the risk of hypertension in normotensive persons. Other factors unrelated to hypertension (e.g. hyperglycemia, inflammation, and endothelial dysfunction) may also be involved in the pathogenesis of retinopathy.

It is important to note that the retinal circulation shares anatomical, physiological, and embryologic features with the cerebral circulation. Patients with stroke showed a frank disorder of retinal and cerebral arteriolar circulation, and dysfunction of retinal blood flow in patients with lacunar stroke have also been reported in majority of cases.

The retinal lesions that make up hypertensive retinopathy can be divided into the following vascular and extravascular retinal lesions, although in some of the latter, the primary factor may be retinal vascular derangement.

Vascular mechanism of hypertensive retinopathy is closely linked to capacity of the retinal vessels to control the transfer of blood pressure load to them adequately keeping vascular endothelium and muscular medium.

Retinal blood vessels have distinct features, which differentiate them from other blood vessels:

- The absence of sympathetic nerve supply.
- Autoregulation of the blood flow.
- Presence of blood-retinal barrier.

Thus, an increase in blood pressure is transferred directly to the vessels which initially constrict. However, a further increase in BP overcomes this compensatory tone and damage to the muscle layer and endothelium ensues.

Hypertensive retinopathy has the following phases:

Vasoconstrictive Phase.

In this phase, the local autoregulatory mechanisms come into play. This causes vasospasm and retinal arteriole narrowing, which is evident by the decrease in the arteriole to venule ratio (normal pattern = 2:3). In older patients with arteriosclerosis, focal arteriolar narrowing develops, as affected vascular segments cannot undergo narrowing. Among

atherosclerosis and hypertensive retinopathy development the retinal arteriole to venule ratio becomes as 1:3.

Sclerotic Phase.

Persistent increase in BP causes certain changes in vessel wall:

- Intima layer: thickening.
- Media layer: hypertrophy.
- Arteriolar wall: hyaline degeneration.

This leads to a severe form of arteriolar narrowing, arteriovenous crossing changes, and widening and accentuation of light reflex. Arteriovenous crossing changes occur when a thickened arteriole crosses over a venule and subsequently compresses it as the vessels share a common adventitious sheath. The vein, in turn, appears dilated and torturous distal to the arteriovenous crossing.

Exudative Phase.

It is seen in patients with highly increased blood pressure and is characterized by the disruption of the blood-brain barrier and leakage of blood and plasma into the vessel wall disrupting the autoregulatory mechanisms. In this stage, retinal signs occur such as retinal hemorrhage, exudate formation, necrosis of smooth muscle cells and retinal ischemia.

Extravascular mechanism of the hypertensive retinopathy is usually observed in the malignant AHT associated with intracranial pressure elevation causing optic disc edema. The main source of blood supply to the optic nerve head is the posterior ciliary artery circulation and not the retinal arterial circulation. Notably, hypertensive retinopathy appeared significantly earlier than hypertensive optic neuropathy or choroidopathy.

Ang II which is quantitatively increased in AHT is directly involved in the pathogenesis of the choroidopathy. Since choriocapillaris are very leaky, the plasma, along with Ang II, leaks freely into the choroidal interstitial fluid, there it causes the vasoconstriction and/or occlusion of the choroidal vessels. The leakage of the Ang II into the choroidal interstitial fluid and vasoconstriction and occlusion of the choroidal vascular bed would produce ischemia of the optic nerve head by two mechanisms:

1. As a part of the choroidal vascular involvement, the peripapillary choroid is also involved. The peripapillary choroid is the main source of blood supply to the optic nerve head,

and vasoconstriction and occlusion of the peripapillary choroid would secondarily cause ischemia of the optic nerve head.

2. In addition, the Ang II from the choroidal interstitial fluid would diffuse into the optic nerve head through the border tissue of Elschnig which is freely permeable. The Ang II in the tissues of the optic nerve would produce vasoconstriction and occlusion by direct action on the capillaries and other vessels in the optic nerve disc. The optic disc or optic nerve head is the point of exit for ganglion cell axons leaving the eye. Because there are no rods or cones overlying the optic disc, it corresponds to a small blind spot in each eye. The ganglion cell axons form the optic nerve after they leave the eye. The optic disc represents the beginning of the optic nerve and is the point where the axons of retinal ganglion cells come together. The optic disc is also the entry point for the major blood vessels that supply the retina. The optic disc in a normal human eye carries 1–1.2 million afferent nerve fibers from the eye towards the brain.

●Arterial hypertension and heart: hypertensive heart a pattern of cardiac remodeling.

Even a mild arterial hypertension has a strong influence on heart leading to evolution of 3 main phenomena:

1. Myocardium hypertrophy.
2. Extracellular matrix growing.
3. Coronary hypertension and coronary remodeling.

Both myocardium hypertrophy and extracellular matrix growing are recognized as key components of AHT induced myocardial remodeling which for a certain time has a positive role in conditions of increased afterload. This inherent pattern of myocardial remodeling in patients with AHT is named as hypertensive heart.

Coronary hypertension is due to elevated aortic blood pressure which claims a higher pumping power of the left ventricle, and this booted aortic jet will increase blood spilling through coronary arteries provoking coronary vessels thickening and respectively their narrowing.

All these phenomena which comprise the entity of hypertensive heart develop in patients with AHT, and are triggered basically by following factors:

- Boosted hemodynamic stress.
- Activated neuroendocrine system.
- Endothelial disorders in a pathogenic interface of boosted inflammatory response and activated oxidative stress.

Boosted hemodynamic stress means increased afterload due to higher peripheral vascular

resistance and in the field of pathophysiology is viewed as a mechanical factor triggering myocardium hypertrophy.

Myocardial hypertrophy as a crucial component of myocardial remodeling in hypertensive heart is triggered by 2 leader factors: (i) mechanical factor and (ii) neuroendocrine factors, such as norepinephrine (NE), endothelin 1 (ET-1) and Ang II. All these factors will activate via some intracellular messengers (e.g. tyrosine kinase, mitogen activated protein, proteinkinase B or akt) the special nuclear genes of cardiomyocyte, named as genes of myocardial hypertrophy (e.g. c-fos, c-jun, c-myc), resulting in activation of proteins synthesis: contractile proteins (actin and myosin) and skeletal proteins (titin, nebulin).

Mechanical factor stemmed from myocardial stretching during increased peripheral resistance and aortic pressure will signalize disc Z by activation of special receptors (integrins and calsarcins) followed by activation of intracellular messengers and, respectively, hypertrophy genes. Myocardium expresses a special subtype of mechanical receptor activated by stretching stress leading to NE release from sympathetic axons resulting in the synthesis of growth factors such as IGF (insulin-like growth factor) and TGF-1β by cardiac cells.

The second type of humoral stimulus involved in cardiomyocyte growth comes from the stimulation of heptahelical G-protein-coupled receptors, particularly the beta 1-adrenergic receptors for epinephrine and norepinephrine, the AT_1 receptor for angiotensin II and the ETA receptor for ET-1. As was above mentioned these neuroendocrine factors play a triggering role in the AHT evolution and quantitatively are markedly increased in hypertensive patients.

The most important change of myocardial remodeling on hypertensive heart is thickening of left ventricle wall with a notable tendency of LV cavity diminution – so called concentric myocardial hypertrophy (fig.8).

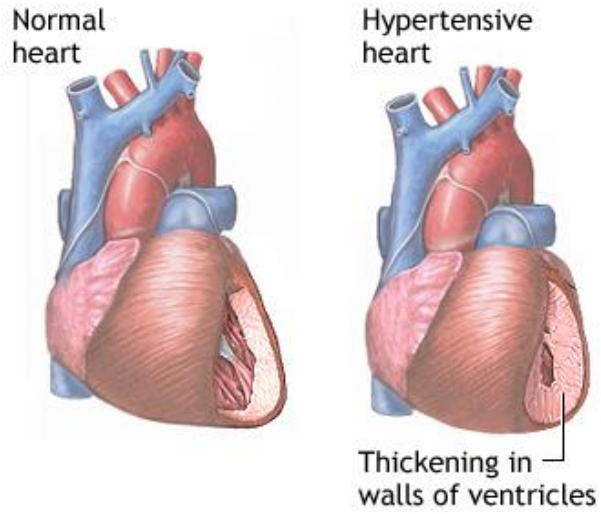

Figure 8. Concentric pattern of myocardial remodeling: LV cavity diminution and LV wall thickening in hypertensive heart

The changes in the myocardium of a hypertensive patient occur not only in left ventricle, which is directly exposed to the hemodynamic overload, but in the interventricular septum and right ventricle, as well. Because myocardial mass and LV wall thickness increase the contractile power increases and systolic pressure elevates. However, due to reduction of the end diastolic volume the ventricular filling is confined, a fact directly compromising efficiency of the Starling phenomenon. As a consequence, the cardiac ejection fraction decreases and it becomes a bases of pathophysiology of hypertensive heart manifested by diastolic heart failure. So, diastolic heart failure is a relevant complication of the arterial hypertension and should be estimated as early is possible. In this regard it is important to note that a rigorous control of the blood pressure will induce the regression of myocardial hypertrophy associated with improvement of the pump performances of the heart. Myocardial hypertrophy regression is also due to mitigation of the neuroendocrine system by applying of ACE inhibitors, sartans (AT_1 receptor antagonists) and blockers of beta-adrenergic receptors.

Noteworthy, both the cardiomyocytes and the blood vessels possess mineralocorticoid receptors, the stimulation of which can activate important physiological and pathological mechanisms. Now is well documented that excess of aldosterone can induce not only cardiac fibrosis, but myocardial hypertrophy also. In AHT activation of the renin-angiotensin-aldosterone system is associated with enhancement of both the Ang II and aldosterone levels.

Among the well proved predictors of the myocardial hypertrophy of hypertensive heart are noted cardiotrophin-1 and calcineurin.

Cardiotrophin-1 is a cytokine member of the interleukin-6 superfamily, produced by cardiomyocytes and non-cardiomyocytes in situations of biomechanical stress that once secreted interacts with its receptor, the heterodimer (also known as leukemia inhibitory factor receptor beta), activating different signaling pathways leading to cardiomyocyte hypertrophy, as well as myocardial fibrosis. Plasma level of cardiotrophin-1 is significantly elevated in patients with AHT and hypertensive heart, and it correlates with the clinical and functional dynamics of the disease. More than that, this marker has a strong predictive power regarding the AHT induced heart failure evolution and tolerance to physical effort. Cardiotrophin-1 also plays an important cardioprotective effect on myocardial damage, is a potent regulator of signaling in adipocytes in vitro and in vivo and potentiates the elevation the acute-phase proteins. Beyond its potential mechanistic contribution to the development of hypertensive heart disease, cardiotrophin-1 offers the opportunity for a new translational approach to this

condition. In fact, recent evidence suggests that cardiotrophin-1 may serve as both a biomarker of left ventricular hypertrophy and dysfunction in hypertensive patients, and a potential target for therapies aimed to prevent and treat hypertensive heart disease beyond blood pressure control. Important to be noted that myocardial hypertrophy regression is accompanied with a reduction of the serum level of cardiotrophi-1 and LV functioning amelioration.

Calcineurin is a calcium-dependent serine–threonine protein phosphatase. It activates the nuclear factor of activated T-cells (NFATs) cytoplasmic, a transcription factor, by dephosphorylating the protein. The activation is then translocated into the nucleus, where it up-regulates the expression of interleukin 2 (IL-2), which, in turn, stimulates the growth and differentiation of T-cell responses.

In the heart, nuclear NFATs bind to the transcription factor GATA-4 and activate transcription of hypertrophic genes. Cardiac overexpression of the constitutively active calcineurin catalytic subunit or a constitutively nuclear factor mutant protein each induced massive cardiac hypertrophy that quickly transitioned to heart failure and death.

It is considered that mechanical stress and both the ET-1 and Ang II trigger the myocardial hypertrophy in patients with AHT by calcium-dependent calcineurin-stimulating mechanism of nuclear hypertrophy genes activation using the main intracellular messengers (mitogen activated protein kinase, *akt* and protein kinase C). Circulating levels of calcineurin elevate in patients with arterial hypertension and administration of the its antagonists share a lot of benefits concerning the state of hypertrophy of the hypertensive heart.

Although left ventricular hypertrophy is an adaptative mechanism to increased load, its development represents a pathological state which can affect patients' health in many ways. The mechanism by which left ventricular hypertrophy impair life expectancy is not completely known; arrhythmias and ischemia may often develop in patients with secondary left ventricular hypertrophy and can contribute to worsen prognosis. Left ventricular mechanics is also affected by hypertrophy. Systolic function is usually normal at rest, but its response to exercise can be blunted when hypertrophy develops. Diastolic dysfunction is early present in patients with hypertension, even before left ventricular hypertrophy occurs, and it can impair systolic function by hampering filling resulting mostly in an impairment in the adjustment to exercise. Effective antihypertensive therapy leads to a decrease in left ventricular hypertrophy and an improvement in diastolic mechanics. Remarkably, that clinical outcomes of many trials show that hypertensive retinopathy and myocardial hypertrophy develop in parallel, and demonstrate a strong correlation, that underline the presence of common inducing factors. Body mass index and maximum systolic blood pressure, appear to

be important determinants of structural ocular and cardiac adaptation in arterial hypertension even in a mild evolution. Hence, myocardial hypertrophy detection in patients with AHT indicates the risk of target organs damage. If concentric myocardial hypertrophy is a factor disturbing LV filling and Starling's mechanism efficiency, the eccentric pattern is a risk factor for cardiac arrhythmias. Expression of the melusin, an integrin β1-interacting protein acting as a biomechanical sensor in the heart is a tool controlling process of LV cavity dilation. If the stimuli providing hypertension induced myocardial hypertrophy do not sufficiently increase expression of melusin the risk of LV dilation is high, resulting in a pathological pattern of remodeling of the hypertensive heart. The melusin overexpression allows prolonged concentric compensatory hypertrophy and protects against the transition toward cardiac dilation and failure in response to long-standing pressure overload. Moreover, melusin overexpression reduces the rate of cardiomyocyte apoptosis in the hypertensive heart.

Melusin is part of the heat shock protein 90 machinery and acts as molecular chaperone in controlling cardiomyocyte survival and adaptive hypertrophy signaling pathways in the heart in response to different stress hemodynamic conditions.

Early diastolic dysfunction in the evolution of the hypertensive heart is determined by extracellular matrix growing because activated fibroblasts begin to synthase excessively fibrillar collagen type I and especially collagen type III leading to reactive fibrosis. Expanded interstitial fibrosis increases diastolic myocardial rigidity that confines LV filling during diastole. So, interstitial fibrosis associates myocardial hypertrophy in AHT, and this phenomenon is important because increased myocardium mass needs a stronger extracellular support. On the other hand, stiffened myocardium reduces the maximal diastolic velocity and the ability of isovolumic relaxation phase, which is so important for achieving of an adequate gradient of LV diastolic filling. Reactive fibrosis increases the distance from capillary network toward cardiomyocyte that results in the oxygen supply diminution and ischemic disorders of the cardiomyocyte, being a factor, which reduces hypertrophied myocardium tolerance to tachycardia and hemodynamic loads with volume and resistance.

Arterial hypertension induced myocardial fibrosis is a result of the activating action of following factors on interstitial fibroblasts:

- endocrine factors, such as NE, ET-1 and especially Ang II;
- mediators of inflammation;
- free oxygen radicals.

Myocardial fibrosis is a complex phenomenon reflecting the loss of the physiological reciprocal regulation between stimulatory (e.g. angiotensin II, endothelin I, catecholamines, aldosterone, basic fibroblast growth factor, insulin-like growth factor, etc.) and inhibitory

factors (prostaglandins, nitric oxide, natriuretic peptides etc.) acting on the turnover of fibrillar collagen. Ang II induces fibroblast proliferation, alteration of fibrillar collagen turnover and stimulation of aldosterone, leading to accumulation of collagen type I and III fibers and fibrosis. This accumulation results in a distortion of tissue structure, which is responsible for the increase in myocardial stiffness leading to diastolic dysfunction, a substrate for ventricular arrhythmias, and ultimately to systolic dysfunction and pump function decline. Aldosterone is also an available factor regarding activation of the fibroblasts and fibrosis space enlarging. Thus, attenuation of the renin-angiotensin-aldosterone system activity markedly alleviates the cardiac structures balance in the hypertensive heart due to blunting of both processes: hypertrophy and fibrosis.

For a long time, the myocardial fibrosis was considered as an irreversible process. However, successful treatment of hypertensive treatment, especially by applying of ACE inhibitors and aldosterone receptor antagonists, has showed a reduction of the fibrosis. This improvement is possible due to at least 2 events tightly linked to stable blood pressure control: (i) attenuation of the fibroblasts activity and collagen synthesis diminution and (ii) activation of the extracellular matrix metalloproteinases.

What are the main circulatory markers and predictors of myocardial fibrosis? Noteworthy, cardiac fibrosis like myocardial hypertrophy secondary to hypertensive heart disease has been identified as a significant cause of morbidity and mortality.

Serum markers of collagen turnover can be classified according to their specific action and their pathophysiological significance.

1. Markers of collagen synthesis, such as CPIP (carboxy-terminal propeptide of procollagen type I) and CPIIIP (carboxy-terminal propeptide of procollagen type III).
2. Markers of collagen degradation CITP (carboxy-terminal telopeptide of collagen type I) and CIIITP (carboxy-terminal telopeptide of collagen type I).
3. Markers of collagen degradation inhibition TIMP I (tissue inhibitor of matrix metalloproteinases type I) and TIMP III (tissue inhibitor of matrix metalloproteinases type III).
4. Proline and oxyproline as precursors of collagen synthesis.
6. Markers of fibroblast activity such as TGF 1β (transforming growth factor 1β) and galectin 3 (a member of the galectin family, is a 30-kDa β-galactoside–binding lectin with a broad repertoire of cellular functions). Both are released by macrophages and their expression correlates with the expression of MCP-1 (monocyte chemoattractant protein), a chemokine which increases population of cardiac macrophages. Remarkably, that TGF 1β level correlates with population of myofibroblasts, but galectin 3 level matches with severity of arterial

hypertension induced diastolic heart failure. Galectin 3 can be also excessively released by fibroblasts, endotheliocytes, eosinophils under the action of proinflammatory cytokines, free oxygen radicals and neuroendocrine factors.

Regarding the pathophysiological pattern of hypertensive heart, it's important to emphasize not only the degree of myocardial fibrosis, but also qualitative aspect, such as ratio between collagen I and collagen III. The last protein has a less compliance, therefore if this ratio decreases due to higher excess of collagen III the myocardium diastolic stiffness enhancement is more conspicuous in detriment of lusitropic function of the heart.

●Arterial hypertension and brain. The AHT impact on brain is very strong, quite early manifests and embraces following main pathophysiological entities: (i) cerebral circulatory disorders and stroke; (ii) hypertensive encephalopathy and (iii) cerebral hemorrhage.

Cerebral artery lesions in AHT are triggered by several factors, such as mechanical factor due to elevated blood pressure, activated neuroendocrine system, progressive endothelial damage, activated oxidative stress and lipid profile disorders. These hard sequelae justify why the brain is a major target of the deleterious effects of arterial hypertension and is responsible for a large dimension of the related mortality and morbidity of persons suffered by this malady. There is a linear relationship between blood pressure and stroke mortality, and in patients with treated hypertension a 1 mmHg increase in systolic blood pressure increases stroke deaths by 2%.

More than that, AHT is a real cause of cognitive decline, dementia and Alzheimer's disease (the most common cause of madness in the elderly) which seriously affect life quality and represent an arduous burden for any society.

Mechanical factor action provides a cerebral vessel distension, which destroys the integrity of the vascular wall and allows plasma insudation into the wall, finally leading to local intumescent derangements resulting basically in quick plaque formation till cerebral artery occlusion. This phenomenon is especially active and steady in the resistive cerebral arterioles facilitating their remodeling according to the specific for brain local system of blood stream control. Arterial hypertension induces fibrinoid necrosis (lipohyalinosis) of penetrating arteries and arterioles supplying the white matter, resulting in small white matter infarcts (lacunes) or brain hemorrhage.

Cerebral arteries and arterioles are innervated by nerve fibers arising from cranial autonomic and sensory ganglia. Smaller arterioles (≤100μm) and capillaries are fully enveloped by the end feet processes of astrocytes. Owing to the blood-brain barrier (BBB), cerebral capillaries are impermeable to most blood-borne substances. Unlike other organs, extraparenchymal arteries and arterioles account for 2/3 of the vascular resistance, while

intracerebral arterioles and capillaries account for the remaining 1/3. Therefore, vessels residing outside the brain have the greatest impact on parenchymal (intracerebral) blood flow. The brain has limited energy reserves and its integrity depends on a continuous supply of oxygen and metabolic substrates delivered through blood flow. Thus, cerebral blood vessels are endowed with adaptive mechanisms that assure that the brain receives an adequate amount of blood at all times. The cerebral blood supply is regionally heterogeneous, reflecting the varying energetic needs of different brain regions. When a brain region is activated, cerebral blood flow (CBF) in that particular region increases, a phenomenon termed functional hyperemia. Neurons, astrocytes and vascular cells release a multitude of vasoactive agents that act in concert to produce vasodilatation of local arterioles during neural activity. These agents include mainly nitric oxide, carbon monoxide, prostanoids, cytochrome p450 metabolites (e.g. epoxieicosatriens), adenosine, and potassium. The vasodilatation of local arterioles is accompanied by vasodilatation of upstream pial arteries that supply the activated area. The coordinated vasodilatation of intraparenchymal arterioles and pial arterioles is essential for increasing CBF efficiently, and may involve intercellular communication between vascular cells or astrocytes.

Cerebrovascular autoregulation keeps CBF independent of changes in arterial pressure within a certain range, about 60–150 mmHg mean level of arterial pressure. Arterial pressure varies markedly during normal daily activities and these changes may lead to potentially dangerous increases or decreases in CBF. To counteract the effects of blood pressure variations on CBF, cerebral arterioles adjust their resistance according to intravascular pressure. Thus, arterioles constrict when the pressure increases and relax when the pressure decreases. Autoregulation is related to the ability of arterial myocytes to constrict when intravascular pressure rises (myogenic response). The myogenic response stems from the fact that an increase in the intravascular pressure depolarizes arterial myocytes, leading to Ca^{2+} influx and vasoconstriction. In addition to Ca^{2+} influx, Ca^{2+} sensitization of the smooth muscle contractile apparatus via protein kinase C also plays a role.

Arterial hypertension induces adaptive changes in systemic and cerebral arteries known as hypertrophic and eutrophic remodeling. In hypertrophic remodeling smooth muscle cells undergo hypertrophy or hyperplasia, and grow inward encroaching into the lumen of the artery. This process increases the wall thickness and reduces the lumen of the vessel. In eutrophic remodeling smooth muscle cells undergo a rearrangement that leads to a reduction of the vessel lumen without changes in total vascular mass or wall thickness. Hypertension also leads to vascular stiffening, a process that increases collagen content and rigidity of the vessel wall. Several factors contribute to hypertrophy in cerebral arteries and arterioles. The

sympathetic perivascular innervation, which exerts a trophic effect on the vascular wall, is required for the development of cerebrovascular hypertrophy. Furthermore, mechanical effects of the elevated intravascular pressure on the vascular wall play a role through growth factors, oxidative stress and NO. Reduced availability of NO, an agent with antiproliferative activity, leads to hypertrophy, as indicated by the vascular growth observed in diverse experiments with NOS inhibition.

It has been proposed that AHT creates a specific endocrine and paracrine precondition of the cerebral arteries hypertrophy based on 2 pivotal tools: NO (natural inhibitor of growing and hyperplasia) and SOD (Cu-Zn-superoxide dismutase, a free oxygen radical scavenger). Interestingly, in experiments provided on animals lacking NOSe and SOD cerebral artery hypertrophy developed without intracranial pressure elevation. Likewise, Ang II plays a crucial role in the arterial hypertension induced cerebral vascular hypertrophy and stiffening, because this octapeptide accelerates degradation of the elastin, an important protein of extracellular matrix, having evident compliant properties. Hypertrophy and remodeling are adaptive responses aimed at reducing stress on the vessel wall and protecting downstream microvessels from the effect of increased pressure. Failure of this protective mechanism leads to blood brain barrier alterations, cerebral edema and cerebrovascular pathology.

Experimentally has been demonstrated that ablation of perivascular sympathetic nerves early in life prevents cerebrovascular hypertrophy in stroke-prone spontaneously hypertensive rats and promotes the development of cerebrovascular lesions. On the other hand, remodeling of systemic or cerebral vessels is potentially damaging because it reduces the vessel’s lumen and increases vascular resistance resulting in a greater propensity for vascular insufficiency. Arterial stiffening is also deleterious because it leads to increases in pulse pressure, a good predictor of stroke and cognitive impairment.

One of the most important mechanisms of AHT induced brain dysfunction and lesion is linked to a new interface of cerebral circulation control. Shortly, arterial hypertension alters cerebrovascular autoregulation leading to a shift of the pressure-flow curve to the right (fig. 9).

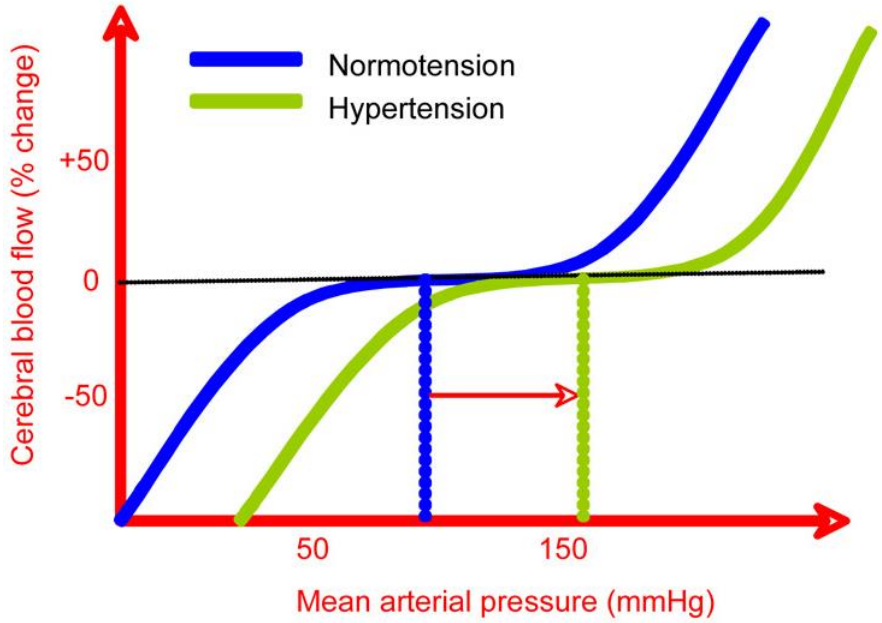

Figure 9. Cerebrovascular autoregulation curve in normo- and arterial hypertension (taken from C.Iadecola and R.Davisson. Cell Metab. 2008; 7(6): 476–484).

Consequently, in AHT higher perfusion pressures are needed to maintain the same level of cerebral blood flow. The shift in autoregulation is related to the increase in myogenic tone induced by an increase in Ca^{2+} sensitivity of myocytes. Drugs having antagonistic effect on calcium demonstrated in experimental and clinical studies brain protecting benefits in arterial hypertension. Remodeling and hypertrophy also contribute to the shift in autoregulation by reducing the vascular lumen and increasing cerebrovascular resistance. It is important to note that, the alterations in autoregulation increase the susceptibility of the brain to cerebral ischemia when blood pressure drops because cerebral blood vessels fail to compensate for the reduction in perfusion pressure. The periventricular white matter is most susceptible to ischemic damage because it is located at the boundary between two arterial territories: penetrating arteries reaching down from the brain surface and basal ganglia arteries arising from the base of the brain. In hypertensive patients, the severity of periventricular white matter injury correlates with the magnitude of autoregulatory dysfunction and with cognitive impairment as well. Impaired autoregulation also leads to more severe ischemia after arterial occlusion. Middle cerebral artery occlusion in spontaneously hypertensive rats leads to larger infarcts than in normotensive rats.

Some new concepts have emerged recently regarding the effects of arterial hypertension on cerebral blood vessels.

The first, hypertrophy of large cerebral arteries in chronic hypertension attenuates increases in pressure of downstream vessels and protects the cerebral microvasculature.

The second, in contrast to large cerebral arteries, which become less distensible during arterial hypertension, distensibility of cerebral arterioles increases during chronic hypertension despite hypertrophy of the arteriolar wall.

The third, dilatation of cerebral blood vessels with disruption of the blood-brain barrier, and not vasospasm, appears to be the critical factor in the pathogenesis of hypertensive encephalopathy. This concept is supported by the finding that cerebral edema in stroke-prone spontaneously hypertensive rats is preceded by vasodilatation and disruption of the barrier.

The fourth, alterations of endothelium-mediated dilatation may impair vasodilator responses in chronic hypertension and predispose to ischemia and ischemic stroke development.

Finally, chronic hypertension impairs dilatation of collateral blood vessels in the cerebral circulation. The implication of this finding is that increased susceptibility to cerebral infarction in chronic hypertension may be related in part to compromised responses of the collateral circulation.

So, because brain functioning is closer linked to feasibility of small arteries and arterioles due to peculiarities of the cerebral circulation autocontrol ischemic stroke and cognitive decline are usually the result of downstream disorders. Pathologic vascular changes, like lipohyalinosis, are inherent to small arteries.

For a long time, degenerative brain diseases, like Alzheimer's disease and senile dementia, have not been linked to cerebral flow disorders. However, in 2004, Bateman demonstrated the key role of vascular risk factors in the development of neurodegenerative diseases, linking vascular pathophysiology and neurological effects on blood pulsation force sent into the arterial tree. The study showed that vascular pathophysiology is related to the strength of the pulse waves induced in the craniospinal cavity by the arterial vascular tree. In 2009, Bell described the crucial role of vascular dysfunction in Alzheimer's disease. Recent data from brain imaging studies in humans and animal models suggest that cerebrovascular dysfunction can precede cognitive decline and the onset of neurodegenerative changes in Alzheimer's disease. Cerebral hypoperfusion and impaired clearance of amyloid β across the blood-brain barrier may contribute to the onset and progression of Alzheimer's dementia. A decrease in cerebral blood flow adversely affects the synthesis of proteins required for memory and learning, and can eventually lead to neuronal injury and death. Inadequate

clearance of amyloid β in the brain by cells of the neurovascular unit can lead to its accumulation in the blood vessels and the brain parenchyma. The accumulation of amyloid β in the cerebral blood vessels, known as cerebral amyloid angiopathy is associated with cognitive decline and is one of the pathogenic mechanisms of brain injury in arterial hypertension, recognized as a target organ damage.

Hypertensive encephalopathy is characterized by signs of cerebral edema that occur after a severe episode of hypertension. This condition is usually diagnosed retrospectively after symptoms dramatically resolve with lowering of the patient's blood pressure, and other causes of neurologic disease have been ruled out. Symptoms of hypertensive encephalopathy include the gradual onset of headache, nausea, and vomiting, followed by neurologic symptoms such as restlessness, confusion, seizures, and potentially coma. If the hypertension is treated promptly, the symptoms of encephalopathy are usually reversible.

Normally, the brain sustains blood flow within a narrow perfusion pressure range without being affected by fluctuations in systemic arterial pressure. For healthy individuals, the pressure ranges are 50-150 mm Hg cerebral perfusion pressure (CPP) or 60 to 160 mm Hg mean arterial pressure (MAP). CPP = MAP – intracranial pressure (ICP). With increased MAP, cerebral arteriolar vasoconstriction occurs, and conversely, with decreased MAP, arteriolar dilation occurs to keep the CPP constant. This adaptive process maintains brain perfusion at a constant level despite systemic blood pressure changes. However, a sudden and severe increase in arterial pressure can exceed this autoregulatory mechanism because the arterioles are limited in their ability to constrict. Then intracerebral elevated blood pressure causes a breach in the blood-brain barrier, and vascular fluid diffuses across the capillary membranes into the brain parenchyma. This leads to the development of cerebral edema, increased intracranial pressure, and neurologic deficits such as altered mentation, visual deficits, and seizures. In patients with chronic evolution of the arterial hypertension, the cerebral vasculature undergoes adaptations, such as arteriolar hypertrophy, to allow for a higher autoregulatory range. Lowering the blood pressure too quickly in these patients can produce cerebral ischemia due to vascular spasm at a higher MAP compared to normotensive patients. In previously normotensive patients, acute episodes of hypertension may induce hypertensive encephalopathy at diastolic blood pressures as low as 100 mm Hg. This scenario may be seen with patients that develop eclampsia or in patients receiving cytotoxic and immunosuppressive therapies. It is hypothesized that these conditions directly elicit a toxic effect on the vascular endothelium and lead to dysfunction of the blood-brain barrier.

When therapy is initiated, it is important to consider the baseline blood pressure in order to avoid excessive blood pressure reduction and prevent cerebral ischemia. It is usually safe to reduce MAP by 25% and to lower the diastolic blood pressure to 100-110 mm Hg. The hallmark of hypertensive encephalopathy is clinical improvement within 12 to 24 hours of adequate BP reduction. The mean arterial pressure should be reduced by no more than 15% over 2 to 3 hours.

● Arterial hypertension and atherosclerosis. It is a well-documented postulate that arterial hypertension accelerates and exacerbates atherosclerosis evolution by 5-10 times, a fact which underlines the importance of rigorous control of blood pressure levels. As the cellular and molecular mechanisms of the pathogenesis of atherosclerosis and the effects of hypertension are being more clearly defined, it becomes apparent that the two processes have certain common mechanisms. The endothelium is a likely central focus for the effect of both diseases. There is increasing evidence that atherosclerosis should be viewed fundamentally as an inflammatory disease. Atherogenic stimuli such as hyperlipidemia appear to activate the inflammatory response by causing expression of mononuclear leukocyte recruiting mechanisms. The gene for one of these, the vascular cell adhesion molecule-1, is controlled at least in part by transcriptional factors regulated by oxidative stress, which modifies the redox state of the endothelial cell. Alterations in the redox state of the arterial wall also may contribute to vascular smooth muscle cell growth.

So, arterial hypertension triggers and boosts main pathogenic mechanisms emphasized in evolution of the atherosclerosis.

1. Arterial hypertension wearies the vascular endothelium to synthesize adequate amounts of the nitric oxide. This repercussion is due to AHT induced increased hemodynamic stress estimated as a mechanical stress able to overactivate NOSe in order to produce more and more NO as a tool limiting vasoconstriction. Tachycardia like AHT is also capable to exhaust feasibility of the endothelial cell regarding NO release. Functional nativity of this phenomenon is based on interaction between NOSe and special mechanical receptors expressed by endotheliocyte whose activation leads to increased expression of NOSe. This mechanism is especially relevant in resistive small arteries. To note in this concern that pulsatile pressure appreciated as a difference between systolic pressure and diastolic pressure has been found as more important pattern of hemodynamical stress. The NO deficiency becomes a crucial pathogenic factor of atherosclerotic plaque progression because the major tools of this process are markedly decrypted, such as oxidative stress, local and systemic inflammation.

2. In the cluster of factors triggering and exacerbating endothelial dysfunction, and subsequently atherosclerosis arterial hypertension is viewed in the reciprocal interface with oxidative stress (fig. 10).

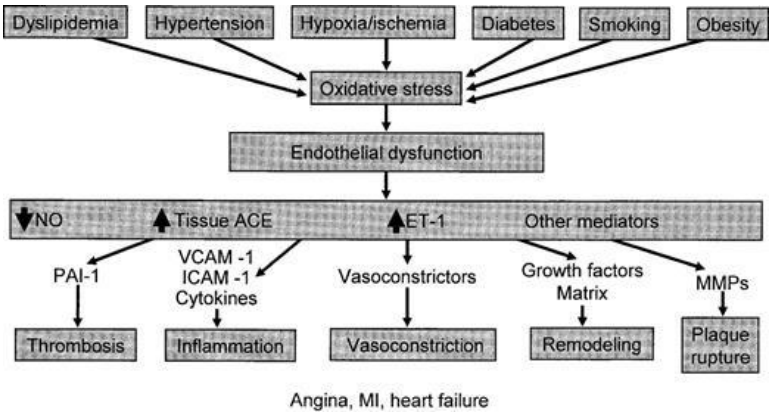

Figure 10. Arterial hypertension a member of cluster factors inducing endothelial dysfunction (taken from: Schiffrin E. *American Journal of Hypertension,* 15(S5): 115S–122S).

Activated oxidative stress in AHT is determined by elevated production of free oxygen radicals due to increase expression of membrane NADPH-oxidase and xanthin-oxidase, enzymes involved in metabolic processes associated with superoxide anion (O_2^-) release by endotheliocytes, vascular smooth myocytes and even the cells of vascular adventice (e.g. fibroblasts). This phenomenon is sustained by Ang II, urotensin II and ET-1 whose levels in arterial hypertension are markedly elevated. Likewise, activated oxidative stress in AHT is linked to depletion of antioxidant enzymes activity or their expression by mitochondrial apparatus which produces most part of superoxide anion. The uncoupling NOSe and mitochondrial dysfunction, which occur in arterial hypertension could be also an important factor of superoxide anion hyperproduction.

O_2^- is poorly neutralized in AHT because the expression of superoxide-dismutase is reduced resulting in excessive accumulation of the radical that conduce to important conditions facilitating atherosclerosis evolution. The first, superoxide anion reduces the life of NO and leads to formation a plenty of peroxynitrite ($ONOO^-$) that collectively provide the overexpression of MCP-1 and accumulation of macrophages in subendothelial layer. They will engulf actively cholesterol and transform in foam cells, an axial plateau for atherosclerotic plaque formation. The second, superoxide anion oxidizes LDL-cholesterol facilitating by this event LDL-oxi crossing through endothelium and access to the intimal macrophages. It has been demonstrated that LDL-oxidation augments repeatedly the evolution of atherosclerosis even when the level of HDL (high density lipoprotein) is not diminished. Furthermore, in arterial hypertension the expression of LDL receptor in the liver

is decreased, that leads to progressive elevation of serum LDL-cholesterol content. In plus, AHT is associated with increased circulating level of free fatty acids because hypercatecolaminemia activates lipases in adipose tissue (beta-adrenergic stimulation leads hydrolysis of triglycerides with release of free fatty acids and glycerol). In isolated fat cells lipolysis proceeded optimally at pH 7.4, was stimulated 3.5 fold by noradrenaline. In the liver free fatty acids will assure cholesterol synthesis. The blood level of free fatty acids is significantly elevated in majority patients with arterial hypertension, and it robustly correlates with the severity of atherosclerosis and risk of vascular accidents.

3. Arterial hypertension affects vascular biology through inflammation which is an omnipresent congener of pathogenic interface of atherosclerosis together with oxidative stress in a mutual relation. Free oxygen radicals increase expression of proinflammatory cytokines, chemokines and intercellular adhesive molecules. Infiltrated neutrophils and monocytes in the intimal layer become a source of radicals. Increased level of free fatty acids enhances expression of Toll-like receptors type 4 which via nuclear factor kappaB activate nuclear genes controlling expression of a lot a lot of mediators referred to inflammatory response and oxidative stress. Inflammation has been shown to downregulate NOSe activity. C-reactive protein (CRP) and TNF-α have both been demonstrated to attenuate NO production by destabilizing NOSe mRNA, which reduces NOS protein expression, and inhibition of TNF-α in contrary restores endothelial-dependent vasodilation in humans and NO reserve. IL-17, a remarkable proinflammatory cytokine, has been reported to cause endothelial dysfunction by activating Rho-kinase, which leads to phosphorylation of the inhibitory NOSe residue, threonine 495. The level of IL-17 correlates with NO amount and severity of atherosclerotic process. The pivotal cytokine using in the cardiovascular risk estimation, CRP, is increased more than 3.0 mg/dL (i.e. high CV risk) in arterial hypertension and it's directly involved in the pathogenesis of atherosclerosis. CRP is found in the atherosclerotic plaque correlatively to population of macrophages and foam cells. Its level positively correlates with the risk of plaque destabilization, erosion and eruption which taken together are triggers of the vascular accidents. CRP inhibits activity of NOSe and respectively contributes to NO decline and activation of lipid and protein peroxidation. Pro-inflammatory state in arterial hypertension is accompanied by increased expression of inducible NOS (NOSi) mostly by macrophages and endotheliocytes, but released NO in concentration 100 hundred more than NO synthesized by NOSe does not fulfil anti-inflammatory and antioxidant functions. As a rule, overexpression of NOSi is associated with troubling of endothelial control on vascular biology.

NO deficit promotes activation of the extracellular matrix metalloproteases (e.g. MMP2, MMP8, MMP9) which degrade reticular collagen IV from structure of the lamina

elastica interna and externa. Under the action of free oxygen radicals and proinflammatory cytokines smooth vascular myocytes escape from the control of system regulating contractile phenotype of muscle cells, because the expression of micro-RNA-143 and micro-RNA-145 progressively decreases. Due to this decline smooth vascular myocytes transform in secretory myocytes which are able to migrate and proliferate. The secretory myocyte migration toward intimal zone is facilitated by destruction of collagen type IV. Their proliferation is a suitable mechanism of atherosclerotic plaque growing, narrowing of arteries and arterioles and blood pressure elevation.

So, arterial hypertension is a homeostasis disorder markedly accelerating atherosclerosis by embracing of main pathogenic factors impairing vascular biology, such as endothelial disfunction and NO penury, excess of free oxygen radicals, boosted inflammation, MMP expression and extracellular matrix disorganization.

12. Bibliography

1. Richard E.Klabunde. Normal and abnormal blood pressure (physiology, pathophysiology and treatment). New-York, 2015, 134 p.

2. Mancia G. A compendium on hypertension. Circulatory Research, 2015; 116, p. 923–1095.

3. Burnier M, Egan BM. Adherence in hypertension: a review of prevalence, risk factors, impact, and management. Circ Res, 2019; 124, p. 1124–1140.

4. Batool A. Risk Factors, Pathophysiology and Management of Hypertension. Int J Pharm Sci & Scient Res, 2018. 4:5, p. 49-61.

13. Tests for auto-evaluation

1. What are the mechanisms of the sympathetic system contribution in arterial hypertension?
a. Activation of the α2 and β2 adreno-receptors.
b. Activation of the mass receptor.
c. Activation of the α1 and β1 adreno-receptors. [*]
d. Activation of the catalase.
e. Hypertrophy of the vascular muscular media. [*]

2. What is facilitation the ET-1 induced arterial hypertension?
a. ETA/ETB receptor ratio increase. [*]
b. ETA/ETB receptor ratio decrease.
c. Alpha-adrenergic activation.
d. Beta-adrenergic activation. [*]
e. Activation of the endotheliocyte actin-myosin skeleton.

3. What are the mechanisms of the ET-1 induced vascular remodeling?
a. Muscular media hypertrophy due to abluminal action of ET-1. [*]
b. Muscular media hypertrophy due to adluminal action of ET-1.
c. Muscular media hypertrophy due to paracrine action of ET-1. [*]
d. NOSe activation.
e. Inhibition of the NF-kB.

4. Underline true links of RAAS role in the arterial hypertension evolution?
a. Ang II acts on blood vessels in an endocrine manner. [*]
b. Ang II acts on blood vessels in a paracrine manner. [*]
c. Ang II production increase is due to juxta-glomerular α1-adreno-receptor activation by NE.
d. Ang II production increase is due to juxta-glomerular α2-adreno-receptor activation by NE.
e. Ang II is synthesized in all tissues excepting the brain.

5. Underline true links of RAAS role in the arterial hypertension evolution?
a. Ang II inhibits vascular fibroblasts.
b. Ang II inhibits extracellular matrix metalloproteinases.
c. Ang II constricts vessels by activation of myocyte AT2 receptor.
d. Ang II constricts vessels by activation of myocyte AT_1 receptor. [*]
e. Ang II increases prostacyclin synthesis.

6. Underline true links of RAAS role in the arterial hypertension evolution?
a. Ang II inhibits progression of atherosclerosis.
b. Ang II inhibits formation of the plasmin. [*]
c. Ang II inhibits formation of the NO. [*]
d. Ang II inhibits expression of integrins.
e. Ang II inhibits cell migration and proliferation.

7. Underline true links of RAAS role in the arterial hypertension evolution?
a. Ang 1-7 activates AT_1 receptors.
b. Ang 1-7 inhibits AT_1 receptor. [*]
c. Ang 1-7 increases production of NO. [*]
d. Ang 1-7 decreases production of NO.
e. Ang 1-7 inhibits cell migration and proliferation. [*]

8. Underline true links of RAAS role in the arterial hypertension evolution?
a. Ang 1-7 stimulates muscular media hypertrophy.
b. Ang 1-7 stimulates production of free oxygen radicals.
c. Ang 1-7 inhibits superoxide-dismutase expression.
d. Ang 1-7 inhibits extracellular matrix metalloproteinases. [*]
e. Ang 1-7 inhibits collagen synthesis by vascular fibroblasts. [*]

9. What are the mechanisms of endothelial dysfunction induced arterial hypertension evolution?
a. Increased tetrahydrobiopterin.
b. Increased dihydrobiopterin. [*]
c. Decreased tetrahydrobiopterin. [*]
d. Decreased dihydrobiopterin.
e. Decreased peroxynitrite.

10. What are the mechanisms of endothelial dysfunction induced arterial hypertension evolution?
a. Increased arginase. [*]
b. Decreased arginase.
c. Increased RAGE (advanced glycation end product receptor) expression. [*]
d. Decreased RAGE expression.
e. Decreased NOSi expression.

11. What are the mechanisms of endothelial dysfunction induced arterial hypertension evolution?
a. Increased asymmetric dimethylarginine. [*]
b. Decreased asymmetric dimethylarginine.
c. Uric acid blood concentration is 5.0 mg/dl.
d. Serum blood homocysteine concentration is 5.0 μmol/L.
e. Increased circulating level of the glucagon-like peptide 1.

12. What events are true in regard to the arterial hypertension pathogenesis?
a. Increased expression of micro-RNA-143 leads to vascular myocyte migration and proliferation.
b. Low expression of micro-RNA-143 leads to vascular myocyte migration and proliferation. [*]
c. Increased expression of Sirtuin sustains availability of the vascular endotheliocyte.
d. Decreased expression of Sirtuin troubles availability of the vascular endotheliocyte. [*]
e. Activation of the ornithine circle for L-arginine use.

13. What is the retinal arteriole to venule ratio in the hypertensive retinopathy?
a. 1:1
b. 1:2
c. 2:1
d. 1:3 [*]
e. 3:1

14. Which glomerular vascular phenomenon triggers glomerulosclerosis in arterial hypertension?
a. Afferent arteriole dilation. [*]
b. Afferent arteriole constriction.
c. Efferent arteriole dilation.
d. Efferent arteriole constriction.
e. Both afferent and efferent arterioles constriction.

15. What is the role of melusin in the arterial hypertension induced myocardial remodeling?
a. Provides eccentric hypertrophy.
b. Provides concentric hypertrophy. [*]
c. Provides dilation of left ventricle cavity.
d. Provides cardiomyocyte apoptosis.
e. Brakes cardiomyocyte apoptosis. [*]

16. Underline the pathophysiological significance of markers of the arterial hypertension induced cardiac remodeling?
a. Galectin 3 predicts myocardial hypertrophy.
b. Galectin 3 predicts myocardial fibrosis. [*]
c. Calcineurin predicts myocardial fibrosis.
d. Increased ratio collagen I/collagen III predicts boosted myocardial diastolic stiffness.
e. Decreased ratio collagen I/collagen III predicts boosted myocardial diastolic stiffness. [*]

17. What changes associate cerebral flow autoregulation in the arterial hypertension?

a. Pressure-flow curve is shifted to left.
b. Pressure-flow curve is shifted to right. [*]
c. Cerebral artery myocyte sensitivity to Ca^{2+} is increased. [*]
d. Cerebral artery myocyte sensitivity to Ca^{2+} is decreased.
e. Increased pulse pressure due to reduced cerebral artery stiffness.

18. What are the consequences of cerebral arteries hypertrophy in the arterial hypertension?
a. Hypertrophy of large cerebral arteries limits the pressure rise of downstream vessels. [*]
b. Hypertrophy of large cerebral arteries boosts the pressure increment of downstream vessels.
c. Hypertrophied large cerebral arteries lose distensibility. [*]
d. Hypertrophied cerebral arterioles lose distensibility.
e. Hypertrophy of large arteries does not shift the pressure-flow curve.

19. What is the pathophysiological support of the hypertensive encephalopathy?
a. Increased intracranial pressure.
b. Decreased intracranial pressure. [*]
c. Hypertrophy of cerebral arteries.
d. Cerebral arteries spasm.
e. Cerebral arteries dilation. [*]

20. What are the mechanisms of arterial hypertension quickening atherosclerosis?
a. Increased expression of micro-RNA-143 and micro-RNA-145.
b. Decreased expression of micro-RNA-143 and micro-RNA-145. [*]
c. Overexpression of NOSi. [*]
c. Deficit of peroxynitrite.
e. Diminution of the Toll-like receptor expression.