

ATHEROSCLEROSIS OF CORONARY BLOOD VESSELS – LOCAL OR SYSTEMIC INFLAMMATION?

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Abstract

The presence of atherosclerotic lesions in the blood vessels is a predisposition for the development and occurrence of acute ischaemic attacks. Bigger atherosclerotic lesions in the coronary blood vessels cause lumen occlusion, which is a cause of acute myocardial infarction. Endothelial dysfunction is defined as an ability of the endothelium to produce vasorelaxing nitric oxide (NO), or deregulation of the other vasoactive substances, such as angiotensin II and endothelin [13]. This definition describes endothelial dysfunction as an improper vasomotor constriction of the vessel, that leads to lumen occlusion of the already existing atherosclerotic lesions. According to the modern model, the development of atherosclerotic plaque and inappropriate endothelial NO production have a synergistic role in patho-physiological and molecular processes in the blood vessels [14]. Lesions in the coronary arteries are deposits of huge quantities of foamy cells and fibrous plaques. The thin fibrous plaques are 10–20% of the total plaque population and are the cause of 80–90% of clinical cases due to their ability to rupture [48]. According to all the results from published studies by far, it has been pointed out that the plaque stability, not the absolute size influences the rupture potential. Elucidating the risk factors that may modify in the atherogenesis and the consequent atherothrombic effect is the first step to this goal.

Key words: Atherosclerotic lesion, endothelial dysfunction, vulnerable lesion, atherothrombosis.

The presence of atherosclerotic lesions in the blood vessels is a predisposition for the development and occurrence of acute ischaemic attacks. Bigger atherosclerotic lesions in the coronary blood vessels cause lumen occlusion, which is a cause of acute myocardial infarction. The erosion or rupture of vulnerable lesions might be the cause of atherothrombic complications, such as acute myocardial infarction, stroke, kidney failure, heart failure, sudden death, and peripheral vascular disease [1, 2]. Although vascular diseases are most frequently considered as orga-

nic systems, nevertheless, atherosclerosis and atherothrombosis are a generalized process.

By the mid 70's, atherosclerosis was considered as a disease of accumulated lipids and the increase of the lesion consisting of lipids was considered to be the primary cause of the lumen occlusion, that led to the occurrence of ischaemic heart and brain events [3, 4]. Actually, the historic and present facts support the role of the plasma lipids (cholesterol and triglycerides) and lipoproteins in the pathogenesis of atherogenesis [5–7]. If the cause of atherosclerosis is lipid accumulation only, then the athe-

rosclerosis level should be proportional to the blood lipid concentration. Undoubtedly, hyperlipidaemia is the main risk factor for the development of cardiovascular; however, coronary disease is present as well in a high percentage of the population without clinical evidence of hyperlipidaemia [8]. The importance of smoking and increased blood pressure, which is almost the same as the importance of hyperlipidaemia in the pathogenesis of atherosclerosis, have to be noted as well.

These facts point out that atherosclerosis is a very complex process and its pathogenesis is associated with the presence of hyperlipidaemia, endothelial dysfunction, and inflammation [9–12]. According to this model, inflammatory cells and cytokines have the essential role in the development of atherosclerotic lesion.

Endothelial Dysfunction

Endothelial dysfunction is defined as an ability of the endothelium to produce vasorelaxing nitric oxide (NO), or deregulation of the other vasoactive substances, such as angiotensin II and endothelin [13]. This definition describes endothelial dysfunction as an improper vasomotor constriction of the vessel, that leads to lumen occlusion of the already existing atherosclerotic lesions. According to the modern model, the development of atherosclerotic plaque and inappropriate endothelial NO production have a synergistic role in the pathophysiological and molecular processes in the blood vessels [14]. Apart from the vasodilatation effects, NO at the same time creates an antithrombotic environment through reduction of the endothelial platelet aggregation [15], prevents endothelial leukocyte adhesion by suppressing the expression of adhesion molecules [16], and maintains the smooth muscles of the blood vessels in a nonproliferative condition [17]. This is a delicate balance where local changes in the blood vessels caused by LDL cholesterol, free radicals, bacteria, angiotensin II-induced hypertension can cause endothelial activation by reduction of the intracellular concentration of NO [18].

It is well established that atherosclerosis exacerbates in the presence of systemic risk factors, such as increased LDL, hypertension, diabetes, or smoking. Although the entire vas-

cular endothelium is exposed to these factors, the atherosclerotic lesions most often develop at the bifurcation points, the point where arteries branch, and the internal bends of arteries, which is another fact proving that local events are of great significance in the development of disease. These predilection sites where atherosclerosis develops are of a complex configuration and their endothelium is exposed to disrupted haemodynamic forces – low shear stress [19], that might cause endothelial disruption and consequential local inflammation [20, 21].

In chronic hyperlipidemic plasma, the blood vessels are exposed to LDL cholesterol which penetrates the cellular endothelial layer at the points with disrupted haemodynamic forces, and enters the intima where under oxidative conditions oxidized LDL (oxLDL) [22] forms. This modified lipoprotein may bind with the endothelium and cause increased O_2 production leading to a decrease of the NO concentration and endothelial activation [23]. The endothelial activation marks the onset of a localized inflammation process, that further causes endothelial extravasation through the production of selectin and integrin. The fast exposition of the Weibel-Palade bodies is caused by expression of P-selectin and E-selectin on the endothelial surface [24]. These selectins poorly bind the Lewis X-antigens on the leukocyte surface, a cause of endothelial barrier attenuation. The endothelial expression of integrins, such as VCAM-1 (vascular cellular adhesion molecule), causes obstruction of -1 adhesion (CD18/CD11b) which recruits monocytes that can extravasate into the endothelial tunic intima [25]. In animal atherosclerosis models, endothelial cells express large quantities of VCAM-1 as part of the initial vascular response to cholesterol accumulation [26]. This expression is not constant throughout the blood vessel and it emerges mostly at the points with disrupted haemodynamic forces and initiates endothelial integrity disruption, which is sufficient to enable lipid migration through the intima. Consequently, the haemodynamic stress may sometimes cause rupture in more complex plaques. The mature monocytes of the tunica intima secrete cytokines, such as $TNF\alpha$, that help the initiation of the immune response and endothelial activation. Chemokines, such as interleukin (IL)-8,

are responsible for monocyte recruitment in the inflammation regions [27].

The mature monocytes develop into tissue macrophages and express receptor cleaners, such as SR-A, CD36, and most importantly, oxLDL receptor-1 (LOX-1) [28]. LOX-1 is especially significant because it provides phagocytosis of the modified sLDL, where the macrophages are satiated with fatty cells and become "foam cells" [29, 30]. Upon arrival and maturation of the monocytes, fatty streaks are being developed in the pro-inflammatory cytokine network.

Angiotensin II, produced by the activated endothelial, is a vasoconstrictor that opposes the NO action. The angiotensin II production is regulated by NO, but this process is disrupted when there is endothelial dysfunction. This molecule is important in the initial development of the pro-inflammatory cytokine network through its action on the smooth muscle cells that produce interleukin 6 (IL-6) and participate in the beginning of the acute stage of systemic response by hepatocyte activation [31].

IL-6 has an autocrine activity as well, which induces the local smooth muscle cells that proliferate further [32, 33]. The smooth muscle cells control the maintenance of the extracellular matrix mainly by collagen production and by establishing balance in the exchange of the matrix substances normally regulated by the matrix-metalloproteinases (MMPs) [35]. Matrix-metalloproteinases are a family of endopeptidase enzymes that contain an atom of zinc and include collagenases, gelatinases and stromelylins. The degradation of the extracellular matrix is controlled by the collagen production and tissue inhibitors of matrix metalloproteinases (TIMPs) from the smooth muscle cells. The matrix homeostasis disruption is the main cause of the vascular pathology.

Thus, the plaque is overfilled with fats and cellular elements. In the early stage of the matrix formation, the proliferative smooth muscle cells provide mechanical support for the lesion development, that further progresses and leads to luminal occlusion. It has long been considered that plaque development is an absolute and progressive process, up until angiographic studies of coronary blood vessels in patients at different time intervals have shown that

the plaque progression is not a unified process. The cause of this is still not clear, but it is assumed that several mechanisms might be involved in this process.

One of the hypotheses is that there is a formation of a new fragile microvascular rupture-prone network in the plaque by neoangiogenesis. The rupture causes thrombosis that leads to thrombin production causing the proliferation of smooth muscle cells and their migration by activating the platelet factor mechanism [36]. The increase of the smooth muscle cell population causes collagen deposition, lesion progression and development of the stenosis.

The presence of T-cells in the plaque was first described in 1985 by Hansson et al. [37] Most of the T-cells found in the lesions belong to CD4+, although some of them are CD8+ effectors or memory cells [38], and the activated cell percentage increases as the disease progresses [39].

The molecular mechanisms that activate these T-cells are poorly understood. The results of recent studies have suggested that, similarly to in infections, dendritic cells migrate from lesion towards the draining lymph nodes and thus activate the T-cells [40]. The dendritic cells ingest the modified LDL similarly to the Langerhans skin cells that ingest the antigens by macropinocytosis. The "dangerous signals" such as cytokines, the toll-like receptors (TLRs) (most probably by the modified LDL) [41], and the apoptotic bodies cause activation of the dendritic cells that direct towards the draining lymph nodes.

Beside the role of oxLDL antigens in the stimulation of the T-cell responses, molecular genetic studies show that T-cells found in the lesions are quite heterogeneous in terms of the specificity of T-cell receptors [42] and 10% only of the clones from the T-cells in the plaque are specific for the oxidized LDL in the MHC II-class [43]. In theory, these T-cells can be activated by some super antigens or by certain inflammatory factors that are present in the lesion.

The native CD4+ T-cells have a potential to be activated in two functional ways: by T-helper cells Th type 1 or by Th type 2. Briefly, Th1 cells are primarily recognized by their ability to produce IFN γ and subsequently to stimulate

the cellular immune response through the macrophages. On the other hand, Th2 cells are recognizable by production of IL-4 and IL-13, necessary to cause B-cell clone expansion and antibodies synthesis. During the immunological response, the T-cell activation has a tendency for consensus, i.e. Th1 and Th2 have an inverse relation. This happens due to (insufficiently resolved) multi-factor mechanisms, perhaps because of the DC-signals for maturation, molecular interactions in the immune cascade, epigenetic limitations, and the response of the cytokines by positive feedback (e.g., IL-12 promotes differentiation of Th1 cells from the macrophages, then TH1 cells produce IFN γ) [44]. In atherogenesis, IFN γ is synthesized by the enormous number of T-cells in the lesion and most of the evidence suggests that the inflammatory component of the atherogenesis is a response to the Th1 cells.

Unlike this, B-cells are also activated in the atherogenic immune response. Several types of potential "altered-self" specific antibodies are described, especially antibodies for various forms of changed LDL. A study of mice with aberrant B-cell response, has proved that B-cells are athero-protective in comparison to the T-cells [45]. This suggests a pro-atherothrombic role of the athero-antibodies, but overall, a protective role of the Th2 response, primarily, and most likely, through consequential limitation of Th1 cytokines.

Vulnerable Lesion and Atherothrombosis

Regardless of the mechanisms for adaptive activation of a response, activated T-cells are present in the lesions in the formation and IFN γ is produced locally, by almost all of them [43]. This cytokine of the Th1 cells characterizes itself by a few pro-atherogenes and pro-thrombic effects, including increased turnover of the matrix through direct SMC activation and activation of MMP-producing macrophages. It is probable that the absence of IFN γ or its inhibition, at least in various mice models, results in reduced vascular pathology [46].

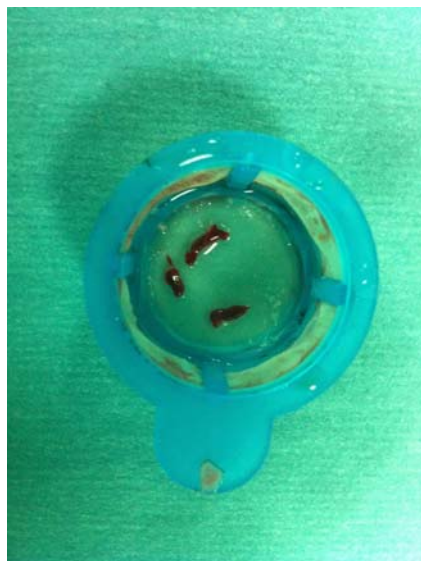
Concomitantly, oxLDL is accumulated in the lesion and causes apoptosis of SMC (and the macrophages, e.g., formation of necrotic core) [47]. SMC are a huge source of TIMPs, and in

their relative absence, MMPs become physiologically more active.

Besides the presence of "scavenger" cells (cells that collect cellular debris), the rest of the debris contributes immensely to the apoptotic cells turning into secondary necrosis that leads to additional inflammation. This creates a micro-environment where matrix degeneration predominates and deregulates the previous balance where collagen deposition allows the creation of stable coarsening. In time, as the fibrin cap weakens, the plaque destabilizes, while the mechanical structure that holds the lesion containing the necrotic core and inflammatory cells is compromised. The Brown study emphasizes that lesions in the coronary arteries are deposits of huge quantities of foamy cells and fibrous plaques. The thin fibrous plaques are 10–20% of the total plaque population and are the cause of 80–90% of clinical cases due to their ability to rupture [48]. According to virtually all the results from published studies, it has been pointed out that the plaque stability, not the absolute size, influences the rupture potential. Since the plaques form in the regions of non-lamellar blood flow, the haemodynamic factors cause mechanism stress of the plaque, creating a mechanism for endothelial erosion and an opportunity for rupture, exposing procoagulant stimuli under the endothelium (tissue factor) in the blood flow [49, 50]. (Fig. 1, Fig. 2).



Picture 1 – White thrombus is mainly composed of platelets and small number of fibrin, red cells and leukocytes it is known as s arterial thrombus



Picture 2 – Red thrombus is produced in the low pressure environment and mainly consist of fibrin network which is entrapped by red cells

Therapeutic prevention (or limitation of the possibility of occurrence) of plaque rupture is the primary goal of vascular medicine. Elucidating the risk factors that may modify the atherogenesis and the consequent atherothrombotic effect is the first step to this goal.

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Резиме

АТЕРОСКЛЕРОЗА НА КОРОНАРНИТЕ КРВНИ САДОВИ – ЛОКАЛНА ИЛИ СИСТЕМСКА ИНФЛАМАЦИЈА?

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Присуството на атеросклеротските лезии во крвните садови е придиспозиција за развој и појава на акутни исхемични атаки. Поголемите атеросклеротски лезии во коронарните крвни садови предизвикуваат оклузија на луменот што е причина за појава на акутен инфаркт на миокардот. Ендотелијалната дисфункција се дефинира како неможност на ендотелот да продуцира вазорелаксирачки азотен моноксид (NO),

или пак присуство на дисбаланс помеѓу другите вазоактивни материи како што е ангиотензин II и оксиданси. Со оваа дефиниција ендотелијалната дисфункција се дефинира како несоодветна вазомоторна конструкција на васкулатурата која доведува до оклузија на луменот со веќе постоечките атеросклеротски лезии. Според современиот модел, развојот на атеросклеротската плака, нарушената продукција на NO од страна на ендотелот имаат заедничка улога во патофизиолошките и молекуларните процеси на ниво на крвните садови. Лезиите во коронарните артерии претставуваат депозити на големи количини на пенести клетки и фиброзни плаки. Тенките фиброзни плаки претставуваат 10–20% од целата популација на плаки и се причина за 80–90% од клиничките случувања поради нивната можност да руптурираат. Според резултатите од објавените студии се истакнува дека стабилноста на плаката а не апсолутната големина влијаат на потенцијалот за руптура. Со идентификација на ризик факторите кои може да се модифицираат во атерогенезата и последователниот атеротромботичен ефект е првиот чекор кон целта.

Клучни зборови: атеросклеротска лезија, ендотелна дисфункција, вулнерабилна лезија, атеротромбоза.