ENDOTHELIAL FUNCTION WITHIN ADOLESCENTS WITH CARDIOVASCULAR RISK

Endothelial function within adolescents with cardiovascular risk

Cardiovascular diseases represent the major medical and social problem. The main idea of this article was to estimate the earliest markers of vascular system injury. Endothelial function among teenagers with arterial hypertension and dyslipidemia were studied by ultrasound method, and von Willebrand factor was determined in blood. Endothelial function was changed in 46.9% of persons. Various characters of disturbances of endothelial functions were revealed.

Key words: Endothelial function, adolescent, cardiovascular risk, ultrasound research, von Willebrand factor.

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Introduction

Cardiovascular diseases represent cardinal medical and social problem that is conditioned by their big prevalence and they take the lead position in the structure of mortality in adult population, as well as they are considerable indicators of disability. Undoubtedly, it is necessary to search for the origin of the given pathology in children and adolescents; many population studies including Muscantine Study, Bogalusa Heart Study, “Know your body” program, indicate on this (Dawson et al., 2009; Urbina et al., 2009). Here inherited factors play essential role as well as modified factors, such as low physical activity, obesity, smoking and others disturbances. Revealed in children and adolescents, these factors are traced through the whole life (“tracking hypothesis”).

It was established that in various cardiovascular diseases in adults (such as arterial hypertension, atherosclerosis, IHD, heart failure) endothelial dysfunction (ED) appears as one of the leading pathogenesis mechanisms of vessel wall injury (PIVUS research, see e.g. Barton, 2010; Lind, 2006). ED represents disbalance between the production of vasodilatating components (such as prostacyclin, nitrogen oxide, fibrinolytic factors, and endothelial hyperpolarizing factor) and vasoconstrictive components as endothelin, superoxide anion, synthesized by the vessel’s wall (Vita and Keaney, 2002). The studies of ED in children and adolescents as early marker of a cardiovascular pathology are occasional (Mimoun et al., 2008; Yilmazer et al., 2010). Many authors (Giannotti and Landmesser, 2007; Mannucci, 1998; Mimoun et al., 2008), comparing prevalence of ED in age aspect, have revealed increase in disturbances from 8% at persons of 15-year-old age to 53% among the elderly people. Authors showed an increase up to 28% in the frequency of ED within adolescents having an arterial hypertension. The results received by Whincup et al. (2005) confirm on the presence in teenagers of correlation between ED, defined on a brachial artery (BA), and indicators of diastolic pressure, levels of the cholesterol and LDL in adolescents age. Jolliffe (2007) testsifies that disturbance of this function definitely can be considered as a marker of early injury of target organs in arterial hypertension among teenagers.

It is necessary to notice that there are various techniques of evaluation of ED. Tool methods include research of peripheral blood-flow by a tetrapolar rheovasography, ultrasonic Doppler research of a blood-flow in a BA and by carrying out various tests
(cold test, nitroglycerine test and other) (Kamran et al., 2010; Mannucci, 1998). Laboratory methods define the substances synthesized by endothelium and a vessel’s wall (Von Willebrand factor (vWF), endothelin, prostacyclin). According to some researches (see, e.g., Kamran et al., 2010) ED in a BA in adults closely depends on atherosclerotic injury of coronary arteries; this fact allows us to use it as model for noninvasive studying of atherosclerotic process, especially at early stages of its development. As a whole, works of the last years convincingly show that ED can be objectively estimated by the means of ultrasonic flow-mediated dilatation (FMD) on endothelial dependent vasodilatation of BA and that is adequate model for endothelial condition studying.

Recently concentration of vWF has been used for the first time as one of the laboratory markers of ED. The hypothesis is based on observation that patients with a peripheral atherosclerosis have a raised level vWF and degree of its increase correlates with prevalence of vessels injury. Further relation of increase in blood vWF concentration and rate of endothelial vessels damage has been proved in a number of experiments in the models of endotoxemia and endothelial mechanical damage. According to some sources, absence of vWF animal’s blood coincides with inability to develop an experimental atherosclerosis. Factor of Willebrand is glycoprotein, synthesized by endothelial cells and circulating in blood in concentration of 10 mkg/ml (Woodward, 1997). In plasma it forms a non-covalent complex with VIII clotting factor. This complex is necessary for stabilization of VIII clotting factor in a blood-flow and further participation in formation of a blood thrombus and its protection from proteolytic inactivation (Mannucci, 1998). Another important function of vWF is forming a platelet blood thrombosis in endothelial damages by sheaf formation between subendothelium and platelets. In a usual condition the basic quantity of the circulating vWF has endothelial origin; however, activation of platelets can lead to increase of their concentrations in blood-flow of thrombocytes pool. The vWF is discharged by endothelial cells inside a blood-flow (supporting concentration in plasma), and aside in subendothelial space, where it joins with a structure of extracellular matrix. Two types of secretion of this factor are distinguished: supporting and fast. Fast secretion is carried out by releasing from special organelles - little Weibel-Palade bodies. The trigger’s of such secretion are hemostatic coagulating (thrombin, plasmin, fibrin) and inflammation factors (histamine, complement’s components C5a and C5b-9, leukotriene, superoxide anion, endotoxin, IL-1,4 and other). Besides, fast, short-term increase in the vWF level is caused by adrenaline, vasopressin, desmopressin injection, physical activity, hypoglycemia and venous occlusion. Its slow and long observable increasing takes place in acute coronary syndromes, hepatic cirrhosis, in postoperative period, oncological diseases, pregnancy, diabetes, hemolytic anemia’s (Mannucci, 1998).

Thus, the data presented in the literature, show that the vWF level in blood is experimentally and clinically verified marker of ED, allowing to estimate the presence and degree of expressiveness of disturbances in functional endothelial condition at various internal diseases and particularly in cardiovascular diseases.

The research of endothelial function was made to search the earliest markers of vascular system damage among adolescents in cardiovascular groups of risk. Research problems included assessment of ED by means FMD ultrasonic test and by evaluation of vWF levels among teenagers with an arterial hypertension, dyslipidemia and in control group.

**Methodology and tools**

Complex clinical, instrumental and laboratory research is executed among 81 adolescents (middle age 15.78±0.30 years). Among them, there were 18 adolescents with an arterial hypertension, 43 adolescents with dyslipidemia, and 20 persons comprised control group. The demographic characteristic of investigated groups is presented in Table 1. It is necessary to notice that the group of persons with dyslipidemia was homogeneous. 15 adolescents had laboratory manifestation of insulin resistance and a forming metabolic
syndrome in background on obesity; 28 adolescents had the burdened heredity of atherosclerosis. Estimation of physical development was made recording to the age and sex on percentile tables with use of criteria of adiposity in teenagers depending of body mass index on Obesity Education Initiative BMI Calculator (1994). For diagnostics of a metabolic syndrome among teenagers the international criteria (Jolliffe, 2007) were used. The diagnosis of an arterial hypertension has been verified by means of monitoring blood pressure (BP) in circadian period, according to classification and criteria of a hypertension at children and adolescents (Lind, 2006; Urbina et al., 2009). All patients were made lipid spectrum research using standard technique with definition of the cholesterol, triglycerides, lipoproteins spectrum in blood. In group with excess weight it was defined fasting concentration of glucose in blood, it was carried out oral glucose tolerance test (OGTT) for a diabetes exception.

Endothelial function was estimated by means of carrying out ultrasonic FMD tests according to technique described by Sorensen et al. (1994). Arterial pressure was measured in an initial condition, after 5 minute rest in a prone position. Then diameter of the BA (d1) and the maximum linear speed of a blood-flow (V1) in it were defined. Then five-minute vessel occlusion was made by compression of a shoulder using cuff sphygmomanometer, visualization of a vessel imposed above a place, and reaching a pressure exceeding initial systolic BP by 50 mm hg. Right after release of air from a cuff during first 10-15 seconds, speed of a blood-groove (V2) was measured in the BA, and through 60 sec - its diameter (d2). Diameter of the BA measured on internal border of adventitia. Later flow-dependent dilatation was counted (percentage BA diameter increase, d, %). Similarly, the degree of increase in speed of a blood-flow (increase V, %) was calculated. Vasodilation more than 10% from initial diameter is considered to be normal reaction of the BA, while vasodilatation less than 10% or vasoconstriction is considered as the pathological. The received results in each group were compared among themselves and to control group.

In 38 persons the FMD research revealed disturbances of flow-dependent dilatation in BA. vWF level was defined using ELISA method. The blood sampling was made by venepunction in horizontal position; the sampling was carried out without syringe use. Blood centrifugation was transferred to a plastic test tube for reception of plasma without thrombocytes. The reactant for definition of vWF represented the carrier of a firm phase covered with monoclonal antibodies against vWF. The research principle combined two-step-by-step ELISA analysis. The result was automatically counted by device according to a curve control.

Statistical processing of the received results was delivered using standard methods. The quantitative data is presented in the form of M±m. Statistical reliability was applied at Р <0.05.

Results and discussion

The laboratory-instrumental examining in patients of the above-stated groups has been revealed number of differences (Table 1) in a condition of vascular hemodynamics. FMD in group of healthy children and adolescents (control group) has found maximum gain of diameter of a vessel (to 11.61±2.65%) in comparison with other compared groups (Р<0.05); this result corresponds to satisfactory elastic properties of a vascular wall and absence of impairment of endothelial function.

It is necessary to notice that reference values of diameter of a vessel (d1) in the given group have appeared as minimal in comparison with other groups (Р<0.05) that was possibly caused by normal values of arterial pressure and absence of a vascular pathology. The tendency of increase in speed of a blood-flow is noted. Values vWF corresponded to hematological norms and averaged between 73.38±6.65%.
In group of adolescents with an arterial hypertension it is noted authentic (P<0.05) increase in diameter of a vessel in initial condition (d1) on 26.1% (in comparison with control). Thus, speeds of a blood-flow both before and after FMD running tended to decrease in comparison with control group. Elastic and vasodilatation properties of vessels appeared to be broken that was demonstrated by considerable decrease in a gain of diameter of a vessel by 87.9% (P<0.001). As a whole, the frequency of disturbances in vasodilatation functions was noted among 17 (60.7%) adolescents in a given group. This was possibly caused by indicators of physical development: thus, the surplus of body weight (98.82±3.54 kg, in comparison with control group, P<0.001) was revealed. Against a tendency to decrease in a gain of speed of a blood-flow (+56.02±13.52%), it was established authentic (P<0.010) decrease in a gain of diameter of a vessel (+4.62±1.44%) and increase (P<0.001) in values vWF to 106.07±6.28%. This testifies to the mixed impairments, i.e. about superfluous endothelial activation and deterioration elastic properties of an arterial vessel.

Similar dynamics of impairments in elastic properties of vessels and endothelial dysfunction was noted in group with displays of a metabolic syndrome. ED was found...
out in 10 persons (66.6%). The increase of speed a blood-flow appeared maximal in the given group in comparison with others and made +82.48±15.81% that had possibly been caused by physical development of patients. The tendency to decrease in a gain of diameter of a vessel (+6.55±2.69%) was established (P<0.05); and authentic increase in the maintenance in blood vWF to 104.60±5.98% was found (P<0.001).

Among adolescents having the anamnesis of atherosclerotic pathology, authentic decrease in a blood-flow speed (P<0.05) and in diameter of a vessel (P<0.05) against authentic increase in vWF values (106.16±7.23%; P<0.001) was revealed. The disturbances of vasodilatation functions were noted among 17 (60.7%) persons.

Thus, the condition of endothelial function in group having laboratory displays of dyslipidemia differs from healthy contemporaries’ by impairments of elastic properties and ED of arterial walls. Essential and more expressed changes (in comparison with control group) are revealed in persons having the burdened heredity by atherosclerosis that is reflected in considerable decrease in blood-flow speed and diameter of a vessel with concentration gain of vWF in blood flow. Thus, authentic increase in vWF concentration by 1.4 times is the general and distinctive among the patients having dyslipidemia. This testifies to more expressed infringement of endothelial function accompanied by endothelial cells. Such dynamics is possibly caused by change in thrombocyte hemostasis.

**Conclusion**

Ultrasonic signs of endothelial dysfunction among 46.9% adolescents with arterial hypertension, a metabolic syndrome and the burdened heredity by atherosclerosis development are revealed. Degree of the given impairments is maximal within the persons having an arterial hypertension, and is minimal within patients with metabolic syndrome. In cases of metabolic syndrome and within the persons with the burdened heredity by an atherosclerosis, laboratory signs of endothelial dysfunction are presented in the form of concentration increase of the Willebrand factors.

The received study observations suggest possibilities of early revealing of vascular channel damage in the form of endothelial dysfunction. This would contribute to better allocation of risk groups at teenage age to provide early preventive maintenance of injury to target organs.

**References**


