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Medical Sciences

Blood Flow Biomechanics and Initial Factors for the Atherosclerosis Development

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ABSTRACT. It is accepted now that hemodynamic forces are the localizing factors in atherogenesis, but conclusions about the reasons of the vessel wall damage are inconsistent. The purpose is to study and reveal the initial factors of atherogenesis in the aortic arch. 25 men from 17 to 45 years old have been investigated by Ì R angiography on Siemens-Avanto.

In the aortic arch at the time of protodiastole the blood flow is separated into opposite directed streams and the flow arrest with the flat flow profile is noted in discrete sites of the aorta. Blood protodiastolic acceleration is 6 times higher than that in the systole, and shear stress exceeds the verge of the endothelial endurance.
The circular blood flow at the aortic arch in protodiastole is characterized by high acceleration, and the local pressure in flat profile can damage internal layer of the vessel. *© 2007 Bull. Georg. Natl. Acad. Sci.*

Key words: *atherosclerosis, shear stress, blood flow separation, magnetic resonance angiography.*

1. Introduction

Recent advances in basic science have established a fundamental role for inflammation in mediating all stages of atherosclerosis from initiation through progression and, ultimately, the thrombotic complications.

Numerous pathophysiologic observations in humans and animals led to the formulation of the response-to-injury hypothesis of atherosclerosis. The most recent version of this hypothesis emphasizes endothelial dysfunction rather than denudation. Whichever process is at work, each characteristic lesion of atherosclerosis represents a different stage in chronic inflammatory process in the artery. If unabated and excessive, this process will result in an advanced, complicated lesion. Possible causes of endothelial dysfunction leading to atherosclerosis include elevated and modified LDL; free radicals caused by cigarette smoking, hypertension, and diabetes mellitus; genetic alterations; elevated plasma homocysteine concentrations; infectious microorganisms and combinations of these or other factors. Regardless of the cause of endothelial dysfunction, atherosclerosis is a highly characteristic response of particular arteries [1,2].

The localized deposition in susceptible zones of the arterial tree is relatively constant and predictable. At the carotid bifurcation, the flow divider is usually spared from lipid deposition in 85% of patients reported in literature. The carotid sinus opposite the flow divider, the preferential site of the lipid deposition, is characterized by oscillatory levels of the wall shear stress, recirculation zones and increased particle residence time. Another important site of deposition of intimae thickening is the end-to-side vascular-bypass graft. These regions of intimae thickening correspond to the regions of the flow oscillation and a relatively low wall shear stress. Wall thickening appears to be the ultimate outcome of any arterial modification due to altered flow patterns [3,4].

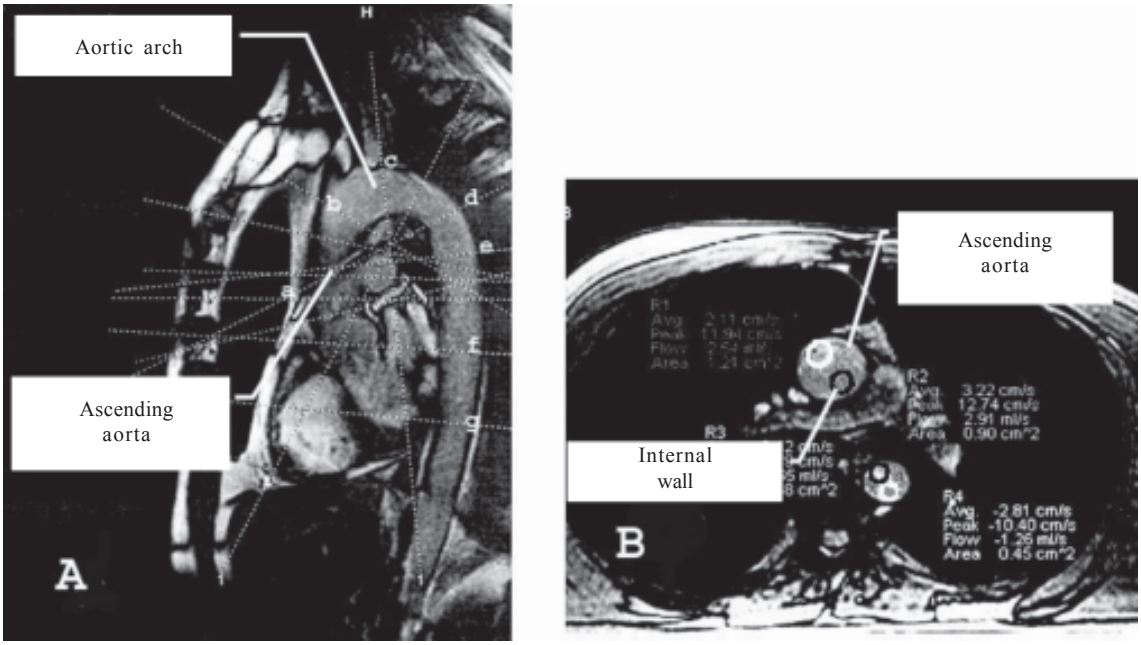

Fig. 1. Sites of measurement of the blood flow in the aortic arch. Dotted lines (a…g.) indicate the imaged slices at different walls of the aorta (Darken circle- internal wall.). Sagital view-1A. Axial view-1B.

New technological innovations enable to build volumetric-parametric models of blood flowing in straight and curved tubes as much as possible resembling the natural process, though a part of these changes is not absolutely clear and creates difficulties in understanding the atherosclerosis development [5].

The purpose of the research is to study the characteristics of the blood flow in the aorta and in the field of the vascular bifurcation by means of magnetic resonance angiography (MRA).

2. Subjects and Methods

25 healthy men aged from 17 to 45 years have been investigated by Magnetic Resonance Angiography (MRA). The phase images were carried out using Siemens-Avanto device. 1.5Ò. fl2D, TR-24.6msec, TE-1.5msec, FoV-348*360, SL6; TR-47ms, TE-2.7msec. TA 19.30, FoV.292*360. SL6.

The imaging was performed with the inspiratory breath hold and ECG triggering. The research of hemodynamic parameters (mean and peak velocity, the mean and net flow) was carried out in different sites and the opposite walls of the aortic arch with the area ≈0.7cm^2 (Fig. 1). Considering technical difficulties of the MRA research of the blood flow in the large arteries, the aorta was selected as the object of the research with typical zones of the flow and wall shear stress. The authors experienced radiologists reviewed all the data of the Siemens MRI flow quantification techniques at random.

3. Results

MRA data of the blood flow are given in Figs. 2,3,4.

For the general explanation of the data obtained, it is necessary to specify that the blood flow profile at the aortic arch is deformed. It is due to the presence of the additional centrifugal force during the circular movement of blood and formation of different velocities of the blood flow at the opposite walls of the vessel (Fig.5A). These changes can be observed precisely during the peak systolic velocities.

At the entrance of the ascending aorta the systolic velocity increases at the site of the external wall (Fig.2). In the central part of the aortic arch, the blood systolic flow velocity is increased at the internal wall (Fig.3).

At the circular movement the direction of the velocity vector is always tangential. At the isthmus area the circular blood flow passes rectilinearly, and at the entrance to the thoracic aorta high systolic velocity on the external wall is noted (place with high accidence of the fatty lines and aortic dissection) (Fig.4).

4. Discussion

Influences, to which arterial walls are exposed, are not identical.

The arterial wall integrity depends, mainly, on the maintenance of normal levels of two components in the large arteries: 1. The wall shear stress (approximately 1.5N/m^2), tangential to the wall. 2. Tensile stress (approximately 100-200N/m^2), normal to the wall.

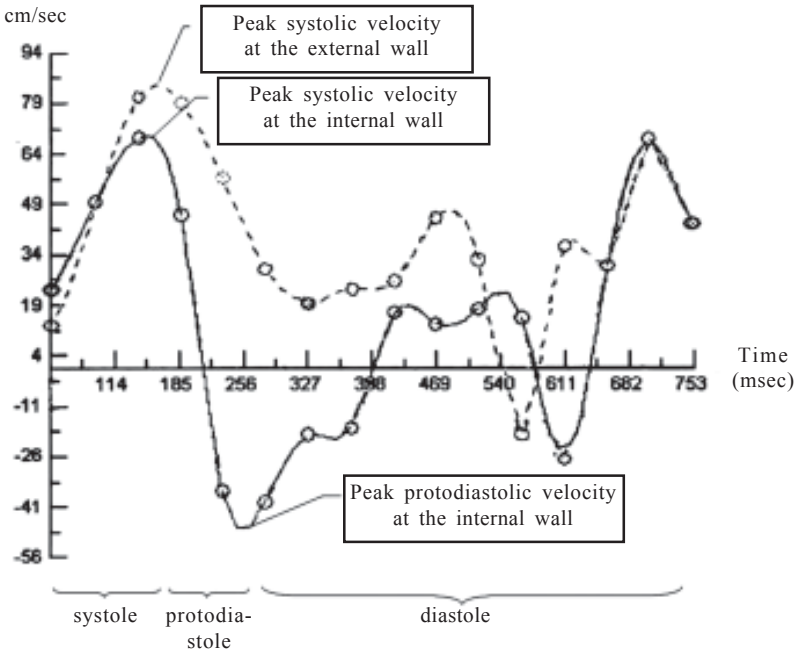

Fig. 2. The peak systolic velocity at the ascending aorta. (Dotted line - external wall). The blood flow acceleration to the retrograde direction at the internal wall exceed 3 times the external one (closing of the aortic valves at 256msec).

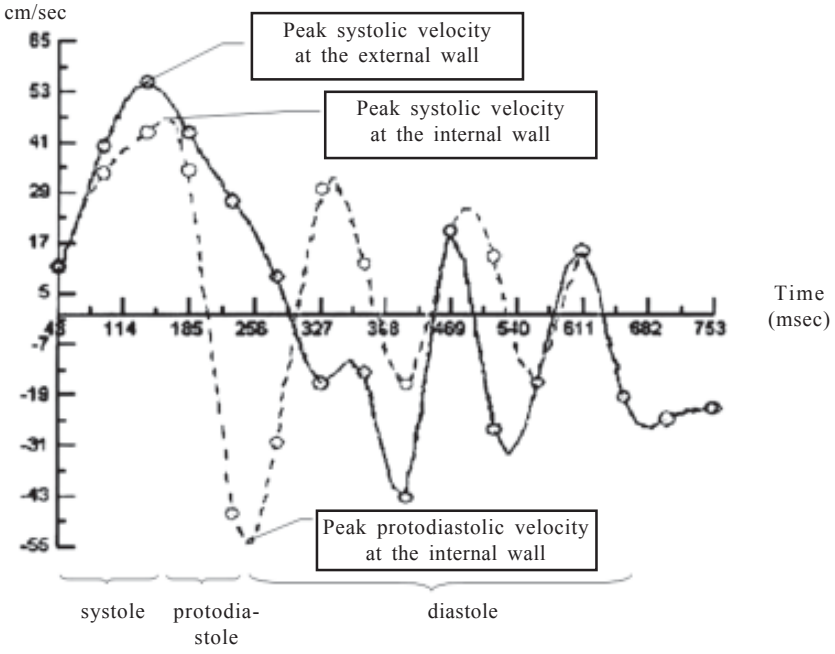

Fig. 3. Peak velocity graph at the central part of the aortic arch. (Dotted line - external wall). Blood flow flat profile at 300msec. Flow velocity 5-7cm/sec. Protodiastolic antegrade acceleration at the external wall 5 times higher than at the internal wall. At 360-700msec blood flow is pendulum like.

The endothelial cell "feels" the tangential stress more than the tensile stress, even if the former is of smaller magnitude. It is established that the wall shear stress, exceeding $40N/m^2$, can damage the endothelial cells. However, according to the references, the wall shear stress in blood vessels is much less than the specified level [6,7].

It is specified that in the presence of completely advanced stream of liquid in a straight pipe with the diameter (d), peak systolic velocity (v), viscosity of blood (μ) and at the flow frequency parameter (Womersley (α)), the amplitude of fluctuations of the wall shear stress is:

$$\vec{\tau} = 2\vec{\alpha}\mu\vec{v}/d.$$

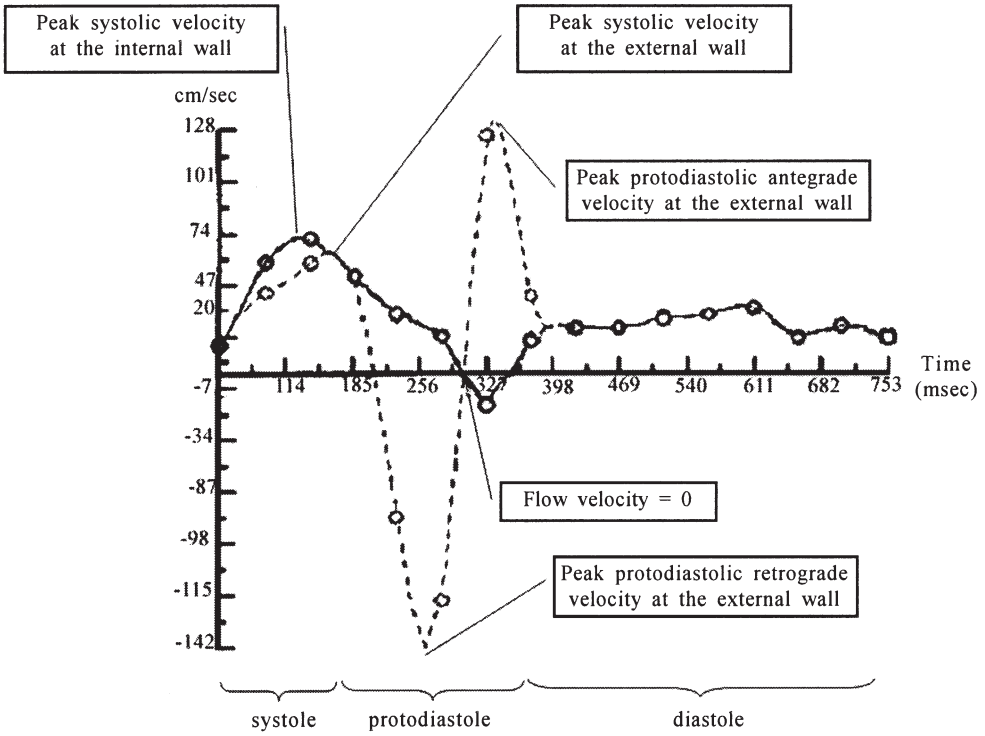

Fig. 4. Peak velocity graph at the isthmus area. (Dotted line-external wall). At 300ms flow velocity = 0, flow profile is flat. Protodiastolic flow acceleration is 6 times higher than that at systole and pressure can damage the internal layer of the external arterial wall. The initial zero velocity with the subsequent high acceleration in protodiastole is marked at the ascending aorta and isthmus area – places where direction of the flow velocity is changed from straight to circular and vice versa.

In the systole peak velocity at the external wall in the isthmus area $v_{sys} = 0.60$ m/s (it is lower than at the internal wall 0.75m/s), $\tau_{sys} = 3.85$ N/m^2, while at the same place the protodiastolic peak velocity is v_{pr}=1.42m/sec (diameter of the separated streams is at least 2 times lower than the aortic diameter), $\tau_{pr} = 18.18$N/m^2 (according to our MRA data, at the ascending aorta $\tau_{sys} = 5.38$N/m^2, at the external wall of the central part of the aortic arch $\tau_{pr} = 7.04$N/m^2).

The hypothesis about the pathogenesis of atherosclerosis in places with a low shear stress seems to be less realistic. It seems impossible that the permeability of the endothelial cells depends only on the systolic low shear stress, while its peak values in protodiastole can be much higher. In our research, the damage of the vessel wall occurs not at the peak velocity, but at the initial stage of the protodiastolic blood movement.

To explain the question it is necessary to specify that the equation for each element of moving liquid is determined as:

$$m\vec{a} = \vec{F}_v + \vec{P} + \vec{F}, \qquad (1)$$

where

m - mass of each element of the moving liquid

$\vec{a}$ - flow acceleration

$\vec{F}_v$ - viscous force (shear stress/adhesion)

$\vec{P}$ - mass force (weight)

$\vec{F}$ - local pressure.

The weight can be neglected in the horizontal position of the vessel.

In this case, acceleration is directly proportional to viscous forces and local pressure:

$$m\vec{a} = \vec{F}_v + \vec{F}. \qquad (2)$$

Taking into account the pulsing character of the blood flow, it should be noted that the direct movement of blood in the ascending aorta starts at the moment of opening the aortic valves together with the blood pumping from the ventricle. The blood flow increases rapidly to the peak value and then decreases sharply; the phase of the retrograde blood flow – protodiastole develops and promotes closing the aortic valves with a subsequent sharp increase of the antegrade blood flow. For an adequate heart beat, the closing of the aortic valves should take place faster (≈0.07sec) than the systolic length (≈0.2sec). It causes high local pressure and acceleration of the blood flow in protodistole.

Not the whole blood mass flows simultaneously to the retrograde direction, but only its part with low systolic velocity: the flow is separated into two unequal parts (Figs. 2, 3, 4).

In the initial stage of the protodiastole fluctuation period for the opposite separated streams is different (for antegrade waves the period is two times less) and waves can interfere. Beside this, for the spiral form of the aortic arch (and heart deformation in systole), separated streams have different directions and thus streams do not resist each other.

After the closing of the aortic valves, fluctuations period and flow direction for the streams gradually become identical: at the changing of the blood shear velocity (and viscosity) the length (or period/frequence) of the fluctuated waves varies (Figs. 3,4.).

To explain the blood flow interaction with the vessel wall, it is necessary to indicate that in specified sites of the vessel wall (isthmus area) in the protodiastole, the opposite flowing streams momentarily arrest each other (Figs. 5B, 4). At the zero velocity the flow profile is flat. These zones have similar patterns to the flow entrance region: the boundary layer is thin, the flow velocity has a flat structure - all parts of the blood move with an identical shape.

Taking into account the parabolic form of the blood velocity curve, at the initial stage of the movement low acceleration can be specified. When acceleration comes nearer to zero (peak/0 velocity) the equation (2) can be written down in the following way:

$$\vec{F} = -\vec{F}_v. \qquad (3)$$

It is known that at the entrance region before the liquid flow the level of the local pressure is much higher and sharply decreases at the time of the formation of the completely developed stream. Thus, for the external wall of the isthmus area the local pressure just before the protodiastolic antegrade flow must be much higher than $18.18 N/m^2$.

Initially high local pressure is equally transferred in all directions, including to perpendicular(tensile stress) and tangential(shear stress) directions. High local pressure at the places with the reduced flow velocity provides high adhesion of the blood elements to the endothelian sheet. Adhesion is calculated from the superficial tension. High adhesion is shown in blood viscosity, which rises more than 80 times when the shear velocity is less than $0.1 sec^{-1}$.

Influence of the local pressure to the vessel walls is not identical and especially is evident at the external wall of the isthmus area where flow (mean) acceleration 6 times exceeds systolic [8].

For high viscosity in the initial stage of the flow blood could not “break up” in sliding layers. Stream division in sliding layers begins with the external surface. In this position, high local pressure is resisted with adhesion (equation 3), which is initially high, and it is more plausible to discuss the endothelial denudation, than the sliding of the blood layers: the superficial endothelian membrane is shifted together with the flowing blood (Fig.5B).

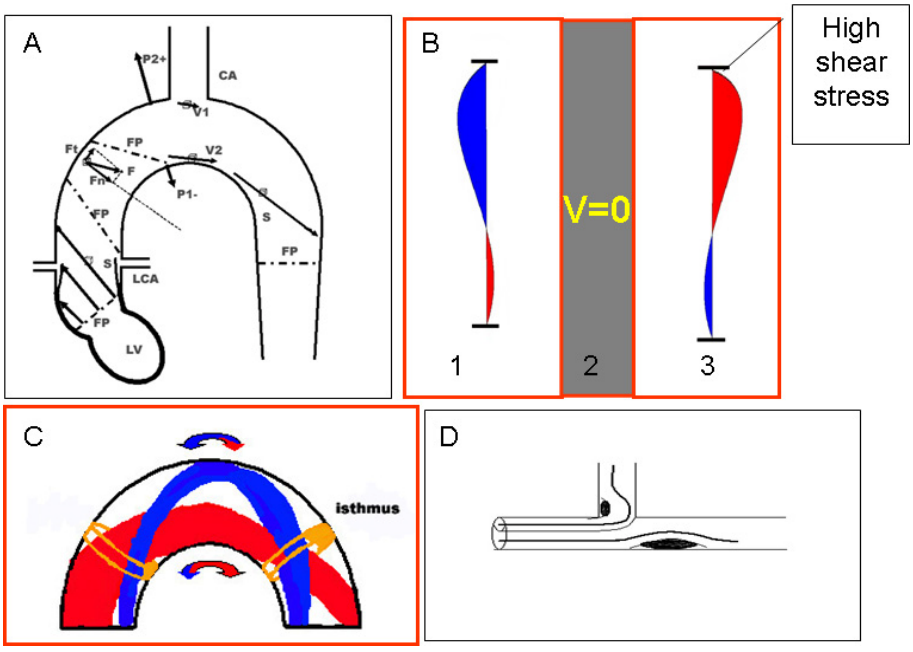

Fig. 5. A. Blood flow in the aortic arch. V1-V2- flow velocity, P1-P2- blood local pressure at the opposite wall; Fn, Ft- normal and tangential pressure; S- places with separation of the border zone and recurrent flow in systole.; LV-left ventricle; LCA-left coronal artery; CA- carotid artery. B. Evolution of the flat flow profile and high shear stress in protodiastole. (External wall of the isthmus. 1,3 just before and after the zero flow velocity). C. Separated blood stream, directions in protodiastole and places with the flat flow profile. D. Blood flow at the places of the arterial bifurcation. (Retrograde direction- bold darkens).

Confirming the above, it is possible to conclude:

1) Superficial tension of ethanol is 4 times lower than water. Ethanol can be freely diffused in the blood and endothelian membrane. In subjects abusing ethanol, atherosclerotic changes in aortic wall are less expressed.

2) In a small circle of blood circulation the venous blood is mixed with lymph that can condition the reduction of the blood superficial tension (contains superficially active substances - bile acids), and atherosclerotic damage of the vessels in a small circle is not observed.

3) High arterial pressure promotes atherosclerotic changes of the large arteries.

The exclusive position for the vessel damage, external wall at the end of the aortic arch, is specified by the inversion of the flow direction for the opposite flowing streams with the changing flow direction.

A similar character of the blood flow can be marked in the sites of the arterial branching (Fig.5D).

Arterial pulsing (beside the muscle and breath movement) is a necessary factor for the extracellular liquid promoting. The pulsatile blood flow in the large arteries promotes the distal transport of the blood mass by the updating length of the boundary layer:

1) The blood flow systolic acceleration is high. At high flow velocity in the vessel there is no space for the completely advanced stream formation (it is a therapeutic effect of glycosides):

The length of an entrance region X=0.03d (Re), where Re=vdρ/μ (provided that diameter - d=2.5cm and Reynolds's number in the initial part of aorta is not less than 2500. X=187.5cm at a real length of aorta ≤ 60cm). The evaluation of the blood flow in the large arteries is formed from the branching sites. The blood flow in the aorta and large arteries has the character of the entrance region.

2) The cone-shaped form of the aorta and large arteries promotes the reduction of the boundary layer.

At the initial stage of fast emission of the blood in aorta the arterial pulse is formed - an oscillatory pressure wave running in a distal direction in the arterial wall. The pulse pressure velocity is 5-10m/sec, and approximately 5-10 times exceeds the blood flow velocity. In the blood and arterial wall pulse pressure velocity lowering blood viscosity and the shear stress to the vessel wall are different. To confirm this it is possible to specify:

1) The frequency of pulse fluctuation and flow shear velocity are measured in identical units - (sec^{-1}), and they are proportional. At the shear velocity greater than $1.0sec^{-1}$ viscosity sharply decreases. The frequency of the pulse fluctuation basic harmonic in aorta is $1.2sec^{-1}$.

2) The Womersley - α number shows how strongly the structure of laminar flow velocity in a long pipe from the Puaseil flow differs when the liquid is exposed to the influence pressure with angular frequency þ:

$$á = d/2\sqrt{þ\,ρ/μ}$$

The Womersley parameter can be presented in another form: the size $á^2$ is equal to the relation of the time during which the viscous forces action is distributed to the whole width of the vessel section ($d^2ñ/4ì$), for the period of fluctuation ($1/þ$), i.e. the faster the pressure wave covers the whole diameter of the vessel the higher Womersley parameter is. For vessels of different diameters it is equal to: ascending aorta - 13.5, abdominal aorta - 8, carotids - 4.4, a femoral artery - 3.5, arterioles-0.04, capillaries-0.005, i.e. in large arteries, outstripping the blood flow, the pulse pressure covers the vessel volume faster, promoting reduction of blood viscosity.

3) The above-stated physiological aspects of the blood flow are lawful for the whole area of large arteries, except for those where the pulse pressure does not outstrip the blood flow. Such places are: a) free edges of the aortal valves in systole (those places simultaneously formed blood flow and arterial pulse), b) isthmus area of the aorta and areas of the arterial branching in protodiastole.

Morphologically it is confirmed that the initial sclerous changes in the child are marked just in the field of free edges of the heart valves, the external wall isthmus area in the aorta and the opposite side of watershed of the large arterial branchings.

Unlike others, in the left coronary artery, the blood flow begins in protodiastole and preliminary pulse is not presented.

Damage of the erythrocytes does not take place, since the threshold size of a shear stress for their membranes is 200-300 N/m^2.

Cellular membrane cholesterol is the natural phenomenon in eukaryotic alive essences. Formation of the atherosclerotic plaque can be an adaptable reaction and is caused by the necessity of increasing the stability of an endothelial superficial membrane in the above-stated mechanisms of the blood flow since: according to the Laplace law the wall superficial tension - F in the cylindrical vessel is directly proportional to the pressure inside the vessel - P and the radius - r (F=Pr/2). At zero velocity, the kinetic energy of the blood flow passes into potential energy, the vessel extends and area/superficial energy of the endothelial sheet/membranes rises (for the prevention surfaces in pulmonary alveolas are covered with the superficial active substances – surfactant). The area also is increased by the shear stress at the initial stage of the blood flow.

However, according to the thermodynamic law, all the spontaneous processes proceed with the reduction of the free (superficial) energy. In the cases of increased tensile and shear stress the sclerotic site reduces the superficial energy of the vessel wall.

The formation of the lipid strips, fibrosis and calcinosis of the vessel wall should be considered as the adaptive response of the body to stressful factors of the blood flow: at the initial stage, cholesterol determines the stability of the endothelian membrane; in cases of the weak stabilization, fibrosis→calcification→ stenosis of the vessel is formed, which changes hemodynamic factors at vessel wall. On the endothelian membrane, wave length in the pulse pressure and fluctuating ions CO_3^{-2} in PO_4^{-3} are identical.

In the evolutionary line of vertebrates, the aortic arch can be caused by the following factors:

1) Aortic arch promotes the flow spectral disassembly by the velocity, flow separation and fast closing aortic valves in the protodiastole with the filling of left coronary artery (Figs. 5A, C), in which the systolic blood flow is not present.

In confirmation to this circular movement of blood determining factor for the filling coronary arteries, the presence of left sided aortic arch in birds can be noted (in mammalian – right sided aortic arch). It can be caused by the fact that the blood flow in the right coronary artery in a bird demands additional expenses of energy: in flight the respiratory mussels are strained, and the filling of the lungs with blood demands hard work of the right ventricle.

2) At the circular movement the blood pressure on the external wall is higher than on the internal (aortic arch, cavernous siphon, subclavian artery). Large vessels are branching from the aortic arch on the external wall and irrigate those organs, which can be lifted to the above horizontally located aorta in birds, mammals (the unilateral aorta and an experimental atherosclerosis are formed only in them), and require pressure to be higher.

5. Conclusion

The aortic arch, being a secondary activator of the blood flow, duly promotes transportation of the blood in all the vessel directions, but in hemodynamic transient moments damages the vessel wall. Similar features of the blood flow can be found in the sites of the arterial bifurcation.

The function of the mammalian arterial endothelium is on the verge of endurance, and the course of time (≈0.5msec periods with high stress 30.10^6 per year) promotes organic pathology of the vessels.

A sclerotic change of the vessel wall with arterial stenosis is an adaptable mechanism against the flow shear stress and warns the vessel of the subsequent functional and structural damage.

The presence of the shorter TR MRI pulse sequences will improve specification of the development of new methods for the atherosclerosis treatment, including:

a) Use of substances lowering the superficial tension of the blood and endothelian sheet.

b) Vessel stents with materials having resonance frequency 1.2Hz.

c) Presystolic vibration of the damaged arterial places.

It is impossible to completely exclude influences of the shear stress to the vessel wall, since a significant reduction of the superficial tension promotes infringement of the cellular membrane metabolism.

სამედიცინო მეცნიერებანი

სისხლის დინების ბიომექანიკა და ათეროსკლეროზის განვითარების ინიციალური ფაქტორები

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დღეისათვის ათეროსკლეროზი განიხილება როგორც არტერიის ქრონიკული ანთებითი დაავადება. ჰემოდინამიკური ძალები მხოლოდ ლოკალიზაციური ფაქტორებია დაზიანების კერის ჩამოყალიბებაში. ათეროსკლეროზული დაზიანების ინიციალური ფაქტორი დადგენილი არ არის.

შრომის მიზანს შეადგენს ჰემოდინამიკის თავისებურებათა შესწავლა აორტის რკალში და ათეროგენეზის შესაძლო ინიციალური ფაქტორების გამოვლენა.

მაგნიტურ-რეზონანსული ტომოგრაფიით (Siemens. MR-Avanto) შესწავლილ იქნა 17-დან-25 წლამდე 25 ჯანმრთელი მამაკაცი.

გამოვლენილია, რომ პროტოდიასტოლის პერიოდში სისტოლური დინება იხლიჩება ორ ურთიერთ-საწინააღმდეგო ნაკადად. დიასტოლის საწყის ეტაპზე ნაკადთა ურთიერთდაპირისპირების დროს ყალიბდება ბრტყელი ტალღა ნულოვანი სიჩქარით. დინების შემდგომი აჩქარება 6-ჯერ აღემატება სისტოლურს. ნულოვანი სიჩქარის დროს დინების კინეტიკური ენერგია ტრანსფორმირდება არტერიის კედლის პოტენციურ ენერგიად. მაღალი ლოკალური წნევა განაპირობებს კოლოიდური მასის ადჰეზიას სისხლძარღვის კედელზე და შემდგომი დინების დროს ენდოთელიუმის დენუდაციას, რაც არტერიის ათეროსკლეროზული დაზიანების მიზეზია.

მიღებული შედეგები საშუალებას იძლევა განისაზღვროს ათეროსკლეროზის მკურნალობის ახალი გზები, რომელიც მაქსიმალურადაა დაახლოებული ფიზიოლოგიურ მოვლენებთან ადამიანის ორგანიზმში.

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