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BIOMECHANICAL ASPECTS OF A ATHEROSCLEROSIS

BIOMECHANICZNE ASPEKTY MIAŻDŻYCY

A b s t r a c t

Pathogenesis of atherosclerosis is a complex multifactorial process of vascular wall injury. It is widely accepted that the local hemodynamic factors, in particular, disturbed flow and low/oscillatory shear stress leads to the plaque development. We present a consistent concept of atherosclerosis aetiology, taking into consideration the four main components contributing in the atheroma formation: geometric, hemodynamic, hemorheological, and mechanical risk factors. Exemplary illustrative flow simulation results for formulated concept have been presented. It assumes the pulsatile non-Newtonian fluid flow and uses realistic coronary artery geometry based on medical imaging and segmentation.

Keywords: *atherosclerosis pathogenesis*, *shear stress*, *computational fluid dynamics*

S t r e s z c z e n i e

Przyczyna miażdżycy jest złożona i wieloczynnikowa. Uważa się, że czynniki hemodynamiczne, a w szczególności przepływy zaburzone, gdzie na ścianę naczynia działają małe i oscylacyjne naprężenia ścinające, odgrywają kluczową rolę w powstawaniu zmian. W artykule przedstawiono spójną koncepcję etiologii choroby, która uwzględnia cztery główne jej komponenty: parametr geometryczny, hemodynamiczny, hemoreologiczny i mechaniczny. Przytoczono przykłady symulacji jako ilustrację do sformułowanej koncepcji. Zakładają one pulsacyjny przepływ płynu nie-Newtonowskiego oraz stosują realistyczny model geometrii tętnicy wieńcowej bazujący na obrazowaniu i segmentacji naczyń.

Słowa kluczowe: *patogeneza miażdżycy*, *naprężenia ścinające*, *numeryczna mechanika płynów*

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1. Introduction

In developed countries every fifth death is caused by coronary artery disease (CAD). Despite tremendous progress in cardiology, biology and basic sciences, atherosclerosis remains an unsolved health and social problem. Atherosclerosis is diffused disease, with predominate location restricted mainly to the aorta, proximal segments of the arteries which originate from the aorta, and both saphenous vein and radial artery aorto-coronary by-passes. The atherosclerotic process is uncommon or almost never occurs in the internal mammary arteries (IMA) even when they are used as conduit for a coronary artery by-pass graft [1]. 10% of remaining IMA graft failure, so-called "string phenomenon" (the narrowing of the whole length of the artery), is attributed to competitive flow in the native artery, and low wall shear stress in the anastomosis [2, 3].

State of the art, routine diagnostic methods are not capable of determining the course of the atherosclerotic process and prediction of when (if ever) acute coronary syndromes will occur, or which lesions will progress into vulnerable plaque or significant hemodynamic stenosis (stable angina). In each individual person, it requires many years to follow the course of the disease. We find about coronary artery atherosclerosis when plaque ruptures or when the plaque restricts the coronary flow during exercise (stable CAD). Plaque visualization at the coronarography allows determination of the status quo only and does not indicate both, when the disease emerged or whether lesion will cause future cardiac events. Therefore, angiography presents the plaques distribution, but does not answer key questions about both the history of the disease and the prognosis. Computational Fluid Dynamics (CFD) seems to be a promising tool, which will efficiently reduce limitations regarding atherosclerosis progression due to the possibility of computer simulation of atherosclerotic plaque growth [4].

2. The biomechanical forces acting on the vessels and atherosclerosis

The vascular wall is exposed to two biomechanical forces. The first one is tensile stress. It is directed perpendicular to the wall and affects all layers of the artery, which causes smooth muscle cell hypertrophy. The second force, much more essential in atherosclerosis, is tangential to the endothelium (endothelial shear stress, ESS). ESS is related to blood viscosity, while tensile stress is relates to arterial blood pressure. ESS depends on velocity gradient (shear rate) and blood viscosity.

On the basis of clinical studies and follow-up coronary angiography, it has been proven that plaque progression relates particularly to those lesions that are exposed to low and oscillatory shear stresses, which clearly implies that biomechanical forces have significant impact on atheroma formation. For example Gibson et al [5] conducted a study to assess the rate of change in coronary arterial diameter in patients over three years. They found a significant correlation between the low shear stress and an increased rate of atherosclerosis progression.

After aorto-coronary by-pass graft surgery, in the native artery segment that had been by-passed the progression of atherosclerosis is rapid. It is caused by the emergence

of reverse flows and oscillatory shear stresses in the by-passed artery [1]. Experimental data confirms that it is possible to reduce the formation of atherosclerotic lesions by lowering the tendency to formation of secondary flows. In animals, adding drag reducing polymers to the blood inhibits the development of atherosclerotic plaques in the mechanism of flow stabilization [6, 7]. Those results support the notion that hemodymamics play the important role in atherogenesis.

The pathogenesis of atherosclerosis is a complex multifactorial process of vascular wall injury. There are four main components involved in the atheroma formation: geometric, hemodynamic, hemorheological, and mechanical [8]. Table 1 presents the importance and contribution of each.

Table 1

The main components involved in the atheroma formation

Risk components	The role in atherosclerotic process
GEOMETRIC	Obtuse angle of bifurcation, unequal cross-sectional area of vessels after bifurcation. Periodic changes of coronary artery curvature due to heart deformation in each cardiac cycle.
HEMODYNAMIC	High flow velocity and centrifugal effect of the flow leads to skewness of the velocity profile, flow separation and oscillatory flow. Formation of disturbed and secondary flows generates regions of low and oscillatory endothelial shear stress.
HEMORHEOLOGICAL	In areas of disturbed flows, non-Newtonian properties including shear-thinning and yield-stress, prolong residence time of blood borne atherogenic particles (LDL, macrophage) and facilitates their penetration to the arterial wall.
MECHANICAL	In the aging process, systemic factors i.e. hypertension, renal insufficiency and diabetes, change the stiffness of arterial wall, and leads to reduced artery compliance, with resulting increase in systolic pressure and decrease in diastolic pressure and hence facilitate generation of the secondary flows.

Despite the fact that the classic risk factors are systemic in nature, arterial lesions are restricted to the points which are exposed on disturbed flow and low and oscillatory ESS. The evidence that blood flow plays a key role in atheroma formation is not at random plaque distribution. Preferred location are lateral walls of the bifurcations, areas near to the side branches and branch ostia (Fig. 1) [9, 10].

Atherosclerotic plaques, particularly at the early stage, are eccentric, and in segments where vessels have no side branches, they emerge from the inner curvature (Fig. 2). That is why, in coronary arteries lesions usually emerge from the epicardial surface (inner curvature). Such plaques localizations indicate their relationship with flow conditions, which are largely determined by complex arterial geometry.

From fundamental mechanics, both the fluid dynamics and the shear stress distribution are dependent on the vessel geometry (Fig. 3).

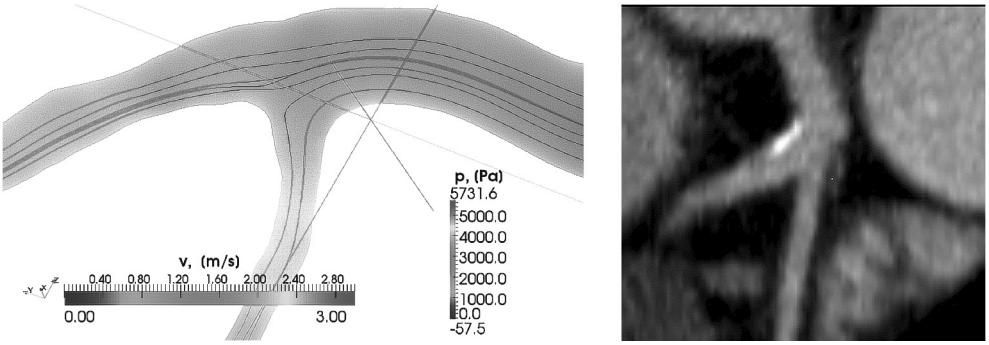

Fig. 1. Plaque formation typically develops at the lateral walls of the bifurcation, as blood tends to separate and form regions of oscillating ESS. Left panel. Calcified plaque at left anterior descending artery (lateral wall). Right panel, schematic representation of calculated stream lines in secondary flow region at the artery bifurcation

Rys. 1. Blaszki miażdżycowe typowo powstają na bocznych ścianach podziałów naczyniowy, czyli miejscach w których dochodzi do oderwania warstwy przyściennej, gdzie ściana naczynia narażona jest na oscylacyjne naprężenia ścinające. Panel lewy. Uwapniona blaszka miażdżycowa przy ścianie bocznej gałęzi przedniej zstępującej. Panel prawy, schematyczne przedstawienie wyznaczonych linii prądu, regionie powstawania przepływu wtórnego w podziale naczyniowym

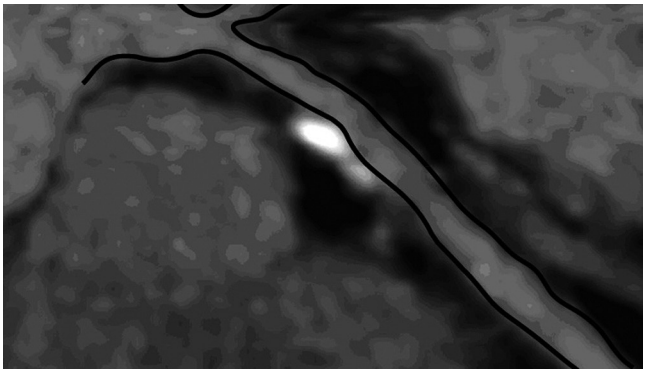

Fig. 2. Left anterior descending artery (imaging with multislice computed tomography). Partially calcified plaque located on epicardial surface of the coronary artery (inner curvature). Human coronary arteries enlarge in relation to plaque area and that functionally important lumen stenosis may be delayed

Rys. 2. Gałąź przednia zstępująca (obrazowanie za pomocą wielowarstwowej tomografii komputerowej) częściowo uwapniona blaszka miażdżycowa na powierzchni nasierdziowej (krzywizna wewnętrzna). Na wczesnym etapie, formowanie się blaszek odbywa się w błonie wewnętrznej, bez zawężenia światła naczynia

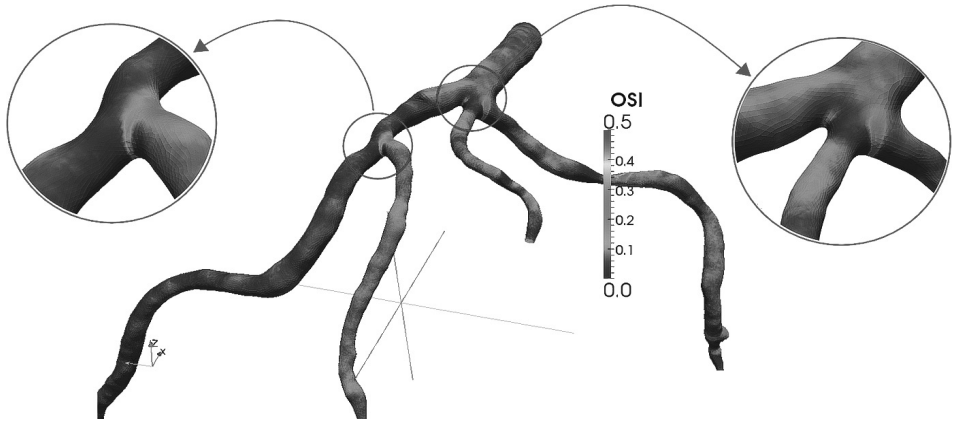

Fig. 3. The numerical simulation (CFD) of oscillatory shear stress distribution in the left coronary artery. The risk points of plaque formation are distributed in segment 6 of the left descending artery, vicinity of the diagonal branch and in the middle segment of circumflex artery – the regions of highest value of the oscillatory shear stress index value, OSI

Rys. 3. Rozkład wskaźnika oscylacyjnego naprężenia ścinającego w anatomicznej geometrii lewej tętnicy wieńcowej zamodelowany za pomocą numerycznej mechaniki płynów (CFD). Miejsca ryzyka powstania zmian miażdżycowych znajdują się w segmencie 6 gałęzi przedniej zstępującej, ostium gałęzi diagonalnej pierwszej oraz w środkowym odcinku gałęzi okalającej – miejscach występowania największych wartości oscylacji przepływu, OS

3. Mechanotransduction

The science that deals with forces associated with biological response of, for example, vessel wall to the flow is mechanobiology. The phenomenon of endothelium sensing ESS and transferring it to biochemical signals is called mechanotransduction [14]. The precise molecular mechanisms remain unknown however, it is believed that mechanoreceptors of cell membrane are involved. Mechanical signals from the flow are being transformed into biochemical signals with the use of transcription factors, like Nuclear Factor kappa B (NF-kB) and Activator Protein 1 (AP-1). It is estimated that hundreds of gene activity depends on the flow velocity profile and ESS distribution [15–17]. Those genes are called shear regulated.

Laminar flow with axially symmetric, fully developed flow velocity profile, activates atheroprotective genes and increases expression of atheroprotective particles. Therefore high ESS is a critical factor in maintaining normal endothelial function. Physiological shear stress stimulates the vascular endothelium to produce mediators of vasodilatation (nitric oxide, prostacyclin, endothelial hyperpolarizing factor) exerting a critical impact in maintaining normal endothelial structure and function. The physiological ESS can be characterized as: anti-inflammatory, antithrombotic, antiproliferative and antioxidant [18–20].

Low and oscillatory ESS tiger unfavorable gene expression and biomechanical response. Reorganisation of endothelial cells and disruption of intercellular connections at the area of low/oscillatory shear stress, facilitates the transport of particles including low density lipoproteins, monocytes, fibrin and other blood-borne atherogenic particles into the intima. It is believed that mechanoreceptors of cell membrane are involved in this process (membrane integrins, ion channels, receptors for tyrosine kinase, protein G, caveolae). Low and oscillatory ESS leads to endothelial dysfunction, which manifests i.e. with increased synthesis of oxygen free radicals, prothrombotic factors, expression of adhesion proteins and chemotactic factors. Disturbed flows facilitate macrophages, leukocytes, and platelets recruitment to the vessel surface. These, in turn, get into intima and release cytokines and growth factors. Increased permeability of the endothelial barrier and reduced thickness of the glycocalix allows infiltration of lipids, fibrinogen, fibrin and other atherogenic particles into the intima. Uncontrolled uptake of oxidized lipids by macrophages leads to formation of foam cells, which become an integral part of plaque. An increase in production of platelet-derived and endothelium-derived growth factors, stimulates smooth muscle cell migration from media to intima. As a response to numerous cytokines and oxidative stress, smooth muscle cells of the vessel wall transform into osteoblasts participating in the plaque calcification process.

In experimental studies low ESS at inner curvatures are being related to the formation of the vulnerable plaque with thin fibrous cap, rich in cholesterol, but poor in smooth muscle cells [21]. This phenomenon is explained by increased inflammation caused by low ESS compared to oscillatory shear stresses [21]. This means that type of shear stress has an impact on plaque metabolism and its susceptibility to rupture. Hence flow modeling methods in vitro may be extremely useful in studies on the pathogenesis and course of the atherosclerotic process [22].

Multislice Computed Tomography (MSCT) evaluation of coronary artery anatomy, and developments in rheometrics, allows us to apply the more robust CDF technology in cardiology applications. It is assumed that computed simulation of flow conditions should take into account viscoelastic properties of arteries, the variable artery geometry, pulsatile nature of flow and blood non-Newtonian properties. The significant progress of CFD technology and improvement in methods for arteries segmentation based on MSCT dataset mean that modeling of the artery blood flow can be the new research tool in cardiology [23, 24].

The aim of using CFD in cardiology is to create a computational model of the cardiovascular system in order to improve the quality of predicting the progression of atherosclerosis (answer on key question plaque stability, progression and hemodynamic significance).

4. Graft failure

Patients with symptomatic CAD require revascularisation, including implantation of coronary artery by-pass grafts. Over the years, since by-pass grafting there is increasing problems of grafts patency. The key risk factors of graft anastomosis patency is too large width of the by-pass graft and type of anastomosis, which determined shear stress distribution.

Clinical practice shows that graft failure is caused not only by plaque formation at the site of anastomosis but very often by atherosclerotic lesions forming along the course of coronary by-pass graft. There are no differences in failure rate between saphenous vein and radial artery grafts [25, 26].

This phenomenon may be related to the appearance of atherogenic flow (secondary disturbed flows) in the aorto-coronary by-pass similar to that which occurs in the native coronary artery originating from sinus of Valsalva. Unlike by-passes outgoing from the aorta, the IMA conduits are resistant to atherosclerosis and are rarely the subjects of closure [27].

In comparison to aorto-coronary by-pass, flow velocity profile in IMA is more stable. It can be assumed that lack of secondary flows and high shear stress are the reason why IMA by-passes are resistant for atherosclerosis [28].

Within aorto-coronary vein by-passes the flow velocity profile is far different. In protodiastolic phase, blood velocity reaches maximum velocity, while at its ending it suddenly slows down, which contributes significantly to forming atherogenic secondary flows in the late diastole.

It may be assumed that venous by-pass implanted for example to subclavian artery instead of aorta, will reveal more stable flow, and it can prevent atheroma formation [1] This type of vascular conduits may be an alternative for by-passes implanted to the aorta, however, there is no experimental or CFD research data revealing benefits of such surgical technique. Coronary by-passes imaging with MSCT and CFD technology may significantly contribute to the understanding of, why aorto-coronary by-passes are atherosclerotic-prone and IMA by-passes are atherosclerotic-resistant.

5. Hemorheology

Hemorheology plays an important role in atherosclerosis. Rheology research allows for determining an appropriate rheological model of blood for its use in computer simulation. Non-Newtonian properties of blood become significant in the zones of disturbed flows, which should be considered in the CFD simulations [29, 30].

Blood rheology has been more difficult to accurately study than other risk factors for cardiovascular disease, explaining why it may be an overlooked factor in our understanding of cardiovascular disease. Rheology of blood depends largely on fibrinogen concentration and hematocrit [31].

The increase in blood viscosity is not relevant at laminar flow (high shear stress), but at risk vascular points of disturbed and oscillatory flow, rheological properties of blood (in particular shear-thinning and yield-stress) hemorheological abnormalities increases the blood residence time near by the vessel wall. Therefore increases in fibrinogen concentration favor the retention and penetration of blood borne atherogenic particles into arterial wall. This phenomenon plays an important role in vascular biology and is an important mechanism in the atheroma formation. Measurement of fibrinogen concentration, hematocrit value and blood viscosity as a function of shear rate must be taken into account when modeling the flow.

A number of researchers measured blood viscosity in patients with CAD, diabetes and myocardial infarction [32–36]. They found that the viscosity of whole blood might be associated with CAD. The hemorheology is now entering a new phase of acceptance with the development of new instruments which, unlike conventional rheometers, easily and accurately determine whole blood viscosity as a function of shear rate, as well as red blood cells deformation and aggregation by laser light scattering technique [37].

6. Conclusions

The initiation and progression of atherosclerosis are determined by a complex interplay between the main risk components: geometric, hemodynamic, hemorheological, and mechanical. The participation of each of them has an impact on plaque progression, stability or vulnerability. CFD is a well-established tool for the simulation of flow fields existing in real complex vascular geometries. The high image quality (MSCT), excellent contrast opacification of the coronary arteries makes CFD as excellent tool for the ESS noninvasive evaluation. The growing understanding of the biomechanical processes responsible for atherosclerosis might allow CFD to aid early identification of a high-risk coronary plaque and thereby provide a rationale for innovative diagnostic and/or therapeutic strategies for the management of coronary patients and prevention of acute coronary syndromes, and planning revascularisation procedures (stent implementation or coronary artery by-pass grafting).

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