Adventitial Atherosclerosis and Calcifications: Surprice and a New Location: Letter to the Editor

Adventisyal Ateroskleroz ve Kalsifikasyonlar: Sürpriz ve Yeni Bir Yerleşim

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Despite steady progress in the treatment of atherosclerotic and atherothrombotic cardiovascular disease, people are still dying of coronary artery diseases and myocardial infarctions. These two problems remain the leading causes of morbidity and mortality particularly in the industrialized countries. Atherosclerosis is the descriptive term for thickened and hardened lesions which have lipids and calcifications of the intimae and medium of elastic and muscular arteries. At the end, it has been accepted that, atherosclerotic and calcified lesions start, occur and grow up within the innermost layer of the arteries (at the intimae). It has been firstly shown in 1995 by American Heart Association (AHA) that, the earliest lesions of atherosclerosis (fatty streaks or type III lesions) were present in the intimae of aorta from childhood. Today, we know that atherosclerosis begins as early as foetal life especially in foetuses of hypercholesterolemic mothers.[1] In any arterial bed of intimae, formation and progression of the atherosclerotic plaques and calcifications were well documented by many authors; like V. Fuster, E. Falk[2-4] and were sub divided several phases by them which are summarised such as at below. Most lipids deposited in the atherosclerotic lesions are derived from plasma low-density lipoproteins (LDLs) that enter the vessel wall through the injured or dysfunctional endothelium. In normal population, from 5 to 10 years of ages, fatty streaks often are present in the aorta and coronary artery, they were accepted the initial points of plaque development. Type I lesion consist of macrophage-derived foam cells that contain lipid droplets; type II lesions contain macrophages and smooth muscle cells with extra cellular lipid deposits; and type III lesions contain smooth muscle cells surrounded by extracellular connective tissue, fibrils, and lipid deposits; Type IV plaques consist of confluent cellular lesions with a great deal of extracellular lipid intermixed with fibrous tissue, whereas Type Va plaques possess and extra cellular lipid core covered by a thin fibrous cap. Either phase III or IV plaque can evolve into fibrotic plaques of phase V, characterized by type Vb or Vc lesions, with or without predominant calcification. Type VI occlusive thrombus over-

laying a superficial erosion of a markedly stenotic and fibrocalcific plaques of phase V.[2-6] In Phase II-V vulnerable lipid-rich plaques are prone to disruption because of the fact that their high lipid content. Raised plaques appear later, by 20 years of age are present in areas, such as, on the endothelium of proximal left anterior descending (LAD) coronary artery, where fatty streaks are most prevalent in early life.[3] The intimal surface of an opened human coronary artery reveals the presence of several types of plaque. Some are flat yellow dots or lines (fatty streaks), and the others are raised above the surface as oval humps, which range in colour from white to yellow (raised fibro lipid plaques).[1-6] An early atherosclerotic lesion (fatty streak or type III lesion) is the aortic root and coronary arteries, the lesion consists of lipid-laden monocyte-derived macrophage foam cells and a few T lymphocytes beneath an intact endothelium. It has been accepted that, only endothelial cells, monocyte-derived macrophages or foam cells and a few T cells participate in the early inflammatory and immune response, giving rise to early atherosclerotic lesions. This early atherosclerotic lesions (fatty streak or type III lesion) represent a dynamic balance of the entry and exit of lipoprotein entry by endothelium injury resulting in a predominance of lipoprotein exit and final scarring.[1-6] In disease progression, the oxidative modified LDL (oxLDL), the inflammatory and immune response is accompanied by a fibro proliferative response in which the vascular smooth muscle cells play dominant roles.[1-11] OxLDL has many proinflammatory properties which explain the local up regulation of inducible endothelial cell adhesion molecules, even before lesion formation, in hypercholesterolemic atherosclerosis and atherothrombotic events.[1-6] OxLDL has proinflammatory and cytotoxic effects. It was recognised by the macrophage scavenger receptor promoting intracellular lipid accumulation and foam cell formation. Such as the endothelial dysfunction or/ activation (vascular cell adhesion molecule 1), monocyte adherence, injuring lipoprotein retention, oxLDL, imflammatory/immune response, macrophage scavenger foam cell formation, endothelial shear stress, turbulent flow, blood pressure on the vessels' walls and the role of nitric oxide (NO), prostacyclin, endotheline-1, acetyl choline, vascular cell adhesion molecule-1 (CAM-1), cell adhesive molecules (CAM or surface glycoproteins), intercellular adhesion molecular-1 (ICAM-1) promote or enter though the injured or dysfunctional endothelium and sub endothelial lipid accumulation and at the end lipid core formations occure. As soon as monocytes (macrophages) adhere to the surface of endothelium (intimae) with the specific molecules, such as monocyte chemotactic protein-1(MCP-1) and macrophage colony-stimulating factor (M-CSF).[1] Macrophage or foam cells, before or after their death, can liberate and accumulate many products including oxLDL and free radicals. Chronic minimal endothelial injury or dysfunction, plasma low-density proteins enter through the injured endothelium, leading to accumulation of lipids (oxLDL) and macrophages are produce atheroma mass or atheromatous component by depend upon of heredity, diabetes, hypercholesterolemia, in tobacco smoke, hypertension, abdominal obesity, gender, aging, hyper urisemia, chemical irritants, infection, circulating vasoactive amines, immune complexes, etc.

So this classical pathway or famous well known cascade of atherosclerosis brings about the formation of atheroma in 1995 by AHA of atherosclerotic lesions.[1-3] This pathway of formation of atherosclerosis and calcifications almost universally were accepted in the sub intimal area (under the endothelium). Atherosclerosis is a focal intimal disease of large and medium sized systemic arteries.

We have recently shown that by the multislice computed tomography (MSCT) using within a device which has a computerised magnifying glass. We strongly emphasized that, the classical cascade of the atherosclerotic and calcified plaques formation begin and grow up not only beneath the intimal endothelium, but also in adventitial sub epithelium on the coronary arteries. We have surprisingly determined that the adventitial side of the calcification develops much faster and severer than that of the intimal side of on the arterial vessels' walls.

MSCT of coronary angiography with 64-slice technology, first described by Leschka et al.[7] Currently, MSCT is a very important tool for the non-invasive evaluation of coronary arterial pathologies (Figure 1). Moreover, the MSCT is an excellent and imported technique to show that the place of the formation of plaques and calcifications on the arteries.[7,8] It has been well documented that in the last three decades, the cascade of atherosclerotic plaques formation start from beneath the intimal cells of coronary arteries.[1-16] The media calcification of the coronary arteries was also described as Mönckeberg's Sclerosis.[8]

We have recently shown that by MSCT, the formation of the atherosclerotic and calcified plaques begin not only beneath the intimal endotels but also under the adventitial epithets on the coronary arteries, surprisingly. The adventitial calcifications grow up the most quickly than the sub endothelial (the intimae) calcified plaques. On the other hand, the medial calcifications much frequently grow up on the aorta and its main branches, such as carotid, vertebral, cerebral, renal, mesenteric, iliofemoral, and peripheral arteries. Interestingly, the formation of calcified plaque much frequently begins beneath the subephitelium of the adventitia and quickly grows up towards to arteherial lumen and keeping same classical and accepted cascade on the coronary arteries. These calcifications mostly begin in the middle of the atheromatous component. The cholesterol (particularly oxLDL) and macrophage cells easily arrive to the adventitia by VASO VASORUM of the coronary arteries. Same pathway occurs in the formation of atherosclerosis obliterans on the other major arteries, such as, aorta and on its main peripheral branches.

Most of the risk factors that apply to the atherosclerotic vascular diseases in all arteries. Herein seven different example of our patients (Figure 2-9) have been shown which were investigated by MSCT and conventional coronary angiography. The atherosclerotic plaques and calcifications begin and grow up beneath the adventitial epithelium though the lumen of vessels on the coronary arteries. It means, our recent studies showed in most patients (approximately 60%), the calcified plaques were started just beneath of the epithelium on the adventitia and grown forward to the lumen of the arteries. Of course, they can make a severe stenosis or occlusion of arterial lumen at the end (Figure 10). In comparison with IVUS, Achenbach et al. found a sensitiv-

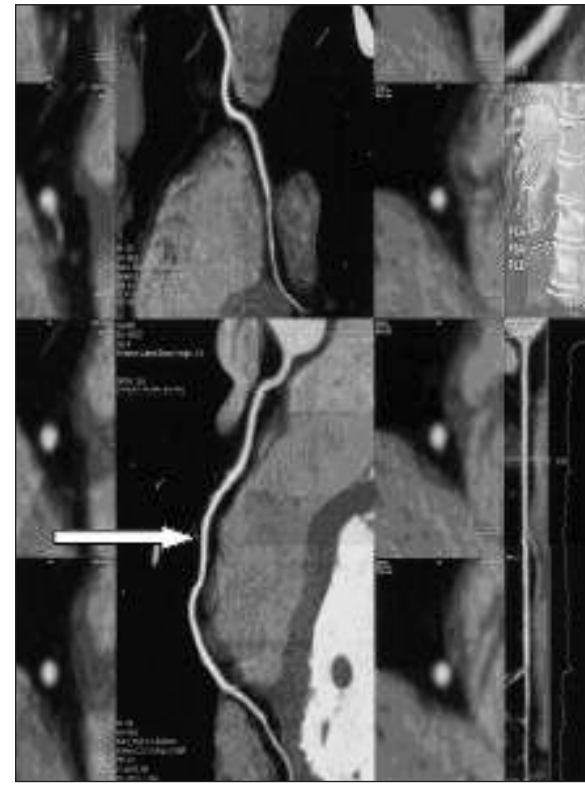

FIGURE 1: A normal Right Coronary Artery (RCA, white arrow) was shown by MSCT with no atherosclerotic plaque and no calcification in a normal case.

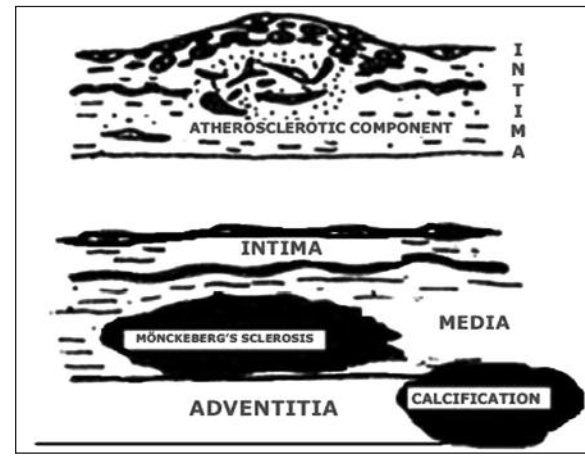

FIGURE 2: This figure is illustrating formation of the atheromathous component in the intima (above) and medial (Mönckeberg's sclerosis), an adventitial atherosclerocalcifications.

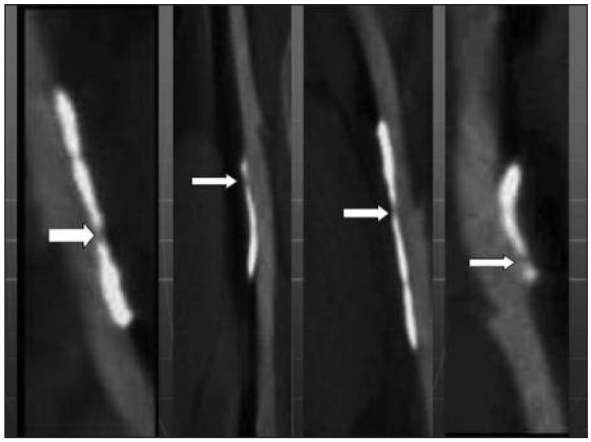

FIGURE 3: This figure shows adventitial calcifications (white areas) and lipid cores in the calcifications (showed arrows) on the coronary arteries which was taken by MSCT and its attachment of computarised magnifying glass.

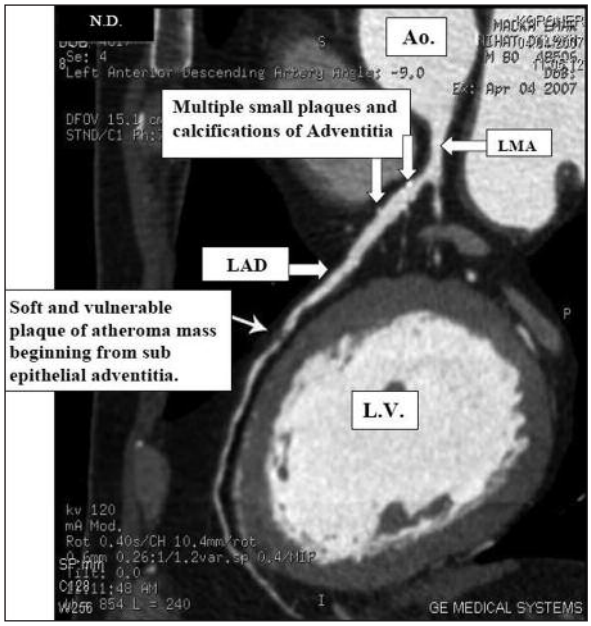

FIGURE 4: The adventitial atherosclerotic plaques with minimal Calcifications on the LAD artery without stenosis and a vulnerable soft plaque of atheroma mass or atheromatous component starting from sub epithelial area of adventitia on the mid LAD artery with significant stenosis.
Ao: Aorta, LAD: Left Anterior Descending, LMA: Left Main Artery, LV: Left Ventricul.

ity of 82% to detect coronary artery segments containing atherosclerotic plaque in patients without significant coronary artery stenosis.[15] MSCT might be useful for the characterization of human coronary plaque morphology by determining tissue density within the lesion non-invasively. Also MSCT is a unique non-invasive method for the detection of coronary atherosclerotic plaque morphology and for the diagnosis of silent ischemia, lumen narrowing calcification of adventitia.[16] Molecular imaging most

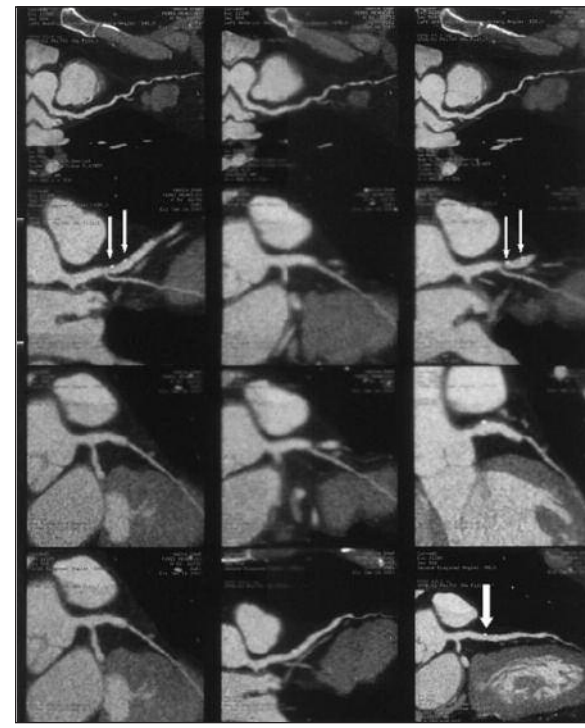

FIGURE 5: The adventitial small calcifications on the LAD (are shown white arrows).

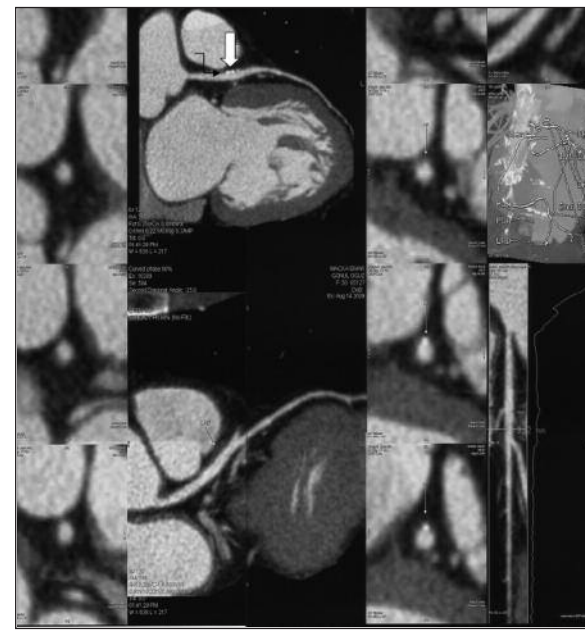

FIGURE 6: The atheroma mass or atheromateous component; minimal calcifications surrounded by some degree of (lipids) soft plaques (have been shown with black and white arrows) were taken place just below the adventitia of LAD artery. (In this case, LAD and Cx arteries were emerging from two separated orifices as a congenital coronary anomaly.)

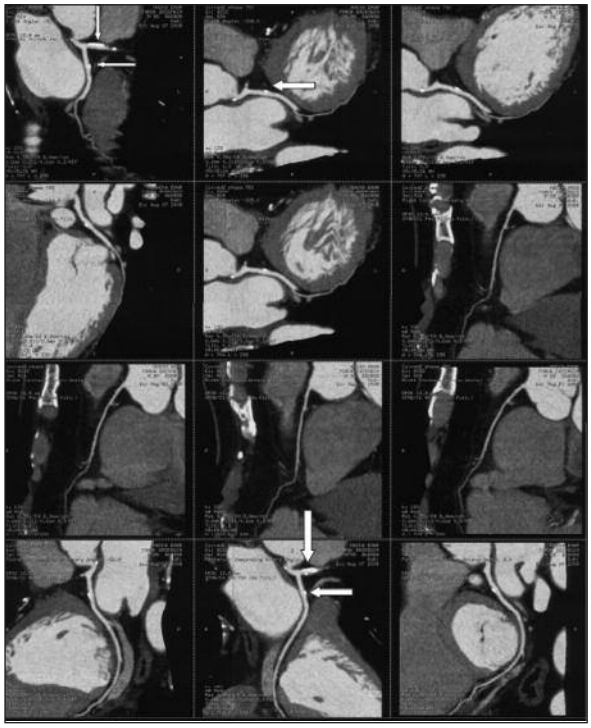

FIGURE 7: Medial calcifications on the LAD and Cx arteries progressing from adventitia with small narrowing of the lumen has been shown (with arrows) in the other case.

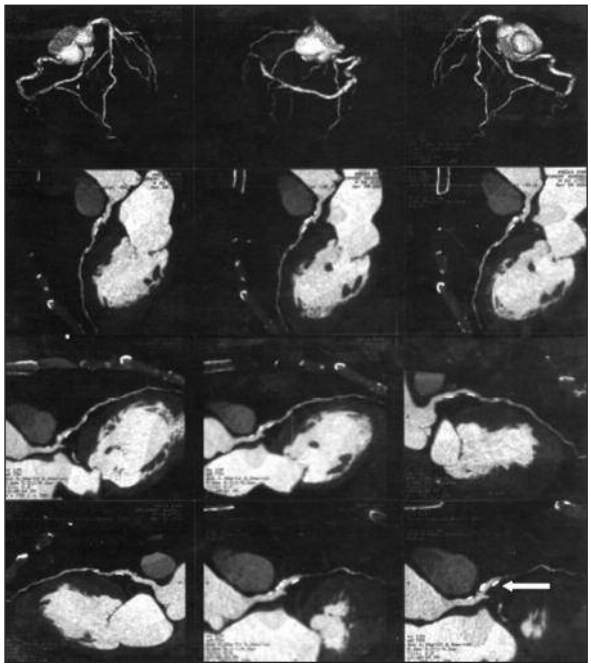

FIGURE 8: Many calcified plaques developing from just on the adventitial epithelium of LAD artery were shown by MSCT in our different case which was published in our Textbook of Internal Medicine on 2007.

probably will be sort it out and help us to show this complex morphology in the near feature.

So we have firstly described here that the second side of the atherosclerotic new pathway, which is, formation of the atherosclerotic plaques start not only from intimal endothelium but also mostly often from adventitial epithelium on the coronary arterial walls. The MSCT is a unique technique to show that unknown opposite side of the classical cascade and pathway of the atherosclerosis. This finding is described firstly in our randomised comparative coronary studies making a comparison between the invasive and non-invasive techniques which is not described in the literature. We have emphasized that MSCT is an important and unique device and is an important tool for non-invasive evaluation of coronary arterial pathologies and plaque formations. Of course, this technique has utilised the radiation (X-ray).

In the first patient, a normal coronary artery was shown (Figure 1). In the second case (Figure 4), it takes place of atherosclerotic soft and vulnerable plaque (atheromatous component) starting from adventitia of the mid segmental part of the

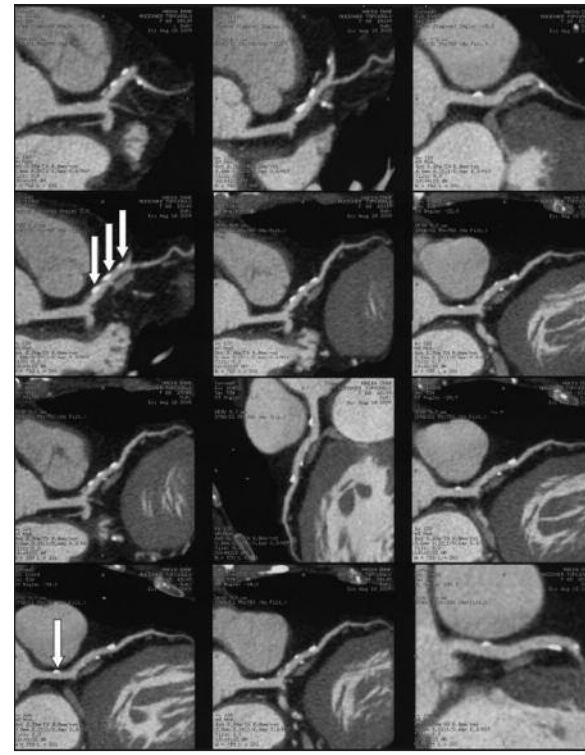

FIGURE 9: Consecutive many epithelial calcifications looks like beads on the adventitia of the LAD artery and one calcified plaque on the adventitia of left main coronary artery.

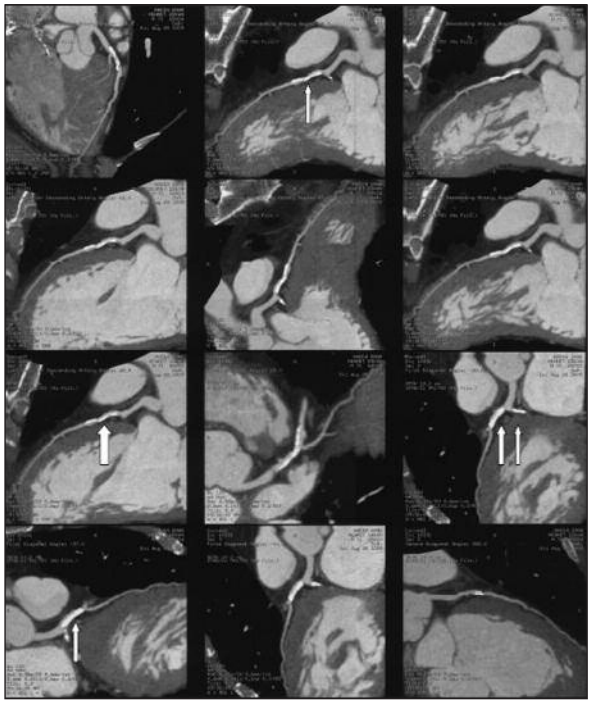

FIGURE 10: Severe calcification (shown arrows) with significant narrowing of the LAD and Cx lumens of arteries beginning from adventitia of the vessels.

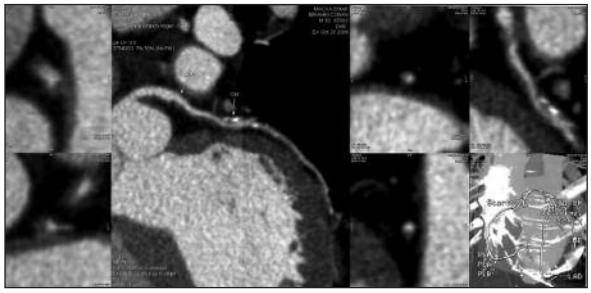

FIGURE 11: The mixed atheroma with small adventitial calcifications surrounded by some degree of lipids (partly soft plaques and partly calcifications) are shown with arrows on the LAD artery.

LAD artery and multiple small calcifications were shown that just beneath the subephitelium of the adventitia on the LAD.

In the third, fourth, fifth, sixth, seventh and eighth cases (Figure 5-9), from minimal to severe degree of atherosclerotic calcifications, mixed plaques and some degree of atheroma were shown which started and took place just beneath the epithelium of adventitia and grown towards to the coronary arterial lumen making some minimal or severe degree of obstructions in the Left Main, LAD and Circumflex (Cx) of coronary arteries (Figure 11). Figure 2 is illustrating the layer (stratum) of coronary artery with some degree of calcifications and formation of atheroma. Figure 3 is showing the adventitial calcification and atherosclerotic component with magnifying glass.

In our studies total 520 patients were investigated by MSCT. In the first subgroup of them (98 consecutive cases, 38 F, 60 M), MSCT and invasive conventional coronary angiography were performed to make a comparison between their results. At the end of this investigation, 66 patients had stent implantations, 22 patients underwent coronary bypass surgery and 10 patients treated medically.

These 520 patients, some of them underwent MSCT and invasive coronary angiography, IVUS, coronary arterial biopsy which was taken in the operating theater during bypass surgery just from the connection (anastomosis) areas of coronary arteries (the arterial biopsy material taken trough cut from connecting bypass area). The taken specimens were send immediately to the pathology for investigation of by the standard, electron and SEM. (The SEM is a very new attachment of the electron microscopy to make for mapping of calcium elements which using microtome, slices of samples might be taken, across the walls of chemical analysis can be taken by means of energy dispersive X-ray while monitoring the surface of specimen by SEM). The specimens particularly were taken from suitable areas of coronary artery during bypass surgery and the investigations were performed to see the localization of atheromas, atheromatous components and calcifications on the arterial level. At the end we have surprisingly seen in this group of patients more than 50% cases; the lipid core, the atheroma or atheromathos component and calcifications were started from just beneath the adventitia of coronary arteries.

Figure 1 is an example of normal coronary artery was demonstrated by MSCT. Figure 2 illustrates formation of the atheromathous component in the intima, medial (Mönckeberg's sclerosis) an adventitial atherosclerocalcifications. Figure 3 shows adventitial calcifications and lipid cores

which was taken by MSCT and examined by magnifying glass. In Figure 4-9 from minimal to severe calcifications, mixed plaques, some degree of atheromatous components were shown which started and were taken placed just beneath the epithelium of adventitia and grown towards to the coronary arterial lumen on the Left Main, LAD and Cx of coronary arteries.

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