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Method for determining the biological age of arteries

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Abstract. Determining the biological age of the human arteries is relevant for timely stratification of the risk of developing diseases, prevention, control of individual aging rate, and geroprotective therapy. To study age-related changes in the echocardiographic examination of the arteries and to develop a formula for estimating the biological age of the human arteries.

Echocardiographic examinations of the heart were performed on 188 practically healthy people aged 30 to 79 years (73 men and 115 women), who signed informed consent and had no clinically significant diseases in the anamnesis or at the moment. The study of the carotid and vertebral arteries of the neck was performed on the Xario SSA-660A device from Toshiba (Japan) according to the standard method using a PLT-704SBT 7.5 MHz probe.

Based on the data of the study by the method of step-by-step multiple linear regressions, a formula for estimating the biological age of the human arteries was obtained. The multiple correlation coefficient after error correction was a fairly high value of R=0.894 ($p<0.00001$). The mean absolute error of age calculation (M±б) is 5.11±3.51 years.

The proposed formula for determining the biological age of the arteries can be used for the early diagnosis of accelerated aging.

Keywords: biological age; ultrasound examination of the main vessels of the neck

Aging is a major risk factor for vascular disease and related cardiovascular and cerebrovascular events. Therefore, it is important to develop tests that effectively identify individuals at high risk of developing an accelerated vascular injury. Such a marker can serve as an assessment of the "vascular age" of the patient [5]. It is well known that aging affects the structure and function of the vascular wall. There is an increase in arterial stiffness (an increase in collagen content and a decrease in elastin), an increase in pulse pressure and pulse wave velocity, endothelial dysfunction, a decrease in NO production, oxidative stress, and local and perivascular inflammation. The earliest manifestation of vascular wall aging is a local increase in the thickness of the intima-media complex (IMC), especially in arterial bifurcation zones, which correlates with an increase in vessel density and structural changes in the vessel wall [1-4, 7, 10]. The thickness of carotid IMC is an important biomarker reflecting atherosclerotic lesions of the vascular system is and related to the parameters of local central arterial stiffness. With the participation of the European Reference Values Collaboration, reference values for the thickness of the IMC of the common carotid artery have been developed. These reference intervals are set depending on age, gender, and blood pressure level, which facilitates the identification of signs of early vascular aging. The increase in IMC thickness at the bifurcation of the carotid artery at the age of 40 to 70 years in healthy individuals is 0.007 mm/year for women and 0.009 mm/year for men [1].

Given these facts, we can say that changes in the arteries are marker characteristics of age-related changes, and therefore, in our work, we analyzed changes in the walls of the main arteries of the vessels of the neck. We also separately singled out and analyzed the significance of IMC thickening in the bifurcation zone of the common carotid artery as the earliest sign of vascular aging.

Measuring the biological age (BA) of the arteries makes it possible to assess the degree of their age-related changes. Deviation of human BA value towards an increase or decrease in relation to chronologic age (CA) can be regarded as an indicator of the studied functional state of the system [5, 6, 8, 9, 14]. Identification of people with an accelerated rate of arterial aging makes it possible to carry out measures to prevent age-related pathology, predict the risk of developing diseases, assess the functional state of the body, and monitor the effectiveness of the use of geroprotectors [11-13].

The purpose of the work: is to study the indicators of age-related changes in the main arteries of the neck and evaluate the possibility of their use to determine the BA of the vascular system.

Materials and methods

188 practically healthy people (73 men and 115 women) were examined. The criterion for inclusion in the study was the signing of informed consent, the absence of clinically significant disease in history, and at the moment. All patients underwent ulan trasound examination of the main vessels of the neck. We used ultrasonic B-mode, color Doppler mapping, and spectral Doppler, which made it possible to study the anatomy of the vessels, the course of the arteries, the size of the lumen, and the condition of the artery wall, the thickness, and morphological changes in the arteries. The study included the study of the carotid and vertebral arteries of the neck: common carotid artery (CCA), external carotid artery (ECA), internal carotid artery (ICA), and vertebral arteries (VA) of the right and left parts of the neck on the apparatus Xario SSA-66 Japan) according to the standard method using sensor PLT-704SBT 7.5 MHz. Measurement of the IMC thickness in the right and left common carotid arteries was carried out 1-1.5 cm proximal to the bifurcation and in the bifurcation zone of the PCA along the posterior wall (in relation to the transducer) of the artery. The threshold value for increasing the thickness of the IMC was considered to be 0.9 mm or more. The IMC value was measured three times, and the average value was calculated from each side, which was taken as the IMC value. In the presence of an atherosclerotic plaque, IMC was determined in the intact area. The general characteristics of the IMC were evaluated: the preservation of layers, and the uniformity of the IMC.

The atherosclerotic plaque was considered to be a local IMC thickening of more than 1.5 mm or an increase in IMC by 50% next to the located part of the vessel.

The percentage of stenosis was measured by ECST (European Carotid Endarterectomy Trial), with transverse scanning of the artery as the ratio of the difference in the diameter of the artery distal to the site of stenosis to the free lumen of the vessel in the area of stenosis, expressed as a percentage. Stenosis was considered the degree of narrowing of the vessel to more than 20%.

The following indicators of the quantitative assessment of blood flow in the arteries of the brain were calculated:

1. Vs – the maximum systolic blood flow velocity in the studied artery;
2. Ved – the end-diastolic velocity, reflecting the level of blood flow in the diastolic phase;
3. Vm – the average blood flow velocity in one cardiac cycle. Based on the above parameters of the characteristics of the spectral curves of blood flow in the arteries, the coefficients were calculated, which made it possible to quantitatively characterize the normal and pathological characteristics of the received signal;
4. RI – circulatory resistance index, resistance index proposed by L. Pourcelot (1974) - the ratio of the difference between the maximum systolic and end-diastolic frequency of the Doppler signal (characterizes the value of peripheral resistance in the studied artery);
5. RI = (Vs-Ved)/Vs;
6. PI – the pulsation index proposed by R. Gosling, 1969, the ratio of the difference between the maximum systolic and end-diastolic frequency of the Doppler signal to the average frequency for the cardiac cycle. The index reflects the elastic properties of the studied artery proximal to the measurement site. The index is calculated by the formula: PI = (Vs-Ved)/Vm;

7. S/D – systolic-diastolic ratio, proposed by S. Stewart, characterizes the elastic properties of the artery. The index is calculated by the formula: S/D = Vs/Ved.

Immediately before the ultrasound examination of the vessels, blood pressure was measured with an LD-60 Little Doctor tonometer (Singapore) with a D-Ring 33-46 cuff according to the standard protocol using the Korotkoff method. Blood pressure was measured three times with an interval of 1-2 minutes and the average value was calculated.

The formula for calculating the biological age was obtained by the method of multiple stepwise regressions. The indicators of arteries were selected, which correlate as much as possible with age and little among themselves.

Statistical processing of the obtained data was carried out with the help of Excel 2007 and Statistica 7 (StatSoft, USA) programs. Standard statistical procedures, including variation and regression analyses, were used.

Results and discussion

The preliminary stage in calculating the formula of biological age was the analysis of the dependence of the studied parameters on the age of the examined people. The table shows the correlation of the studied indicators with the age (Table 1).

Table 1

Pearson Correlations between chronological age and biomarkers (Marked correlations are significant at p<0.05)

Biological markers	**Right arteries**	**Left arteries**
Common carotid artery (CCA)		
The thickness of the IMC	**0.62**	**0.50**
The thickness of the IMC of bifurcation	**0.58**	**0.58**
Vs	**-0.32**	**-0.33**
Ved	**-0.23**	-0.14
Vm	-0.09	-0.10
PI	**-0.32**	**-0.29**
RI	-0.09	-0.07
SD	-0.12	-0.06
Internal carotid artery (ICA)		
Vs	**-0.31**	-0.13
Ved	-0.15	-0.18
Vm	-0.19	-0.12
PI	-0.08	0.03
RI	-0.02	0.09
SD	0.001	0.15
Vertebral arteries (VA)		
Vs	0.11	0.01
Ved	-0.04	-0.14
Vm	0.02	-0.05
PI	0.18	**0.24**
RI	0.17	**0.25**
SD	0.17	0.17

The use of stepwise multiple regression made it possible to select the most informative indicators and obtain an equation linking the age of the examined people with several indicators of arteries (Tab. 2).

Table 2

Regression summary for dependent variable: Age
(Marked correlations are significant at $p<0.05$)

Regression Summary for Dependent Variable: Age. R= 0.784; R^2= 0.615; Adjusted R^2=0.595; F(5,100)=31.88; p<0.00001; Std. The error of estimate: 8.52						
	Beta	SE of Beta	B	SE of B	t(100)	p-level
Intercept			41.0929	9.7157	4.2295	0.0001
The thickness of the IMC (bifurcation of common carotid artery), mm	0.3518	0.0787	10.3925	2.3261	4.4678	0.00001
The thickness of the IMC (common carotid artery), mm	0.2971	0.0773	20.8108	5.4178	3.8412	0.0002
PI (common carotid artery);	-0.3398	0.0684	-14.3336	2.8859	-4.9667	0.00001
Ved (common carotid artery), m/s	-0.2405	0.0663	-0.7431	0.2049	-3.6265	0.0005
RI (left vertebral arteries).	0.2124	0.0661	33.8518	10.5351	3.2132	0.0018

Note: R – correlation coefficient of indicators with the model; R^2 – coefficient of model determination; Adjusted R^2 – adjusted R-square (taking into account the number of predictors in the model); F – Fisher's test; t – Student's test; p – assessment of the significance of the model; SE of the estimate – standard error of estimation; Intercept – a free member of the equation; B – regression coefficient; Beta – standardized regression coefficient; SE of Beta – standardized error of the coefficient; SE of B – standardized error of the regression coefficient.

$$Y = 10.39\,X1 + 20.81\,X2 - 14.33\,X3 - 0.743\,X4 + 33.85\,X5 + 41.09$$

Y – Predicted age, years;
X1 – Thickness of the IMC (bifurcation of common carotid artery), mm;
X2 – Thickness of the IMC (common carotid artery), mm;
X3 – PI (common carotid artery);
X4 – Ved (common carotid artery), m/s;
X5 – RI (left vertebral arteries).

Note. The formula uses the average values of the parameters of the right and left arteries.

The systematic error in calculating the age, associated with the peculiarities of constructing the multiple regression equation is calculated using the regression equation: prognosticated age - chronological age [15]. For our data, this error is calculated by the formula:

Age predicted error = 19.696 – 0.358 CA (r = -0,601; p = 0,001).

In turn, BA is calculated as the difference between the predicted age and the error in its calculation.

BA = Predicted age – Age calculation error.

The figure shows a graph of the correlation between BA after error correction and CA. It can be seen that the dispersion of points around the regression line is small and the multiple correlation coefficient is high ($r = 0.894$; $p < 0.00001$).

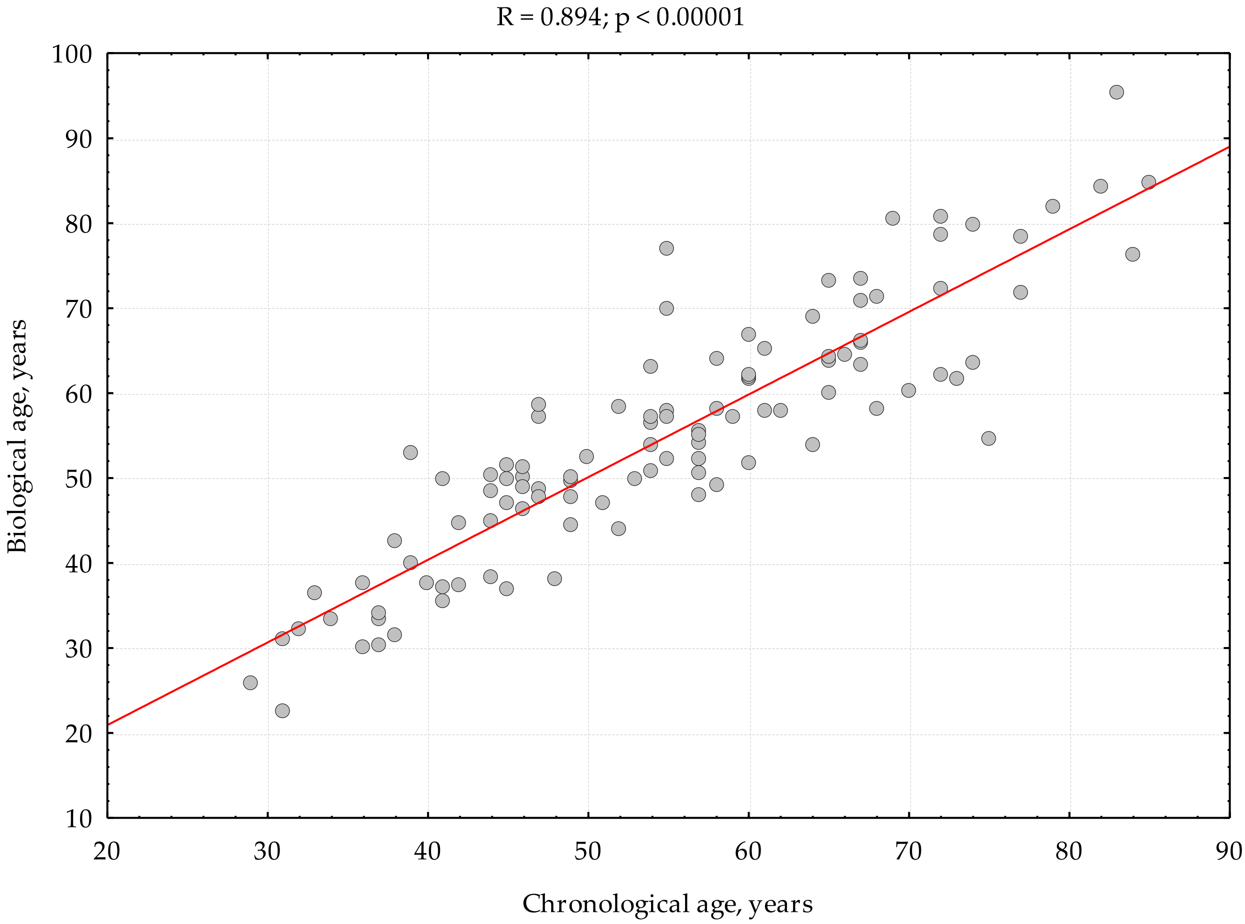

Figure. Correlation between biological age (after error correction) and chronological age.

The average absolute value of the error of BA calculation, in this case, is 5.11±3.51 years. If we consider, as it is used to believe, people with accelerated ageing, whose BA exceeds CA by 10 years, then the proportion of such people among the surveyed people is 8,3 %.

Thus, the method for assessing the rate of ageing developed by us has high accuracy and can be used to assess the risk of developing age-dependent cardiovascular pathology. The implementation of the proposed method will allow not only to identify people with the risk of developing pathology but also to assess the effectiveness of treatment, and prophylactic and rehabilitation measures.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Buljan, K.; Butkovic-Soldo, B.; Janculjak, D., et al. Relationship between age and thickness of carotid arteries in a population without risk factors for atherosclerosis. Coll Antr 2015, 39, 3, 779-784. URL: https://hrcak.srce.hr/166380
2. Cermakova, P.; Ding, J.; Meirelles, O.; Reis, J.; et al. Carotid Intima–Media Thickness and Markers of Brain Health in a Biracial Middle-Aged Cohort: CARDIA Brain MRI Sub-study. The Journals of Gerontology 2020, 75, 2, 380–386. https://doi.org/10.1093/gerona/glz039
3. Chirinos, J. A. Ventricular–arterial coupling: invasive and non-invasive assessment. Artery research 2013, 7, 2-14. https://doi.org/10.1016/j.artres.2012.12.0021
4. Danmei, He; Lan, Gao; Ying, Yang; Jia, Jia; Yimeng, et al. Brachial-ankle pulse wave velocity as a measurement for increased carotid intima-media thickness: A comparison with carotid-femoral pulse wave velocity in a Chinese community-based cohort. The Journal of Clinical Hypertension 2022, 24, 4, 409-417. https://doi.org/10.1111/jch.14448
5. Hamczyk, M; Nevado, R; Barettino, A., et al. Biological Versus Chronological Aging. J Am Coll Cardiol 2020, 75, 8, 919–930. https//doi.org/10.1016/j.jacc.2019.11.062
6. Jia, L.; Zhang, W.; Chen, X. Common methods of biological age estimation. Clin Interv Aging 2017, 12, 759–772. https://doi.org/10.2147/CIA.S134921
7. Maillard, P.; Mitchell, G.F.; Himali, J.J., et al. Effects of arterial stiffness on brain integrity in young adults from the Framingham. Heart study. Stroke 2016, 47, 1030–1036. https://doi:10.1161/strokeaha.116.012949
8. Mamoshina, P.; Kochetov, K.; Putin, E.; Cortese, F.; Aliper, A.; Lee, W.S. et al. Population-specific biomarkers of human ageing: a big data study using South Korean, Canadian and Eastern European patient populations. J Gerontol Ser A 2018, 1, 1–9. https://doi.org/10.1093/gerona/gly005
9. Murabito, J.M.; Zhao, Q.; Larson, M.G.; Rong, J.; Lin, H.; Benjamin, E.J. et al. Measures of biologic age in a community sample predict mortality and age-related disease: the Framingham offspring study. *J* Gerontol Ser A Biol Sci Med Sci 2018, 73, 757–762. https://doi.org/10.1093/gerona/glx144
10. Na, Wu; Haibin, Lv. Observation of the Clinical Correlation between Carotid Artery Intima-Media Thickness and Cardiovascular Risk Factors in Hypertensive Patients under Microscope Images. Journal of Sensors 2021, 1-14. https://doi.org/10.1155/2021/8919824
11. Nilsson, P.; Boutouyrie, P.; Laurent, S. Vascular aging a tale of EVA and ADAM in cardiovascular risk assessment and prevention. Hypertension 2009, 54, 3-10. https://doi:10.1161/hypertensionaha.109.129114
12. Nilsson, P. M. Early vascular aging (EVA): consequences and prevention. Vasc Health Risk Manag 2008 ,4, 547-52. https://doi.org/10.2147/VHRM.S1094
13. Nilsson P.M. Early vascular ageing - a concept in development. European Endocrinology. 2015, 11, 1, 26-31. https://doi:10.17925/EE.2015.1 1.01.26
14. Sebastiani, P.; Thyagarajan, B.; Sun, F.; Schupf, N.; Newman, A.B.; Montano, M. et al. Biomarker signatures of aging. Aging Cell 2017, 16, 329–338. https://doi.org/10.1111/acel.12557
15. Pisaruk, A.V. A simple method for correction of the systematic error in calculating biological age by the multiple regression equation. Ageing and longevity 2021, 2, 11-16. https://doi.org/10.47855/jal9020-2021-1-2