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REVIEW ARTICLE

Atherosclerosis in Animals is a Separate Type of Atherosclerosis that Has Nothing to do with the Two Types of Atherosclerosis in Humans

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ABSTRACT

The article is presented in the form of a review and analysis of the literature, which additionally helps to reveal the mechanisms of the pathogenesis of the development of atherosclerosis in humans. A contemporary vision is refuted that animal models of atherosclerosis are completely similar to the two types of human atherosclerotic lesions. The use of incorrect information about the etiology and pathogenesis of atherosclerotic lesions in humans reduces and even completely interferes with the possibility to carry out effective treatment and prevention of cardiovascular diseases associated with atherosclerosis. The two types of human atherosclerotic plaques have very different characteristics compared to atherosclerotic plaques in animals. They have a completely different etiology, pathogenesis, have a completely different appearance and location relative to the artery wall, have a different structure of the fibrous cap, a different pathway of LDL and macrophages, a different location of lipid core, a different way and time of arterial occlusion, a different type of endothelial dysfunction, they interact in totally different way with the walls of the artery and still have many additional differences that make both human atherosclerotic lesions completely different from atherosclerotic lesion in animals. Types IV atherosclerotic lesions consist of one lipid core with molten extracellular lipid. Type V atherosclerotic lesions type is a long, concentric, soft, strong, elastic, yellow, uniform structure. Due to the large number of inconsistencies between atherosclerotic lesions in animals and the two types of atherosclerotic lesions in humans, it is neither possible nor reasonable to use animal models to study the development of atherosclerotic lesions in humans. The plaques appear in the lumen of the artery in just a few days, in places of a sharp narrowing of the artery caused by hyperstimulation of the nervous system. The plaques consist of LDL, which were glued together with fibrin filaments. It also doesn't allow to detect a very simple mechanism accountable for the pathological increase in LDL levels in people who do not have genetic abnormalities. This mechanism proposed by the author is described in the first article dedicated to the type V atherosclerotic lesions ("Cylindrical cholesterol plaque").

Keywords: Atherosclerosis; LDL; Atherosclerotic plaque; Heart attack; Stroke; Artery dissection; Stress; Atherosclerosis in animals; Atherosclerosis in humans.

Abbreviations

ASL		atherosclerotic lesions;
ASL(I)	-	type I atherosclerotic lesions;
ASL(IV)	-	type IV atherosclerotic lesions;
ASL(I-IV)	-	types I-IV atherosclerotic lesions;
ASL(V)	-	type V atherosclerotic lesions;
ASL(VI)	-	type VI atherosclerotic lesions;
ASL(V-VI)	-	types V and VI atherosclerotic lesions;
LC	-	lipid core with molten lipids;
LDL	-	low density lipoproteins;
CCP	-	cylindrical cholesterol plaque;
ED	-	endothelial dysfunction;
FC	-	fibrous cap;
FCCP	-	friable cylindrical cholesterol plaque;
SCCP	-	soft cylindrical cholesterol plaque;
DCCP	-	dense cylindrical cholesterol plaque;
OCCP	-	old cylindrical cholesterol plaque;
MFC	-	macrophage foam cells;
VV	-	vasa vasorum.

Introduction

The history that describes mechanism of formation of atherosclerotic lesions (ASL) in animals began more than 100 years ago.[1] Anichkov used cholesterol dissolved in vegetable oil. Such a diet resulted in appearance of ASL in t rabbit's aorta and clinical manifestations appeared that coincided with clinical manifestations in humans.[2] After numerous studies dedicated to animal models of atherosclerosis, scientists have concluded that atherosclerosis (AS) must be treated as a chronic and multifactorial inflammatory disease.[3] Since ASL caused similar clinical manifestations in rabbits and humans and there was an external resemblance of plaques, the main conclusion was that the animal model of AS is identical to AS in humans, and that the study of AS in animals allows to study and fully transfer all knowledge about animal models of AS on human AS.[4] For 100 years, surrogate instrumental measurements, as well as coronary artery calcification and carotid intima-media thickness, clinical manifestations of ischemia have been used as endpoints to assess the direct effect on atherosclerosis.[5-7]

As it was mentioned in the previous article, a person has two separate types of atherosclerotic plaques, which are also not related to each other.

Types I-IV atherosclerotic lesions consists of one lipid core with molten extracellular lipid. Stretches the middle and outer layers of an artery from one side and protrudes beyond the anatomical artery dimensions over the years.

In contrast, type V atherosclerotic lesions type is a long, concentric, soft, strong, elastic, yellow, uniform structure, in the form of a tube with a hole in the middle, located in the lumen, which is easily removed from the artery. Type V atherosclerotic lesions is an independent pathological structure that appears in a short period of time (few minutes) in the lumen of a healthy artery in case of artery spasm and appearance of a strong obstruction to blood flow.

Animal models of atherosclerosis look different - diffuse intimal thickening with multiple lipid nuclei, which are covered with damaged endothelium and fibrosis, which appears due to the inflammation of the intima after artificial effect on the arterial wall by a human during the experiment. Such effect on walls of vessels are absent in an ordinary person when type V atherosclerotic lesions appears.

It is the misconception about the development of atherosclerotic lesions in animals and atherosclerotic lesions in humans that makes it impossible to study, treat and prevent types V-VI atherosclerotic lesions in humans for 100 years, which contribute the most to the development of dangerous and common diseases of the cardiovascular system in humans, such as stroke and heart attack, and ensures a "pathological increase in the level of low-density lipoproteins (LDL)" in the blood.

The atherosclerosis in animals

At present, several successive stages of ASL development are being determined in animals (Figures 1.8-1.10).[4, 6, 8, 9] The development of AS is called "Atherogenesis". This means that monocytes penetrate into the intima layer of arteries, from the side of the blood, which then undergo differentiation into macrophages.[10] Together with monocytes, LDL pass into the intima, through the endothelium.[11,12]

Macrophages absorb LDL and turn into macrophage foam cells (MFC).[10] When MFC is degraded, a lipid core (LC) is formed from extracellular lipids with various admixtures. The penetration of blood elements into the intima is explained by the fact that the epithelium is damaged and inflamed due to the blood pumping in the zones of turbulent flow.[13] It is also believed that systemic factors such as chronic systemic inflammation, smoking, obesity, type 2 diabetes, sedentary lifestyle, and eating of "harmful" food have a direct impact on penetration of the shaped elements into the intima layer of arteries. Smooth muscle cells migrate to the area of atheroma after an injury to the artery wall and the appearance of inflammation.[14] At sites of endothelial damage and inflammatory reactions, a fibrous layer is formed, which contains smooth muscle cells and extracellular matrix.[14] The increase in the size of ASL in the vessel causes occlusion of the vessel by the ASL itself and causes organ ischemia.[15,16] Damage and rupture of the fibrous layer leads to the formation of a thrombus .[15] Calcium deposition leads to ASL calcification.[17-19]

Thus, after the impact of traumatic factors on the artery wall, a diffuse intimal thickening appears with multiple mast cells and lipid nuclei, which are covered by damaged endothelium and fibrosis. The location of such ASLs in the arterial lumen in animals can be either concentric or eccentric.

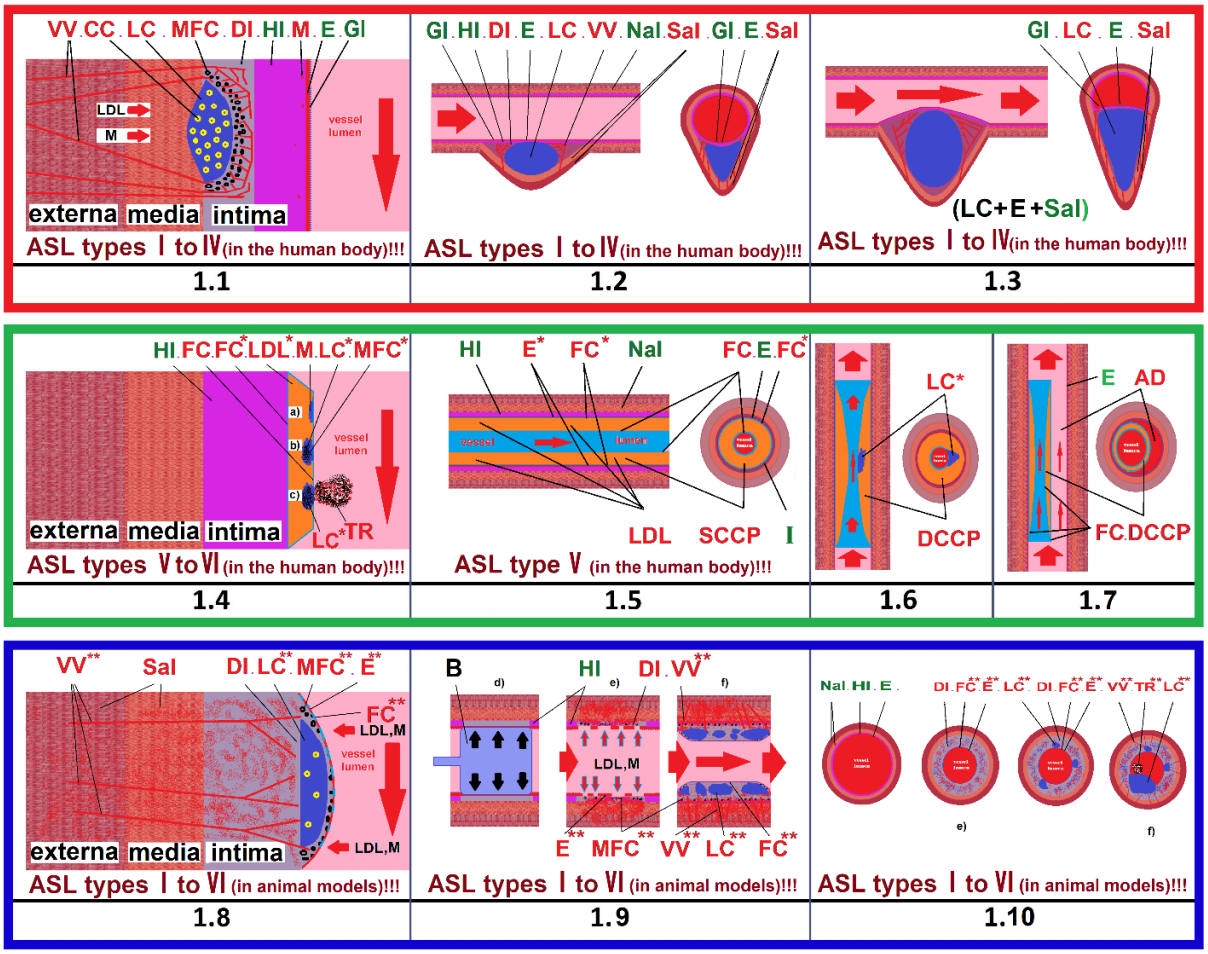

Figure 1: Three types of atherosclerotic lesions have nothing in common with each other. A person has two types: ASL IV - with long-term stretching of the walls of the artery and ASL V (Cylindrical cholesterol plaque) - an elastic tube in the lumen of the artery. One (separate species) in animals - immediately grows into the lumen of the artery.

1.1 -1.3) **Type IV atherosclerotic lesions (ASL IV) in artery in human:** 1.1 The real location of the LC in intimate part. Type IV atherosclerotic lesions in artery. The LC is located far from the endothelium, close to the middle layer of artery. The MFCs are located close to the LC. There is an area of healthy intimate region (HI) without inflammation, without MFC, LDL, with a very small number of macrophages Between the MFC and the lumen of the artery. LDL and macrophages enter the lipid nucleus only from the outer layer of the artery, through the "vasa vasorum" [22]; 1.2-1.3) The longitudinal and transverse section of

the types I-IV atherosclerotic lesions, according to the classification, looks like a tubercle that protrudes beyond the anatomical dimensions of the artery. Also looks like a tubercle protruding inward (into the lumen) of the artery in the type IV atherosclerotic lesions. Always limited to a few millimeters LC length. Always contains liquid lipids in the lipid core. There is always an area of healthy intima near the endothelium. Always has a whole endothelium. Never has a fibrous cap. Always stretches the middle and outer layer of the artery. It always has blood vessels that start from the outer layer of the artery.

1.4-1.7) **Type V atherosclerotic lesions (ASL V) (Cylindrical cholesterol plaque) in artery in human:** 1.4) ASL V (Cylindrical cholesterol plaque) is an independent pathological structure that appears in a short period of time in the lumen of a healthy artery, consists entirely of LDL. The wall of the artery that surrounds the CCP has a normal structure, without damages, inflammation, sprain and without necrotic nuclei. From the side of the blood, the CCP is gradually covered with a fibrous cap (FC). On the outside of the CCP, a fibrous layer is also formed between the CCP and the artery wall. a,b) When FC is damaged from the blood, macrophages penetrate into the CCP wall, MFC and LC are formed. The LC is located only inside the CCP wall; c) Blood clot formation at the site of FC damage; 1.5) The anatomical dimensions of the artery do not change. There is a hole located in the center of the CCP through which blood flows. When appearing the CCP has a form of a tube (cylinder) inserted into an artery. After its appearance, ASL V has no LCs; 1.6) When FC is damaged from the blood, macrophages penetrate into the CCP wall, MFC and LC are formed. The LC is located only inside the CCP wall; 1.7) Dissection of the artery. The strong outer wall of the CCP can break away from the inner artery wall so that blood can fly ow between the CCP and the artery wall, forming a pathology - an arterial dissection;

1.8 - 1.10) **Atherosclerotic lesions in animals (ASL Animal):** 1.8) LDL enters the “intima” through the damaged endothelium. The lipid nucleus is located just behind the damaged endothelium. The endothelium is stretched and damaged. The middle and outer layers of the artery are never stretched. The LC size increases only in the lumen of the artery; 1.9) d) Balloon or wire injury are the two commonly accepted injury modalities used in animals’ models; e) damage to the endothelium and the formation of "endothelial dysfunction"; f) plaque formation in an animal; 1.10) Atherosclerotic lesions (Animal) crosssection. Similar to paragraph 1.8;

AD - Arterial Dissection; B- balloon; CC - cholesterol crystals; DCCP- Dense Cylindrical Cholesterol Plaque; DI - damaged artery intima; E - whole endothelium in a human artery; E* - endothelium between plaque and arterial wall in humans; E** - damaged endothelium in an animal artery; ED - endothelial dysfunction; FC - fibrous cap (in the lumen of the artery); FC*- fibrous cap (between plaque and artery wall); FC** - fibrous cap (above the plaque in an animal); GI - glycocalyx; HI - healthy intima of the artery; I - intima; LC - lipid core with molten lipids in human intima; LC *- lipid core with molten lipids in Cylindrical Cholesterol Plaque; LC** - lipid core with molten lipids in animal intima; LDL - low density lipoprotein in human intima; LDL* - low density lipoprotein in Cylindrical Cholesterol Plaque; LDL** - low density lipoprotein in intima of an animal; M - single macrophages; MFC - macrophage foam cells in human intima; MFC* - macrophage foam cells in Cylindrical Cholesterol Plaque; MFC** - macrophage foam cells in animal intima; Nal - normal artery layers; S - stretched artery layers; SCCP- soft cylindrical cholesterol plaque; TR - thrombus in the plaque lumen after a rupture of the fibrous lid in a human; TR** - thrombus in the lumen of an artery after rupture of the fibrous cap in an animal; VV - vasa vasorum in the wall of an human artery; VV** - vasa vasorum in the wall of an animal artery.

Two types of atherosclerosis in humans

The two types of ASL in humans have many differences both in relation to ASL in animals and with each other. The mechanism of formation of the 2 type of atherosclerosis in humans is described in the first article of the author.[20] Differences between separate types of ASL in humans are described in a previous article of the author.[21]

In accordance with the classification,[22] type IV atherosclerotic lesions (ASL IV) (Figures 1.1-1.3) consists of one LC with molten extracellular lipid and a small number of macrophage MFC. "Vasa vasorum" (VV), which grow from the outer layer of the artery and gradually sprouts around ASL IV. ASL IV stretches the middle and inner lining of an artery and protrudes beyond the anatomical artery dimensions over the years. ASL IV looks like a small tubercle outside the artery which protrudes above the artery wall. It is impossible to separate ASL IV from the artery wall, while maintaining its shape and structure.[22] Extracellular lipids in LC do not have a strong bond with each other. In case when lipids are squeezed out, LC lose their shape. The intima with MFC, when removed from the vessel, also cannot retain its shape, since MFCs do not have a fibrous connection with each other.

In contrast, type V atherosclerotic lesions (ASL V) tube in the form of a hollow cylinder (Figures 1.4-1.7, 2.1-1.10, 3.1-3.6),[23-42] often without a "lipid core".[23,24-30,31-36] ASL V type is a long, concentric, soft, strong, elastic, yellow, uniform structure, in the form of a tube with a hole in the middle, located in the lumen, which is easily removed from the artery without damaging its wall. This types V and VI atherosclerotic lesions (ASL V-VI) - the author suggests calling "cylindrical cholesterol plaque" (CCP).[21] Only ASL V-VI (eccentric and concentric) are featured in all the videos made during removal of atherosclerotic lesions. In the process of ASL V-VI removal, there are no signs of ASL IV in the artery wall, which, in accordance with the modern view, must be there. The artery wall near ASL V-VI does not have inflammation, VV and LC, bleeding sites, protruding parts, sprain of the artery membranes, has a normal appearance of the inner and outer surfaces. In accordance with the theory proposed by the author, ASL V is an independent pathological structure that appears in a short period of time in the lumen of a healthy artery. ASL V has its own unique structure, its reason for its appearance, its own mechanism of formation and its developmental stages, which have nothing to do with types I-IV atherosclerotic lesions (ASL I-IV). After its appearance, ASL V has no LCs. The artery wall, next to ASL V, is easy to turn inside out and can be easily taken off ASL V. From the side of the blood, the CCP is gradually covered with a fibrous cap (FC). On the outside of the CCP, when the glycocalyx and endothelium are destroyed, a fibrous layer is also formed between the CCP and the artery wall. When part of the CCP wall is separated from the artery wall, arterial dissection occurs. The CCP can be cut, in whole or in layers, with the help of multiple modern instruments during intravascular surgery. It also can be separated from the artery wall with the help of an instrument in the form of a ring, pulled out as a tube from the artery, expanded with a balloon and fixed in this form with a help of stent. All these procedures take place without damaging or changing the artery walls.[21]

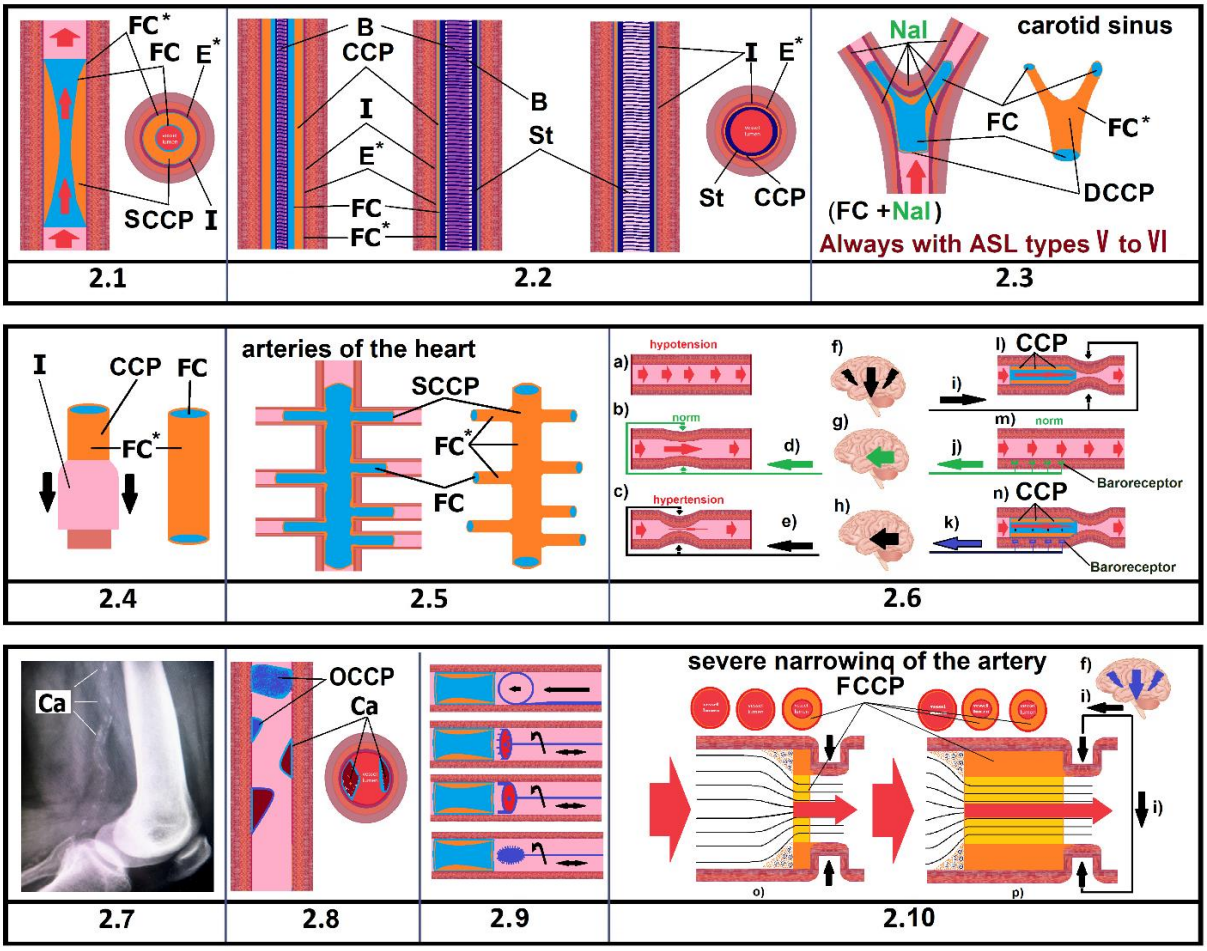

Figure 2: Concentric cylindrical cholesterol plaque (CCP). CCP is an independent pathological structure in the lumen of a healthy artery, consists entirely of LDL.

2.1) There is a long, soft, elastic, strong, solid, yellow tube in the form of a hollow cylinder located in the arterial lumen, have a concentric arrangement. Endothelium is located between "intima" and the external wall CCP. CCP pinches the artery evenly on all sides of the artery. The blood passes through a narrow passage in the center of CCP. Always has FC; 2.2) CCP has a concentric shape, is easily stretched in different directions with a balloon and fixed with a stent. The anatomical dimensions of the artery do not change; 2.3) Branching of the CCP in the lateral branches of the artery in the carotid sinus. CCP follows the contours of the artery, is located on all sides, close to the artery wall. Blood flows inside the CCP and moves away from the artery walls. The anatomical dimensions of the artery do not change; 2.4) The artery wall that is intact, without inflammation, without tubercles and necrosis, can be easily turned inside out; 2.5) Branching of the CCP in the lateral branches in the arteries. The anatomical dimensions of the artery do not change; 2.6 Cylindrical cholesterol plaque (CCP) is formed in the lumen of an artery within a few minutes in case of artery spasm and appearance of a strong obstruction to blood flow. Beyond the constriction all blood cells easily pass into formed narrow opening, and only low-density lipoproteins (LDL) are retained within the wall, in front of the site of arterial narrowing, and quickly create a CCP in the form of a hollow cylinder. a) hypotonicity - the walls of the artery are even; b) normotonus - the walls of the artery are slightly narrowed to maintain normal blood pressure; c) hypertonicity - a strong narrowing of the lumen of the artery. The appearance of a strong obstruction to the movement of blood; d) normal signal from the nervous system; e) increased signal level from the nervous system; l) accumulation of LDL in the form of a tube, in front of the site of narrowing of the artery; f) overexcitation of the central nervous system leads to over excitation of the autonomic nervous system and leads to narrowing of the lumen of the artery; i) a strong signal to compress the lumen of the artery when the nervous system is overexcited; m) signal from baroreceptors shows the level of blood pressure on the walls of the artery; n) in a thinner tube, the pressure on the wall is lower; k,h.e) baroreceptors transmit incorrect information, which leads to an increase in systemic blood pressure; 2.7) X-ray - calcium crystals deposition in the CCP wall; 2.8) All subsequent forms of types V and VI atherosclerotic lesions, concentric and eccentric, are the result of the destruction of the original concentric structure of the CCP. The artery wall near CCP does not have inflammation, VV and LC, bleeding sites, protruding parts, sprain of the artery membranes, has a normal appearance of the inner and outer surfaces; 2.9) Use of instruments having a form of ring and cylinder to remove CCP; 2.10) Formation of CCP in the vortex when a strong narrowing of the arterial lumen occurs. All blood cells easily pass into formed narrow opening, and only low density lipoproteins (LDL) are retained within the wall, in front of the site of arterial narrowing, and quickly create a CCP in the form of a hollow cylinder. o) the first ring, which consists of LDL, which lingered in the zone of turbulence in front of the place of severe narrowing of the artery; p) many adherent rings of LDL, which form a plaque in the form of a tube - cylindrical cholesterol plaque. The entire plaque consists of only LDL.

B- balloon; Ca- calcium crystals deposition; CCP- cylindrical cholesterol plaque; DCCP- dense cylindrical cholesterol plaque; E- endothelium; E* - endothelium between plaque and arterial wall in humans; FC - fibrous cap (in the lumen of the artery); FC*- fibrous cap (between plaque and artery wall); FCCP- friable cylindrical cholesterol plaque; I- Intima; LC*- the lipid core is located not within the arterial wall, but within the wall of the CCP itself; OCCP- old cylindrical cholesterol plaque; SCCP- soft cylindrical cholesterol plaque; St- stent; TR- blood clot.

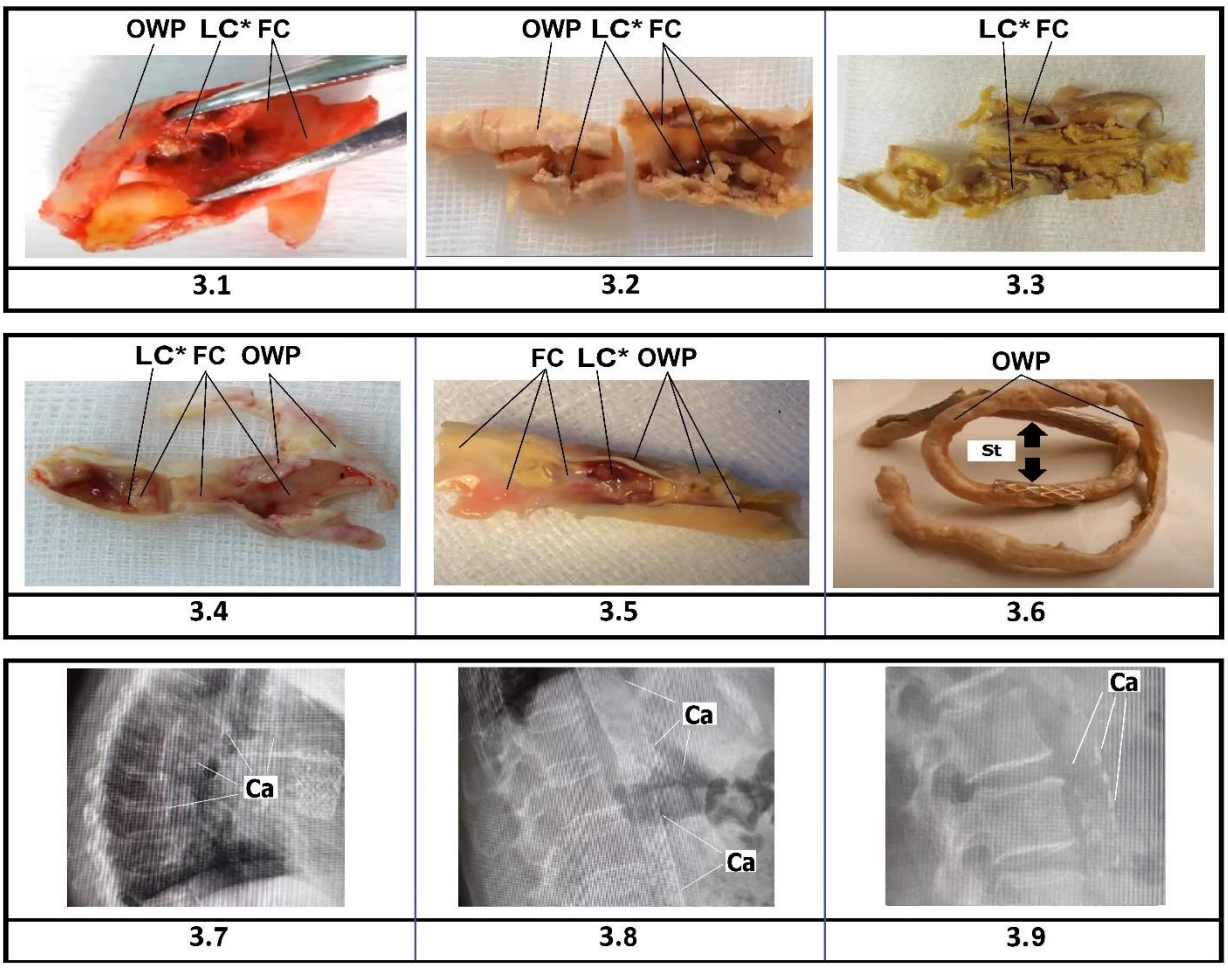

Figure 3: Concentric cylindrical cholesterol plaque (CCP) after removal of from the artery retains its shape.

3.1-3.6) There is a long, soft, elastic, strong, solid, yellow tube in the form of a hollow cylinder located in the arterial lumen, have a concentric arrangement. CCP follows all the contours of the artery. The blood passes through a narrow passage in the center of CCP. Always has FC. CCP can have any length - from a centimeter to tens of centimeters. The outer wall of the CCP is always smooth and does not depend on the presence of an LC inside the wall of the CCP. On the inner surface of the plaque, areas of damage to the fibrous cap, foci of necrosis are visible. After removal of from the artery retains its shape and looks like a "solidified silicone". 3.6) The CCP was removed from the superficial femoral artery 2 weeks after stent implantation. 3.7-3.8) X-ray - calcium crystals deposition in the CCP wall in one patient. 3.9) X-ray - calcium crystals deposition in the CCP wall.

FC - fibrous cap (in the lumen of the artery); FC*- fibrous cap (between plaque and artery wall); LC*- the lipid core is located not within the arterial wall, but within the wall of the CCP itself; St - stent.

Figure 3.1-3.6 Images courtesy of Dr. Mikhaylov I. Ph.D. in medicine. Leading vascular surgeon. Clinical Hospital of the Academy of Sciences in St. Petersburg.

Methods for rendering influence on animals which lead to the formation of atherosclerosis

In order to cause the appearance of ASL in animals, several variants of effect on the vascular wall of rabbits, rats, chickens, and monkeys were used (Figures 1.9 d) [4,43,44,45,46,47]:

1. animals were fed with a special food containing a big amount of cholesterol, which led to a change in the cholesterol levels and LDL in the blood;

2. they caused an increase in blood pressure, which caused damage to sections of vessels with difficult hemodynamic conditions;

3. the arterial wall was artificially injured using a balloon to form inflammatory zones in the intima and damage the endothelium;

4. various combinations of traumatic factors were used, including the stress on rabbits.[15]

Inflammation is the leading theory that explains the ASL development in animals

At the moment, based on the study of ASL in animals, the main theory that explains the appearance of ASL is accepted - "Inflammatory theory".[48-51] According to many authors, such systemic inflammation of the artery wall can be caused by different factors like smoking, obesity, diabetes mellitus and elevated LDL levels. Due to the fact that all these factors have impact on absolutely all vessels in the body, damage can be caused to "absolutely all arteries and veins."

Numerous studies have examined various aspects that affect inflammation, the development of ASL, and the regulation of blood lipids, such as: oxidative stress,[52] the Diabetes Mellitus.[53] The impact of the following drugs on ASL development such as probucol,[44] iron,[54] PCSK9,[55] circRNA expression pattern and circRNA-miRNA-mRNA,[43] β-Elemene,[56] human apolipoprotein A-II,[57] testin,[58] cyclodextrin,[59-61] TPM2,[62] colchicine,[63] copper,[64] clopidogrel[65], puerarin,[66] different doses of CETP vaccine,[67] kaempferol,[68] losartan,[69] ezetimibe,[70] chondroitin sulphate,[71] PJ34, a PARP1 inhibitor,[72] MCC950,[73] ursodeoxycholic acid[74] have been examined. The pathways of cholesterol release from macrophages[75] and varieties of LDL have been studied with the help of animal models.[76] As a result of these studies, some drugs have begun to be used in humans.[77]

Despite the effectiveness of AS anti-inflammatory therapy in animals, regression of atherosclerosis in humans has proven to be a difficult task. Quantitative angiographic studies with statins have shown a very modest reduction in stenosis, about several RBC diameters.[78] Anti-inflammatory interventions do not have a pronounced effect on humans - large clinical trials have not been able to demonstrate the benefit of antioxidants in cardiovascular outcomes. Studies investigating the possibility that classical antioxidants such as vitamin C, vitamin E, selenium, or folic acid may improve the prognosis for patients suffering from heart disease have shown mostly neutral and sometimes negative results.[79]

In practice, not "all" vessels are inflamed. Numerous studies show that ASL appear only in certain places of the vascular bed, and at the same time there are arteries and veins without ASL. This arrangement of ASL refutes the systemic nature of the process in AS and shows that absolutely all systemic factors cannot be the causes of ASL.

Inference: the findings refute the theory that ASL in humans appears because of inflammation, just as it has been seen on an example of the ASL development in animals. All of the above-mentioned factors and risks thus may simply be seen in the patient that do not contribute to the formation of ASL, but can affect the functioning of the central nervous system (CNS) and create constant nervous tension.

Difficult hemodynamic conditions are the main cause of atherosclerosis development

Such places are in healthy people, and also the same places were observed in this patient at a time when he was still absolutely healthy.

Inference: difficult hemodynamic conditions also cannot be described as the main reason for the formation of ASL.

Psychological stress in a human is the main cause of the development of atherosclerosis

Nervous tension induced by stress rapidly results in hyperactivity of the sympathetic nervous system, which can be the cause of sudden death due to vasospasm.[80] It has been shown that spasm of the coronary artery plays an important role in the pathogenesis of not only variant angina, but also AMI and sudden death.[81]

Acute, extreme stress can provoke acute, lethal myocardial infarction[82] or cardiac arrhythmia in very short periods of time. Above-mentioned diseases cold arise in people because of earthquakes,[83,84] missile strikes,[85] and football penalties broadcasted on television.[86] During the 60-day period after September 11, 2001, there was a statistically significant increase in the number of patients with acute myocardial infarction.[87,88] The presence of psychosocial stressors is connected with increased risk of acute myocardial infarction.[89] The presence of anxiety worsens the prognosis for patients with coronary heart disease.[90] Mittleman et al.[91] have shown that acute myocardial infarction can be triggered by anger. Goodman and his colleagues examined hostility separately.[92] The memories of personal stressful events triggered a response of the autonomic nervous system in AMI patients, and therefore events of personal significance are associated with the onset of coronary heart disease.[93] Depression is common in patients with heart disease, with prevalence rates nearly three times higher than in the general population.[94,95] Depression is also linked to worse cardiac prognosis and higher

mortality.[96] Kaptein et al.[97] showed that patients with chronic depressive symptoms were exposed to higher risk of occurring of new cardiovascular events after myocardial infarction than those who had depressive symptoms and then they disappeared.

Inference: thus, the main external factor which has an impact on the nutrition of the heart and brain is the disruption of the CNS and ANS.[20,21]

Stress in animals is the cause of the development of atherosclerosis in animals

The study of stress in animals[15] cannot be used to conduct a study of stress in humans, since the aorta of rabbits, before exposure to stress, was artificially injured with a balloon. Such damage is not present in a healthy person with psychological stress without surgical intervention.

Inference: stress caused by pressure on the arterial wall, foods that are high in cholesterol and "cold stress",[98] cannot be equally attributed to psychological stress in humans.

Endothelial dysfunction - the cause of the development of atherosclerosis

It is necessary to consider a very significant indicator that is used in humans as a criterion for endothelial damage - endothelial dysfunction (ED).[100-105] At the moment, it is assumed that in the absence of a reaction to the stimulus, there is a damage of the endothelial layer in the human vessels. Therefore, many techniques have been developed that allow to determine the degree of ED in human vessels. The criterion for the presence of ED in human vessels is the absence of a reaction of the vessel wall to certain substances, which should, on contact with the endothelium, expand the artery.[103-106] Acetylcholine and adenosine are used[107] for these purposes, intracoronary infusions of acetylsalicylic acid,[108,109] peak velocity is measured, which is linearly related to the blood flow and can be calculated with the cross-sectional area of the vessel[110,111], and the "cold pressor test" is used[112]. Currently, there are several non-invasive approaches that include imaging methods such as the use of dipyridamole, or adenosine through non-endothelial mechanisms,[113,114] using transthoracic Doppler echocardiography,[115,116] PET,[117] MRI,[107,118,119] high resolution ultrasound.[120,121]

Inference: Despite the obtained results (lack of response to the stimulus), it is impossible to state that the result is ensured to damage to the endothelium on the artery wall due to inflammation. The same result can be obtained in a situation where there is a plaque inside the artery, which separates blood around the perimeter and other substances from the real wall of the artery, including intact endothelium. Such a plaque completely repeats the inner surface of the artery, and thus does not allow substances dissolved in the blood to have impact on the endothelium. As seen in the author's previous articles,[20,21] there is a long, soft, elastic tube inside the artery, completely repeating the contour of the artery and its branches. It is this plaque that mimics ED in a human artery. Real damage to the endothelial layer in the coronary vessels in humans can only occur during coronary angioplasty,[122,123] and therefore it does not make sense to consider it as a natural change in the endothelium.

"Coincidences" that make it impossible to see the difference between ASL.

A closer look at human and animal ASL raises many questions that cast doubt on whether the animal model of AS, and both types of human AS, have anything in common.

In a previous article the modern vision is refuted, which states that all types ASL in human are developed successively, one after another. The article sheds a light on a significant difference between type IV atherosclerotic lesions and between types V and VI atherosclerotic lesions.

Type V atherosclerotic lesions (CCP) has nothing to do with types I-V atherosclerotic lesions. Type V atherosclerotic lesions (CCP) is an independent pathological structure that appears in a short period of time (few minutes) in the lumen of a healthy artery in case of artery spasm and appearance of a strong obstruction to blood flow.

Just «7 coincidences» were described in the previous article », that create a false impression that the ASL IV and ASL V types in humans, are similar to each other.[21]

Looking at all the characteristics of AS in animals, it is clear that ASL in animals is another separate type of ASL that is completely different from any of the types of atherosclerotic lesions in humans. But at the same time, it also has many imaginary "coincidences" that create a false impression of similarity with both ASL I-IV and ASL V-VI in humans.

Coincidence 1.

ASL (Animal), ASL IV and ASL V always appear in the same places - carotid artery, cerebral arteries, heart, aorta and the lower extremities. Such places have difficult hydrodynamic conditions, but at the same time ASL (Animal), ASL IV and ASL V look different:

- ASL (Animal) - intimal thickening happens because of the appearance of a large number of mast cells and LC inside the intima; the intima is covered with defective endothelium and fibrous areas[123-225]; the middle and outer lining of the artery are not extended; when the arterial wall is stretched with a balloon, in the experiment, the location of the ASL is determined by the site of injury to the wall. In case of an elevated LDL level in an animal, in the experiment, the location of ASL depends on the site of inflammation in the endothelium; ASL in animals can be found not only in arteries, but also in veins (Figures 1.8-1.10)[126,127];

- ASL IV - a single tubercle, which consists of stretched middle and outer membranes with liquid lipid content, which is visible outside the artery, as well as a tubercle with normal endothelium, which is visible inside the artery; never appears in the veins (Figures 1.8-1.10)[22];

- ASL V - a long, elastic, strong, yellow tube in the lumen of the vessel, not connected with the arterial intima; completely repeats the internal contours of the artery and its branches[20, 21,23-42]; never appears in the veins (Figures 1.4-1.7, 2.1-2.10, 3.1-3.9).

Coincidence 2.

LDL are present in ASL (Animal), ASL IV and ASL V:

ASL (Animal) - LDL enter through the damaged endothelium. Immediately after the endothelium, it is absorbed by macrophages (Figures 1.8-1.10)[10,11,12, 43];

- ASL IV - LDL enter through the VV from the outer arterial wall to the intima, near the medial tunic of the artery. The endothelium is always intact (Figures 1.8-1.10)[22];

- ASL V - LDL immediately accumulate inside the lumen of the artery, in front of the site of a strong narrowing of the artery wall. The entire plaque consists of LDLs stick together by fibrin threads (Figures 1.4, 1.5, 2.1, 2.3-2.6, 2.10).[20, 21]

Coincidence 3.

ASL (Animal), ASL IV and ASL V always have macrophages:

- ASL (Animal) - macrophages enter through the damaged endothelium (Figures 1.8-1.10)[10,11,12,43];

- ASL IV - macrophages enter through the VV from the outer layer; the endothelium is always intact (Figures 1.8-1.10)[22];

- ASL V - macrophages enter the cracks in the FC inside the CCP (cylindrical cholesterol plaque) itself, which consists only of LDL; the endothelium is always intact, located between the plaque and the intima (Figures 1.4, 1.6).[20,21]

Coincidence 4.

ASL (Animal), ASL IV and ASL V might have LC:

- ASL (Animal) - contains a lot of LC located in the intima; at sites of damage to the arterial wall by the balloon, LCs are located at the site of injury; when conducting experiments without causing damage to the artery wall, LCs are located diffusely (Figures 1.8-1.10);

- ASL IV - ASL consists of only one nucleus, which appears at the border of the intima and the middle layer of the artery, grows for decades without affecting the lumen of the artery (Figures 1.1-1.3)[22];

- ASL V - when a plaque appears - LC is completely absent. LC appears inside the CCP in case of aging and damage to the FC. LC develops under the fibrous cap of the CCP itself. It is not connected in any way with intima (Figures 1.4-1.7, 2.1, 2.3-2.6, 3.1-3.6).[20,21]

Coincidence 5.

ASL (Animal), ASL IV and ASL V may mechanically overlap the arterial lumen:

- ASL (Animal) - after the appearance of inflammation, the intima increases in size and blocks the lumen of the vessel from all sides where damage with balloon happened; when conducting experiments without causing damage to the artery wall, a diffuse increase in intima occurs; the intima increases in volume, unevenly protruding the endothelium and FC into the lumen of the vessel; grows within several weeks (Figures 1.8-1.10)[10,11,12,43,19];

- ASL IV - one single LC first grows outside the artery, stretches the middle and outer wall, only then, after many years, grows into the lumen of the artery, stretches the intima, and blocks the lumen of the artery only from one side of the artery. Grows for decades (Figures 1.1-1.3)[22];

- ASL V - immediately after the appearance (within a few minutes) it blocks the blood flow along the perimeter of the artery and allows blood to pass only through the center of the ASL (Figures 2.6, 2.10).[20,21,23-42] Appears within a few minutes, no longer increases in size, collapses and decreases in size when an aging (Figures 2.6, 2.8, 2.10).

Coincidence 6.

ASL (Animal), ASL IV and ASL V may cover an artery due to blood clotting:

- ASL (Animal) - FC is being torn with difficulty without mechanical impact[124], a thrombus may form in case of rupture;

- ASL IV do not cause blood clots - the unicellular endothelium is never damaged[22];

- ASL V a blood clot is formed by rupture (erosion) of a thin TCFA (thin-cap fibroatheroma) above the LC (Figures 1.6).[29,30,40-42]

Coincidence 7.

ASL (Animal), ASL IV and ASL V can theoretically be removed from the artery:

- ASL (Animal) - can be removed (peeled off together with the intima), since the middle and outer shells are not stretched (Figures 1.8-1.10)[19];

- ASL IV - impossible to remove, since the liquid core protrudes beyond the outer anatomical dimensions of the artery, and stretches the middle and outer shells (Figures 1.1-1.3)[22];

- ASL V - easily removed, since the walls of the artery remain unchanged, and the plaque itself is located inside the lumen of the artery, and is not associated with the wall of the artery (Figures 2.4, 2.5, 2.9, 3.1-3.6). [20,21,23-42]

There are also a few more ostensible coincidences that create a false impression that the ASL IV and ASL V types are similar to each other in humans.[21]

Coincidence 8.

Presence of FC:

- ASL (Animal) - damaged fibrous lid is located only on the side of the lumen of the artery, covers the lipid cores at the sites of endothelial damage.[123-125] Formed when rabbits are not feeded with cholesterol[128]; It breaks only when mechanical action is applied (Figures 1.8-1.10)[124];

- ASL IV - FC is always absent. There is always a whole, intact endothelium above the ASL, on the blood side (Figures 1.1-1.3)[22];

- ASL V - FC always covers the LDL glued together from the side of the lumen of the artery ("internal FC"), and from the side of the arterial wall ("outer FC"). When the "outer FC" is pulled away from the artery wall, an additional cavity is formed through which blood flows - arterial dissection or aortic dissection (Figures 1.4-1.7, 3.1-3.6).[129-133,21,23-42]

Coincidence 9.

Calcium deposition:

- ASL (Animal) - in animals, calcium deposition occurs diffusely, in all places of intimal thickening[19];

- ASL IV - there is no calcium deposition[22];

- ASL V - before the appearance of calcium in the arteries, during surgery, an elastic long tube (CCP) is visible, in which, LDL is replaced by calcium over time (Figures 2.7, 2.8, 3.7-3.9).[21]

Coincidence 10.

Presence of endothelial dysfunction:

- ASL (Animal) - traumatic factors cause damage to the endothelium and loss of endothelial cells – ED (Figures 1.8-1.10)[10,11,12];

- ASL IV - the endothelium is always healthy[22];

- ASL V - there is no endothelium in the lumen of the artery, since it is located between the plaque and the intima; the plaque separates the endothelium from the blood and mimics the presence of ED in the vessel during the research (Figures 1.4-1.7, 2.1-2.10, 3.1-3.9).[20,21]

Coincidence 11.

Damage to the intima:

- ASL (Animal), the intima becomes inflamed throughout its thickness after arterial wall injury; in case of an increased level of LDL in the blood, the intima is more inflamed near the endothelium (Figures 1.8-1.10)[11,12];

- ASL IV - the intima is damaged only near the median membrane of the artery, while, on the other side (near the endothelium), there is intimal area without inflammation and damage (Figures 1.1-1.3)[22];

- ASL V - the intima is not damaged in any way, since all processes occur in the lumen of the artery (Figures 1.4-1.6, 2.10).[20,21]

Coincidence 12.

Change in blood pressure:

- ASL (Animal) - the intimal thickening causes a increase in blood pressure in front the ASL itself (Figures 1.8-1.10)[134-136];

- ASL IV - sprouting of the plaque in the lumen of the artery causes a increase in blood pressure in front the ASL itself (Figures 1.1-1.3)[134-136];

- ASL V - causes an increase in blood pressure; ensures constant easing of the pressure on the walls of the artery in the area of the plaque itself, due to a decrease in the lumen of the vessel for blood flow (Bernoulli's law)[134-136]; such reduced pressure in the region of baroreceptors causes a reflexive blood pressure increase (Figures 1.4-1.7).[21]

Coincidence 13.

The appearance of plaque, but for different reasons:

- ASL (Animal) - artificial hypertension in the experiment; artificial damage to the endothelium in the experiment; artificial diet high in cholesterol in

rabbits, monkeys, chickens and rats; selection of animals with a gene mutation that ensures a permanent increase in the level of LDL in the blood (Figures 1.8-1.10)[125-137,43,46,47];

- ASL IV - not known; presumably, long-term average compression of the vessel due to stimulation from the autonomic nervous system, and the appearance of an inflammatory process in the middle and outer shells of the artery (Figures 1.1-1.3);

- ASL V - prolonged strong compression of the vessel due to stimulation from the autonomic nervous system, accumulation of LDL in front of the constriction site, and further fastening of LDL between each other by fibrous filaments (Figures 1.4, 1.5, 2.6).[20,21]

There are two separate types of ASL in humans that have no connection with each other, and one type in animals. All these three types of AS are different from each other. Each type has its own reason for the appearance, its own mechanism for the formation of ASL, and its further development. ASL in animals and ASL in humans occlude the arterial lumen in different ways. Even the appearance of ASL in an animal and ASL in human, which 100 years ago was "approximately similar", on closer examination shows the absolute differences between all three types of ASL. Inflammation, as the main cause why AS appears, is only relevant for AS in animals, and has no role in the development of AS in humans. The method of "determining the degree of ED" in humans gives a positive result only by separating the whole, intact endothelium of the artery from substances dissolved in the blood.

All three types of ASL affect the increase in blood pressure in different ways, and, in different ways, respond to an increase in blood pressure in the circulatory system. In order to ensure the appearance of AS in animals an artificial increase in the level of LDL in the blood is created. Such situations, in humans, occur only in case of familial hypercholesterolemia, and they cannot have them without these genetic abnormalities. On the contrary, the same conditions that give rise to CCP development in humans ensure a pathological increase in LDL levels in the blood.

Use of the results of studies that are positive for animals, do not have a positive effect for humans, or have a negative effect on the state of the cardiovascular system.

The significant difference between AS in animals and AS in humans suggests that all studies of AS development in animals cannot in any way be used for the treatment and prevention of AS in humans. Since diseases of the vascular system stay on one of the first places in terms of mortality, it is necessary to study the "real" ASL (soft cylindrical cholesterol plaque (SCCP)), which causes severe diseases of the vascular system. The appearance of primary friable cylindrical cholesterol plaque (FCCP) is independent of inflammation, and thus independent of systemic “factors” and “risks” such as obesity, smoking, type 2 diabetes, and so on. CCP mimics the presence of ED because healthy endothelium hides behind plaque and doesn't know what substances circulate in the blood. CCP ensures a decrease in diameter of the arterial lumen in the region of baroreceptors, and thus, can disrupt the normal arterial pressure regulation and ensure a persistent reflex increase in blood pressure. It is not necessary to have the “factors” and “risks” generally accepted today that contribute to the development of CCP, it can appear in the lumen of an artery in a previously absolutely healthy person, even maintaining a healthy lifestyle, in just a few minutes.

To form a strong, elastic SCCP in the form of a tube, a person only needs to get into a difficult psychological situation, which will lead to colossal nervous tension, overstimulation of the central and autonomous nervous system, and as a result, will lead to a strong narrowing of the artery lumen. It is CCP that creates problems in the people's arteries and puts millions of people a year in danger of becoming disabled or dying within a few days in case of severe nervous strain. Restoration of the normal functioning of the vasomotor center can stop not only the development of CCP, but also restore the natural level of LDL in the blood, the violation of which is connected with the appearance and dissolution of friable cylindrical cholesterol plaque (FCCP).[20] Preventing CCP from occurring can prevent its natural aging and the formation of a dense cylindrical cholesterol plaque (DCCP), which can detach from the artery wall and cause serious disease such as artery dissection or aortic dissection. Also it can prevent the appearance of old cylindrical cholesterol plaque (OCCP), which is characterized by further destruction of the CCP with the formation of an embolus, replacement of LDL in the plaque with calcium, the appearance of a thin FC and its rupture with the formation of a thrombus in the arterial lumen.[20,21]

Conclusion

This article shows that AS in animals is another, separate structure and therefore, the results of the study of AS development in animals cannot be used for the treatment and prevention of AS in humans.

Understanding that AS in animals and AS in humans are completely different processes will help to conduct a focused examination of the true ASL that

causes problems in human arteries ("cylindrical cholesterol plaque"). Understanding and preventing the appearance and development of CCP can significantly reduce the number and severity of diseases associated with AS in human arteries, such as stroke and heart attack, prevent the appearance of emboli and blood cloths, prevent artery calcification, and prevent artery dissection and aortic dissection, help naturally restore LDL levels in the blood.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

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