REVIEWS

Correlation between Anatomic Parameters of the Aorta and Manifestations of Atherosclerosis

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A new risk factor of atherosclerosis — distal narrowing and shortening of the aorta — is described. The following parameters are analyzed in aortas collected from 1098 men and 1059 women aged 20-89 years: visual and planimetric estimations of the severity of atherosclerotic lesions and the perimeter, length, area, and angles of narrowing at different levels of the aorta. Atherogenic effect of inadequate aortic narrowing is more pronounced in young healthy individuals and is aggravated by hypertension. The narrowing of abdominal aorta promotes progression of atherosclerosis in the aorta, iliac, right coronary, and superior mesenteric arteries to a greater extent than in the left coronary and inferior mesenteric artery.

Key Words: *atherosclerosis; aorta; ischemic heart disease*

Public health service markedly reduced mortality from infectious diseases; however, urbanization and industrialization are associated with increased incidence of cardiovascular pathologies [7,14,17]. Atherosclerosis and atherosclerosis-related pathologies, such as ischemic heart disease, cerebrovascular and arterial pathologies are the major causes of cardiovascular disorders.

Comparative studies carried out under aegis of the WHO in the 1960s and 1980s revealed numerous risk factors of atherosclerosis [7,8,18]; their presence, however, accounts for not more than 50% cases of atherosclerosis [23]. The effects of blood vessel anatomy on atherogenesis have been poorly investigated, although a relationship between biomechanical properties of vascular wall and hemodynamics has been established [6,10]. The dependence of blood vessel radius and vascular wall thickness on the intravascular blood pressure can be interpreted in several ways, particularly in arterial hypertension, which may account for focal character and specific localization of atherosclerotic lesions. A turbulence zone that practically overlaps blood flow is formed in short vessels. This factor is taken into account in reconstructive surgery to prevent thrombosis. A relationship between branching and geometry of bifurcation of the aorta, on the one hand, and age, sex, height, and body weight index, on the other [4,13,22], as well as the effects of these factors on atherogenesis [24] were studied. A relationship between the size of artery and atherosclerotic lesions was established [12]. On the basis of integral morphometric parameters, an approach to the elucidation of the mechanisms responsible for initiation and development of atherosclerosis has been proposed. However, this approach is labor-consuming, requires complex mathematical calculations, and a series of biophysical transformations and cannot be used for predicting the development of atherosclerosis.

Out method is based on the determination of the shape and size of the aorta. It is simple and can be employed in clinical practice. Our hypothesis that atherogenesis is influenced by aortic anatomy was confirmed by investigations of aortas from 1098 men

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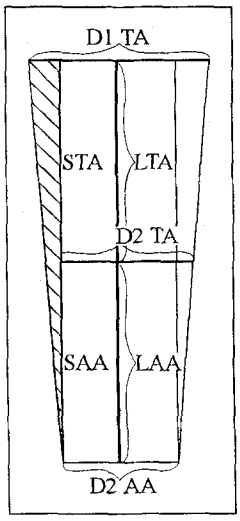

Fig. 1. A scheme of the aorta. Maximum (D1) and minimal (D2) perimeters of thoracic aorta (TA, *aorta thoracica*) longitudinal section; D2AA — minimal perimeter of abdominal aorta (AA, *aorta abdominalis*); LTA — length of thoracic aorta; LAA — length of abdominal aorta; STA — area of thoracic aorta; SAA — area of abdominal aorta.

and 1059 women aged 20-89 years, taking perimeter, length, area, and angle of narrowing as basic parameters (Figs. 1 and 2).

Atherosclerotic lesions (lipoidosis, fibrous plaques, complicated lesions, and calcinosis) were identified using the visual-planimetric method recommended by the WHO [21].

The information regarding aortic anatomy, atherosclerotic lesions (occurrence and area), age, sex, ethnicity, and some risk factors was analyzed using Statistic Analysis System (SAS) and General Linear Model (GIM) software based on analysis of variance and covariant and regression analyses. Calculations were performed at the Laboratory of Biostatistics of the Cardiology Research Center.

The mean diameter of thoracic aorta (TA) in 20-89-year-old individuals varied from 12.6 to 30.1 mm (from 13.4 to 22.0 mm according to the literature data [9]). In very few cases the perimeter (diameter) of the abdominal aorta (AA) was greater than that of TA. The greatest difference between the maximum and minimal perimeters was 16 mm for TA, 18 mm for AA, and 39 mm for the entire aorta. The maximum length of TA was 240 mm in men, and 213 mm in women; the maximum length of AA was 191 mm. The minimal length was 98 mm for TA and 76 mm for AA. In 2% of the cases, abdominal aorta was longer than thoracic aorta.

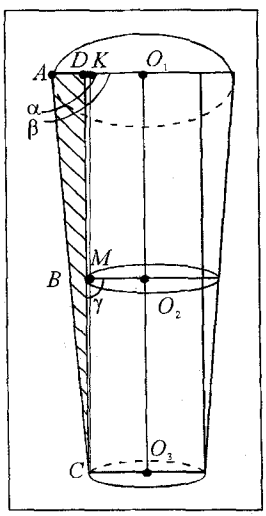

Fig. 2. Some parameters of the aorta. O_1, O_2, O_3 — points on the middle line; *A*, *B*, *C*, *K*, *M* — deviation points from the middle line; α — angle of deviation of thoracic aorta between lines connecting points *A*, *D*, *B*; β — angle of narrowing of the entire aorta; γ — angle of narrowing of abdominal aorta.

The area of the intima increases with age up to 2.5 times, reaching a value of 205 cm^2 (76.6 cm^2 for AA and 132.5 cm^2 for TA), reaching 171 cm^2 in some cases.

The length, perimeter (diameter), and intimal area in TA and AA positively correlated with age, although the rate of increase of these parameters dropped at the age of 40-59, when intense progression of atherosclerotic lesions has been observed.

It should be noted that a slight distal narrowing of the aorta occurs in the norm in accordance with the number, diameter and angle of branches. However, inadequate narrowing and shortening of the aorta were documented, i.e., mild aortic hypoplasia was adequately compensated by high elasticity of the aortic wall and numerous arterial branches.

We observed pronounced distal narrowing of the aorta or almost a 2-fold shortening of AA relative to TA in 20.3% men: in 13.9% of them by the difference in the area, in 4.9% by the difference between perimeters, in 1.5% by the difference between the lengths of TA and AA. These parameters were slightly lower in women. The difference (>1.6-fold) between the same parameters of TA and AA was revealed in 27.4% of the aortas (the difference between maximum and minimal perimeters in 21.8% of them, the difference between the lengths of TA and AA in 2.5%, different area in 1.8%, and different combinations of parameters in 1.3%). In 7.2% of individuals, the narrowing of aorta (angle β) was hemodynamically significant.

Various methods have been developed to characterize the aorta: Broca and Erisman indices and their modifications, etc. There is a relationship between body constitution, on the one hand, and diameter and length of blood vessels and age, on the other [2]. For example, in people with brachymorphic constitution thoracic aorta is shorter, while the abdominal aorta is longer than in people with in dolichomorphic constitution. It was found that the correlation between blood vessel parameters and type of constitution is weaker in case of short vessels.

We have analyzed the size of aorta in relation with disease and cause of death. The greatest differences between these parameters was revealed in individuals died from atherosclerosis and ischemic heart disease (the greatest difference between the lengths of TA and AA was 30.33 mm, between

their perimeters 22.32 mm, and between their areas 31.10 mm^2). The smallest difference between these parameters was observed in individuals died from diabetes mellitus or from complications of nephropathy during pregnancy. In general, the occurrence of the differences between the same parameters of the aorta was 1.6-fold higher (71.1%) in persons died from atherosclerosis than in persons died from other diseases. This relationship was stronger in the foreign than in the indigenous population, which positively correlated with severity of atherosclerosis.

Variable correlations were revealed between aortic parameters, risk factors, and atherosclerotic lesions (Table 1). The correlation between lipoidosis and age (0.29 for TA and 0.44 for AA) was weaker than that between age and fibrous plaques (0.68), while the correlation between rhythmic structures and age was negative (0.02).

The strongest positive correlations was established between the TA perimeter, on the one hand, area (0.90-0.93), age (0.82-0.84), and fibrous plaques (0.67-0.69), on the other; the maximum perimeter correlated with calcinosis (0.36-0.40).

TABLE 1. Coefficients of Correlation Between Atherosclerotic Lesions and Aortic Parameters

Characteristic	Lipoidosis	Fibrous plaques	Complicated lesions	Calcinosis	Rhythmic structures	Length	Perimeter		Area	Ratio between			Angle of narrowing
							maximum	minimal		lengths	perimeters	areas	
Thoracic aorta													
Age	0.29**	0.68**	0.27**	0.36**	-0.01	0.60**	0.82**	0.84**	0.78**	0.07**	0.08*	0.07*	0.13
Lipoidosis		-0.35**	-0.17**	-0.18**	-0.04	-0.21**	-0.27**	-0.29*	-0.27*	-0.04	-0.07*	-0.05	0.02
Fibrous plaque			0.28*	0.38*	0.11*	0.49**	0.67**	0.69**	0.65**	0.14*	0.12**	0.15**	0.21
Complicated lesions				0.27**	0.04	0.18**	0.29**	0.31**	0.28**	0.04	0.01	0.04	-0.06
Calcinosis					0.03	0.21**	0.36**	0.37**	0.33**	0.06**	0.07	0.06	0.02
Rhythmic structures						-0.04	0.01	-0.01	-0.01	0.01	0.06	0.01	0.17
Length							0.70**	0.65**	0.90**	0.28**	0.09*	0.27**	-0.14
Perimeter maximum								0.93**	0.93*	0.12*	0.23**	0.13**	0.37**
minimal									0.90**	0.11*	0.06*	0.10*	0.17
Area										0.21**	0.14**	0.21**	0.10
Ratio between													
lengths											0.11*	0.99**	0.01
perimeters												0.22**	0.87*
areas													0.13
Abdominal aorta													
Age	0.44**	0.65**	0.27**	0.43**	-0.24*	0.42**	0.84**	0.73**	0.72**	0.07*	0.08*	0.07*	0.09
Lipoidosis		-0.49**	-0.22*	-0.29*	0.06	-0.18*	-0.44*	-0.37**	-0.35**	-0.07*	-0.04	-0.07*	-0.18*
Fibrous plaque			0.13**	0.27**	-0.13*	0.26**	0.64*	0.56**	0.52**	0.11*	0.04	0.11*	0.10
Complicated lesions				0.20**	-0.06	0.13**	0.30**	0.34**	0.28**	0.01	-0.07*	0.01	0.14
Calcinosis					-0.08*	0.16**	0.40**	0.25**	0.30**	0.01	0.18*	0.01	0.25
Rhythmic structures						-0.13*	-0.19*	-0.19*	0.18**	0.01	0.06	0.02	0.01
Length							0.44**	0.41**	0.83**	-0.48*	-0.01	-0.46**	0.12
Perimeter maximum								0.85**	0.83**	0.10*	0.06*	0.10*	0.43**
minimal									0.81**	0.06*	-0.36**	0.01	0.27**
Area										-0.22**	-0.08*	-0.23**	0.29*
Ratio between													
lengths											0.11*	0.99**	0.35**
perimeters												0.22**	0.86**
areas													0.51**

Note. *p<0.05, **p<0.0001 between atherosclerotic lesions and aortic parameters.

Covariant analysis showed that fibrous plaques are the most informative parameter. The coefficient of multiple determination (R^2) for fibrous plaques was high; their occurrence and area were much higher compared with those for lipoidosis, complicated lesions, and calcinosis. Therefore, in other analyses fibrous plaque was chosen as a marker of atherosclerosis. Strong correlations were established between fibrous plaques, age, angle of narrowing for the entire aorta (β, ATA) and the areas of TA and AA.

Analysis of the relationships between aortic parameters and various risk factors of atherosclerosis showed that the significance of individual risk factors is lower than that of their sum. For example, the *F* test for the heart weight was equal to 12.11 ($p<0.001$); however, when arterial hypertension was taken into account, it decreased to 1.10, i.e., became insignificant (Table 2), which is due to a strong correlation between heart weight and arterial hypertension (10.18, $p<0.001$).

Thus, heart weight is influenced not only by arterial hypertension, but also by cardiac defects, hypertrophic cardiomyopathy, etc. The multiple determination coefficient in this model was high (0.57, $p<0.0001$). Table 2 shows that there is no relationship between the parameters characterizing the constitution of a patient (height 0.03, body weight 0.04, and Cattle index 0.01) and the occurrence and area of fibrous plaques, while the age, angle of narrowing, and some other parameters are significant for the development of atherosclerosis.

TABLE 2. Covariant Analysis (Relation with Fibrous Plaques)

Parameter	*F* test of inclusion in model	Statistical significance
Age	36.85	0.0001
Angle of narrowing of entire aorta (β, ATA)	29.52	0.0001
Perimeter		
maximum	25.52	0.0001
minimal	15.93	0.0001
Area TA	22.25	0.0001
Height	0.03	0.8648
Body weight	0.04	0.8487
Index of Cattle	0.01	0.9098
Mass of heart	1.10	0.2951
Arterial hypertension	10.18	0.0015
Diabetes mellitus	10.85	0.0010
Cause of death (primary disease)	4.14	0.0024

Then we attempted to evaluate the significance of size and shape of the aorta for atherogenesis and to find out whether these parameters influence this process individually or in association with other risk factors (age, etc.). For this purpose we have employed a three-step procedure of multivariant analysis. Firstly, we calculated the complete model according to the following formula:

FPTA k=1NT+α_1×AGE+α_2×ATA+α_3×STA+α_4×DTT+Bidr+Eik, where FPTA is the fibrous plaque in TA, k is the number of observation, 1NT is the free member (constant), $\alpha_{1,2,3,4}$ are the regression coefficients, AGE is the age of individual, ATA (β) is the angle of narrowing of the entire aorta, STA is the area of TA, DTT is the difference between the maximum and minimal perimeters of TA, Bidr is the effect of the cause of death at this level, Eik is the error.

The multiple determination coefficient was 0.5456 ($p<0.0001$), i.e., 54% of dispersion in this model is associated with the studied characteristics. $R^2=(\sigma^2_{ini}-\sigma^2_{model})/\sigma^2_{ini}$.

Other 46% are associated with the phenomena that were not included in this model (unknown risk factors, clinical and anatomical information that was not taken into consideration, random errors, etc.). In this model, the *F* test characterizing the inclusion of the given parameter in the model was 86.72 for the age of an individual, and 39.48 for the angle of narrowing, 67.41 for the area; the difference between maximum and minimal perimeters of TA and AA was 22.82 ($p<0.0001$).

Secondly, three regressive models were considered. ATA=γ_1×AGE+C_1; STA=γ_2×AGE+C_2; ATT=γ_3×AGE+C_3, where the linearity between the parameters characterizing size and shape of the aorta and age are taken into account. Regression analysis of individual parameters was carried out according to the following model:

RATA=ATA k—(γ_1AGE k+C_1)=ATA k—(2.5591×AGE k+0.0046);

RSTA=STA k—(γ_1AGE k+C_2)=STA k—(93.2496×AGE k+2984);

RDTT=DTT k—(γ_3AGE k+C_3)=DTT k—(0.2677×AGE k+6.5818);

ATA (angle β)=LTA+LAA D1TA—D2TA;

STA=LTA D1TA—D2TA;

DDT=D1TA—D2TA, where: $\gamma\sigma_{1,2,3}$ are the coefficients of regression, $C_{1,2,3}$ are the constants, k is the number of observation, AGE is the age, LTA is the length of TA, LAA is the length of AA, and DTT is the difference between the maximum and minimal perimeters of TA.

There was no direct relationship between RATA, RDTT and age. The calculated R^2 is 0.1028 for ATA (angle β) and 0.0209 for DTT, i.e., there is a very

weak relationship between this parameter and age. Statistical significance of these values was very high ($p<0.0001$). Thus, the influence of age is 10 and 2%, respectively, for angle of narrowing of the entire aorta and the difference between maximum and minimum perimeters, while the area of TA, as it was expected, strongly depended on age (61%).

Thirdly, another model of covariant analysis, which was similar to the first model, but without the influence of age on the shape and size of aorta on the development of atherosclerosis, was calculated as follows:

$$FPTA=1NT+\gamma_1\times RATA\ k+\gamma_2\times RDTT\ k+\gamma_3\times RSTA+Bidr+Eik,$$

where 1NT is the constant (20.88), k is the individual, Bidr — is the effect of the cause of death at this level, Eik is the error, RATA, RSTA, RDTT are the regression residues of the parameters after correction for age, $\gamma_{1,2,3}$ are the coefficients of regression: 3123.92, 1.2530, and 0.0003, respectively. R^2 is equal to 2138 ($p<0.0001$), i.e., 21.4% in comparison with the initial value and after taking into consideration all the studied parameters (54%, model that includes age), indicating that this model reflects the relationship between fibrous plaque and aortic parameters after correction by age. The F test is 26.49 for the angle ATA, 33.89 for the area of TA, 22.57 for the difference between the perimeters, and 75.90 for the cause of death ($p<0.001$ for all studied parameters).

Thus, this model with a high degree of reliability demonstrates the significance of shape and size of the aorta in the development of atherosclerosis. The contribution of the angle of narrowing of the entire aorta (ATA or β), which is a stable parameter of the aorta irrespective of age and type of atherosclerotic lesions, is the greatest.

Atherosclerosis (the area occupied by fibrous plaques and calcinosis and the total area occupied by elevated lesions) is much severe in individuals with maximum difference between aortic parameters than in individuals with minimal differences (Table 3).

For example, the occurrence of fibrous plaques in TA of individuals with minimal difference of the lengths of TA and AA was equal to 65.6% and 71.2% in those with maximum difference, the mean area occupies by the plaques being, respectively, 21.1 and 30.7% of the aortic surface. The significance of the shape and size of aorta and its biomechanical properties are higher in young age, since the effects of other risk factors (age-related alterations, arterial hypertension, etc.) increase when various manifestations of atherosclerosis are leveled.

We believe that pronounced and inadequate distal narrowing of the aorta is an important risk factor of atherosclerosis. When the difference between similar parameters of TA and AA reaches the values of 1.6 and higher, blood flow disturbances and distention of aortic wall result in regional hypertension [5]. Changes in hemo- and hydrodynamics [6,10,20] are associated with increased permeability of the intima and development of vascular lesions, leading to hemorrhages and other vascular disorders [15,19].

Among the four major mechanisms of atherosclerosis, Schwartz *et al.* (1989) have stressed the importance of mechanical and hemodynamic loading

TABLE 3. Occurrence and Area Occupied by Atherosclerotic Lesions in Aorta Relative to Its Anatomy (%)

Parameter of aorta	Segment of aorta	Difference	All lesions		Fibrous plaque		Complicated lesions		Calcinosis	
			occurrence	area	occurrence	area	occurrence	area	occurrence	area
Length	TA	minimal <1.2	99.4	31.6±1.6	65.6	21.1±1.4	26.5	1.5±0.3	24.5	1.0±0.4
		maximum >1.6	98.4	41.3±1.8*	71.2	30.7±1.7*	40.2*	1.8±0.3*	38.0	1.6±0.3
	AA	minimal <1.2	99.4	44.8±1.8	74.4	26.9±1.6	37.8	2.6±0.5	38.4	4.2±0.6
		maximum >1.6	99.4	54.3±1.9*	74.0	35.4±1.8*	41.5	4.2±0.7	42.5	5.3±0.6
Width	TA	minimal <1.2	98.1	34.1±1.6	69.4	23.5±1.5	30.0	1.4±0.3	26.8	1.0±0.3
		maximum >1.6	100.0	41.7±1.8*	72.3	31.1±1.7	40.6*	1.6±0.3	37.3	1.8±0.4
	AA	minimal <1.2	98.7	47.7±1.8	76.0	31.5±1.7	37.8	3.9±0.6	37.4	2.8±0.6
		maximum >1.6	100.0	52.7±1.9*	77.7	33.8±1.7	45.3	3.2±0.5	44.9	6.4±0.9
Area	TA	minimal <1.2	99.4	32.4±1.6	67.2	21.5±1.5	26.2	1.4±0.3	28.2	1.0±0.3
		maximum >1.6	99.0	41.6±1.8*	69.7	30.7±1.7*	39.7*	1.6±0.3	40.0	1.8±0.3
	AA	minimal <1.2	99.4	45.8±1.8	76.7	27.8±1.6	37.8	3.4±0.6	30.1	3.9±0.6
		maximum >1.6	99.7	53.4±1.9*	73.2	34.2±1.8*	41.3	3.9±0.6*	42.4	5.6±0.6

Note. *$p<0.05$.

and the sensitivity of vascular receptors to low-density lipoproteins. Thus, an increase in the difference between the parameters of TA and AA increases the probability of early initiation and rapid progression of atherosclerotic lesions, which potentiates the effects of other risk factors, particularly of arterial hypertension.

We studied the effect of aortic anatomy on atherosclerotic changes in coronary, iliac, and mesenteric arteries. A pronounced relationship between atherosclerosis in right coronary, common iliac, and superior mesenteric arteries, and in abdominal aorta has been established. The relationship was weak in the inferior mesenteric artery and left circumflex coronary artery and was absent in the descending coronary artery.

A strong relationship was established between atherosclerosis, the area of TA, and the angle of narrowing. This relationship was stronger in patients with arterial hypertension and in healthy subjects (R^2=0.4763 and 0.4591, respectively, p<0.0001).

Fibrous plaques in AA correlated with the ratio of the difference between the maximum and minimal diameters of AA to its length as well as with angle of narrowing of AA (R^2=0.1860, p<0.0001).

The effect of aortic anatomy on the occurrence and area occupied by fibrous plaques in the common and internal iliac arteries (R^2=0.41-0.43, p<0.0001) was higher than in AA and external iliac and mesenteric arteries (R^2=0.11, p<0.0001). Thus, different deviations of aortic anatomy from the norm were revealed in 27.4% individuals aged 20-89 years. The occurrence and severity of atherosclerotic lesions increased with the degree of aortic narrowing. Thus, distal narrowing of the aorta can be regarded as a new risk factor of atherosclerosis which is not associated with age-related vascular modifications. Prognostic validity of this factor is greater in healthy subjects and in young people than in patients with cardiovascular diseases and old people.

Our findings provide more insight into the mechanisms of atherogenesis, primarily, biomechanical, hemo- and hydrodynamic, rheological and some others.

The peculiarities of aortic anatomy can be revealed using anthropometric methods, functional and X-ray diagnostics, tomography, ultra-sound imaging, etc. The shape and size of the aorta should be taken into consideration in reconstructive surgery and in clinical and anatomical analysis of cardiovascular diseases.

REFERENCES

1. M. N. Anichkov and I. D. Lev, *Clinico-Anatomical Atlas of Aortic Pathology* [in Russian], Leningrad (1967).
2. D. B. Bekov and Yu. N. Vovk, in: *Individual Anatomic Variability of Human Internal Organs, Systems, and Constitution* [in Russian], Kiev (1988), pp. 132-159.
3. Kh. T. Kaarma, *Arkh. Anat.*, **85**, No. 9, 67-70 (1983).
4. V. A. Kolpakov, R. S. Polishchuk, P. B. Solov'ev, *et al.*, *Arkh. Pat.*, **55**, No. 3, 39-43 (1993).
5. O. Yu. Marina, *Diagnostics of Aortic Coarctation* [in Russian], Moscow (1961).
6. I. F. Obraztsov and M. A. Khanin, *Optimal Biomechanical Systems* [in Russian], Moscow (1989).
7. R. G. Oganov, *Arkh. Pat.*, **54**, No. 4, 13-15 (1992).
8. R. G. Oganov and G. S. Zhukovskii, in: *Preventive Cardiology* [in Russian], Moscow (1987), pp. 68-91.
9. B. A. Purinya and V. A. Kas'yanov, *Biomechanics of Human Major Blood Vessels* [in Russian], Riga (1980).
10. V. I. Savich, *Pathological Changes in Extra- and Intracranial Arteries and Brain Infarction* [in Russian], Minsk (1987).
11. V. S. Smolenskii, *Aortic Diseases* [in Russian], Moscow (1964).
12. Kh. E. Fernandes-Britto and P. V. Karlevaro, *Arkh. Pat.*, **51**, No. 11, 74-76 (1989).
13. N. M. Fruntash, *Biomorphosis of Human Aorta* [in Russian], Kishinev (1982).
14. E. I. Chazov, A. M. Vikhert, and R. G. Oganov, *Trudy Akad. Med. Nauk SSSR* [in Russian], Vol. 1, Moscow (1986), pp. 36-52.
15. G. K. Cambell and P. K. L. Mosse, *Exp. Mol. Pathol.*, **45**, No. 3, 227-244 (1986).
16. F. N. Epstein, *Ann. Clin. Res.*, **20**, 21-25 (1988).
17. F. N. Epstein, *Prev. Med.*, **12**, No. 1, 210-217 (1983).
18. P. N. Hopkins and R. A. Williams, *Atherosclerosis*, **40**, No. 1, 1-24 (1981).
19. R. M. Nerem and J. F. Cornhill, *Ibid.*, **36**, No. 2, 151-157 (1980).
20. C. Norden and U. Krunes, *Klin. Med.*, **41**, No. 18, 1413-1416 (1986).
21. *Protocol for an International Study of the Pathological Determinants of Atherosclerosis in Youth. WHO, Geneva* (1983).
22. A. M. Raso, *Panminerva Med.*, **23**, No. 1, 33-37 (1981).
23. R. H. Rosenman and M. A. Chesney, *Act. Nerv. Super. (Praha)*, **22**, 1-45 (1980).
24. K. Skullerud, *Acta Neurol. Scand. Suppl.*, **71**, No. 102, 94 (1985).