Journal of Siberian Medical Sciences 1 (2017) 3–6

Journal of Siberian Medical Sciences

Journal homepage: http://jsms.ngmu.ru

Endothelial hemostatic predictors of cardiovascular risk in patients with vibration disease in combination with the arterial hypertension

Shpagina L.A.[1, 2], Gerasimenko O.N.[1], Drobyshev V.A.[1]*, Kuznetsova G.V.[1]

[1]*Novosibirsk State Medical University*
[2]*City Clinical Hospital No. 2, Novosibirsk*

ARTICLE INFO

Article history:
Received 11.01.2017
Accepted 12.02.2017

Keywords:
Arterial hypertension
Vibration disease
Endothelium
Hemostasis
Adhesion molecules
Thrombospondin
Fibronectin
Predictor
Growth factors

ABSTRACT

We have investigated levels of vascular endothelial growth factor, thrombomodulin, platelet-derived growth factor BB, transforming growth factor β1, fibronectin, thrombospondin, alpha-2-macroglobulin, fibrinopeptide A, and adhesion molecules in patients with vibration disease (VD), hypertension, and with combination of both diseases.
It has been revealed that the blood serum of VD patients with hypertension has the high content of endothelial cell indicators (vascular endothelial growth factor BB, transforming growth factor β1, platelet-derived growth factor BB, fibronectin, thrombomodulin, thrombospondin, alfa-2-macroglobulin, fibrinopeptide A, and adhesion molecules), which are responsible for the membrane platelet activation, and intracellular synthesis of endogenous proaggregants and thrombogenesis, and that allows us to consider them as early markers of increased cardiovascular risk.

Introduction

Microhemocirculatory violations on the background of vibration disease are to a great extent caused by of endothelial disfunction and hemostasis parameters involved in the remodeling of the vascular wall, and hence in the process of atherogenesis and thrombosis [1, 2]. Increased serum concentrations of platelet-derived growth factor, thrombomodulin, adhesion molecules, transforming growth factor β1, fibronectin, thrombospondin indicates the changes resulted from endothelial dysfunction [3]. Activation of adhesion molecules on endothelial cells is accompanied by the involvement of circulating leukocytes, the development of inflammation (sVCAM-1), adhesion of platelets and leukocytes to the endothelium (sPECAM-1), and accelerating endothelial lesion [4, 5]. More and more attention is paid to increase of plasma P-selectin participating in the development of blood vessel inflammation and hemostasis disorders, as well as monocyte chemotactic factor, which has a definite impact on the proliferation of vascular smooth muscle cells with their secretion of proinflammatory cytokines [6—8]. The study of endothelial cellular early predictors of endothelial lesions and pre-endothelial hemostasis disorders in vibration disease combined with hypertension is an urgent task due to the high incidence of vascular complications of comorbid forms of pathology.

Aim of the Research

The study of early endothelial hemostatic markers of dysfunction of endothelium and hemostatic changes in patients with vibration disease combined with arterial hypertension.

*Corresponding author. Novosibirsk State Medical University, 52, Krasny Prospect, Novosibirsk, 630091, Russia.
E-mail address: doctorvik@yandex.ru

Materials and Methods

The Department of Professional Pathology at the City Clinical Hospital No. 2 in Novosibirsk (the head physician is professor L.A. Shpagina, MD) surveyed 253 male workers, including 116 riveters (45.8%), 28 mechanical fitters (11.1%), 109 labourers not affected by the vibration and noise factor (43.1%).

Exclusion criteria were acute and chronic non-communicable diseases in the acute stage; symptomatic forms of atherosclerosis, coronary heart and cerebral diseases; congenital and acquired malformations of the heart and blood vessels; diabetes.

All subjects were divided into 4 groups: 1st group — 75 patients exposed to local vibration with vibration disease (VD) of I degree, the average age was 47.0 ± 2.4 years, work experience with vibration 15.3 ± 1.4 years; 2nd group — 69 patients exposed to local vibration with VD of I degree in combination with hypertension I–II, risk of 2–3, mean age was 47.6 ± 2.1 years, work experience with vibration — 15.7 ± 1.2 years ; 3rd group — 72 workers out of contact with the vibration and the noise factor, with a diagnosis of hypertension I–II, risk of 2–3, mean age was 46.4 ± 2.8 years; control group — 37 people out of contact with the vibration working in the same enterprise, the average age was 47.5 ± 2.2 years.

VD diagnosis was verified taking into account the characteristics of sanitary conditions of work, working term, the results of complete clinical examination of patients. The diagnosis of hypertension was perfomed in accordance with the recommendations of the All-Russian Society of Cardiology (2010) and European Society of Cardiology (2013). The study was approved by the Local Ethics Committee.

Evaluation of patients included an examination by the physician and pathologist with subsequent laboratory study of endothelial cell markers. To study adhesion molecules we used the method of enzyme linked immunosorbent assay (ELISA) of sandwich type. The study was conducted with the immunoassay analyzer Expert Plus (ASYS HITECH, Austria), the measured wavelength is 450 nm. We used the following ELISA kits: sP-selectin (catalog number BMS219, manufacturer Bender MedSystems, Austria, measuring range 0.06—30.0 ng/ml, sensitivity 0.06 ng/ml); sVCAM-1 (catalog number BMS232, manufacturer Bender MedSystems, Austria, measuring range 2.2—100.0 ng/ml, sensitivity 2.2 ng/ml); sPECAM-1 (catalog number is BMS229, manufacturer Bender MedSystems, Austria, sensitivity 0.06 ng/ml, measuring range 0.06—30.0 ng/ml).

Solid phase sandwich ELISA was employed to study vascular endothelial growth factor (VEGF), transforming growth factor β1, fibronectin, thrombospondin, thrombomodulin, and platelet derived growth factor BB in the blood serum.The study was conducted with the same the Expert Plus immunoassay analyzer (ASYS HITECH, Austria), the measured wavelength is 450 nm. We worked using of the following ELISA kits: VEGF (manufacturer VECTOR-BEST, Novosibirsk, Russia, catalog number A-8784, measuring range 0–2000 pg/ml, sensitivity 10 pg/ml); PDGF-BB (catalog number DBB00, measuring range 15–2000 pg/ml, analytical sensitivity 15 pg/ml, manufacturer R&D Systems, USA); TGF-β1 (catalog number BMS249, measuring range 9–2000 ng/ml, sensitivity 9 ng/ml, producer Bender MedSystems, Austria); thrombomodulin (soluble receptor CD141, catalog number E90529Hu, measuring range 0.041–6.0 ng/ml, sensitivity 0.041 ng/ml, manufacturer USCN Life Science, USA); thrombospondin (catalog number DTSP10, measuring range 0.944–500 ng/ml, sensitivity 0.944 ng/ml, manufacturer R&D Systems, Germany); fibronectin (catalog number TC12030, manufacturer Cusabio BIOTECH, measuring range 10–2000 μg/ml, sensitivity 10 μg/ml).

The study of blood serum alpha-2-macroglobulin was conducted with the Expert Plus immunoassay analyzer (ASYS HITECH, Austria), the measured wavelength is 450 nm. We worked using ELISA kit: alpha.2-MG (catalog number is K6610, manufacturer Immundiagnostik AG, Germany, measuring range 0.058–5 g/l, sensitivity 0.058 g/l).

The study of fibrinopeptide A was conducted with the Expert Plus immunoassay analyzer (ASYS HITECH, Austria), the measured wavelength is 450 nm. We used such ELISA kits as Sekisui Diagnostics (American Diagnostica, measuring range 0.78–50 ng/ml, sensitivity 0.78 ng/ml).

The statistical package SPSS 11.5 was used for statistical data processing.

Results and Discussion

Examination of endothelial cell concentration showed the following data (Table 1). In the hypertensive patients the level of transforming growth factor β1 (TGF-β1) exceeded 1.3 times the control values, in the VD patients exceeded 1.6 times, while in the VD patients with hypertension exceeded 1.8 times ($p < 0.05$).

The highest levels of platelet-derived growth factor BB were in the blood of VD patients with hypertension. They were 1.5 times higher than the control values, where as in the group of isolated VD the indicators were 1.4 times higher than standard figures, and in hypertensive patients they were 1.3 times higher ($p < 0.05$). VEGF in the blood was 2.7 times higher than the upper limit for the group of hypertensive patients,

Table 1
Endothelial cell indicators in the serum of patients examined

Indicator	Control group	Hypertension group	VD group	Hypertension + VD group
Transforming growth factor β1, ng/ml	29.8 ± 4.7	37.4 ± 5.2*	46.9 ± 6.4*	53.7 ± 6.9*
Platelet-derived growth factor BB, pg/ml	196.9 ± 25.54	249.5 ± 29.42*	279.4 ± 32.7*	302 ± 36.8*
Vascular endothelial growth factor, pg/ml	49.6 ± 6.9	132.4 ± 11.3*	175.9 ± 13.7*	197.6 ± 12.6*
Fibronectin, mg/ml	225.6 ± 22.5	339.7 ± 23.5*	392.5 ± 26.3*	412.8 ± 28.5*
Thrombospondin, ng/ml	38.5 ± 4.9	53.7 ± 5.8*	64.5 ± 6.4	76.8 ± 7.2
Thrombomodulin, ng/ml	0.96 ± 0.09	1.39 ± 0.07	1.69 ± 0.08	1.98 ± 0.07
α-2-macroglobulin, g/l	1.73 ± 0.05	1.89 ± 0.06	1.98 ± 0.04	2.15 ± 0.03
Fibrinopeptide A, ng/ml	0.92 ± 0.05	1.16 ± 0.08	1.48 ± 0.09	1.82 ± 0.08

* Differences are significant in comparison with the control group ($p < 0.05$).

3.5 times higher for VD group, and 4.0 times higher for group with both VD and hypertension ($p < 0.05$).

Imbalance of fibronectin levels also had statistically significant differences from the benchmarks and exceeded the latter 1.5 times in the hypertensive patients, 1.7 times in the VD group, and 1.8 times in VD patients with combined hypertension ($p < 0.05$). We have recorded unidirectional changes of serum thrombomodulin and thrombospondin, which exceeded the reference values for the group of hypertensive patients, VD group, and those of VD patient with hypertension by 1.4; 1.7 and 2.0 times respectively ($p < 0.05$).

It should be noted that in the VD patients with hypertension levels of α-2-macroglobulin exceeded 1.2 times the control figures ($p < 0.05$), while in patients with isolated VD — only 1.14 times ($p > 0.05$). Bad trend was observed in relation to fibrinopeptide A, the values of which were higher than values of the control group (1.3 times higher in the hypertensive patients; 1.6 times in the VD patients, and 2.0 times in hypertensive patients with VD; $p < 0.05$). These findings allow to assume of an increased risk of thrombosis.

The maximum concentration levels of adhesion molecules sPECAM-1 were also observed in the serum of hypertensive patients with VD. They exceeded 3.4 times the reference values, while in the group with VD — only 1.2 times, and in the hypertensive group — only 1.3 times (Table 2).

The concentration of sVCAM-1 proved to be the highest in the blood of VD patients with comorbid hypertension and was 1.9 times above the reference value. Identical rates in groups of patients with isolated forms of the VD and the hypertension were 1.4 and 1.5 times respectively. The maximum concentration of sP-selectin which is an adhesion molecule accelerating the interaction of activated endothelial cells with leukocytes [7] was recorded in the group of patients with the VD and in the VD group combined with hypertension. The latter's sP-selectin concentration differed 2.2 times from the control values, and was 1.2 and 1.3 times higher than concentration in the group of isolated VD and that of hypertension respectively ($p < 0.05$).

Conclusion

Elevated levels of endothelial cell parameters were revealed in the blood of vibration disease patients combined with hypertension. Among these parameters are vascular endothelial growth factor, platelet-derived growth factor BB, transforming growth factor β1, fibronectin, thrombospondin, alpha-2-macroglobulin, thrombomodulin, fibrinopeptide A, and a high concentration of adhesion molecules. This situation allows us to consider them as the early marker of increased cardiovascular risk.

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Table 2
The content of the adhesion molecules in the serum of patients examined, ng/ml

Indicators	Control group	Hypertension group	VD group	Hypertension + VD group
sP-selectin	32.6 ± 4.1	53.8 ± 4.6*	61.7 ± 6.5*	79.5 ± 10.3*
The adhesion molecule sPECAM-1	2.3 ± 1.1	5.9 ± 2.3*	6.5 ± 2.6*	7.8 ± 3.1*
The adhesion molecule sVCAM-1	9.3 ± 2.5	13.8 ± 3.8*	14.1 ± 5.9*	20.4 ± 5.3*

* Values significantly different from the control group ($p < 0.05$).

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