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Estimating the functional age of the cardiorespiratory system

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Abstract Based on our data on age-related changes in indicators of blood pressure, ECG, HRV, capillaroscopy, and spirography developed a methodology for assessing the biological (functional) age cardiorespiratory system. The study included 116 apparently healthy people aged 20 to 90 years. The formula for calculating functional age was obtained by stepwise multiple regression. Multiple correlation between predicted age and chronological age is large ($r = 0.891$; $p < 0.00001$). The mean absolute value of the BA calculation error, in this case, is 6.12 ± 4.36 years.
The method developed by us for assessing the functional age of the cardiorespiratory system has sufficiently high accuracy and can be used to assess the risk of developing an age-dependent pathology of the cardiorespiratory system. The implementation of the proposed method will allow not only to identify individuals at risk of developing pathology but also to evaluate the effectiveness of therapeutic, preventive, and rehabilitation measures.

Keywords: functional age; cardiorespiratory system

Biological age (BA) is a measure of the rate of aging [1-4]. For this, BA is compared with the person's chronological age (CA). The difference between BA-CA characterizes the rate of aging. If this difference is positive, accelerated aging takes place. In this case, it is possible to predict the risk of developing age-related pathology and premature death [1].
One of the most important physiological systems of the body is the cardiorespiratory system. It combines two systems, the cardiovascular and respiratory systems. Both of these systems can be functionally combined into one cardiorespiratory system. The purpose of such an integrated system is to transport O_2 to cells and remove CO_2 from the body. With aging, the function of the cardiorespiratory system decreases, which leads to the development of hypoxia.

For an integral assessment of age-related changes in the cardiorespiratory system, you can use the calculation of BA according to indicators characterizing the function of this system. Therefore, BA in this case can be called functional age. A simple method for evaluating the function of the respiratory system is spirography [5]. A well-known regular decrease with age of spirography indicators: VC, FVC, FEV1, and others. The function of the cardiovascular system is evaluated by various methods: blood pressure measurement, ECG, HRV, capillaroscopy, and others [6-12]. These methods were used in our study. The purpose of the work is to develop a method for assessing the rate of development of age-related changes in the cardiorespiratory system.

Materials and methods

The study included 116 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». 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. Anthropometric indicators and body composition were measured by Bioelectrical Impedance Analysis Technology. Blood pressure (BP) and ECG measurements were taken from 10:00 to 12:00 in the afternoon, in the supine and standing positions (at the 5-minute). During the ECG recording, the subject was instructed to breathe according to his normal rate. 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 PQ and QT interval was measured by recording ECG in the supine position at 5 minutes. HRV scores were calculated in the time-domain and frequency-domain [11]:

SDNN – The standard deviation of NN intervals; 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;

TP –Total power (≤ 0,40 Hz); variance of all NN intervals;

VLF – Power in a very-low-frequency range (0,003-0,040 Hz); humoral influences;

LF – Power in the 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;

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 lung function was determined by the method of spirography on the device “Spirometer MIR Spirobank II” (Produce MIR S.r.l., Italy). For the assessment of bronchial patency was used, the analysis of the “flow-volume” curve of the forced expiratory [5]. The indicators of the ventilation function of the lungs and the “flow-volume” curve of the forced expiratory were secured:

1. VC - Vital Capacity;
2. FVC - Forced vital capacity;
3. PEF – Peak expiratory flow;
4. FEV1 - Forced Expiratory Volume in one second;
5. FEF 25% -75% - Forced inspiratory flow 25–75%.

Microcirculation of the bulbar conjunctiva was observed under an additional photoelectric lamp, Zeiss, Germany) with further morphometric processing of recordings taken from the freeze-frame mode [12].

The formula for calculating the biological age was obtained by the method of multiple stepwise regression. The indicators of the cardiorespiratory system 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. Our article [13] presents the correlation coefficients of indicators of the cardiovascular systems with age. Tab. 1 shows the correlation of the coefficients of the respiratory indicators with the age.

Table 1

Correlation coefficients between chronological age and respiratory indicators (Marked correlations are significant at p<0.05)

Biological markers	Pearson Correlations
Vital capacity of the lungs (VC), l	**-0,44**
Forced VC (FVC), l	**-0,49**
The volume of forced expiratory for 1 s (FEV1), l	**-0,53**
Peak expiratory flow (PEF), l/s	**-0,42**
FEV1/FVC, %	0,05
Forced expiratory flow 25-75% (FEF25-75), l/s	**-0,44**
Respiratory delay time on inspiration (Ti), s	**-0,35**
Respiratory delay time on expiration (Te), s	-0,14

Tab. 2 shows the correlation of the coefficients of the capilaroscopy indicators with the age.

Table 2

Correlation coefficients between chronological age and capillaroscopic indicators (Marked correlations are significant at p< 0.05)

Biological markers	Pearson Correlations
Diameter of arterioles, μm	**-0.44**
Diameter of venules, μm	**0.27**
Diameter of arterioles / Diameter of venules	**-0.60**
The density of functioning capillaries on 1 mm^2	**-0.68**

The use of stepwise multiple regression makes it possible to select the most informative indicators and obtain an equation linking the age of the examined people with a number of cardiological, capillaroscopic, and respiratory 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= 0.801; R^2= 0.637; Adjusted R^2= 0.617; F (6.109) = 3.,88; p< 0.00001; Std. Error of estimate: 7.834						
	Beta	Std. Err. of Beta	B	Std. Err. of B	t(109)	p-level
Intercept			44.620	12.161	3.668	**0.0003**
Waist/hips	0.192	0.065	33.054	11.233	2.942	**0.0039**
FEV_1/Height, l/m	-0.346	0.072	-10.604	2.217	-4.783	**0.0001**
The density of functioning capillaries on 1 mm^2	-0.216	0.069	-1.362	0.435	-3.127	**0.0022**
Diameter of arterioles / Diameter of venules	-0.222	0.064	-36.379	10.449	-3.481	**0.0007**
PQ, ms	0.157	0.066	0.084	0.0353	2.384	**0.0188**
SBP-DBP, mm Hg	0.211	0.064	0.282	0.0861	3.278	**0.0014**

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; Beta – standardized regression coefficient; B – regression coefficient.

$$Y = 0.282\ X1 + 0.084\ X2 - 10.604\ X3 - 36.379\ X4 - 1.362\ X5 + 33.054\ X6 + 44.62 \text{ (Model 1)}$$

Y – Biological (functional) age, years

X1 – SBP-DBP, mm Hg;

X2 – PQ (*supine position*), ms;

X3 – FEV_1/Height, l/m;

X4 – Diameter of arterioles / Diameter of venules;

X5 – Density of functioning capillaries on 1 mm^2;

X6 – Waist/hips (ratio of waist circumference to hip circumference).

The average absolute value of the error of BA calculation, in this case, is 6.12±4.36 years. If we consider, as it is used to believe, people with accelerated aging, whose BA exceeds CA by 10 years, then the proportion of such people among the surveyed people is 10.34%.

Fig. 1 shows a graph of the correlation between BA and CA. It can be seen that the dispersion of points around the regression line is small and the multiple correlation coefficient is high ($r = 0.801$; $p < 0.00001$).

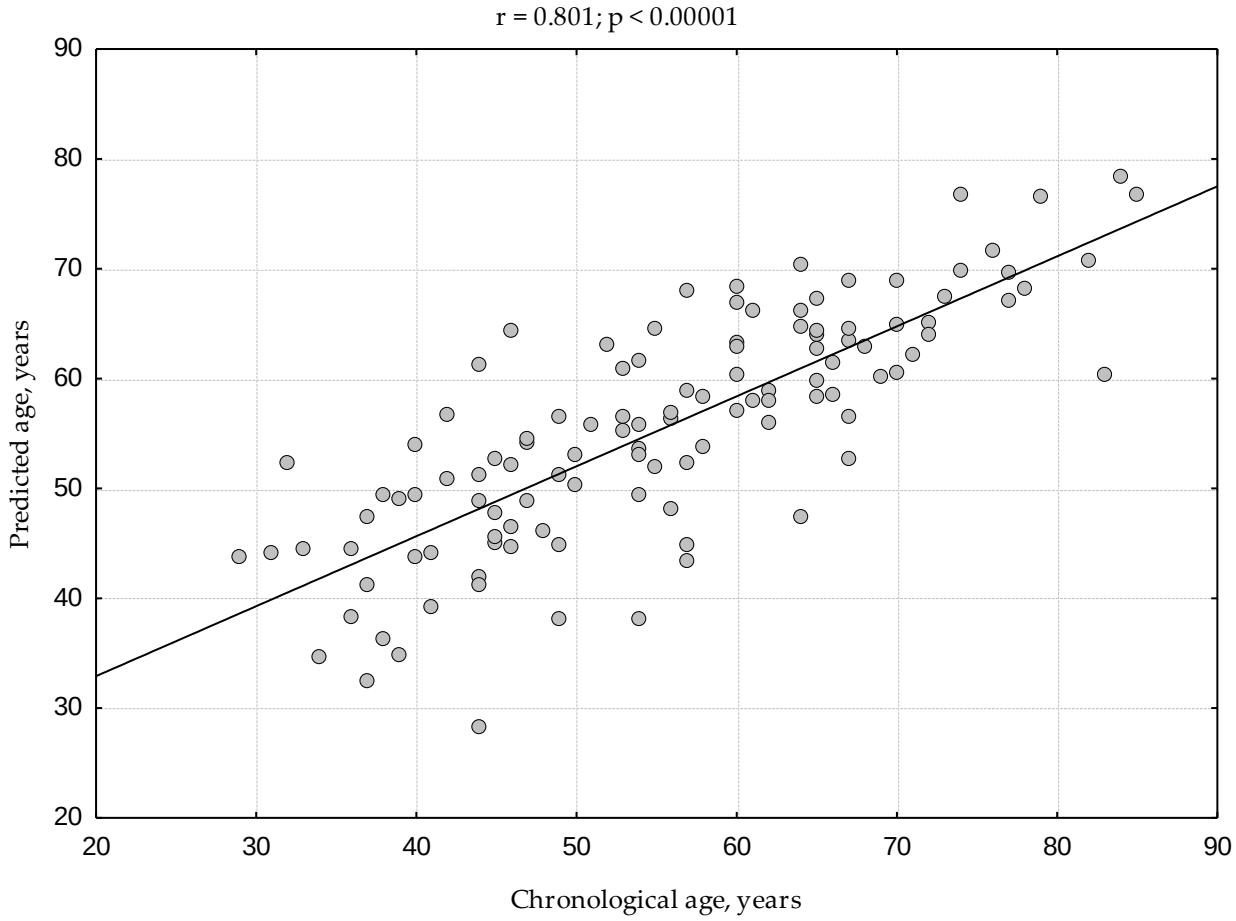

Figure 1. Correlation between predicted (biological) and chronological age of people (Model 1).

The resulting formula is fully consistent with the known age-related changes in the indicators of the cardiorespiratory system. So, with aging, the following increase: pulse BP, PQ ECG interval (impulse

conduction from the atria to the ventricles of the heart slows down), the ratio of waist circumference to hip circumference (Waist/Hips). At the same time, the forced expiratory volume in 1 second (in relation to body height, FEV1/Height), the ratio of the diameter of arterioles to the diameter of venules, and the density of functioning capillaries in the bulbar conjunctiva of the eye decrease.

Calculation of the functional age cardiorespiratory system according to the Model 1 formula requires capillaroscopy. This method is not available in many hospitals. Therefore, Model 2 was calculated, which does not include capillaroscopy values (Tab. 4). Instead, HRV in supine and standing positions, as well as the proportion of visceral fat, were used.

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=0.791; R^2= 0.625; Adjusted R^2= 0.594; F (10.105) = 19.661; p< 0.000001; Std. Error of estimate: 8.359						
	Beta	**Std. Err. of Beta**	**B**	**Std. Err. of B**	**t(105)**	**p-level**
Intercept			31.800	12.026	2.644	**0.009**
Waist/Hips	0.164	0.073	28.140	12.609	2.232	**0.028**
Visceral fat, %	0.224	0.077	0.681	0.235	2.892	**0.005**
FEV_1/Height, l/m	-0.523	0.075	-16.017	2.306	-6.947	**0.000**
Respiratory delay time on inspiration, s	-0.128	0.067	-0.104	0.054	-1.923	**0.049**
PQ, ms	0.143	0.071	0.077	0.038	2.031	**0.045**
SBP-DBP, mm Hg	0.209	0.067	0.279	0.090	3.102	**0.002**
HF (*supine position*), ms^2	-0.117	0.061	-0.006	0.003	-1.918	**0.049**
VLF (*standing position)*, ms^2	0.179	0.067	0.006	0.002	2.690	**0.008**
LF (*standing position)*, ms^2	-0.138	0.062	-0.011	0.005	-2.212	**0.029**

Note: Designations as in Tab. 3

$$Y = 31.80 + 28.14\ X1 + 0.68\ X2 - 16.02\ X3 - 0.104\ X4 + 0.077\ X5 + 0.279\ X6 - 0.006\ X7 + 0.006\ X8 - 0.011\ X9$$

(Model 2)

Y – Biological (functional) age, years;

X1 – Waist/Hips (ratio of waist circumference to hip circumference

X2 – Visceral fat, %;

X3 – FEV_1/Height, l/m;

X4 – Respiratory delay time on inspiration, s;

X5 – PQ (*supine position*), ms;

X6 – SBP-DBP, mm Hg;

X7 – HF (*supine position)*, ms^2;

X8 – VLF (*standing position)*, ms^2;

X9 – LF (*standing position)*, ms^2;

Fig. 2 shows a graph of the correlation between BA 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 = 0.791; p< 0.00001). The average absolute value of the error of BA calculation, in this case, is 6.54±4.61 years. If we consider, as it is used to believe, people with accelerated aging, whose BA exceeds CA by 10 years, then the proportion of such people among the surveyed people is 10.34 %.

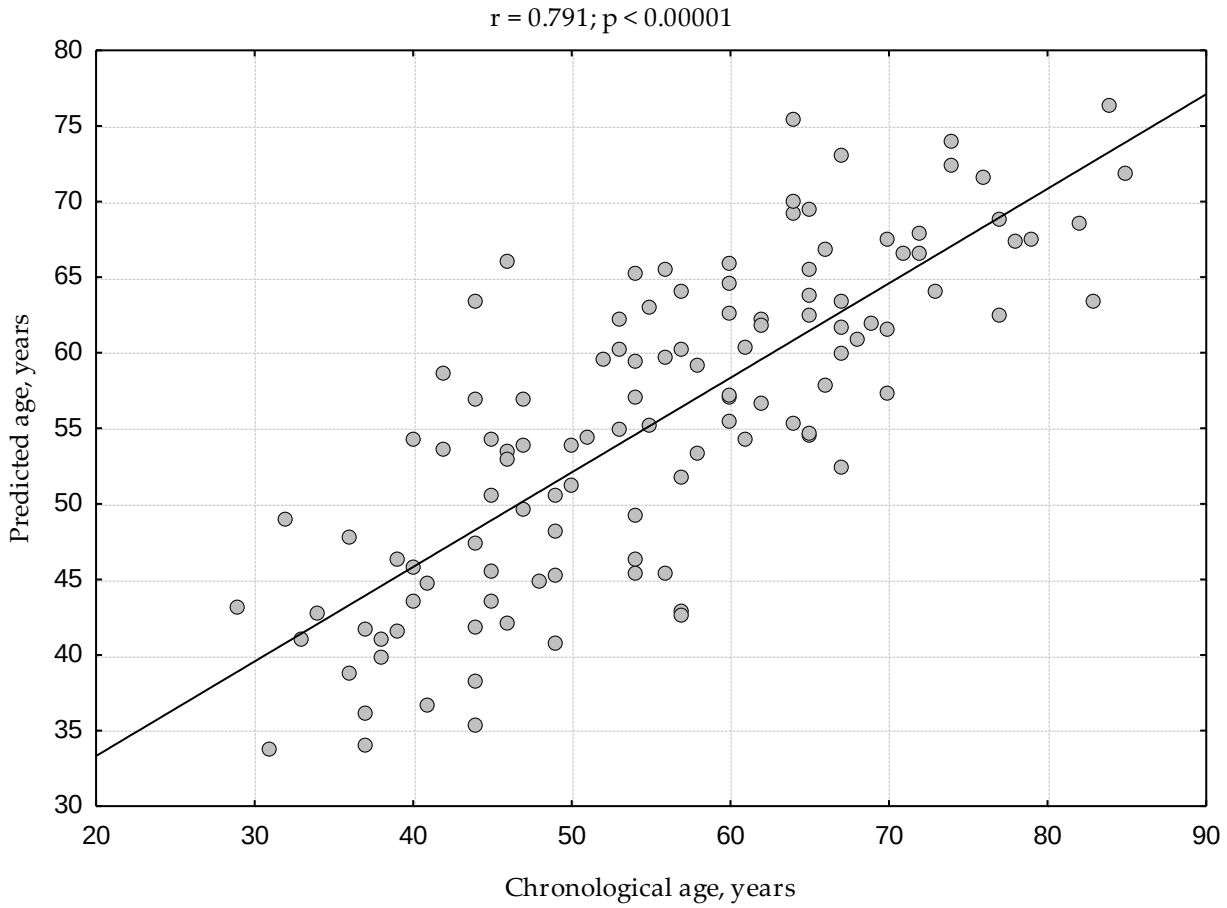

Figure 2. Correlation between predicted (biological) and chronological age of people (Model 2).

Our formulas for calculating the functional age cardiorespiratory system are sufficiently accurate to estimate the rate of aging. The first formula requires capillaroscopy, which is not available for many medical institutions. The second formula includes simple, accessible tests, so it can be used more widely.

Functional age models are calculated on a small dataset, so they need to be refined and tested on a larger amount of data.

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

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