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Estimating biological age of the autonomic regulation cardio-vascular system

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Abstract. Based on our data on age-related changes in blood pressure, ECG, and HRV, we developed a method for assessing the cardiovascular system's biological (functional) age. We set ourselves the task of finding a simple non-invasive method for the integral assessment of the state of the cardiovascular system, which allows us to quantify the degree of age-related changes in this system. The essence of the method lies in the fact that the BA of the cardiovascular system is calculated according to the indicators of BP, QT and HRV. The study included 108 practically healthy people aged from 20 to 90 years. The formula for calculating BA was obtained by multiple stepwise regression. The multiple correlation between biological age and chronological is high (r = 0.895; p <0.00001). The average absolute value of the error of BA calculation, in this case, is 5.19 years.

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, prophylactic and rehabilitation measures.

Keywords: biological age; heart rate variability

Many methods determine a person's biological age (BA) [1–4]. They allow assessing the degree of development of age-related changes in the body as a whole and it's functional systems. The definition of BA is important in geriatric practice, allowing predicting life expectancy, the risk of developing pathology, evaluating the effectiveness of preventive measures, and the effect of geroprotectors.

To assess the BA of the cardiovascular system, data from various research methods are used: blood pressure (BP) measurement, ECG recording, heart rate variability (HRV) analysis, echocardiography. HRV analysis allows assessing the state of autonomic regulation of the heart rate. It is known that with ageing, BP increases, the QT interval on the ECG lengthens, and HRV decreases [5]. With ageing, the autonomic regulation of the heart rhythm changes: the reaction of the heart to vegetative influences, mainly parasympathetic, decreases with ageing, the baroreflex component of the heart rhythm decreases [6-9]. The work aimed to develop a simple, non-invasive method for measuring the degree of age-related changes in the cardiovascular system.

Materials and methods

The study included 108 practically healthy people aged from 20 to 90 years, who were examined at the Department of Clinical Physiology and Pathology of Internal Organs of the State Institution «D.F.

Chebotarev Institute of Gerontology of the National Academy of Medical Sciences of Ukraine». People with pathologies of the cardiovascular, respiratory, endocrine and central nervous systems, chronic liver and All subjects were instructed to avoid alcohol or caffeinated drinks after 10:00 pm. (22:00) the night before the examination. In addition, they refrained from smoking 1 hour before the measurement. BP and ECG measurements were taken from 10:00 to noon, in the supine and standing positions (at 5 and 3 minutes). The subject was instructed to breathe according to his normal rate during the ECG recording. ECG registration was carried out using the ECG-recorder DiaCard (Solvaig, Ukraine). ECG and HRV analysis was performed by program DiaCard v. 1.0.0.73. The duration of the QT interval was measured and QTc (Bazett) was calculated by recording ECG in the supine position at 5 minutes. HRV scores were calculated in the time-domain and frequency-domain [10] (Tab. 1).

Table 1

HRV scores in the time domain and frequency domain

Time-domain methods		
SDNN	The standard deviation of NN intervals	The variance of all NN intervals
RMSSD	The square root of the mean of the squares of the successive differences between adjacent NNs	Parasympathetic activity.
pNN50	The proportion of pairs of successive NNs that differ by more than 50 ms	Parasympathetic activity.
Frequency-domain methods (Power spectral density)		
TP	Total power (≤ 0,40 Hz).	The variance of all NN intervals
VLF	Power is very low frequency range (0,003-0,040 Hz).	Humoral influences.
LF	Power in low frequency range (0,040-0,150 Гц).	Sympathetic and vagal influences.
HF	Power in high frequency range (0,150-0,400 Hz).	Parasympathetic activity.
LFn	LF power in normalised units: 100 LF / (TP - VLF)	Relative sympathetic activity
HFn	HF power in normalised units: 100 HF / (TP - VLF)	Relative parasympathetic activity
LF / HF	Ratio LF / HF	Sympathetic-vagal index

Note: the term "NN" is used in place of RR-interval ECG to emphasize the fact that the processed beats are "normal" beats

The formula for calculating the biological age was obtained by the method of multiple stepwise regression. The indicators of BP, ECG and HRV 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 2).

Table 2

Correlation coefficients between chronological age and biomarkers (Marked correlations are significant at p<0,05)

Biological markers	Pearson Correlations	Spearman Rank Order Correlations
Registration in the supine position, for 5 minutes		
Systolic blood pressure, mm Hg	**0.25**	**0.24**
Diastolic blood pressure, mm Hg	-0.12	-0.15
Heart rate beats per minute	0.02	0.00
QT, ms	**0.24**	**0.26**
QTc, ms	**0.22**	**0.25**
NN, ms	-0.07	-0.01
SDNN, ms	**-0.27**	**-0.26**
RMSSD, ms	-0.17	-0.19
pNN50, %	**-0.31**	**-0.30**
TP, ms^2	**-0.30**	**-0.31**
VLF, ms^2	-0.19	**-0.22**
LF, ms^2	**-0.29**	**-0.29**
HF, ms^2	**-0.20**	**-0.25**
LF/HF	0.02	-0.12
LFn,%	-0.11	-0.12
HFn,%	0.11	0.12
Registration in a standing position, for 3 minutes		
BPS, mm Hg	0.12	0.13
BPD, mm Hg	**-0.22**	**-0.26**
Heart rate beats per minute	-0.17	-0.16
NN, ms	0.08	0.13
SDNN, ms	-0.09	**-0.39**
RMSSD, ms	-0.04	**-0.24**
pNN50, %	**-0.35**	**-0.24**
TP, ms^2	-0.00	**-0.37**
VLF, ms^2	-0.15	**-0.30**
LF, ms^2	-0.08	**-0.55**
HF, ms^2	0.04	**-0.22**
LF/HF	**-0.40**	**-0.46**
LFn,%	-0.11	**-0.44**
HFn,%	**0.32**	**0.41**

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 cardiological indicators (Tab. 3).

Table 3

Regression summary for dependent variable: Age (Model 1)
(Marked correlations are significant at p<0,05)

Regression Summary for Dependent Variable: Age. R=0.752; R^2=0.566; Adjusted R^2=0.540; F(6,83)=21.89; p<0.000001; Std. Error of estimate: 9.110						
	Beta	**Std. Err.**	**B**	**Std. Err.**	**t(83)**	**p-level**
Intercept			-6.0851	13.8761	-0.4385	0.6621
Pulse blood pressure (*supine position*), mm Hg	0.3106	0.0745	0.3832	0,0920	4,1660	**0,0001**
QT (*supine position*), ms	0.2963	0.0729	0.1400	0.0345	4.0643	**0.0001**
LF/HF (*supine position*)	0,2133	0.0775	1.1854	0.4308	2.7517	**0.0073**
pNN50 (*standing position)*, %	-0.3809	0.0743	-0.6985	0.1362	-5.1295	**0.0000**
LF/HF (*standing position)*	-0.4566	0.0805	-2.8006	0.4935	-5.6754	**0.0000**

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; b* – standardized regression coefficient; SE of b* – standardized error of the coefficient.

Y = 0.383 X1 + 0.140 X2 + 1.185 X3 – 0.699 X4 – 2.801 X5 – 6,085 (Model 1)

Y – Predicted age, years

X1 – Pulse blood pressure (Systolic blood pressure - Diastolic blood pressure), mm Hg;

X2 – QT (supine position), ms;

X3 – LF/HF (supine position);

X4 – pNN50 (standing position), %;

X5 – LF/HF (standing position).

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 [11]. For our data, this error is calculated by the formula:

Age predicted error = 22.448 – 0.409 CA (r = -0,648; p = 0,00001).

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 average absolute value of the error of BA calculation, in this case, is 5.19 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 11.1%.

Figure 1 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 = 0.895; p <0.00001).

A simplified formula for calculating BA is obtained from the data in the supine position (Tab. 4).

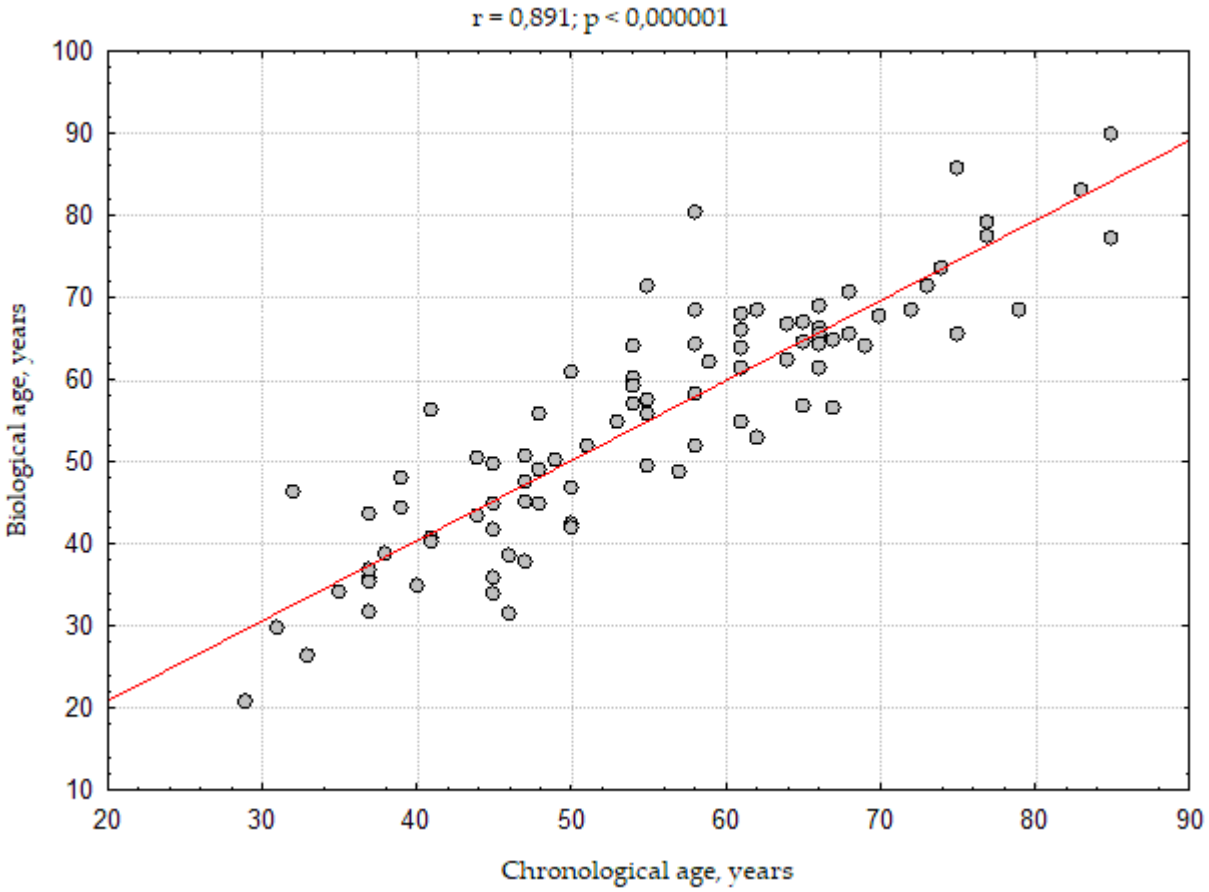

Figure 1. Correlation between biological and chronological age of people (Model 1).

Table 4

Regression summary for dependent variable: Age (Model 2)
(Marked correlations are significant at p<0.05)

Regression Summary for Dependent Variable: Age. R=0.569; R^2=0.324; Adjusted R^2=0.300; F(3.86)=13.753; p<0.000001; Std. Error of estimate: 11.23						
	Beta	**Std. Err.**	**B**	**Std. Err.**	**t(86)**	**p-level**
Intercept			-5.1596	17.0135	-0.3033	0.7624
Pulse blood pressure, mm Hg	0.4249	0.0888	0.5242	0.1095	4.7864	**0.0000**
QT, ms	0.2085	0.0892	0.1034	0.0442	2.3377	**0.0217**
pNN50, %	-0.3197	0.0891	-0.2693	0.0750	-3.5888	**0.0006**

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; b* – standardized regression coefficient; SE of b* – standardized error of the coefficient.

$$Y = 0.524\ X1 + 0.103\ X2 + 0.112\ X3 - 0.269\ X3 - 5.16 \text{ (Model 2)}$$

Y – Predicted age, years

X1 – Pulse blood pressure (Systolic blood pressure - Diastolic blood pressure), mm Hg;
X2 – QT, ms;
X3 – pNN50, %.

The systematic error in calculating of the age, for our data, calculated by the formula:

Age predicted error = 36.19 – 0.661 CA (r = -0.818; p = 0.00001; model 2).

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

BA = Predicted age – Age calculation error (model 2)

Figure 2 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 = 0.890; p <0.00001). The average absolute value of the error of BA calculation, in this case, is 5.67 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 12 %.

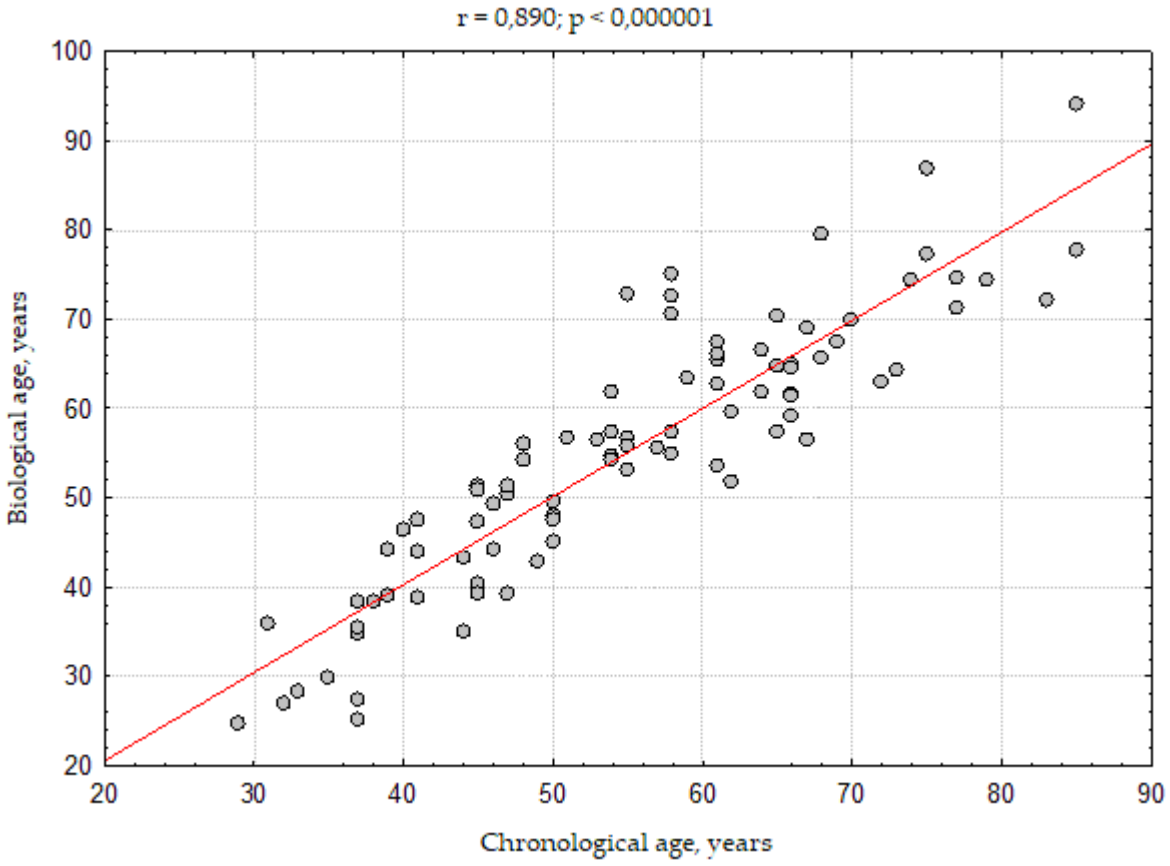

Figure 2. Correlation between biological and chronological age of people (Model 2).

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, prophylactic and rehabilitation measures.

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

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