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Diagnosis of Aging. Report II. Age Dynamics of Correlation between the Biological Markers of Aging

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Abstract—The correlation analysis of the relationship between the biological age markers in three age groups revealed alterations in the number and rate of correlations up to the inversion of these relations in some cases. As a whole, the observed changes can be characterized as a rearrangement at the regulatory interactions with an increase at the strain of the functioning of the body organs and systems at the middle age and an alteration in the coordination of the body system functioning at the elderly age. The ways of the optimization of the standard methods for the biological age measurement are discussed with regard to these changes.

One of the main tasks of the age physiology, gerontology, and geriatrics is to determine a marker of aging that can effectively reflect the fact that organisms with the same chronological age (ChA) can be characterized by different vitality. A search for such a marker, called the biological age (BA), has continued for several decades [1]. The conclusion that the unique factor, which can serve as a measure of the biological time and the criterion of a reduction in vitality of the whole body, cannot exist among the great number of the body parameters can be attributed to the unfavorable results of investigations in this field [2, 3]. Considering this conclusion, some investigators reject the expediency of the BA determination [4]. However, practical demands for the evaluation of the rate of heterogeneity of the risk of death among subjects with the same ChA gave rise to a wide variety of methods for the determination of the integral value of the BA as a function of some finite set of the body functional parameters regarded as the biological markers of aging ($M_1, M_2, ..., M_n$):

$$BA=f(M_1,M_2,...,M_n). \quad (1)$$

In practice, the most simple mode of presenting the BA as a set of biological markers, the so called multiple linear regression, is used mostly:

$$BA = A + B_1M_1 + B_2M_2 + ... + B_nM_n, \quad (2)$$

in which the A, $B_1, B_2, ..., B_n$ are the constants or the parameters of the linear model of the BA.

Different parameters of the essential body functions can be chosen for the biological markers. These parameters must change significantly with the age in the interval between puberty and extreme old age. The variability of these parameters due to the aging must be significantly greater than the interindividual variability. The following parameters can be singled out among the biological markers used: morphological, psychological, neuropsychic, biochemical, immunological, pathological, parameters of the physiological functions at rest and during performance of tests with loads, and also the subjective indices of condition self-rating [1, 5].

Commonly, the multiple linear regression formulas for the BA evaluation are constructed for men and women separately (quite often the sets of markers for men and women differ) but are applied with the same coefficients for the integral adult population in the age range between puberty and extreme old age. This approach is reasonable in the case that the contribution of each marker in the complex process of the body aging does not depend on the age. However, in fact, aging is just related to alteration in the system organization. The simplest example of such an alteration is the change in correlation between the most important functional parameters. Therefore, the elaboration of specific methods for the quantitative and qualitative evaluation and interpretation of the systemic organization of the body integrity and of the ontogenetic changes in this organization seems to be of great importance.

The investigation of the relationship between the aging markers is also important for the optimization of the methods for the BA measurement. Evidently, in the case of the high correlation between the two markers reflecting the linear interrelationship, one of these markers can be excluded from consideration. Moreover, markers, which correlate with the ChA weakly, can also be excluded because of the significant excess of their intefindiyidual variability over the mean population age alterations. However, the question of including the markers with low correlation coefficients with the age into the formula for the BA calculation should be considered in terms of the results of a more subtle analysis than the simple linear regression, because their age dynamics has a significantly nonlinear character.

It should be kept in mind that the parameters included in (2) as independent variables are not functionally independent. All the informative biological markers of aging are related to the age. Thus, the existence of functional relationships between them is natural. In the majority of the cases, these relationships cannot be reduced to the linear function, but, frequently, there is a strong enough correlation. This is why the construction of effective methods for the BA evaluation should apply the mathematical apparatus of the regression analyses for models, which are linear in parameters but not in variables [6].

This paper presents an analysis of a set of biological markers of aging used in the so-called Kiev method for the BA determination, which is widely used in Russia [7]. The study was aimed at the detection of changes with age in the pattern of interrelations in the set of markers and also in the type of association of these markers with age.

PROCEDURE

We examined 153 practically healthy women in the 25-69 age range who applied for assistance to the geriatric preventive center, which worked in the Medical and Sanitary Unit № 169 administered by the Office on Medical-Biological and Extreme Problems, and to the National Center of Gerontology over a period of time between 1995 and 1999. A set of parameters specified by the type method (the so called Kiev method) for the BA determination was recorded [7]: (1) systolic, diastolic, and pulse blood pressure (BP_S, BP_d, and BP_{pulse}); (2) rate of the pulse wave propagation along the elastic-type vessels (RPW_e) in the zone of carotid-femoral arteries; (3) rate of the pulse wave propagation along the muscle-type vessels (RPW_m) in the zone of carotid-radial arteries; (4) vital lung capacity (VLC); (5) breath-holding (BH) time at expiration; (6) lens accommodation according to the nearest view point distance (Ace); (7) auditory threshold (ATh) at 4000 Hz; (8) static balancing (SB) on the left leg; (9) body weight (BW); (10) Wexler symbolic-digital test (WT), the number of cells filled in correctly within 90 s; and (11) self-rating of health (SRH).

The particular methods for the examination and recording of the physiological functions were applied strictly in compliance with recommendations for this procedure. The height of the subjects examined was also recorded. Three age groups were singled out of the test subjects with 15-year intervals: 25-39 years (young age), 40-54 years (middle age), and 55-69 years (old age). The groups comprised 53, 76, and 24 subjects, respectively.

The data were analyzed by means of the standard statistical methods: correlation and variance analyses. Contingency tables were analyzed by the chi-square test.

RESULTS AND DISCUSSION

The correlation rate of the set of the aging markers with the age appeared to be significantly irregular (Table 1). The RPW_e and the RPW_m parameters had the strongest association with age. This result supports the hypothesis advanced earlier several times on the leading role of changes in the connective tissue of vessels in the general process of the human body's aging [8-10]. The rate of association between the age and the blood pressure value, VLC, and the parameters related to the analyzer functions and the intellectual activity was significantly lower but reliable and approximately the same. The relationships of the anthropometrical parameters and the level of the health self-rating (SRH) to the age were still less pronounced, whereas the BH did not correlate significantly with the age. None of the correlation coefficients exceeded the module value 0.7. Since the square correlation coefficient between the two parameters characterizes the variation ratio of one of them, which can be explained by the linear dependence on the other, this result is compatible with the conclusion that the linear relationship between the chronological age and the parameters studied explains their age dynamics in less than one half of cases. The differences in the types of these relationships in various age groups can determine the low, though reliable, relationship between the markers and the age (Table 2).

Pronounced changes in the age dynamics of various parameters have been noted with the transfer from one age group to another. No reliable associations with the age were seen in the young group. The most probable explanation to this fact is the relatively low value of age alterations in the age range between 25 and 39 years compared to the interindividual differences. The middle-aged subjects were characterized by a significant increase in the blood pressure values with the age, which reflected a more pronounced significance of the age alterations in the cardiovascular system in this group of subjects, compared to the individual variability. A decrease in the intellectual activity revealed by the worsening with the age of the Wexler test performance was also significant in this group. Positive correlation between the age and accommodation may reflect the development of the age hyperopia. The characteristic feature of this group was the negative correlation between height and age, which could be probably associated with the fact that this group comprised subjects born during the period between 1941-1959. During this period of time, the life conditions in childhood changed, which could have had an impact on general growth and development. In general, the maximal number of reliable correlations between the age and the parameters studied characterized the middle age group, which could be explained by the almost linear type of their age dynamics. The number of parameters corre-

Table 1. Coefficients of correlation between the aging markers and the age with significance evaluation of their difference from 0

Parameter	Coefficient of correlation with the age
BP_S	0.43***
BP_d	0 38***
BP_{pulse}	0. 31***
RPW_e	0.70***
RPW_m	0.70***
VLC	-0.40***
BH	-0.04
Acc	0.30***
Ath	0.36***
SB	-0.32***
BW	0.28**
SRH	0.24**
WT	-0.35***
Height	-0.27**

Note: For abbreviation expansion here and in Tables 2 and 3 see the "PROCEDURE" section.
here and in Tables 2 and 3 $^0 0.05 \leq p < 0.10$.
*p<0.05.
**p<0.01.
***p< 0.001.

Table 2. Age correlations of the parameters examined in three age groups

Parameters	Coefficients of correlation with the age		
	young	middle age	aged
SRH	0.20	-0.09	0.16
BW	0.15	0.20	0.31
Height	-0.07	-0.26*	0.03
BP_S	0.04	0.27*	-0.42°
BP_d	0.14	0.30*	-0.27
BP_{pulse}	-0.06	0.12	-0.45*
BH	-0.08	-0.14	0.30
SB	-0.13	-0.12	-0.19
RPW_e	-0.16	0.11	-0.26
RPW_m	-0.13	0.03	-0.08
VLC	0.01	-0.18	0.11
Acc	-0.02	0.34**	0.24
Ath	0.25	0.11	-0.15
WT	0.02	-0.34**	-0.48*

lated significantly to the age is reduced in the old age group; i.e., the individual differences prevail over the general regularity of the age dynamics. Similar to the middle age group, the deterioration of intellectual activity with the age is significant. The most important dissimilarity from the previous group is the inversion of the sign of the correlation coefficient between blood pressure and age. This result reflects pronounced age alterations in the structural organization.

Fig. 1. shows the age dynamics of blood pressure with more detailed age division of groups, in 5-year ranges.

Analysis of the variance in the case of the blood pressure averaging in every 5-year age range showed that in the 25-69 year range, there was a significant relation between this parameter and the age *($p < 0.001$)*. However, there are differences in various segments of this range. According to the correlation analysis, in the age range between 25 and 39 years, the relationship is insignificant; in the age of 40-59 years, the relationship is positive; and in the age of 60 years and older, the relationship is negative. The observed BP reduction in subjects from the oldest age group can be explained by the fact that we examined only subjects who were practically healthy and applied to the Gerontology preventive center. The level of BP, which is not accompanied by pronounced cardiovascular pathology, is very likely to be decreased in the old compared to the mean normal value for this age. The idea of the existence of the crucial value of the BP_S compatible with normal body functioning is in good accord with the aging model of a single individual [11]. According to this model, aging is associated with the overrun of one of the crucial systems of the body (including the cardiovascular system) beyond the limits of homeostasis.

Table 3 presents the pattern of correlation coefficients between the aging markers revealed without dividing of the cohort of test subjects into the age groups.

An extremely high correlation coefficient was noted between the RPW_e and RPW_m values, which pointed to the near linear relationship in the course of the total age range. This fact opens up possibilities of reducing the number of markers at the expense of excluding one of these parameters without noticeable loss of information. Within the group of cardiovascular system parameters (BP_S and BP_d) and between the parameters of the general physical development (VLC and height) correlations were rather high. For the other pairs of parameters, the correlations were not high; however, they were significant in many cases. A nonlinear type of relationship between the parameters can be one of the causes for a nonlinear character of correlation.

An analysis of the correlation between the markers in the individual age groups confirmed the assumption that the character of relations between them changed with the age (Fig. 2).

The main feature of the correlation pattern is the strengthening of interactions on transfer from the young age group to the middle age group. This event is accompanied by the breaking down of the set of parameters examined into two groups: the mere physiological parameters and the parameters of the analyzer function and the intellectual activity. These groups are practically not interrelated. There is a great number of intrinsic correlations in the group of physiological parameters, whereas in the group of nonphysiological parameters, the intrinsic relations are significantly weaker. This fact could be related to the coordinated activation of the physiological mechanisms in the middle age. The number of reliable correlations is the least in the old age group. The type of interrelations between certain parameters changes with the age. Thus, BH does not correlate with VLC in the young and the middle age but correlates with weight in the young group and with weight and blood pressure in the middle group. In the old group the correlation of BH with VLC is positive and significant. These results reflect the fact that an oxygen providing system capacity is restricted to the anatomical structure in the young, to the cardiovascular system capacity in the middle-aged, and to the lung function in the old age group.

The number of significant ($p < 0.05$) correlations between the markers in the young, middle, and old age groups is 10, 19, and 5, accordingly. In terms of the fact that the total number of paired correlations between 14 parameters equals 14 x (14- l)/2 = 91, the chi-square test reveals a statistically significant ($p < 0.01$) relation between the age and the number of reliable correlations. The greatest number of significant intrinsic correlations was observed in the middle age group, and the least number of correlations was observed in the old age group. A considerable number of the correlations between different parameters is typical for a condition of coordinated mobilization of different functional systems of the body. Thus, the small number of correlations can occur in two cases: when the living conditions are not stressful and do not require mobilization or when the coordinated functioning of different subsystems of the body can not be maintained due to the overrun of some of them beyond the limits of the extreme permissible level (there are no correlations in this case) or due to approaching to the extreme level (when the functional relations between the subsystems are significantly nonlinear). The first case is typical of the young age group. Correlations between certain parameters absent at rest can possibly be revealed under the conditions of functional loading tests. An imbalance of the functional systems of the body is more likely to occur in the old age group and may be related to different mechanisms of aging: with the accumulation of diversity due to the insufficiency of the selection

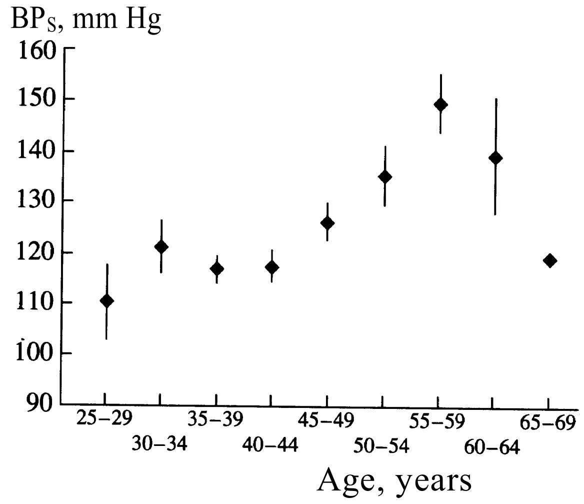

Fig. 1. Age dynamics of BP_S in women (means and SEM).

forces inside an individual, or with reduction in the number of the reviving structures [12].

The nonmonotonic type of age dynamics of biological markers obliges to analyze more carefully the existing approaches to the BA determination. Thus, the age ranges should be singled out precisely for all the linear BA models characterized by the absence of the nonmonotonic and significantly nonlinear segments for all the markers used, because the linear models are inadequate beyond the limits of such ranges. The nonlinear effects can be taken adequately into account in models regarding the BA deviation from the ChA as a weighted total of particular deviations, which characterize the difference between the ChA and the BA of specific body systems [9]. Moreover, the particular BA is measured in terms of the mean population relations between the functional parameters of appropriate systems and the age. Here, the weight coefficients are not constant but increase as the particular markers approach their crucial level. The unequivocal determination of the particular BAs for such models is only possible in the case of the monotonous age dynamics of the markers. The decisive rules for the determination of the BA for certain subsystems (e.g., the determination of the cardiovascular system BA for an individual value of the BP_S =135 mm Hg) with nonmonotonic fluctuating markers in the course of aging can be elaborated. In addition, they should include some additional relationships, which characterize interaction of various functional systems.

CONCLUSIONS

The analysis of the correlation between the biological markers of aging in three age groups revealed alterations in the number and rate of correlation relationships between particular markers and also between markers and age. There was a nonmonotonic type of relationship between BP_S and age. The age alterations

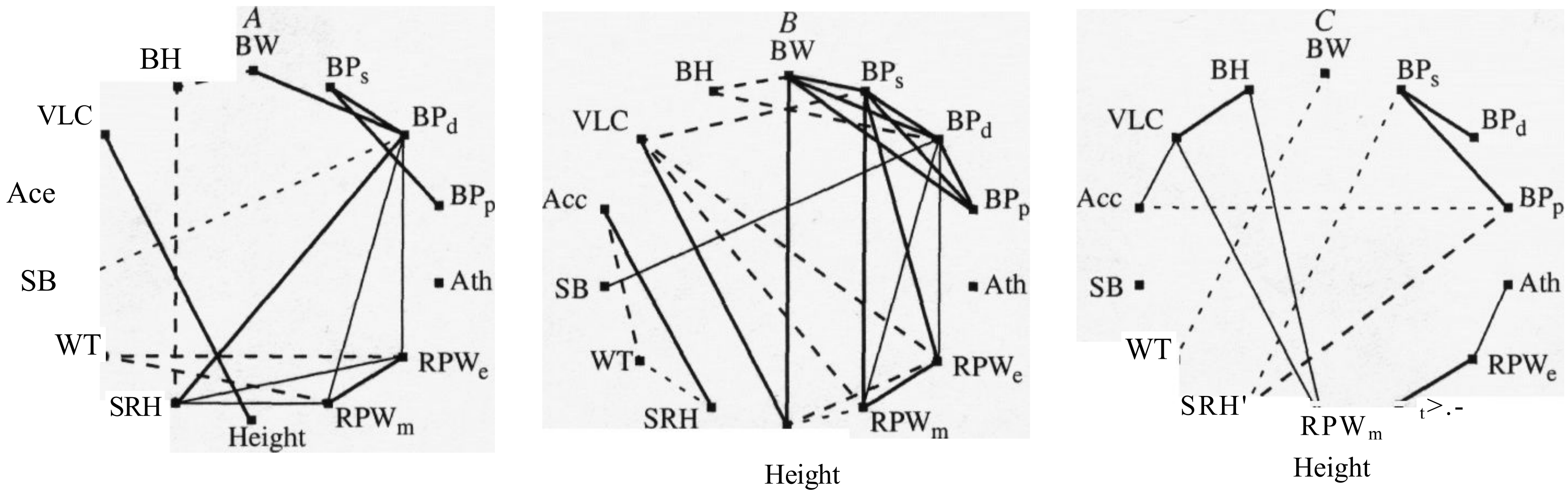

Fig. 2. Pattern of correlations between the aging markers in the *(A)* young, (B) middle, and (C) old age groups. Note: Solid lines show the positive values of correlation coefficient *r* between the given parameters, and the dotted lines shows the negative values. Bold lines indicate correlation coefficients, which differ from 0 with the $p < 0.05$ significance; thin lines, with the $0.05 \leq p < 0.10$ significance. For abbreviation expansion see the "PROCEDURE" section.

in correlations between the biological markers of aging may be related to a rearrangement in regulatory interactions at the level of particular functional system or at the integral body level. This rearrangement can become apparent as an increase in the functional strain of organs and systems in the middle age and as disturbance in coordination of the body system functioning in the old age. Another reason for the differences in correlations between the aging markers seen in different generations is the historical change in the health conditions of people. The observed alterations point to limitations of the methods for the BA measurement, which use the models of multiple linear regression. There are three ways for increasing the validity of the BA determining methods: specializing the parameters in the linear regression models of the BA for particular age ranges, the application of nonlinear models, and the

Table 3. Coefficients of correlation between the aging markers

Parameters	SRH	BW	Height	BP_S	BP_d	BP_{pulse}	BH	SB	RPW_e	RPW_m	VLC	Ace	Ath
BW	0.08												
Height	-0.22*	0.16°											
BP_S	0.12	0 30***	-0.07										
BP_d	0.24*	0.42***	-0.09	0.68***									
BP_{pulse}	-0.04	0.15	-0.02	0.78***	0.08								
BH	-0.23*	-0.32**	0.28**	-0.16°	-0.25*	-0.01							
SB	-0.17°	-0.25**	0.06	-0.16°	-0.09	-0.16	0.19°						
RPW_e	0.30**	0.29**	-0.35***	0.40***	0.32**	0.27**	-0.08	-0.27**					
RPW_m	0.31**	0.31**	-0 33***	0.39***	0.31**	0.26**	-0.08	-0.25**	099***				
VLC	-0.26**	-0.17°	0.69***	-0.21*	-0.22*	-0.10	0.36***	0.19°	-0.50***	-0 47***			
Ac	0.35***	0.07	-0.11	0.12	0.10	0.08	-0.04	-0.03	0.21*	0.22*	-0.06		
Ath	0.03	0.06	-0.08	0.01	-0.04	0.05	0.10	-0.09	0.30**	Q 22***	-0.15	0.02	
WT	-0.21*	-0.14	0.06	-0.15	-0.07	-0.15	0.10	0.10	-0.30**	-0.28**	0.01	-0.35**	-0.15

development of BA models using approaches other than the multiple regression.

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