FACTORS IN FIBRINOLYSIS IN THE HUMAN VASCULAR WALL AT DIFFERENT AGES DEPENDING ON THE SEVERITY OF ATHEROSCLEROSIS

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Changes in the fibrinolytic properties of the vascular wall during aging and in atherosclerosis in man are an as yet incompletely solved problem. In previous investigations [5-7] changes in this parameter have been studied under the influence of two factors on the same autopsy material, grouping it on the basis either of age period or of the severity of the atherosclerotic changes. Since the severity of atherosclerosis depends directly on age [1], the same conclusion was drawn in both cases, namely that fibrinolytic activity of macroscopically unchanged areas of arteries was increased. No comparative study of fibrinolysis factors in the walls of arteries and veins in elderly and old people has yet been undertaken. However, the wall of veins is a more appropriate object with which to study age processes than the wall of arteries, for it is not prone to undergo atherosclerotic changes in such a gross morphological form as in arteries.

The object of this investigation was to compare activity of tissue fibrinolysis factors in the vascular wall of the aorta and inferior vena cava in young subjects and in persons over 60 years of age with different degrees of severity of atherosclerosis of the aorta.

EXPERIMENTAL METHOD

Pieces of vessels from macroscopically unchanged regions of the aorta and inferior vena cava taken from subjects dying suddenly from various causes (70 persons) were investigated. The material was divided into three groups depending on age and the severity of the atherosclerotic changes in the aorta. When material was chosen for visual assessment of atherosclerotic changes in the intima of the aorta, special schemes of standard autopsied segments of the aorta suggested by Avtandilov [1] were used. The control group consisted of 20 young persons aged 17-29 years. Atherosclerotic changes in this group consisted of lipoidosis, accompanied in some cases by single fibrous plaques. The total area of aorta affected was 3-10%. Groups 2 and 3 consisted of elderly subjects (age 66.2 ± 1.43 and 68.1 ± 1.48 years respectively). In group 2 (26 subjects) the atherosclerotic changes were minimal for that age and, as in the control group, they were restricted to lipoidosis and atherosclerotic plaques. There were no complicated lesions in this group but the area involved was greater than in the young subjects, namely 10-30%. Group 3 consisted of 24 persons with severe morphological changes in the surface of the aorta, including complicated atherosclerotic formations (ulceration, hemorrhages, juxtamural thrombosis), and also areas of calcification. The total area of intima involved in this group exceeded 50%. In all cases the venous wall was free from any distinct morphological changes.

Tissue extracts obtained from the vascular fragments were used in the ratio of 1:5 (1 part of tissue material and 5 parts of isotonic solution). Activity of the vascular plasminogen activator and proactivator [8] was determined with the aid of kabikinase (a highly purified preparation of streptokinase marketed by the firm "Deutsche KABI Gmbh"); antiplasmin activity [2], the fibrin-stabilizing action [3], and also the clotting (thromboplastin) activity (from the substrate plasma recalcification time [4]) also were determined. In the last case, platelet-free bovine plasma was used. The results of the tests were subjected to statistical analysis by Student's nonparametric t test.

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TABLE 1. Parameters of Activity of Tissue Fibrinolysis Factors in Aorta and Inferior Vena Cava of Young and Elderly Subjects with Different Degrees of Severity of Aortic Atherosclerosis (M ± m)

Parameter	Young subjects		Elderly subjects with moderate atherosclerosis		P	Elderly subjects with severe atherosclerosis		P	P_1
	aorta	vena cava	aorta	vena cava		aorta	vena cava		
Vascular activator, mm^2	30±7,0	40±8,0*	58±8,7	39±7,0*	$\frac{<0,02}{>0,5}$	60±8,8	41±6,8*	$\frac{<0,02}{>0,5}$	$\frac{>0,5}{>0,5}$
Vascular proactivator, mm^2	494±14,5	512±27,9	546±20,0	467±23,1*	$\frac{<0,05}{>0,2}$	596±11,2	472±22,7*	$\frac{<0,001}{>0,2}$	$\frac{<0,05}{>0,5}$
Antiplasmin activity, %	8±2,0	5±1,5	15±2,2	13±2,5	$\frac{<0,05}{<0,01}$	19±2,0	20±1,9	$\frac{<0,001}{<0,001}$	$\frac{>0,1}{<0,05}$
Index of activity of fibrin-stabilizing factor	2,4±0,31	1,5±0,17*	2,5±0,25	1,6±0,14*	$\frac{>0,5}{>0,5}$	2,5±0,31	1,5±0,14*	$\frac{>0,5}{-}$	$\frac{-}{>0,5}$
Index of clotting activity	3,7±0,20	3,1±0,13*	4,4±0,26	3,7±0,17*	$\frac{<0,05}{<0,01}$	4,8±0,17	4,1±0,22*	$\frac{<0,001}{<0,001}$	$\frac{>0,2}{>0,1}$

Legend. Numerator shows significance of differences between values for aorta, denominator the same for vena cava; P) significance of differences compared with young group; P_1) significance of differences compared with elderly group with moderate atherosclerosis; *) values for aorta and inferior vena cava differ significantly.

EXPERIMENTAL RESULTS

In the healthy young subjects the ratio of vascular plasminogen activator and proactivator activities in the walls of the aorta and inferior vena cava was 5.7 and 95.3%, and 7.2 and 92.8% respectively. These figures indicate that the fibrinolytic potential of the large blood vessels is due mainly to proactivator.

The lowest content of vascular plasminogen activator in the aortic wall was found in the young subjects (Table 1). Activity of this factor in this group in the inferior vena cava was significantly higher than in the aorta.

In intact areas of the aorta in the elderly subjects (groups 2 and 3) there was a considerable increase (on average twofold) in vascular activator activity, whereas in the vein it remained the same as before. This led to a change in their arteriovenous difference for the content of this factor in the direction of substantial predominance in the wall of the aorta. No significant differences were found between vascular activator activity in the aortic tissues of subjects with moderate and severe atherosclerosis.

The proactivator content in the wall of the aorta and vena cava in the young subjects was equal. In persons over 60 years of age, the concentration of this factor was significantly increased in macroscopically unchanged areas of the aorta. The degree of increase depended on the severity of the atherosclerotic changes: The more severe the morphological changes, the higher the proactivator content in unchanged areas of the vessel. This led to the appearance of a statistically significant difference between the proactivator content in the aorta and vein, in which its concentration remained unchanged in the elderly group of subjects irrespective of the severity of their atherosclerosis.

Consequently, in the wall of the vena cava, which had no visible changes of an atherosclerotic character, no disturbances of activity of fibrinolysis stimulators (plasminogen activator and proactivator) could be observed. It must be emphasized, in this context, that the tissues of a vein do not undergo age-induced structural changes, for the aging process is to some degree absolute for all tissues of the body. By contrast, the content of the activator and proactivator in the intact regions of the aorta was substantially increased in the elderly subjects. Proactivator is known to be distributed in the intima and media of blood vessels. That is probably why its content in the intact tissue of the aorta depends more on the spread of atherosclerosis, which affects precisely these layers of the vessel wall, than the content of activator, which is located mainly in large vessels of arterial type in the endothelium of the vasa vasorum of the adventitia.

There were no arteriovenous differences of antiplasmin activity in any of the groups. At 60 years of age it rose sharply in the wall both of the aorta and of the inferior vena cava. The increase in antiplasmin activity was directly dependent on the severity of atherosclerosis and, evidently, associated with the accumulation of a certain substance (or substances) selectively inhibiting plasmin in the vascular wall in this disease.

In each group activity of the fibrin-stabilizing factor in the aortic wall was significantly higher than in the wall of the vena cave. Neither age nor atherosclerosis had any effect on this ratio, for the index of activity of fibrin-stabilizing factor in elderly subjects with differences in the severity of atherosclerosis of the aorta was the same as in the young subjects.

The clotting activity of aortic extract was higher than that of extracts of the vein. It was increased in elderly subjects in accordance with the severity of the atherosclerotic changes both in intact parts of the aorta and in the tissue of the vein.

These results are evidence that the changes observed in late ontogeny in fibrinolysis factors in the intact zones of the vascular wall are due mainly to atherosclerosis and they depend quantitatively on the severity of the pathological process. In particular, age-induced structural changes in the vascular wall have no definite effect on the activity of fibrinolytic components contained in them. These findings are in agreement with the views of Perlick [9] who concludes from the results of his own investigations that morphological and biochemical atherogenic changes induce a compensatory-adaptive response of parts of the vessel not affected by atherosclerosis. This response is manifested as an increase in the activity of tissue factors of hemostatis, facilitating both clotting and fibrinolysis of the blood; the larger the total area of involvement, the more marked this response.

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