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AGE RELATED CHANGES IN THE WALLS OF ARCUATE ARTERIES OF KIDNEY: A LIGHT MICROSCOPIC STUDY

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Abstract. *Although there are many published papers on macro- and microvascularization of the kidney, there has not been a single study that would describe the histological characteristics of the arcuate arteries in specific periods of life. Our motivation to do this study derived from the need to explain the genesis of the ischemic nephropathy and determine the morphological changes on the arcuate arteries. Tissue samples were taken from the kidneys of 50 different cadavers of both sexes. They were divided into five groups, according to their age. The kidneys were of average size and did not show any macroscopic pathological changes. After embedding in paraffin, 5 μm cross-sections through the arteries were prepared. The specimens were analyzed under standard light microscopy, after different staining. The first significant changes are characterized by the widening of the subendothelial layer and the progressive enlargement of the intima. Media gradually shows atrophy, increase of the volume of collagen fibers and reduction of cell numbers. Internal elastic lamina undergoes changes that in time make it wrinkled with denser waves to the point of multiplication. The arcuate arteries, of all the larger intrarenal arteries, undergo the biggest amount of changes. In the beginning, the arcuate arteries suffer a "JET phenomenon", and that is why the age-related mechanical changes are more prominent in them. The dynamics of the change in their walls accelerates during aging. All described changes that start as a non-atherogenous fibromatosis of the tunica intima is a prerequisite for the development of an atheromatous plaque.*

Key words: *Age changes, kidney, arcuate arteries, histology*

Introduction

Every organ works with the appropriate capacity and has a certain functional reserve, which, mainly, expresses itself in older age. The change of the functional state of each organ is caused and/or accompanied by the changes in the morphological level. Age changes lead to increased probability for the occurrence of disease or deadly outcome. They affect the parenchyma and stroma of the organ, together with the changes in blood vessels supplying it, or without them.

All parts of the vascular system are subject to the influence of aging, but most attention focuses on the changes of large distributive arteries, responsible for the development of hypertension and increased pulse pressure, and potential effects on hemodynamics of left ventricle and changes in peripheral resistance and microcirculation [1]. Changes in the renal artery are mainly examined as one of the cause of the terminal renal failure, without clear marks of their dynamics, intensity and quality. During aging, kidney becomes sensitive to many influences from the external environment (high body temperature, lack of entry of liquids, physical load, nephrotoxic drugs, etc.), as well as to the different diseases accompanied by increased body temperature, greater loss of fluids, or massive destruction of cells, which all leads to more frequent occurrence of renal diseases, which are in this age more intense, more dangerous and difficult to heal [2–5]. It often happens that older people develop chronic renal failure without clear and visible symptoms and signs of previous disease of kidneys and other organs. Recently, a renal disease called ischemic nephropathy was established. It is often present, although often overlooked syndrome that is a potentially curable cause of terminal renal failure in elderly persons and includes reduced kidney function due to inadequate flow of blood through the kidneys [3,6]. Based on the observations of many authors [7–15] that in renal cortex of elderly people there is a standard phenomenon of sclerosis and hyalinosis of glomeruli, with consecutive changes in tubules, moderate fibrosis of renal interstitium, as well as the general reduction of kidney volume, mainly in the absence of hypertension or in the presence of corrected hypertension, one can suppose that the causes of these phenomena are in the morphological as well as functional changes in the larger arteries of kidney (renal artery, segmental arteries, interlobar–arcuate arterial complex). Numerous authors suggest that ischemic nephropathy arises mainly due to

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hemodynamically significant renal artery stenosis [16–20]. However, the opinion noted that renal ischemia can be caused by a stenosis or obstruction of the main renal arteries and/or a stenosis/obstruction of intraparenchymal preglomerular arterioles [21].

The arcuate artery of kidney is any of the branches of the interlobar arteries that turn at the junction of the cortex and medulla and proceed at right angles to the parent stem and approximately parallel to the surface of the kidney. Starting from the hypothesis that the morphological changes in the larger kidney arteries during aging may be responsible for the development of ischemic nephropathy, this research is focused on examining the morphological characteristics of, in particular, arcuate arteries of kidney in various ages.

Material and Methods

The research was carried out on the cadaveric material originating from people of different ages and both sexes. The renal tissue material from Institute for Forensic Medicine in Niš, was used.

Kidney tissue samples were taken always in the same way, from 50 cadavers, of both sexes, sorted in five age groups, each containing 10 pieces, in the following way: I group — age 20–29 years, II group — age 30–39 years, III group – age 40–49 years, IV group — age 50–59 years, and V group — over 60 years. Period of time from the moment of death to sampling was not longer than 24 hours. The most common cause of death was accident or a primary malignant tumor localized far from the kidney. At the same time, there was no positive anamnesis or visible signs of diabetes and hypertension, and it were strictly observed that there are no visible signs of atherosclerosis of larger arteries. The kidneys had expected dimensions, and did not show macroscopic image of scarring process or large cyst or deformities of pyelocaliceal system. In each individual case, contralateral kidney was similar in dimensions.

Histological examination was performed on the initial part of arcuate artery, which is muscular type artery. For the purpose of examination, a sample of kidney tissue from Bertini's column in the level of bases of neighboring Malpighi's pyramids, exactly in the middle distance between the upper and lower poles of the kidney, was used. The cadaveric material was fixed in 10% neutral formalin immediately after sampling. Then, the material was molded in paraffin by standard histological procedure. After molding, the cuts with thickness up to 5 μm and normally to the long axis of vessel (cross-section) were made. Afterwards, staining was done by following methods: Hematoxylin-Eosin (HE), elastic fibers by Weigert's resorcin-fuchsin method, Van Gieson's method for collagen, and Gomori's impregnation for reticulin [22]. By Van Gieson's method, nuclei are stained brown/black; collagen red and other tissues are yellow. According to Weigert's resorcin-fuchsin method, elastic fibers are stained brown. By Gomori, reticular fibers are stained black; collagen pale red; nuclei gray, and other tissues are stained differently, depending on the contrast. At the end, the histological analysis was done using the light microscope. All the layout and distribution of smooth muscle cells in the media, the amount and quality of collagen fibers and the presence of abnormal plaques in the arterial intima have been examined. We also evaluated the ratio of vessel lumen to the wall thickness, as well as state of endothelium, subendothelial space, internal elastic lamina, smooth muscle cells of the media (atrophic, hypertrophic, hyperplastic), interstitial space, and adventitia. On the basis of impressions, created by interpretation of the structures, using a number of staining techniques, the histological features of the arcuate arteries are contemplated.

Results

Basic information about the cadaveric materials used is shown in Table 1. It is evident that the length of the kidney slightly decreases during aging.

Within age groups, sorted by decade, there are variations in the wall structure from the youngest to the older age, so the absolute identity within a group is impossible. With some variations, the findings related to the artery within a group are as follows:

I group (*period of 20–29 years*). The intima of arcuate arteries is present only as an endothelial layer that leans on thin and real internal elastic lamina (IEL). In some arteries (24 years) the intima shows mild thickening. In the older age (28 years) of this group, in relation to the circumference, it is moderately expanded, and possessed in one quarter, mainly with collagen structures and rare smooth muscle cells (SMCs) (Fig. 1). In one branch of the arcuate artery (29 years), in circumscriptly thickened intima, the reticular network is thickened. IEL is shallowly wavy bent and sporadically duplicated. The media has the appropriate width, with well-expressed SMCs in the circular or inclined longitudinal schedule and slight partial fibrosis. In the small number of cases, SMCs are sparse and atrophic in

Table 1. Basic data about the materials used for histological examination (mean values ± standard deviation)

		Age group				
		20–29 (n=10)	30–39 (n=10)	40–49 (n=10)	50–59 (n=10)	60+ (n=10)
Mean age (years)		25.8 ± 3.6	35.1 ± 3.1	43.2 ± 1.8	54.4 ± 3.0	71.7 ± 6.9
Mean height (cm)		178.4 ± 4.8	177.8 ±13.3	174.9 ± 6.7	175.2 ± 8.5	165.8 ± 9.6
Kidney length (cm)	R	11.12 ± 0.63	11.52 ± 0.98	11.45 ± 1.17	11.38 ± 1.11	11.07 ± 1.23
	L	11.20 ± 0.91	11.87 ± 0.71	11.74 ± 0.83	11.63 ± 1.03	11.40 ± 1.14

the level of thickened intima, sporadically with collagen among them. The external elastic lamina (EEL) is hardly observable, thin, linear and aplated. The adventitia is relatively wide.

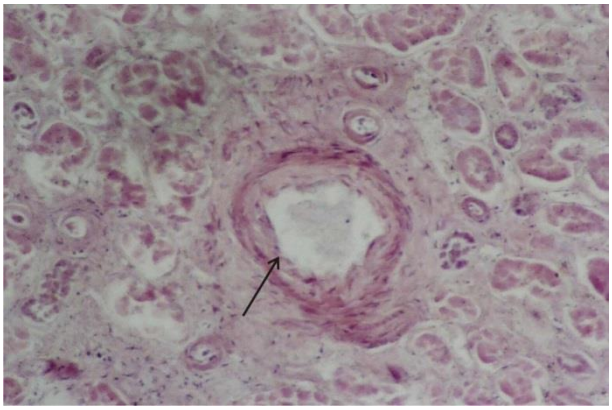

Fig. 1 Transverse section of the arcuate artery with relatively preserved structure and mild collagenization of wall (arrow). HE, × 100

II group (*period of 30–39 years*). The arcuate arteries have uneven caliber, appropriate size, well-expressed lumen, sometimes without intima or they show (older kidneys of this group) slightly partial cellular-fibrous type of thickening of the intima, with rough reticular network. In part, IEL is shallow, wavy, with uniform width, well acceptable to color, and partly duplicated and serrated. Some arteries have tortuous and partially duplicated IEL. In most cases, the media has uniform width, corresponding cellularity, and is knited by reticular fibers, with some reduction of number of SMCs in the level of fibrous thickening of the intima. One-fifth circumference of the inner part of the wall are reduced SMCs, and they are replaced by pink collagen fibers (Fig. 2), and there are collagenized reticular fibers in this level. EEL is clearly outlined, with shallowly serrated small part, and flattened in the other part. The adventitia is primarily collagenized.

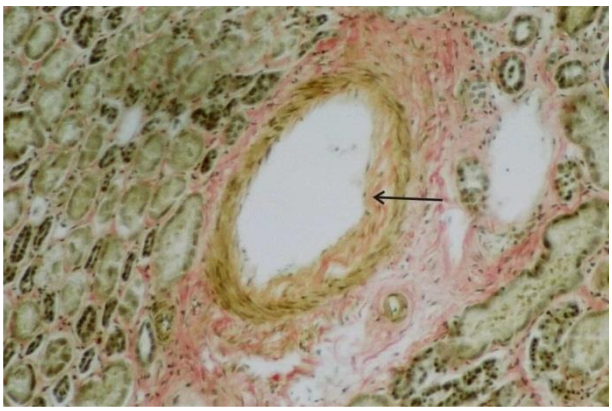

Fig. 2. Transverse section of the arcuate artery with asymmetrically widened intima in which collagen fibers (arrow) are seen. Van Gieson, × 100

III group (*period of 40–49 years*). The spectrum of arcuate arteries' caliber is wide but they show similar characteristics, depending on diameter. In the larger arteries asymmetric homogenous fibrous widening of the intima is observed, with rare spindle cells in it. These cells are periodically placed orthogonally to the lumen, and gentle and coarse elastic and collagen fibers are also present, as well as SMCs. Reticular network in intimal thickening is roughened and collagenized (Fig. 3). IEL is very shallow, wavy, in some cases partially fragmented, sometimes duplicated. In the media there is a slight reduction of cells only in places where intima is changed (homogenized), which is conditioned by changes in intima. There are no collagen fibers in the media but sometimes one can note the relative and absolute reduction of SMCs of media. EEL is clearly outlined and flattened. The adventitia in larger arcuate arteries shows the width equal to that of media, while in very small arteries it is reduced.

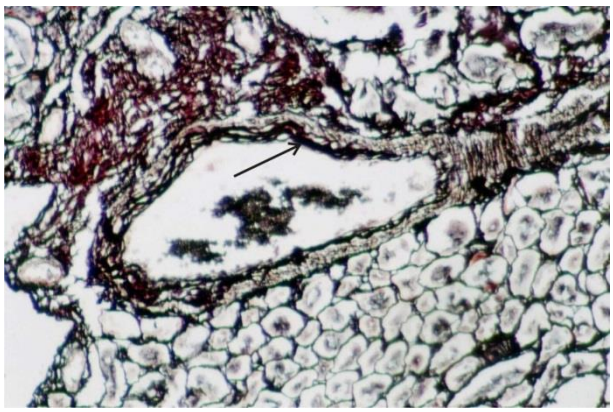

Fig. 3. Tangentially affected arcuate artery with asymmetrically fibrous intima made of rough reticular fibers (arrow), with reduction of media. Gomori, × 120

IV group (*period of 50–59 years*). The arcuate arteries do not have all the same properties. Some show complete fibrosis of the wall and visible reduction of SMCs in media. The intima is difficult to distinguish from the media; it changes more than other layers (Fig. 4). Some arteries show acellularity of inner part of wall, where there are asymmetrically affected parts of the intima and media (Fig. 5). Some arcuate arteries, however, have a minimal expansion of the intima with thickened reticular fibers. The intima is relatively broad, as well as media, and collagenized. SMCs are attended, as well as wavy and coarse reticular fibers. IEL is slightly wavy, partially indinstinct. The media is partially to almost completely acellular. Some arteries have wide media and moderately reduced SMCs. In relatively atrophic media there are rough reticular fibers. EEL is the right circular line. It outlines media under broader adventitia and at some places it is wavy above collagenized intima. The adventitia is emphasized and collagenized.

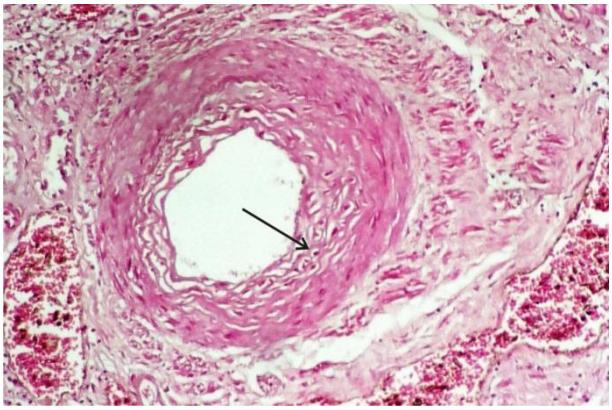

Fig. 4. Transverse section of the arcuate artery. Loosely widened intima (arrow) with a moderate number of cells asymmetrically suppresses atrophic media. HE, × 120

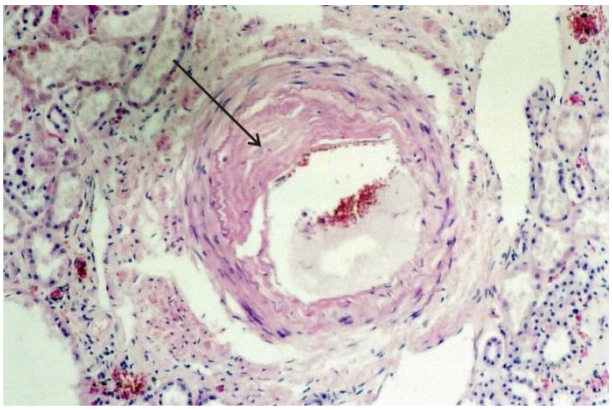

Fig. 5. Transverse section of the arcuate artery. Asymmetrically markedly widened hyaline-collagen intima (arrow) partially reduces media and makes subocclusion of lumen. HE, × 120

V group (*over 60 years*). The arcuate arteries are of unequal size and morphological characteristics, most of them are overall highly increased and with thickened walls. In two thirds of the expanded intima the arcuate arteries show markedly asymmetric fibrocollagen thickening with homogenized content and rare spindle cells, sometimes with the SMCs (Fig. 6). Cuts along the length of the vessel show the minimal and slightly asymmetric thickening of intima. The intima has the fibrocollagen and belongs to suboclusive type. In the broader intima, the reticular network is roughened (thickened) and replaced by collagen (Fig. 7). In the level of intimal thickening, IEL is sometimes multiply decomposed (Fig. 8), in other cases is suppressed by intimal widening, condensed and shallow wavy, and in many cases it is duplicated. The media is in some cases droningly wide, but it is narrowed in the level of fibrous thickening of the intima, until complete fibrocollagenization of the entire wall, with the ultimate reduction of its cells. Where fibrosis has overtaken the inner zone of media, SMCs are sporadic, rarely bundled and drowned in collagen mass (see Fig. 6). In third type of cases, the

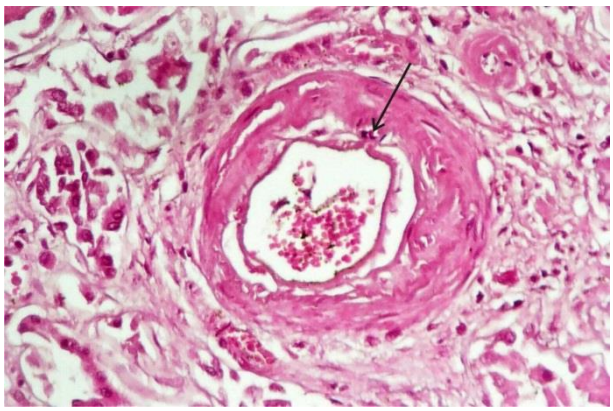

Fig. 6. Transverse section of the arcuate artery. Lumen stenosis and thickening of the arcuate artery wall due to subtotal fibrosis and hyalinization of its wall, with rare atrophic smooth muscle cells (arrow). HE, × 120

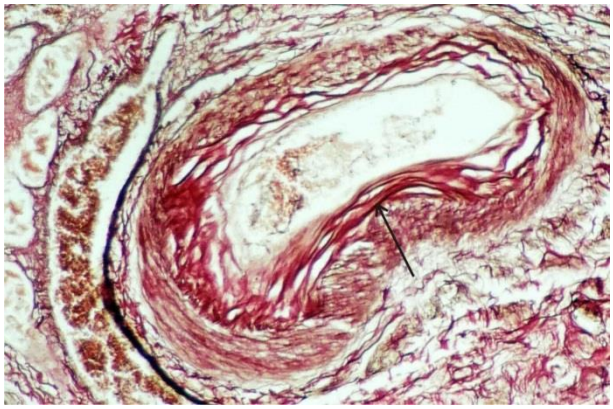

Fig. 7. Tangential section of the arcuate artery shows coarsening of reticular fibers (arrow) and their collagenization in the intima and part of media. Gomori, × 150

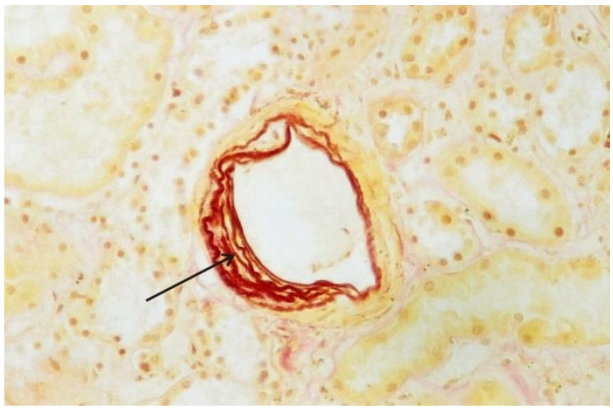

Fig. 8. Transverse section of the arcuate artery. Assymetrical multiplication of IEL (arrow), which reduces media. IEL, internal elastic lamina; Weigert, × 100

media is in general slightly asymmetric, its two-thirds are widened, and one third is narrower, with fewer cells due to moderate atrophy and reduction of SMCs number, only slight fibrous fibers can be seen through the media. Reticular network is gentler or slightly thickened in the media (see Fig. 7). EEL is almost completely absent or is well outlined, with wavy monotonous rhythm. The adventitia is narrow, loose, partially with areas of arteriolohyalinosis.

Discussion

The kidney has an essential role in hypertension, taking into consideration that its blood vessels are sensitive to different types of pathological changes that are directly associated with increased blood pressure. At the same time and independently of that, the progressive reduction of blood flow through the kidney arteries has significant influence on atrophy of renal parenchyma. These changes need not always be directly related to pathological processes, but may be an expression of aging events [23–25]. In the above-mentioned processes, extreme sensitivity reflects, first of all, in the small arteries and arterioles, especially in preglomerular vessels. Narrowing of kidney blood vessels leads to glomerular sclerosis, tubular atrophy and interstitial fibrosis (nephrosclerosis).

Despite numerous works about the macro- and microvasculature of the kidney in the world literature, until now, no studies have described the histological characteristics of arcuate arteries of kidney for certain periods of life, starting from the time when the kidney is fully ripe for all of its functions, to the old age. According to our results, one of the characteristics of aging by years, if the age shows changes such as fibrous thickening of intima, is that they first appeared focal, then spread in circumference, i.e. increased the width (thickness) of the intima and enriched the content. Haemodynamical factor in the process of aging changes is significant, in addition to positional situations (branching blood vessels and platelet aggregation) in normal conditions, due to duration. This means that in relation to duration, i.e. elapsed time, the effects of this factor are evident. This excludes pathological factors.

Within age groups there are variations in the composition of the wall from the youngest to older age, so that the absolute identity of the findings within a particular group is impossible. On the other hand, although there are regularities in the appearance of certain changes, they are subject to variation, too, so that some appear inadequate in relation to time and blood vessel, but this can be attributed to unequal genetic texture of the people, and to the existence of individual difficulties and physical burdens of the people who are unknown to us. Of course, the body height of a person, its constitution, obesity and other variations affect the changes to the structure of the wall of blood vessels. Therefore, the number of seemingly unusual findings within a group should not be surprising, because it is a wide range of time (range 10 years), with unequal genetic potential, type of diet, physical form of the load, and more.

There is no doubt that all layers of the vessel wall "suffer" age changes, but we believe that the initial, primary and most visible changes are taking place in the intima, IEL and media (in some cases even EEL suffers changes). According to this, one can consider three questions: the question of the intima, IEL and media.

The question of the intima. Due to diffusional supplying of internal half of the media, the intima is presented only by the endothelium, which is close to IEL. The example is the case of the aorta that is going to 10^{th} year [26]. From that period its thickening begins by creating subendothelial layer, which is a prerequisite for further compromising of nutrition and developing further changes in the intima, and consecutive repercussions to the media, through the development of atheromatous changes. The intima of most segments of all artery types is mainly reduced to the endothelial layer lying close to the IEL, which means that it is in principle almost absent, except in some cases where it shows initial partial thickening in the form of cushion widening, where the reticular network is well expressed about SMCs, but even outside them, at the earliest age groups. In older age there are increased values of parameters of intimal fibroplasia [27]. Changes in the composition of the intima reduce diffusional process which is reflected in the ingredients of vessel's wall. With aging, the endothelial cells become heterogeneous in size, shape and orientation, resulting in reduction of laminar flow and increasing receptivity to lipid deposits, and this endothelium becomes more sensitive to oxidative stress and damage by free radicals [13].

It appears that changes in the properties of IEL are dependent on state of the intima i.e. that are only in close correlation with its thickening (increased jaggedness of IEL, its duplication and fragmentation). In places where thickening of intima starts, one can see strong reinforcement of amplitude and density "plication" of IEL, probably due to the increased need for communication between the intima and media. This happens through the IEL, which, we assume, increases the surface exchange of communication between the media and intima, which is growing, initially only in the form of mucopolysaccharides, and later the cell contents.

Morphogenesis of the intima secondarily depends on the action of the media: in the beginning, it is possible that the subendothelial layer is possessed by diffusion of polysaccharide content, eventually by lymphocytes, but in the further course, media fills the content of the intima, because the former affects the condition of IEL, which is its product, sending the SMCs into the subendothelial layer. For these reasons, cell content near the IEL is much more common than below the endothelium.

The question of the IEL. Elastic lamina of arteries is the organizational structure whose role is primarily supportive, not only for the maintenance of lumen contours, but also for support of the main parenchymatous functioning part, i.e. media. So, it significantly follows changes of the lumen diameter and on the other hand it

maintains the media. SMCs of media are fixed for IEL and EEL and they are, among other things, the structural support of the media and its product. IEL is undoubtedly an important component in the narrowing and widening of the walls of blood vessels, but on the post mortem microscopic preparations, in normal circumstances, it is more or less aplated or slightly wavy [28]. We observed that the existence of larger or smaller amplitudes (waves) is an equivalent of age changes, often associated with changes in the intima. One possible presumption is that in this way it is trying to increase the area of exchange between progressively expanded intima and inner parts of the media. It is understandable that, with increasing width of intima and its "dramatic" events during the formation of larger fibromatous or atheromatous plaques, there is a duplication of IEL, decreasing the wall properties (loss of receptivity to color, fragmentation), which is a sign that, under these circumstances, the mechanisms of adaptation and compensation are absent.

It is interesting that the IEL is most commonly one-pieced, ie. homogenous, evenly broad structure. During the aging, i.e. by the influence of long acting hemodynamic factors (through time, with age), it is among the first structures which opposes damaging factors of duration of circulation, and begins to change. As an expression of its damage or attempt to confront the present long-term burden of mechanical pulse wave, it shows compensatory duplication or triplication [28]. This is often observed in places of strong shock, such as initial segments of arcuate arteries which stand at right angles to the shock wave from interlobar artery. These changes are slightly reduced with the reduction of caliber of arcuate artery in the horizontal position. It looks like some form of vessel's defense to load, because it can not produce these effects in a short-term action. This raises the question: does the blood current – blood blow provoke production of growth factors?

The continuity of the presence of changes in the IEL (such as low receptivity to color, thinness, duplication, possibly fragmentation) in the level of cushion widening of intima testifies about insufficiency of process of diffusion, which is repercuted to the morphofunctional state of SMCs at this level and its inner part, as well as to the reduction of production of IEL. These age changes may not be accompanied with changes of its thickness and may include increased number of collagen fibers that overlap fenestrae of IEL and/or reduction of total surface area of these fenestrae by changes in the structure of elastic layers [29]. IEL of arcuate arteries in the kidney in old age particularly acts — multiplies, divides into layers. This phenomenon may be called the multiplication of IEL.

The question of the media. Tunica media is adapted adequately to distribution of blood vessels, in fact, it is adapted according to hemodynamic wave - prevalently it is elastic in conductive types and muscular in distributive type. Media content is appropriate to topographic location: in elastic arteries — elastic fibers, in muscular arteries — SMCs. The tunica media is mainly formed by SMCs and elastin, and the latter is arranged in fenestrated lamellae between which are collagen fibers, extracellular matrix, and SMCs [30]. These parenchymatous components almost contain a minimum of collagen fibers. In relation to time we have observed directly and indirectly that there is a change in their content. In arcuate (muscular) arteries there occurs reduction of their SMCs or their deterioration due to atrophy, especially in the level of thickened intima (nutritional factor). However, in the process of aging it was progressively noted that reticular network knitting SMCs can be collapsed, bold or collagenized. The question of the presence of collagen fibers in a larger quantity is interesting considering that the media does not have fibroblast cells. It is possible that collagen fibers arise from reticular network which got coarse. It could be stated under the presumption that the influence of growth factors induces the development of fibroblast cells from undifferentiated mesenchymal cells of intima.

Eventual thickening of the media could be relative, due to the presence of edema and lipid content in the case of atheromatosis, but absolute widening of the media was not often observed. So, we can say that in the process of aging there occurs reduction of functional part of the vessel, ie. media, probably and primarily due to intima fibrosis and consecutive atrophy of SMCs, with accompanying coarsening of reticular network, which in turn further reduces nourishment of cells because it prevents access of nutritious substances to the muscle cells due to the creation of "armor" from the bolded reticular network. In the level of bold intima, the media is easily reduced. Media repairs and maintains the quality or permanence of IEL structural integrity.

One can pose a question about proliferative capacity of SMCs of media, i.e. the existence of stem cells. A number of SMCs, under the influence of cytokines and growth factors in the process of intimal fibrosis, migrate from media to intima [31]. It is clear that, under the influence of chronic hemodynamic stimuli, the SMCs of media experience changes. These changes resemble "dedifferentiation". With the loss of capacity for contraction, SMCs acquire the ability to divide and synthesis of extracellular matrix increases. SMCs in the intima lose their thickness and filaments containing myosin, and increase the amount of organelles involved in protein synthesis [31]. So, there is a phenotypic modulation from "contractile" phenotype to the "synthetic-proliferative" phenotype. Therefore, it is considered that mutations and phenotypic modifications of SMCs of media reach the intima [32]. This transformation happens in atherosclerosis, where SMCs synthesize collagen in the scale characteristic for fibroblast cells [33]. SMCs, which migrate from the media, are primarily proliferative cells in the intima, though in some cases, their proliferation may arise from ancestral myointimal cells [32]. There is no doubt that, in some cases, migrations of SMCs are very numerous.

Considering the normal age changes, all under the influence of hemodynamic factors, it seems that among the major intrarenal arteries, arcuate arteries show the largest changes. The arcuate arteries are damaged be-

cause of their position and effect of hemodynamic factors, which is described by other authors [34]. The arcuate arteries at the beginning suffer "JET phenomenon" – a stronger shock wave pulse, because they are at a right angle to the straight interlobar arteries, and therefore, age "mechanical" changes are more expressed in them. However, in the further course, due to the depreciation of shock pulse wave, they have fewer changes. Many textbooks show uniformity of arcuate artery's caliber which is almost impossible, because this artery is shown as a continuing arc of the interlobar artery in a flat section, and the question arises: where are their side branches in terms of space (stereometrically) in the corticomedullary border in a light of the total thickness of the kidney? Therefore, it is necessary to perform a comprehensive research of arcuate arteries and standardization of their size, because, undoubtedly, they are not all of equal caliber or thickness of the wall.

Conclusion

The first significant changes are recorded in the third decade in the form of enhancement of subendothelial layer and progressive widening of the intima, which is gradually possessed by an amorphous mass; then the cells appear in it.

With aging, the internal elastic lamina (IEL) becomes less susceptible to color and wrinkled with larger and denser extent, to the fragmentation and multiplication. With the weakening of the media, IEL suffers changes, which means that the media maintains morphological integrity and permanence of IEL.

Media shows atrophy and gradual reduction of SMCs, and increased collagen content. Reticular network which initially gently knits each smooth muscle cell but with aging it gets coarse and collagenizes. A universal finding is the existence of circumscriptive reduction of media in the level of thickened intima.

The dynamics of changes in the layers of the arcuate artery wall accelerates and becomes difficult with age. All described changes that begin as non-atherogenic fibromatous plate of intima, are a prerequisite for the development of atheromatous plate. All these changes reduce the diameter of the lumen, i.e. they lead to narrowing of the arcuate arteries in older age.

Age changes in the wall of arcuate arteries of kidney in the elderly, combined with other factors in the external and internal environment, may be responsible for the occurrence of ischemic kidney disease.

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