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Not at random location of atherosclerotic lesions in thoracic aorta and their prognostic significance in relation to the risk of cardiovascular events

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Summary

Thoracic aortic calcium deposits are frequently detected on tomography of the chest, and in other imaging modalities. Numerous studies indicated the correlation of hemodynamic parameters such as wall shear stress in relation to distribution aortic calcifications. This publication discusses similarities and differences of two distinct pathomechanisms of arterial calcifications: intimal associated with atherosclerosis and medial knows as Mönckeberg's arteriosclerosis. This review also analyzes the frequent coexistence of aortic calcification and coronary artery disease in terms of risk of cardiovascular events.

Key words: aortic calcification • atherosclerosis • arteriosclerosis

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Atherosclerosis and Calcific Sclerosis. Two Causes Leading to Formation of Vascular Calcifications

Arterial calcification shows many similarities to bone mineralization. It is considered to be an active process that involves numerous regulatory mechanisms, although exact pathophysiology is not exactly known. Two independent processes: atherosclerosis and Mönckeberg's arteriosclerosis lead to formation of calcifications [1]. Calciphylaxis – calcification of medium-sized and small blood vessels is a rare disorder of progressive skin necrosis usually seen in the setting of end-stage renal disease.

Despite the fact that risk factors for atherosclerosis are systemic in character, locations of atherosclerotic plaques are not at random. Locations of plaque formation may be predicted based on numerical methods of blood flow simulation [2,3]. It means that localization of lesions is related to hemodynamics. The plaques are formed in precisely defined localizations (so-called risk points) within the aorta and other arteries originating from the aorta (Figure 1). In those points endothelium is exposed to the influence of atherogenic low shear stress (SS), whereas calcified plaques are formed in locations of oscillatory shear stress. It is so because oscillatory SS activate, among other inflammatory factors, osteogenic factors, including bone morphogenic proteins (BMP) [4,5]. They are credited with participation in osteoblastic transformation of vascular smooth muscle cells. Low non-oscillatory SS facilitate formation of fatty infiltrations and poorly calcified, cholesterol-rich plaques. In calcified plaques calcium salts are deposited in the intima (intima calcification) and histological features often resembles bone or cartilage structures [6].

Arterial calcific sclerosis is a pathological process, which should be differentiated from atherosclerosis but also leads to vascular calcification. In this case calcium salts are deposited in tunica media (media calcification) [7]. It is not the only difference (Table 1). As opposed to atherosclerosis, calcifications encompass the entire cross-section of the vessel and involve long, straight segments of peripheral arteries. Such localization of calcifications is fundamentally different from local, eccentric, occasionally non-calcified atherosclerotic plaques (Figure 1). In exceptional cases Mönckeberg calcifications appear in coronary arteries and are unaccompanied by cholesterol esters. Abdominal aorta and peripheral elastic arteries such as temporal artery and lower limb arteries are particularly susceptible to

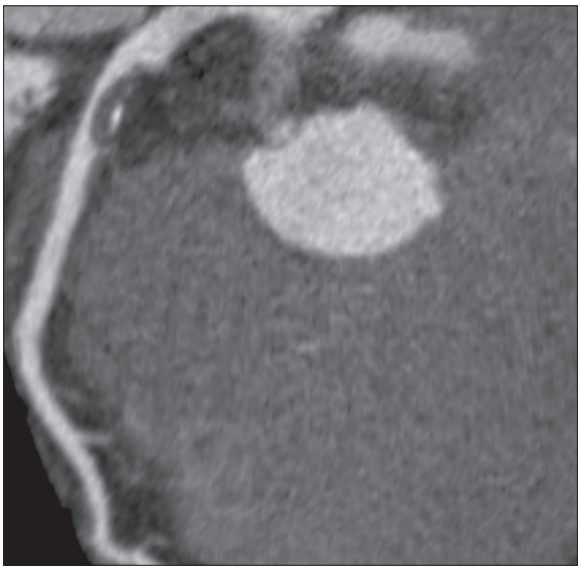

Figure 1. Left coronary artery in multi-slice computed tomography imaging. There is an eccentric atherosclerotic plaque in proximal part of left anterior descending artery. As opposed to arteriosclerosis, atheromatic lesions are localized near bifurcations and places of origin of lateral branches as well as on inner curvatures of vessels. At certain point in their development, most atherosclerotic lesions become calcified. Arteriosclerosis is not accompanied by infiltration of vascular walls by lipids.

arteriosclerosis [8,9]. This type of calcification leads to loss of vascular elasticity, which leads to increased wave velocity and pulse pressure. On plain x-ray Mönckeberg calcifications are described as railway tracks, since calcifications are visible along the entire course of the vessel (Figure 1).

It is thought that arteriosclerosis calcifications are secondary to disturbances of calcium and phosphorus metabolism, which accompanies renal failure, hypoparathyroidism and osteoporosis [1]. Calcifications are not only caused by calcium and phosphorus overload, but it is assumed to be an active process. This view is supported by higher activity of factors that promote mineralization (alkaline phosphatease, BMP, receptor activator of NF-kappaB ligand, leptin) and deficiency of factors inhibiting calcification (matrix Gla protein, fetuin A, osteopontin, osteoposteoprotegrin), which is observed in such states [10]. In diabetes and connective tissue diseases formation of vascular calcifications are ascribed to intensification of systemic inflammation and change in phenotype of vascular smooth muscle cells into bone-forming cells caused by an increase in activity of pro-inflammatory cytokines and free oxygen radicals.

Despite the differing pathogenesis of atherosclerosis and arteriosclerosis, both processes often occur simultaneously. It is difficult to differentiate calcifications in the course of atherosclerosis and arteriosclerosis based on radiological imaging, although the character and topography of lesions and medical history (e.g. renal failure) might be a suggestion [8].

It should be emphasized that increased arterial stiffness, by influencing blood flow profile, may constitute an important factor promoting atherosclerosis. It may be one of the mechanisms responsible for increased risk of cardiovascular events in renal failure and diabetes.

Topography of Atherosclerotic Lesions in Thoracic Aorta

Atherosclerotic damage of the aorta is usually asymptomatic. It is often discovered accidentally during various radiological examinations or in ultrasonography. A precisely defined location of thoracic artery calcifications is related to blood flow profile. Formation of secondary flows is the causative factor for atherosclerotic damage to the aorta as well as proximal fragments of arterial branches originating from aorta. Location of calcifications indicates their close relationship to hemodynamics and distribution of shear stress. The flow profile are largely determined by aortic shape, including curvature of the arch and angles, at which large arterial branches leave the aorta (Figure 1) [11].

The aorta are not equally susceptible to atherosclerotic damage and subsequent formation of calcifications [12]. The lesions are more frequently encountered in abdominal aorta than in thoracic aorta. In the thoracic region calcifications are more often formed in the aortic arch and descending rather than ascending aorta [12]. In a large study (mean age 52.9 years) aortic arch calcifications were found in 19.6% of subjects, while the descending aorta was involved in 10.1% of people and the ascending aorta in as little as 2.7% of patients [13]. It means that proximal aorta is resistant to formation of lesions. This phenomenon is explained through a so-called helical flow pattern in ascending aorta. Aortic geometry and hemodynamic conditions forcing such movement of blood flow [14]. There is a theory that helical blood flow facilitates endothelial oxygenation and prevents gathering of LDL (low-density lipoprotein) cholesterol particles

Table 1. Some differences between calcifications in atherosclerosis and Mönckeberg arteriosclerosis.

	Atherosclerosis	Arteriosclerosis
Location of calcifications	Intima	Media
Cause	Hemodynamic	Metabolic
Site	Muscular arteries	Elastic arteries
Histopathological picture accompanying calcifications	Lipids + monocytes + foam cells	Absence of lipids, monocytes and foam cells
Hemodynamics	Stenotic lesions	Non-stenotic lesions

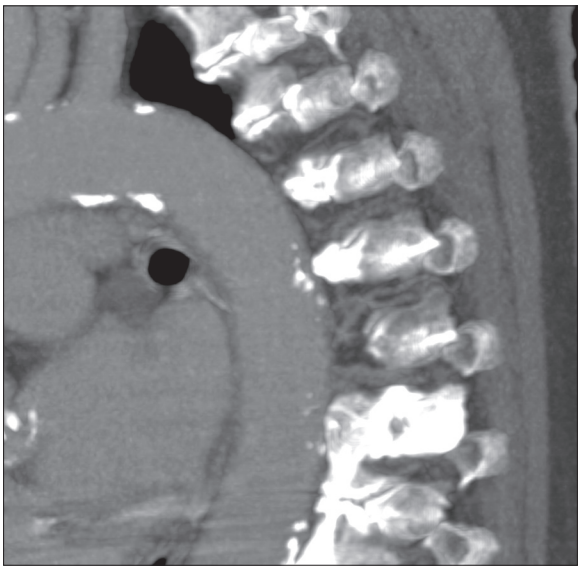

Figure 2. Multi-slice computed tomography examination. Calcifications are visible on the inner aortic curvature, in proximal parts of large arteries originating at the arch and on posterior wall of descending aorta.

and other blood-borne atherogenic particles close to vascular wall [15]. It counteracts their diffusion into intima. This observation became an inspiration when designing vascular stents, as their architecture determines blood flow profile and the value of shear stress within the stent [16]. If the structure of stent struts produces helical flow, the expected risk of neointimal proliferation and restenosis is lower [17].

Inner curvature of the aortic arch is a typical location of calcifications in the thoracic aorta (flow separation and reversal flow) [18]. Other predisposed locations include the posterior wall of descending aorta, where reversal flow develops in the diastolic phase (oscillatory shear stress). In the arteries originating from the outer curvature of the arch secondary flows appears adjacent to the lateral walls near the orifice of brachiocephalic trunk, left common carotid artery and left subclavian artery (Figure 2). Inner aortic curvature, proximal segments of arterial branches leave the arch and posterior wall of the descending aorta constitute a typical localization of calcifications in the thoracic aorta (Figure 3).

In animal models of atherosclerosis with additionally induced aortic insufficiency, presence of regurgitation is a factor contributing to increased severity of atherosclerotic damage to the aorta compared to animals with normal aortic valve function [19,20]. This phenomenon is explained by increased aortic retrograde flow and impact of oscilltory shear stress [19,20]. This observation is confirmed clinically. Studies by Shimoni et al. showed more severe atherosclerosis of descending aorta in patients with aortic regurgitation (regardless of etiology and risk profile) in comparison to a control group similar with regard to age and presence of risk factors [21]. These observations corroborate contribution of hemodynamics and reversal flow to development of aortic calcifications.

Mechanotrasduction is an increasingly recognized phenomenon explaining the association of hemodynamics with

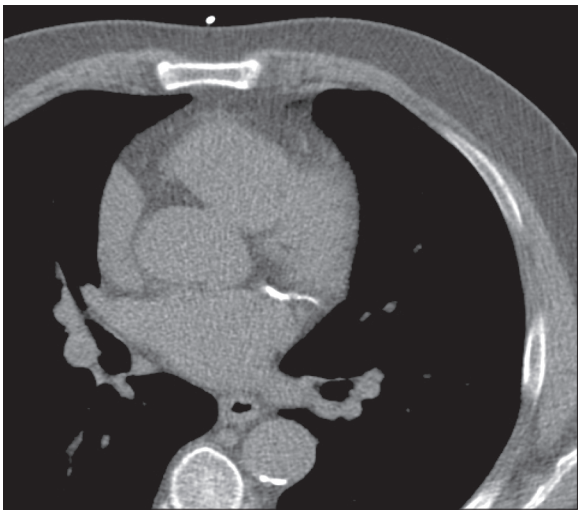

Figure 3. CCS study. Calcification is visible on the posterior wall of descending aorta and along the course of circumflex branch of left coronary artery.

atherosclerosis [22]. This phenomenon involves transduction of signals produced by flow through endothelial mechanoreceptors into the vessel wall. As a result, endothelial cell change phenotypes as well biochemical respons. Low-amplitude oscillatory SS contribute to increased endothelial expression of proatherogenic factors such as: adhesion proteins, chemotactic factors or BMPs promoting calcification [22]. Moreover, lack of the continuity of adhesions between endothelial cells and reduced glycocalyx thickness in points exposed to secondary flow promotes formation of atherosclerotic lesions [22,23]. All that facilitates transmission of blood-borne particles into the vascular wall, which is regarded as the main issue of atherosclerotic plaque formation (Figures 2 and 3).

Risk Factors for Aortic Calcifications and Their Prognostic Significance

Risk factors for thoracic aortic calcification (TAC) are the same as risk factors for coronary artery disease, while the most prominent ones include hypertension and smoking [13,24]. Frequency of occurrence of TAC and severity of calcifications increase with age [13,25].

Regardless of other factors, thoracic aortic calcifications are strong predictors of coronary calcification [26]. Severe thoracic aortic calcifications, especially when accompanied by numerous cardiovascular risk factors, are important indicators of presence of advanced coronary artery disease [12,27,28]. This observation explains why calcifications of the descending aorta are associated with almost four-fold increase in the risk of coronary artery disease [29].

In a prospective cohort study involving patients with stable coronary artery disease, coronary calcium score (CCS) was higher in the group with TAC and amounted to $565 \pm 177;736$ compared to $241 \pm 177;339$ ($p<0.001$) in patients without aortic calcifications. In one of the analyses sensitivity and specificity of thoracic aortic calcifications as a predictor of presence of severe coronary artery lesions were estimated at 56% and 72% respectively [29]. In a

population of patients with positive CCS or stable coronary artery disease aortic calcifications are encountered in 70% of patients, while their severity correlates positively with CCS [30,31]. In the Healthy Women Study project, which included women before menopause, high initial severity of coronary artery calcifications correlated with progression of aortic calcifications [32]. This observation indicates common pathogenesis of coronary and aortic calcifications.

Beside hemodynamic predispositions, classical risk factors also play an important role in development of atherosclerotic plaque. Increased blood viscosity that accompanies most of them leads to prolonged residence time of atherogenic particles in the proximity to endotelium at the points were disturbed flows results on low or low-oscillatory endothelial shear stress [33]. It facilitates mass transport of particles making up atherosclerotic plaque, including LDL cholesterol, into the vessel wall.

Prognostic Significance of Aortic Calcifications.

TAC constitutes a negative predicting factor for cardiovascular events [34,35]. Regardless of classical risk factors, presence of aortic calcifications increases the risk death from all causes, including cardiovascular ones [29,36–42]. The risk of death among men older than 45 years is six fold higher when plain chest x-ray shows aortic calcifications [43]. Interestingly, this risk does not depend on other factors [44]. A study involving analysis of over 60 thousand people between 30 and 89 years old revealed that presence of atherosclerotic plaque in the aortic arch was associated with high risk of coronary artery disease [36].

Conclusions

There are two pathological processes leading to formation of vascular calcifications: atherosclerosis and arteriosclerosis. Localization of atherosclerotic plaque and aortic calcifications in thoracic aorta is not at random. It is closely related to formation of secondary flows in the area where endothelium is subjected to low or low-oscillatory shear stress in particular. Visualization of aortic calcifications in the aorta is associated with high probability of severe atherosclerotic lesions in other locations, including coronary arteries. That explains the observed increase cardiovascular risk in patients wih TAC.

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