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Polysystemic Approach to School, Sport and Environment Medicine

Edited by

Mikhail Karganov

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Preface

One of the basic research objectives of the present monograph is to update multidisciplinary specialists on contemporary instrumental and analytical means and methods of automatic polysystemic sanogenetic monitoring. The unique advantage of this monitoring lies in not only information capacity of dynamic criteria registered, but also its ability to automate measurement and indication procedures and to ensure simultaneous operation and development of technical facilities. Substantiation of the sanogenetic theory, creation of automatic examination facilities for individual sanogenesis and large-scale approbation of these methods in school, sport and environment medicine required cooperation of specialists from many scientific fields.

Thank you,

Mikhail Karganov

About Editor

Mikhail Karganov was born 13.11.1956 in Odessa, USSR. In 1980 he was graduated from Moscow Mendeleev Institute of Chemical Technology, organic-fuel faculty, technology of microbiological production. At the age of 28, he presented his Ph.D Theses “Study of the role of peptides in the regulation of muscle tone in vestibulopathy” at the Institute of General Pathology and Pathophysiology, Russian Academy of Medical Sciences. In 2001, he accomplished his postdoctoral studies “Peptidergic mechanisms of occurrence and elimination of experimental neuropathologic syndromes” at the same institute and was given Dr. Sci. degree. From 1980 till 1988 – assistant researcher, from 1988 till 2000 – senior researcher at the Institute of General Pathology and Pathophysiology, since 2001 - head of Laboratory of Polysystemic Investigations of Institute of General Pathology and Pathophysiology. M. Karganov has published more than 100 papers in reputed journals and works as an editorial board member. Since 2006, works as a professor. The sphere of his scientific researches over the last 15 years includes the development of new biophysical methodologies that enable rapid detection in a noninvasive mode of the functional status of regulatory systems responsible for preservation of its adaptive potencies of the body.

Forewords

The modern world throws humanity new challenges. Go change the environment is changing information environment. People try to adapt to this changes, developing science and technology. In turn, the new generations have to learn all these achievements. All this places high demands on the education system, it will have to change following the changes of our world. The only way to evaluate the effectiveness of changes in education and the "cost of adaptation" is medical-biological research. The book is devoted to the description of the general principles, methodological approaches and tools of biomedical monitoring of adaptive changes.

Nataliya Pankova

One of the indicators of health status is considered the body's ability to adapt to the environment and implement adaptive capacity of the body. This book reports new facts and their original interpretations. It is interesting and addresses useful methods to evaluate the cardiovascular, breathing, psychomotor and metabolic systems. Since the transition from health to illness is associated with low adaptive capacity, high practical significance of this book does not cause doubts.

Alchinova I

This book is devoted to substantiation of new concepts of fundamental mechanisms of sanogenesis. Polysystemic sanogenetic monitoring is a technology to evaluate adaptive and compensatory capacity of an organism as a biological system in response to variation of the external or internal conditions. The developed concepts and approaches open new prospects in predictive diagnostics and medicine.

Semenov AL

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Introduction

According to current views, human body is a self-organizing system capable of maintaining its homeostasis and open for energy and information exchange with the environment. Individual norm for this system is an optimal level of functioning ensuring homeostasis maintenance with consideration for the age, sex, biological (constitutional) type, climatic, geographic, and ecological factors. Technical progress necessitates continuous control over the quality of life and health of the population, especially, children as its most susceptible part. Due to individual variability of sanogenetic processes, the same anthropogenic factor in equal doses and concentrations will cause certain effects in some individuals (sensitive), will not cause in others, and will induce resistance in the thirds. This implies that at the population level three subpopulations should be determined at relatively low-dose and low-concentration exposures: sensitive, neutral, and super resistant. The ratio between these subpopulations can eventually serve as a criterion of population risk for the corresponding exposure.

Reduction of health reserve impairs adaptive capacities of the organism, which determines the first stage of transition from health to disease. At this stage (prenosological state), functional parameters of the body are within the normal range, but the mechanisms of adaptation work in a strained mode to maintain health parameters at the required level. Sanogenetic monitoring makes it possible to diagnose prenosological states and to identify risk groups. Polysystemic monitoring implies repeated examinations of individuals including simultaneous evaluation of the functional state of several physiological systems. For evaluation of the individual sanogenetic status, we chose the major functional systems that can be examined by modern non-invasive express-tests and reflecting the dynamic state of the body. Monitoring is carried out using computer-aided measurement instrumentation and data processing systems, which provides the basis for strict quantitative assessment of the dynamics of risk for the studied populations.

Due to stochastic features of risk assessment, its applicability to the diagnosis, prevention, and protective or compensatory measures in some cases can be very limited. The proposed concept combining approaches based on the risk analysis and sanogenetic analysis is aimed at increasing the efficiency of both approaches in addressing issues of risk prediction.

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Chapter: I

Fundamental Principles of Health Support Regulation Mechanisms (Sanogenesis)

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Abstract

Contemporary theories of sanogenetic adaptation, epigenetic management and constitutionality of biological regulation systems are discussed. An organism has special sanogenetic systems designed to analyze the changing internal and external conditions and to ensure the most efficient mode of interaction. This means that the state of health basically depends on the priority of functions that may be sacrificed for adaptation. It is valid for a wide range of external conditions (climate change, harmful influences, school problems, social transformation, etc.) and internal conditions (diseases, growth and development of organs and systems, etc.). The problem of polysystemic monitoring of the body's sanogenetic potential may, therefore, be solved through the creation of a program and tool complex that would allow identifying individual functional sufficiency of organisms based on the functional connection between basic health systems. Tasks of this complex include diagnostics of causal factors of pathologies in order to detect relevant risk groups (first approach) and identification of danger levels in these risk groups (predicted pathology gravity) by the degree of modification of defense mechanisms (second approach).

Keywords: Adaptive Reserve; Health Status; Polysystemic Monitoring; Sanogenesis

Introduction

One of the basic research objectives of the present monograph is to update multidisciplinary specialists on contemporary instrumental and analytical means and methods of automatic polysystemic sanogenetic monitoring. The unique advantage of this monitoring lies not only in the information capacity of dynamic criteria registered, but also in its ability to automate measurement and indication procedures and to ensure simultaneous operation and development of technical facilities.

It is clear that the theoretical justification of the sanogenetic theory, creation of automatic examination facilities for individual sanogenesis and large-scale approbation of its methods required cooperation of specialists from many scientific areas. These are listed as the numerous authors of this study. It is important to note that this cooperation was based on the single fundamental theory laid down below.

While creating and exploring the general theory on sanogenesis regulation in children, we faced a number of problems that required advanced knowledge of molecular genetic fundamental concepts of cell management and organismic adaptation and understanding of their role in evolution mechanisms and the degree of their inter-correlation with external and internal environment factors on constitutive and inducible levels.

This knowledge is required due to the progress of pedagogical technologies, the risks of which tend to raise more and more generally unfounded disputes. The problem is that the danger is discussed only in terms of the so called "stress" impacts, damaging important survival processes and abilities. However, at the same time, it is ignored that stress is a physiologically adequate generator of the functional growth of an organism that is vital for successful development in many spheres of human activities.

This situation led us to a wider range of questions as compared to those 30 years ago, when our research was started. On the one hand, it is a common biological problem covering general regulation in living organisms, homeostasis, one of the origins of classical cybernetics, as well as regulation and self-regulation of the biological evolution. On the other hand, there is an even more interesting and unexpected, but already classical, problem of the nature of "scientific revolutions". We now happen to take part in a revolution with a non-traditional change of paradigms, when all processes evolve much slower than it was expected by the science of the twentieth and particularly the twenty-first century. These considerations directly relate to the present text. In order to clarify the ideas in this study meant for the wide audience from leading genetics professionals and prominent figures on the global sanitary and hygiene scene to teachers and parents we have to recollect the history and methods of science.

Contemporary theories of sanogenetic adaptation, epigenetic management and constitutionality of biological regulation systems have long been in contradiction to traditional deterministic provisions of selectogenesis and the ideas of direct genetic determination. This entailed a more detailed analysis of nomogenesis [1,2], epigenetic regulation mechanisms and unavoidable significant errors in ensuring individual adaptogenesis.

Conceptual Framework of Health Science

The general concept of health is based on the idea of a biological object in general or a human being in particular "not being ill". We will try to explain the weak points we see in such a theory. For this, we shall have to clarify the term of "not being ill".

First and foremost, the body of each particular person may not reach the state of "not being ill", since each illness is the body's resistance to the changing external and internal environment. Moreover, the states that we describe as "chilly" or "tired" may not be separated from those described as "ill". Hippocrates said (and this idea finds more proof with time) that a person gets only the illness he or she can have. The whole history of civilization proves this idea: on battle fields, the same injuries would kill one man, cripple another man, and leave a third one with his body and spirit strengthened by the experience. In times of universal pests, many would die; others would survive and become even stronger. Therefore, we can see that even in extreme conditions illnesses and injuries were both killers and healers! What may be the nature of this phenomenon, appearing in the two opposite aspects simultaneously?

It was already in the nineteenth century that people understood the need for a comprehensive approach to treating illnesses. They started to use malaria injections to treat complicated cases of syphilis (Spirochaeta would die in malaria fever, and malaria itself would be treated with quinine). Later, Louise Pasteur started immunization against yssa (by injecting relatively harmless agents of the disease, its so-called mitigated forms).

According to the WHO, “health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” (Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19-22 June, 1946; signed on 22 July 1946 by the representatives of 61 States (Official Records of the World Health Organization, no. 2, p. 100) and entered into force on 7 April 1948). This definition seems more practical than the common one. It turns out that in order not to be ill (not to resist), the body needs a harmony of almost contradicting well-beings.

Let us clarify the term of “well-being” through its physical aspect. If we understand well-being as the availability of “a benefit” (what is probably meant in the WHO’s definition), a basketball-player would see being tall as a benefit, while a gymnast would enjoy being short; a weightlifter would require hypertrophic (rippling) muscles, while a marathon runner would not require big musculature; and, for example, a boxer would see an acromial skull and thick cheekbones as benefits. As we can see, benefits differ for different people.

We hope you will excuse our pretentiousness in argumentation with vague definitions, as we are not pioneers and such definitions are often criticized, but keep reappearing again and again. An alternative example of health definition, which we support, was suggested by the prominent physiologist and academician G.N. Kryzhanovsky. He wrote that heal this “The state of an organism ensuring optimal execution of its functions to the extent required for efficient interaction with the environment” [3]. This definition is based on the idea that an organism has special systems designed to analyze the changing internal and external conditions and to ensure the most efficient mode of interaction. This means that the state of health basically depends on the priority of functions that may be sacrificed for adaptation. This explanation is valid for a wide range of external conditions (climate change, harmful influences, school problems, social transformation, etc.) and internal conditions (diseases, growth and development of organs and systems, etc.).

Therefore, diseases play a less significant, a subordinate part to health. They only serve as reconstruction factors of health mechanisms (which we call sanogenetic mechanisms).

The sanogenetic theory requires an evidential base that would determine the choice between the “rational selection” and “direct practicability”, which is discussed in the next sub-chapter.

Evolution: Alternative Approaches

From the biological point of view, each living being aims to guarantee survival of its species. For this, several tasks shall be solved to ensure functioning of the biological object. The present section covers various evolution-based aspects of this problem.

Before discussing the evidential base, we should provide the reader with brief descriptions of some of its participants. Charles Darwin hardly needs an introduction; however, he personally did not participate in the discussion, his zealous supporters did. They all considered themselves as evolutionists not because they supported Darwin’s ideas, but because they supported the idea of “safe career-making” [4]. Therefore, we shall only introduce Berg LS (1876-1950) [1] and Goldschmidt R (1878-1958) [5], major zoologists, who lived in the same times, but in different social epochs. The similarities and differences between the two scientists are numerous. One of the differences is that Berg’s fundamental work of Nomogenesis was published in 1922 in Petrograd in collected works of the Russian Geographical Society, and already in 1926 it was published in London by a London publishing house with a foreword by the famous evolutionist and mathematics biologist D’Arcy Thompson [6-8]; while Goldschmidt’s work was published much later [2].

The social function and internal development logic of science reject not only the beginners. In crucial areas, theories may be rejected even when proposed by most prominent scientists belonging to the scientific elite in terms of their position, achievements and knowledge. This is what happened with Berg's Nomogenesis. We have every reason to trust the opinion of the reputed and respectful genetics expert N.N. Vorontsov, who said that: "It's out of the question at the level of scientific expertise of those of his contemporaries who criticized nomogenesis was much lower than his own. It took as long as half a century for his idea of the direction in evolution to gain significant support" [9]. Other great discoveries had to suffer the same fate, for example, Mendel's laws and McClintock's mobile genes [10].

Doubts in the Darwin's theory emerged when in the thirties of the twentieth century his followers were trying to interpret the recovering theory of chromosomal heredity. It was then that E.Myer [11] mentioned "the confirmation of the universal importance of natural selection" as the most essential feature of the synthesis of the Darwin's theory and genetics(please note, Myer, not Darwin). This is why, in his Nomogenesis, Berg does not contend the Darwin's theory (in its initial version), but challenges the selectogenesis suggested by his followers. (Note that it was Berg who offered the term of selectogenesis instead of Darwinism).

But what is the vital difference between the two theories of evolution?

According to Berg: "Evolution of organisms is a development according to fixed laws (nomogenesis),as opposed to the evolution by chance suggested by selectogenesis. The effects of struggle for survival and natural selection are of secondary importance in this process" [1].

In the struggle for survival, natural selection only seems to be accidental, and Darwinism states that only useful evolution-based characteristics are selected. The nomogenesis concept envisages the ability of life forms to adapt through the respective inherent (immanent) ability of living organisms (direct practicability) rather than through the selection of accidental useful deviations. It is clear that the main battles between selectogenesis and nomogenesis were and are still fought in the field of biological principles behind the formation and development of living organisms (ontogenesis).

It is impractical for us to examine the actual facts behind any theory, but the main conclusion with regard to direct practicability shall be mentioned: a developing organism is not a passive victim of its interactions with the environment, but an active life form with self-regulation programs.

Determinism of Characteristics and Vital Necessity in Prognostic Diagnostics

First we should describe the terms of "determinism of characteristics" and "vital necessity" and explain why we find the problem of approaches behind these terms so relevant.

Deterministic characteristics predict a pathological process with a high probability (of at least 70-80%) and are more known as "ethiopathogenetically connected", "pathology markers". An example characteristics availability of specific antibodies.

Vitally necessary characteristics accompany many pathological (or other) processes and are, therefore, have lower priority as compared to deterministic characteristics. These are called "non-specific characteristics", "non-differentiating the nature of a pathological process". An example characteristic is a body temperature rise.

It may seem that these definitions preclude any competition between characteristics in prognostic diagnostics; therefore, we shall clarify the meaning of competition with regard to the approaches. First of all, we shall try to set the application limits of each approach with account of the pluralism of hypotheses used in gnoseology.

For this, we shall once more refer to Meyen SV [12,13], who, using the "sympathy principle" suggested for scientific communication, insisted on the fact that "there should be competition between various hypotheses and rational research has its limits and provides incomplete knowledge".

The competition of views is, therefore, not a fight of different concepts, but establishment of relations for rational research, which shall be covered in more detail in the next paragraphs.

First, we shall refer to the opinion by Puzyrev VP [14]:

"The impressive successes in gene and human genome decoding and evident successes in the application of genomics in practical research dangerously combine with the genomania and'genetic determinism', which claim to entirely explain the complicated structural and functional organization of living systems and organisms".

Thus, taken as a fundamental truth, the seemingly appealing achievements of the deterministic diagnostics are largely disputable, though included into the practice of the "evidence based medicine".

Primarily, it shall be noted the weakest point of deterministic characteristics predicting a high probability of a process is that they absolutely require evaluation of their deviations from the normal values. This was emphasized by the prominent molecular biologist Erwin Chargaff, who saw "normative biology" as the cause for "fast dogmas". It was the Chargaff's Rule (the rule of deterministic complementarity of purines and pyrimidines) that allowed Watson and Crick to create their epochal theory of the double-stranded DNA structure. We should take our hats off to this visionary philosopher, who discovered a deterministic (!) rule for the structural organization of the gene and voluntarily rejected dogmatization of the "normologic gene structure", as he foresaw the future of science forty-fifty years ahead.

We tried to organize our discussion on the competition between deterministic characteristics and vital necessity within the general cognitive theory, which accepts "the entire multitude of partly intersecting and adequate, but mutually incompatible theories" [15]. Moreover, a detailed analysis of modern general principles of the cognitive theory may be found in works by Polani M [16] and Feyerabend P [15], who argue, though in a rather respectable manner, with the triumvirate of great scientific methodologists of the middle of the last century: Karl Raimund Popper (1907-1994), Thomas Samuel Kuhn (1922-1995) and Imre Lakatos (1922-1974). In their mutual criticism, they often get carried away when "explaining the frequent intersections in their views". (In this context one of the remarks by Kuhn T is interesting [17]: "I cannot define precisely the amount of my intellectual debt to Sir Karl, but I have no doubts that I owe him").

Genetic Invalidity of Deterministic Views on Gene Mutation Prognostic Efficiency

The validity and highly specific nature of mutation process parameters (at least with regard to the occurrence of chromosome and chromatid mutations) tend to play the main role in contemporary diagnostic prognosis.

Deviations of the parameters from the so-called "spontaneous" level are evaluated: the probability of a prognosis is assessed depending on the degree of deviations from the spontaneous level.

Critical evaluation shall not be applied in all prognostic approaches covering chromosome disorders, but only in those intended to interpret predictions at a level that slightly (several times) exceeds the spontaneous level. Thus, there are no doubts as to a prognosis of the Down syndrome upon detection of the 21^{st} extra chromatid (trisomy of the 21^{st} chromosome), as well as to an almost complete chromatin dispersion in predictions of Progeria, Werner disease, xeroderma pigment osumor Falconi's anemia. There can be no doubts as to the corrects ex-detection based on the X-chromosome or unpredictable sexual orientation in case of extra “sex coherent” chromosome options.

Similarly, there is no clinical sense in considering a probabilistic prognosis based on fundamental (non-specific) parameters in the presence of such factors as blood pressure of over 200mmHg, Cheyne-Stokes respiration, ventricular and atrial fibrillation, high glucose and urea rates, clearly visualized metastasis in all organs, etc., that are clearly indicative of a close death. In this case, only early prognosis of moderate hypoglycemia, uremia, hypoproteinemia, hypo and hypertension, heart blocks, etc., becomes the fundamental tool of preventive medicine and rehabilitation, with their efficiency depending on the accuracy of individual predictions.

Thus, the scope of competition between deterministic (specific) and necessary (non-specific) approaches is limited to those deregulated states requiring probabilistic and strictly individualized prognosis at early stages.

Predictive diagnostics of risks of gene mutations and chromosome-chromatid aberrations requires correlating the recorded level with the spontaneous (normalized) level. This raises the first question: Is the spontaneous mutation level constant or does it experience sharp fluctuations not only from person to person, but also throughout one’s life?

Fundamental molecular genetics gives the following answers to this question:

1. An outbreak of mutations occurs in separate locuses of the eukaryotes genome or a gene group with similar phenotypes.

2. Outbreaks of mutations may be local or global.

3. An outbreak lasts 7 to11 years.

4. There may be recurring “trends” for mutations of a specific gene.

5. Some mutation outbreaks are based not only on external influences, but also on deregulation upon an endogenic transposon invasion.

Most importantly, stable and non-stable mutations occurring during outbreaks are due to the activation of mobile (regulated) elements that are able to induce internal gene reconstructions and contribute greatly to the general gene variation.

A spontaneous mutation may be considered as a staged process. “First, optional genome elements are activated; those elements are most sensitive to weak, non-mutagenic environmental influences. This may cause a generalized genotype response to external and internal environmental factors, resulting in gene and genome mutations” [6].

It is important to note the following: the variability of mutagenesis is due to the physiologically adequate regulation mechanisms of the gene architectonics and is often a source of hyper sensibility to those influences that may be preliminarily rated as non-mutagenic.

The concept of a genome as a system of interacting information macromolecules and of the existence of various forms of hereditary variations (dynamic storage and translation of hereditary information) naturally includes facts and phenomena that earlier seemed purely specific (non-canonical). One of the contemporary researchers [15] called this process – the ability of a hereditary system “for natural genetic engineering”. Genetic engineering (in its literary sense) suggests the creation of highly resistant individuals through genetic perturbations (mutations). Genetic changes detected do not always evidently show whether they are aimed at degrading the state of the organism or at increasing its resistance (e.g. to a disease).

Thus, according to the fundamental genetics, it is widely believed that the concept of the prognostic role of increased mutability being a determinist conclusion of its negative effect brings about at least two major uncertainties:

1. How can it be proven that the mutability level increases under the influence of the exported state (if the spontaneous level is highly variable)?

2. How can a predicted "poor" criterion be proven if the modern analysis of non-canonic hereditary variability is far from decoding the mechanisms of such phenomena in the human hereditary pathology as clinical polymorphism, genetic heterogeneity, or pleiotropism?

Moreover, there appear such independent phenomena as genetic imprinting, inactivation, X-chromosome, expansion of trinucleotide repeats (this is where the visionary power of Erwin Chargaff [18] is confirmed), cytoplasmic heredity in new forms of human diseases: mitochondrial diseases, diseases of expansion of trinucleotide repeats, genetic diseases of somatic cells. Even though a regular medical practitioner is not quite familiar with these forms of pathologies, such widespread diseases as Alzheimer's, Parkinson's and Huntington's disease a priori are, in their tentative nature, genetic function deregulations. Therefore, they may not be predicted solely using the parameters setting the causes of accompanying deregulations (the more so, as the cause lies in the ultimate variability of functional regulation processes). This is where alternative approaches introducing a functional reserve of non-specific organism protection systems are vital.

Finally, not for a compromise, but for the scientific evaluation of the situation, it may be predicted that the methodology for identifying reserve possibilities of the non-specific resistance of individuals will be more efficient in combination with the detection of conventional determinant characteristics.

This statement, however, requires a separate discussion.

Sanogenesis as a System for Managing Functional Errors in Development and Adaptation of an Organism

In the previous section, we discussed the difficulties arising in prognosis of the only predictable (deterministic) consequence both during development of an organism and its adaptation to the changeable external and internal environmental factors. Using contemporary theories of molecular regulation mechanisms of gene processes as the basis, it is easy to prove that both the cell and the organism levels have numerous systems that are vital for the adaptation process, but function with the highest error risks.

The above transposon regulation model is one of the sources of such errors. In our opinion, especially at the level of somatic cells where (homo and hetero) transposition and recombination processes are suppressed considerably, errors may occur in activation of reparation systems, heat shock systems, and systems controlling the level of cell differentiation and activation of cell death programs. These aspects have been thoroughly studied in fundamental genetics.

Most importantly for us, all gene control systems studied, without exceptions, have significant error rates, even though they are intended to eliminate errors. This situation remains unchanged both on the cell level and on the level of organs or organisms, where the systems of immunopoesis, hormones regulation, oxygen transportation, sensorineural and cardiorespiratory control and many other systems serve as the sources of error.

Similarly to genetic systems, their purpose is to eliminate errors (e.g. caused by diseases); however, the systems themselves are erroneous.

As it follows from the above, an organism emerges, develops, struggles for adaptation (e.g. to diseases) and dies due to the single accompanying process – occurrence of an error and a struggle with it. This error shall be understood in a broader sense: it includes not only morphometric defects of important cell and organism structures, but also erroneous actions of regulating systems (due to their non-participation or excessive intensity).

What is the biological meaning of life under the principle of unavoidability of errors?

This question is not new. It has been bothering people for many centuries now.

Recall that the Darwin's theory was based on the idea that constant errors (in evolution) are divided into useful and useless errors, with only the former remaining. According to Darwinism, an evolving biological object undergoes an errors election process aimed at identifying the most practical errors (purpose-based "necessary practicability").

It is, therefore, not surprising that the counter arguments to the "necessary practicability" (due to errors) suggested by Berg and Goldschmidt were accepted only in the eighties of the twentieth century. This was due to the triumph of molecular genetics in the sphere of decoding of molecular mechanisms behind errors and their elimination methods: not all errors have "necessary practicability"; most of them have "vital necessity". The difference between the two terms is that, according to nomogenesis, errors may be impractical.

In other words consequences of errors are multivariate. The same errors may lead to "useful" outcomes (e.g. to sufficient adaptation),"disputable" results (e.g. aggravating and non-aggravating compensations) or, in many cases, to "bad" outcomes (e.g. to adaptation failure, cancerogenic transformation and lethality). The above system of views shows that mere detection of errors (the basic purpose of the deterministic prognostic diagnostics that identifies the specific nature a pathological locus, i.e. error) does not always allow predicting its outcome. Clinical experience offers numerous arguments supporting this idea. We will mention only some which refer to the most significant achievements of the evidence based medicine.

Thus, the presence of cancer markers, activate telomerases, "pathological" cytokines and other specific oncogenetic features does not necessarily guarantee cancer. Hypercholesterolemia, high density hypolipoproteinemia and low density hyperlipoproteinemia do not always guarantee atheromatosis. Histocompatibility disorders in generic tissue cells do not always guarantee toxemia of pregnancy. More simple and traditional arguments include that hypertension does not always guarantee hypertensive disease, hyperglycemia does not guarantee diabetes, *Bacillus Kochii*-tuberculosis, mycobacteria-diphtheritic myocarditis, and so on.

If direct specific error detection does not have sufficient prognostic efficiency, than ethiopathogenetic diagnostics may not have absolute significance when describing the the gravity of a pathological process.

Under the basics of the nomogenesis concept, the vital necessity of an error lies in the fact that it includes a control system. However, the control system itself is not error-free and may entail other errors involving another system, etc.

It will be discussed later that the range of systems that control errors is extensive, even on the cell level, and it is even larger on the organism level. Still, the development path is not selected by accident. In each particular situation and conditions, the selection depends on what is a) coded in the genetic apparatus or b) considered more adequate.

The function and direction of a regulatory system may be determined using diverse biochemical, biophysical and other approaches. Since the same regulatory systems control different errors, their functional competence with regard to the errors is not specific, though it is the functional quality (adequacy) that eventually determines the outcome of the error detected.

The vitally necessary characteristics included in the title of this section as competing with deterministic characteristics indicate inclusion of regulatory systems, without differentiating the nature of the pathology initiating them.

Thus, with certain difficulties due to the complicated historical evolution in biology and medicine, we have approached the problem of competition between deterministic (pathology-specific) and vitally necessary (non-specific) characteristics of successful predictions: the use of specific diagnostics for detection of risk groups of the presumable a etiology, with a further analysis of non-specific internal processes indicating individual risk rates. Most frequently the latter approach is considered as non-specific symptomatic diagnostics that is of secondary significance to the first approach.

Sanotyping is used as a brief definition in sanogenetic diagnostics. It is based on the traditions established by Hippocrates, the founder of the health science, who proved the high ambiguity of illness predispositions in people with different psychological and neurological makeup and different body types.

Predictability of the future is due to the rapidly developing methods of genetic errors detection, applied as early as in prenatal development. Still, the possibilities of prenatal diagnostics are limited by rare monogenetic diseases, which are numerous in number (many thousands), but few in percentage of the rest of current diseases. We tend to disagree with the populist views of many ecologists who forecast an increasing number of dangerous monogenetic deterministic pathologies in the nearest future. There is every ground to believe that the increased number of variants of such predetermined states (often ending in fetal death) is directly caused by the application of successful detection methods. Under all circumstances, in reasonable predictions of polygenic diseases without clarifying sanogenetic monitoring, the future of accurate prognosis is still unclear. Moreover, polygenetic pathologies include oncological diseases, diseases of the cardiovascular system, brain diseases (the easily forecasted problem of many civilized societies), diseases of the immune system, hormone system, etc. These are only the diseases for which the gene-related origin is presumed based on serious arguments. Only traumatism, human intolerance and abuse have not yet been included into this list (however, the resistance of some individuals and high vulnerability of others may also turn out to have a gene-related origin).

Contemporary Concepts of Regulatory System Disorders as the Basis of Many Deregulatory States

When analyzing the development of biology and medicine, we can trace their "spiral" evolution from functional deterministic views of the early days of science to the brilliant achievements in ethiopathogenic mechanisms in the end of the ninetieth – middle of the twentieth century (and to a certain degree back in time, to the problems of deregulatory states in the end of the twentieth century). At present, we see two development lines of technical means of diagnostics:

1. We have reached the ultimate specificity and sensitivity in ethyopathogenetic nosology differentiation (the top achievements include X-ray, ultrasound, neutron, positron, and NMR imaging).

2. We have not yet reached success in multifactor assessment of early deregulatory states, which are the basis of many contemporary diseases (70-80% as per different sources).

Thus, despite current prospects, the methods under approach 2 are still less credible than those under approach 1.

In our opinion, it is not the struggle but the right balance of both approaches based on the differentiation of tasks that shall ensure success to polysystemic functional diagnostics. These tasks shall include diagnostics of causal factors of pathologies in order to detect relevant risk groups (first approach) and identification of danger levels in these risk groups (predicted pathology gravity) by the degree of modification of defense mechanisms (second approach).

Even though the principle of individual development was introduced in the beginning of the medical history, its most impressive results were achieved in examining causal factors of pathologies on the population level. It was not before the end of the last century, mainly due to the rapid development of express diagnostics methods (pathology markers), that it became possible to return to the basic fundamental development principles of an individual organism as a solid functional and dynamic system. The need for such a change was due to the fact that even in identification of purely specific pathology markers, individual prognosis of a disease form used to be uncertain.

On the theoretical level, the cause of unreliability of individual predictions for consequences of strictly determined markers is rather obvious and is due to individual development features of the systems that ensure resistance (or sensitivity) of the organism towards the causal factors identified. The purpose of these systems, from the point of view of classical physiology, is to ensure dynamic body homeostasis (dynamic maintenance of a constant internal environment) in the process of individual development, including in constant interactions with external and internal factors that may potentially initiate pathology.

The general homeostasis theory was discovered in the second half of the twentieth century; its biophysical concepts for physiological mechanisms of individual development are represented in the works of Bauer, Prigozhin, Arshavsky, etc. Dynamic homeostasis is "the most essential quality of living systems, ensuring the state of non-equilibrium, and is constantly supported by its structures, acting to prevent a balanced state" [19]. Postulation of this "structural energy" as a characteristic feature of living systems is one of the greatest achievements of E. Bauer. In terms of practical implementation of individual variants of the "dynamic non-equilibrium" [19] (negentropy states), little was done over more than a century.

Dogmatic and simple views of Bauer E may be expressed in the following statement: "The total amount of calories that may be transformed by an organism throughout its life depends only on the free energy of the ovicell and is proportional to it". These views were criticized by another expert in biochemistry and physiology, Meyerhoff O. He noted the absence of difference in calorific values of dead and living proteins (it does not exceed 0.02%, if any) [19]. No experimental proof was also found to the conclusions for Prigozhin's theory that suggests that general development of the whole organism, as a process, is characterized by a constant decrease in the specific metabolic rate and, therefore, reduced entropy generation. This statement contradicts the facts confirming a constant increase in metabolic rates per unit of mass of the differentiated organism in embryogenesis [20]; although a decrease in heat production is registered [21-23] in antenatal development of mammals (according to indirect calorimetry data), as well as at early stages of embryo development [24]. With regard to identification of systemic individual development principles, experimental proof was found not only against the direct energy consumption measurement methods, but also against methodically simpler measurements of morphometric parameters of a developing organism.

The seemingly solid surface principles of M. Rubner that describe surface energy rules based on the assumption that regulation levels for biological thermodynamics (as any other simple physiological process) are nothing more but consequences of correlations between the mass and the surface of the body, changing in time. Identification of the role of skeletal muscles(i.e. existing forms of physical activities) casted a doubt over the Rubner's rule and allowed establishing a specifying energy rule for skeletal muscles [19]. Thus, an attempt to predict individual organism development peculiarities basing only on integral biophysical parameters has failed.

The individual functional division offered is currently used in some of its options, more frequently not as a deterministic parameter, but as a specific measuring scale for specific features of regulation in other vitally important regulatory systems of the body.

We have briefly covered only traditional basic approaches in the attempt to justify the individual changeability of the body. It shall be noted here that the main difficulties were not due to any problems in methodic repeatability, but due to the inadequacy of monosystemic identifications in general problems of system typing of organisms examined.

The problem of monosystemic typing is becoming more complicated in prognosis of the body's susceptibility to pathological exogenous and endogenous factors. Based on classical energy supply and regulation systems, it is possible to approximately predict body sensitivity to certain factors. The surface and energy supply rules for certain ontogenesis stages envisage a certain degree of susceptibility to current diseases and external anthropogenic effects in the so-called sensitive age periods (high sensitivity of young, developing organisms in certain periods of time) and for non-typical body structures (excessive or insufficient weight and height). However, even in these cases, a reliable individual prognosis is not always justified.

The problem of polysystemic monitoring of the body's sanogenetic potential may, therefore, be solved through the creation of a program and tool complex that would allow identifying individual functional sufficiency of organisms based on the functional connection between basic health systems.

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Chapter: II

Methodology, Hard-and Software of Polysystemic Monitoring

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Introduction

Health hazard from natural and anthropogenic sources has begun to be analyzed years ago. Until recently this analysis was primarily applied for human safety in incidents. However, due to stochastic features of risk assessment its applicability to the diagnosis, prevention, and protective or compensatory measures in some cases can be very limited.

The proposed concept combining approaches based on risk analysis and sanogenetic [1] analysis is aimed at increasing the efficiency of both approaches in addressing issues of risk prediction.

There are several reasons necessitating integrated approach to risk analysis:

1. Identifying of risk groups in the population subjected to anthropogenic influences is associated with the formation of groups in which the frequency of fixation of certain pathological processes is dramatically increased. However, modern approaches of epidemiological analysis are based on statement of the accomplished fact (prevalence of cancer, hematological diseases, congenital and hereditary abnormalities, reduced life span, etc.). Most these consequences are long-lasting (sometimes for many years) and state the hazard rather than predict the risk.

2. In cases when anthropogenic influences are evaluated on the basis of detection of undesirable biological responses (e.g. chromosome aberrations, accumulation of lipid peroxidation products, changes in activity of some enzymes etc.) the recorded shifts usually ambiguously determine the expected consequences. Biological aftereffects of the detected shifts can to a certain degree reflect both desirable (development of resistance) and undesirable (fixation of certain pathologies) outcomes.

3. In most cases, the above-listed approaches are informative only in relatively high doses and concentrations of this or that anthropogenic factors and are almost irreproducible in case of low-dose and low-concentration influences.

4. Many effects (mortality, pathologies) as consequences of anthropogenic risk factors are unspecific, i.e. it can be caused by other factors.

5. The data on the effect of some harmful factors suggest that the probability of this effect

is proportional to the probability of spontaneous appearance of the same effect, caused by a complex of other factors of human life. We can speak about synergism of various factors.

6. Modern industrial conditions practically exclude single-factor exposure. Existing methods of epidemiological risk assessment practically cannot differentiate between chemical, radiation, climatic, noise, vibration, and other impacts. Hence, they do not provide a reliable argument for choosing optimal preventive measures.

7. The method of documentation of pathological consequences rules out the possibility of early prophylactic protection of the population contacting with hazardous industries and school environment, which is a priori more efficient and less costly than treatment of the realized risks.

By the wide range of effects, all existing real dangers of radiation, physical, chemical, and biological nature can be divided into two categories: 1) risks in the deterministic range of doses and concentrations (doses and concentrations far surpassing than the established thresholds), 2) risks in a stochastic range of doses and concentrations (doses and concentration near the established thresholds). In the deterministic range of doses and concentrations, the biological effects strictly depend on doses and concentrations of anthropogenic factors and can be detected by existing methods of epidemiological analysis. In the stochastic range of doses and concentrations of anthropogenic factors, the consequences strictly depend on individual sensitivity of biological objects, including humans.

In the human body, many regulatory systems operating at different levels of organization provide sensitivity or resistance to both external and internal factors. On the results of analysis of functional adequacy of sanogenesis systems predicts the level of resistance or sensitivity to relatively tolerable doses and concentrations of anthropogenic influences. Hence, sanogenetic monitoring is more informative for the range of doses and concentrations that cause stochastic effects, especially in children.

Due to individual variability of functioning of sanogenetic processes, the same anthropogenic factor in equal doses and concentrations will cause certain effects in some organisms (sensitive), will not cause in others, and will induce resistance in the third. This implies that at the population level three subpopulations should be determined at relatively low-dose and low-concentration exposures: sensitive, neutral and super resistant. The ratio between these subpopulations can eventually serve as a criterion of population risk from this exposure.

Any stable fixation of the pathological trace is preceded by processes of dysregulation of the corresponding functions. The most probable pathological outcomes can be predicted on the basis of the results of polysystemic sanogenetic monitoring by detecting dysregulation in certain systems of the organism (cardiorespiratory, psychomotor, and metabolism systems). Monitoring is carried out using computerized measurement instrumentation and data processing systems, which provides the basis for strict quantitative assessment of the dynamics of risk for the studied populations [2-4].

Methods

Hardware base of the sanogenetic monitoring complex includes three major appliances adapted to non-invasive screening survey:

- Spiroarteriocardiorhythmograph for continuous non-invasive recording of blood pressure, expiration and inspiration air flows with a highly sensitive ultrasonic transducer, and electrocardiogram;

- Computer-aided device for express-evaluation of psychomotor activity from motor tests;

- Laser correlation spectrometer intended for identification of the pattern of regulation of metabolic and immune processes.

All tests are performed with strict adherence of general bioethical standards.

Individual functional status of the cardiorespiratory system is evaluated using a Spiroarteriorrcardiorhythmograph instrument complex (SACR, recommended by Ministry of Health Care and Social Development of the Russian Federation for clinical use; registration certificate #29/03020703/5869-04, St. Petersburg) allowing simultaneous recording of the heart, vascular, and respiratory rhythms (Figure 1). The method makes it possible to calculate the relative contribution of sympathetic and parasympathetic Autonomic Nervous System (ANS) into heart rate and BP regulation, integrated values of cardiogram intervals, parameters of lung ventilation, baroreflex parameters, etc.

The circulatory system is one of the main systems that determine the adaptive reserves of the body. The state of the circulatory system should be considered as an integral marker of adaptive reactions of the body, because its main function, adequate oxygen and nutrient supply to tissues, directly correlates with the level of functioning of other body systems. Adverse environmental influences induce changes in the function of various systems of the body that require, before pathological trace appearance, restructuring of the circulatory system and cause shifts in many mechanisms of its regulation. In view of close anatomical and functional interrelationships, the state of circulation and its autonomic regulation should be assessed as part of the integral respiratory and cardiovascular systems. For solving this problem, a special device, Spiroarteriocardiorhythmograph, was developed.

The noninvasive methods of blood pressure measurement can be divided into two types: discrete measurements or long-term continuous PB pulse wave monitoring. Two methods for noninvasive measurements of BP are widely applied: Korotkov's method and oscillometry. The main drawback of these methods is that BP cannot be measured more than once within 30-60sec. The Penaz principle of "unloaded artery" [5,6] realized in the device for pressure measurement implies continuous photoplethysmographic evaluation of the volume of digital vessels and an electropneumatic servo system creating a pressure preventing changes in the diameter of the digital arterial vessels under the cuff. In this case, constant diameter of the digital arteries is provided and the pressure in the cuff repeats arterial blood pressure in the finger, which gives a unique possibility of long-term recording of the whole BP curve. Available commercial devices for continuous BP recording are based on the "unloaded artery principle" [7]. The major drawback of this method is its sensitivity to peripheral vascular resistance, because BP is measured in peripheral digital vessels and the readings can differ from the central pressure [8].

Electrocardiogram (ECG) was recorded in standard lead I over 2 minutes. The time-amplitude parameters of PQRST complex and Heart Rhythm Variability (HRV) were evaluated using statistic, geometric, and spectral parameters [9]. HRV power in different frequency bands determined using Fourier-transform analysis characterizes ANS activity and the function of the central mechanisms of heart rate regulation. Three frequency bands can be distinguished in spectra: Very Low Frequency (VLF, 0-0.04Hz), Low Frequency (LF, 0.04-0.15Hz), and high frequency (0.15-0.4Hz), which are measured in absolute values of power ($msec^2$). These values can also be presented in standardized units (LFn, HFn) calculated as the ratio of each spectral component to their sum. Index of Autonomic Balance (AB=LF/HF) and index of centralization (C=(VLF+LF)/HF) were calculated from HRV spectral parameters.

Peripheral Systolic and Diastolic Blood Pressure (SBP and DBP, respectively) and their variability were measured on middle phalanx using the method of Penaz. From the parameters of BP pulse wave, hemodynamic parameters, stroke volume, and cardiac output were calculated using phase analysis of cardiac cycle and BP. Spontaneous arterial Baroreflex Sensitivity (BRS=LFM/LFSBP) was also evaluated. From geometric parameters of HRV (mode, mode amplitude, amplitude of oscillations, etc.), autonomic balance index, parameter of adequacy of regulation processes, autonomic rhythm index, and regulatory system Strain Index (SI) were calculated.

Figure 1: Spiroarteriocardiorhythmograph.

For evaluation of functional reserves of the cardiovascular system, a functional test with increased "dead space" was used [9]. Reactivity of the cardiovascular system was evaluated by changes in the parameters describing its function (in %) during ECG recording in spirometric mask in comparison to ECG recorded without the mask. The time of inspiration and expiration, volume rate of inspiration and expiration, and respiratory volume of quiet breathing in an averaged cycle were evaluated. Parameters of forced expiration (vital capacity of the lungs and volume of forced expiration) were also measured.

The only analogs of Spiroarteriocardiorhythmograph, Finapress Medical System [10] and its portable modification Portapress [11] manufactured by TNO company (The Netherlands), have no measuring spirometric channel, which makes impossible simultaneous analysis of respiration and circulation, but this is successfully realized in Spiroarteriocardiorhythmograph.

The study of the latent period of simple sensorimotor reaction and other psychomotor parameters are performed using a specific instrument called "KMM" (computer movement meter, Figure 2), Registration Certificate No. 29/03041202/5085-03. Locomotion requires coordinated activities of various systems of the brain directly regulating the implementation of the motor act and associated with processes of perception, attention, and memory [12]. Hence, psychomotor testing should be aimed at multidimensional analysis of the studied function; the tests should have sufficient differential sensitivity allowing evaluation of the contribution of different types of psychophysiological processes into the formation of the locomotion sphere.

Before discussing the tests implemented in KMM instrument, let us consider the existing ideas about the organization of the target executive action that is realized in any psychomotor testing. All models of this activity analyze various characteristics of human movement aimed at rapid attaining the target after signal presentation [13,14]. Motor characteristics include temporal, speed, and spatial parameters and the number of repetitions (in case of repeated act). These characteristics allow assessing some integral parameters, such as quality tracking motion, its accuracy, and success; conclusions about nervous and mental processes can also be made [15,16].

Targeted action can be divided into latent and motor stages. In turn, the latent stage consists of a number of functionally different periods. For visually controlled movements, according to Welford's classification [17], the latent stage consists of two processes: the first process is related to perception of a visual stimulus (40msec) and information processing (+75msec) and the second process includes the time of central organization of the motor act (+75msec) and the time of bioelectric activity of muscles before the start of movement (+60msec). Thus, the total duration of the latent stage is 250msec. The duration of this latent stage can vary depending on the type of visual information (number of stimuli, brightness, noise, etc.) and the type of the movement (simple or complex, single or multiaxis, discrete or tracing, single or repeated, etc.), but the time of bioelectric activity (60msec) remains unchanged.

The motor component of the action consists of two phases: the first stage is realized according to the program developed during the latent stage within 250-300msec without proprioceptive and visual feedback, i.e. via open loop regulation, and represent a ballistic phase). The second phase consists in precise adjustment of the movement (cursor) to the target and involves the feedback mechanisms. The response time for movement correction is 108-169msec relative to the kinesthetic feedback [18] and 190-260msec relative to the visual feedback [19]. The motor output, among other things, is based on inertia of the kinematic chain elements that often hampers motor act implementation [20,21]. Taking into account the structure of the target action, the tests designed for KMM instrument focus on different phases of the latent or motor stages of the movement, which allows analyzing the status of various mechanisms controlling the psychomotor act. The examination includes three different tests for both the right and left hands. The accuracy of measuring the time of simple sensorimotor reaction was 1ms. A subject was placed in a comfortable chair, while his/her hand was placed on a special handle and lever, which, in turn, may revolve around a vertical axis. The fulcrum of the rotating segment was treated as the upper third of the forearm. In this position the forearm and wrist could commit abduction and adduction.

Figure 2: Computer movement meter.

Mechanical resistance to rotational movement of the forearm was insignificant and therefore ignored in the calculations. Initially, the lever with forearm and wrist resting on it was fixed on the zero position by electromagnetic stoppers. Participants were instructed to focus on the cross in the centre of the screen, and to adduct the handle of the lever with their forearm and wrist as quickly as possible in response to the visual signals started at random intervals (4-8 seconds). The visual signals (vivid light) were slightly peripheral to the central visual field, in order to potentially speed up sensor motor reaction. At the instance of switching on light the electromagnetic stoppers were simultaneously removed and the lever was able to move freely. The latent period of the motor response (Reaction Time-RT) was measured from the moment of switching on light until the angular displacement of the handle with forearm at 1° was recorded by a computer. The subjects were not limited in the amplitude of translation of the lever. The study was performed for both dominant and subdominant hands. Each subject received 16 signals for reaction with each hand. Training before the experiment included reaction for 10 visual stimuli which were randomly distributed in time.

Subfractional composition of blood serum and other biological fluids is analyzed using Laser Correlation Spectrometer (LCS, certificate of Committee on New Medical Instrumentation, Ministry of Health Care and Social Development of the Russian Federation, RU.C. 39.003.A N 5381, St. Petersburg). The method is based on changes in spectral characteristics of monochromatic coherent helium-neon laser radiation due to light scatter in disperse system (blood serum, urine, and other biological fluids) [22,23]. The degree of this scatter is proportional to particle speed, which depends on its hydrodynamic radius. Visual analysis of histograms is low-effective for screening studies; special classification programs are required to enable analysis of data bulk over a short time. The algorithm of classification analysis is based on methods of the theory of groups. In case of blood plasma or serum, the total spectrum range is divided into 5 discrete intervals (by the size of scattering particles): I - 0-10nm; II - 11-30nm; III - 31-70nm; IV - 71-150nm; V - >150nm (Figure 3). The first interval primarily includes low molecular weight monomer albumins and free glycolipid complexes; the second interval comprises globular proteins and low molecular weight lipoprotein complexes; the third interval contains larger lipoprotein complexes, RNP and DNP particles, and immune complexes with the lowest molecular weight; the fourth interval includes constitutive medium molecular weight immune complexes; the fifth interval is filled in case of immunopoiesis activation with the formation of high-molecular-weight immune complexes (usually associated with allergisation or autoimmune sensitization).

The same method is applied for the analysis of urine samples and Oropharyngeal Washout Fluid (OPWF), but in these cases other informative intervals are used. For OPWF the spectrum is divided into 4 intervals: I - 0-50nm; II - 51-400nm; III - 400-2000nm; IV - >2000nm; for urine: I - <75nm; II - 76-220nm; III - 221-1500nm; IV - >1500nm. According to data obtained during studying of various pathological states, these intervals contain molecular components of cells: from polypeptide fragments to high-molecular weight protein complexes. It is assumed that increased areas in low- and medium-molecular-weight intervals of LC spectra reflect predominance of biosubstrate degradation processes, while increased areas in high and very high molecular weight intervals indicate predominance of biosubstrate polymerization processes.

Basing on the increase (or decrease) in the percent contribution of particles of a certain fraction into light scattering, a semiotic classification of LCS spectra was proposed including identification of 8 types of shifts in homeostasis and humoral immunity.

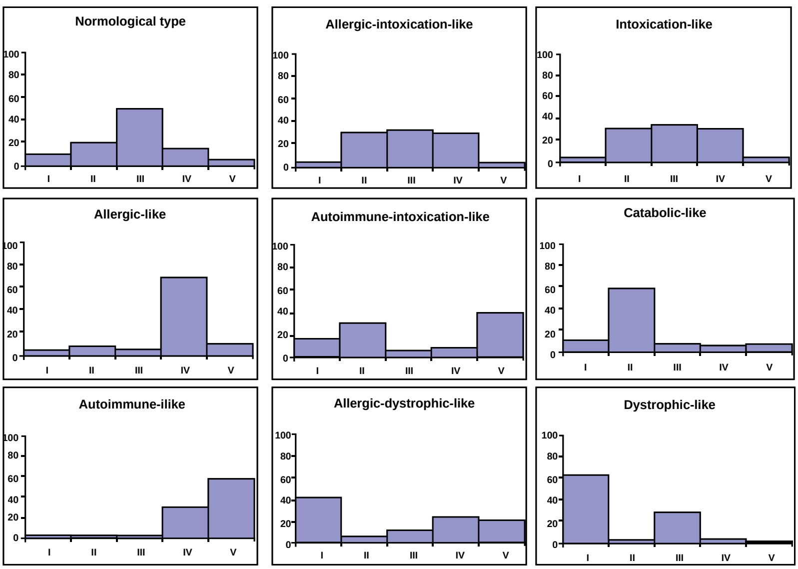

Figure 3: Scheme of metabolic shifts, used in semiotic classifier. Ordinate – contribution of particles of the corresponding zone into light scattering (%).

Analysis of LC spectra of blood plasma (>600 samples) from individuals of different gender, age, and ethnicity living in populations not burdened with verified pathologies has allowed us to identify a conventionally normological distribution. The difference of individual histogram from conditionally normological distribution determines the direction and extent of different shifts. Table 1 presents variants of these shifts in patients with verified diagnoses [23-27].

Direction of the shift	Type of semiotic shift	Redistribution between spectrum zones
Hydrolytical	Intoxication-like	accumulation of fraction II particles (11-30 nm) and fraction III particles (31-70 nm)
	Catabolic-like	accumulation of fraction II particles (11-30 nm)
	Dystrophic-like	accumulation of fraction I particles (<10 nm)
Synthetic	Allergic-like	accumulation of fraction IV particles (70-150 nm)
	Autoimmune-like	accumulation of fraction V particles (>150 nm)
Mixed	Allergic-intoxication-like	accumulation of fraction IV and fraction II particles
	Autoimmune-intoxication-like	accumulation of fraction V and II particles
	Allergic-dystrophic-like	accumulation of fraction V and fraction I particles

Table 1: Spectral shifts in various symptom complexes.

The data are processed using an expert system. The core of the expert system is formed by a program executing autonomic evaluation of the results and database filling and management. It is based on relational database in Microsoft Access format (mdb). The expert system allows scoring the measured parameters using the hypo/hyperfunction scale taking into account the "individual norm" calculated from partial correlations and identification of the most important systems of sanogenesis and the source of strain.

The expert system in the automatic mode provides parameters of electrical activity of the heart, heart rhythm, blood pressure, respiration, and psychomotor activity on the basis of patterns, spectral characteristics, transition processes, kinematograms, etc.; sex and age dependent statistical relationships; and takes into account intra and intersystemic nature of interactions between functional systems of the organism.

The level of functional sufficiency for each system was scored using a 3-point scale: 1-balanced; 2-suffi cient; 3-strained.

In a population not burdened by verified pathologies and intoxications, the proportion between these groups is 50% - 40% - 10%.

The actual parameters are ranked using centile tables. Centile table is constructed for each ranked parameter and includes the following data obtained for k age subgroups and separately for men and women:

$$\begin{pmatrix} v_1 & c_{11} & c_{21} & c_{31} & c_{41} \\ v_2 & c_{12} & c_{22} & c_{32} & c_{42} \\ . & . & . & . & . \\ v_k & c_{1k} & c_{2k} & c_{3k} & c_{4k} \end{pmatrix}, \tag{1}$$

where v_k is the mean age in the k^{th} subgroup, c_{1k}, c_{2k}, c_{3k}, c_{4k} are values of the ranked parameter corresponding to $P\{c<c_{ik}\}\times 100=5^{th}$, 25^{th}, 75^{th}, and 95^{th} centile. The size of the subgroups is chosen on the basis of sample representativeness for attaining adequate 5^{th} and 95^{th} centiles and peculiarities of the age-related dynamics of the parameter, which yields group distribution of the physiological balance 50% - 40% - 10%. The centile table is corrected with increasing the number of observations. By the present time, the sample includes more than 20000 examinees at the age of 5-70 years.

The integral functional balance of sanogenesis by a 3-point ranking was determined by the summary score for seven regulatory systems:

1. Balanced (score from 7 to 10);
2. Sufficient (score from 11 to 12);
3. Strained (score ≥ 13);

Monitoring was carried out using computerized measurement instrumentation and data processing systems, which provides the basis for strict quantitative assessment of the dynamics of risk for the studied populations [28-30]. The risks assessment goes from the instrument of control to the rank of controlled processes, which is the basis for successful operation of potentially hazardous industries.

Reduction of health reserve impairs adaptive capacities of the organism, which determines the first stage of transition from health to disease. At this stage (preclinical state), functional parameters of the organism are within the normal range, but the mechanisms of adaptation work in a strained mode to maintain health parameters at the required level. This leads to enhanced expenditure of functional reserves of the body.

Sanogenetic monitoring makes it possible to diagnose preclinical states and to identify risk groups. Sanogenetic monitoring implies repeated examinations of individuals including simultaneous evaluation of the functional state of several physiological systems. Examination of employees of the nuclear fuel cycle plant using the LCS method revealed a risk group for hematological diseases (anemias, erythremia). Of 300 examinees, 11 and 5 individuals were included into these groups, respectively. The accuracy of risk group isolation was confirmed by routine hematological studies [31]. Screening of 130 workers of a potentially hazardous plant by analyzing serum and urine LC spectra and standard eosinophil count detected a risk group for allergic diseases (5 women and 8 men). This group included individuals with moderate or pronounced allergic-like shifts and mixed shifts with allergic component. Since our objective was isolation of the risk group by brochopulmonary pathologies, further functional testing was performed on a Spiroarteriocardiorhythmograph hardware-software complex. It revealed reduced vital lung capacity in 5 examinees and reduced Tiffeneau index in 4 individuals (the latter parameter is more important for evaluation of allegric bronchopulmonary pathologies). In 2 examinees, reduced Tiffeneau index was associated with increased eosinophil count (Arkhipova et al., this book). The method of LSC was successfully used for evaluation of the disease severity and efficacy of therapy in bronchial asthma [32] and diabetes mellitus [33,34].

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Chapter: III

Effect of Motor Load on Health and Adaptive Capacity of School Children

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Introduction

The comparative analysis of the results of sanogenetic monitoring of the health of adolescents from various regions of the Russian Federation (Moscow, Moscow and Novgorod oblasts, and the Republic of Adygea) has demonstrated disturbances of the state of the cardiac muscle, vascular tone, and the systems of autonomic control of heart rate and peripheral blood pressure in schoolchildren in Moscow [1]. It has been shown that life in a megalopolis changes the course of the formation of the basic systems of the body in adolescents and modifies the mechanisms of this process. The assessment of the cardiovascular system's reactivity in functional tests shows that the main factor of development under conditions of insufficient motor activity, which are typical of life in a big city and result in a decrease in the activity of peripheral regulatory mechanisms, is the activity of the higher divisions of regulatory systems, including emotional and psychogenic ones, rather than the functional maturation of the sympathetic part of autonomic control [2].

The goal of this research was to study the state of the cardiovascular system in adolescents in Moscow with different levels of motor activity: (1) students of the schools of general education, with motor activity restricted to two physical education classes per week, and (2) young athletes (basketball, swimming, sport dancing, figure skating, and taekwondo) who had be entraining for more than two years. The objectives of the examination were to assess the indices at rest and the reactivity of the cardiovascular system of adolescents' to a moderate influence (difficulty of pulmonary ventilation due to increase in the "dead" respiratory volume) as a test of the functional state of this system.

Methods

Healthy adolescents residing in Moscow were examined. The group of athletes included adolescents going in for basketball, swimming, and sport dancing at school no. 1953 (Southwest Administrative District), taekwondo (Southeast Administrative District), and figure skating (Central Administrative District) (14 girls and 22 boys at an age of 13–14 years and 4 girls and 16 boys at an age of 15-16 years). They had been participating in sporting activities for 2-13 years. The control group included students from school no. 1357, Southeast Administrative District of Moscow (20 girls and 9 boys at an age of 13-14 years and 13 girls and 8 boys at an age of 15-16 years). We report summary data, because gender differences were absent for most of the studied indices. The cases where gender differences have been found are specially indicated. Examination was performed with a spiroarteriocardiorythmograph. This device allows simultaneous recording of the indices of respiration, peripheral Blood Pressure (pBP) in the finger artery by the Penaz method, and electrocardiogram in standard lead I, assessment of the Heart Rate (HR), stroke volume, and cardiac output calculated on the basis of cardiac cycle phase analysis and BP indices. Continuous recording of the indices during 75-300s makes it possible to analyze the spectral (by the algorithm of the parametric estimator of the power spectral density), geometrical and statistical indices of heart rate variability and, concurrently, spectral indices of systolic and diastolic pBP (pBPs and pBPd) variability. The total spectral power is calculated in the range of 0-0.40Hz; the limits of separate spectral ranges coincide with the generally accepted limits: the High Frequency (HF) range (0.15-0.40Hz), Low Frequency (LF) range (0.04–0.15 Hz), and Very Low Frequency (VLF) range (0-0.04Hz) [3]. On the basis of the spectral indices of Heart Rate (HR) variability, the Autonomic Balance (AB = LF_{HR}/HF_{HR}) and Centralization Index (CI = $(VLF_{HR} + LF_{HR})/HF_{HR}$) are calculated. The stress index is calculated by geometric values of HR variability (mode, modal amplitude, etc. [3]). The α-index reflecting the value of spontaneous arterial Baroreflex Sensitivity (BRS) is calculated on the basis of spectral indices of HR variability and BPS (the square root of the ratio of the absolute powers of the LF ranges of HR and BPS variability spectra [4]). The technical characteristics of this device also permit direct BRS measurements in voluntary breathing and in the moments of coherence of pBD_S and HR changes.

Testing with the spirometric mask of the spiroarteriocardiorythmograph in voluntary breathing was used as a functional test; recording without a mask was used as a control (only HR and pBP indices). The test consisted of two successive 2min recordings: control and testing. Our previous studies have shown that the test with the spirometric mask is a functional test causing the reaction of the cardio respiratory system (mainly the changes in HR variability and peripheral BD spectra) to a light form of mixed hypoxia and hypercapnia. The mask tube diameter provides easy breathing though increasing the “dead” volume of the lungs about two fold (tube volume, 75ml). Oropharyngeal lavage samples were taken in some of the adolescents from both groups (76 subjects) to determine the character of the main metabolic processes on the level of the whole body by the method of laser correlation spectrometry [6]. This method permits the calculation of the function of light scattering distribution depending on the presence and relative quantity of biological macromolecules and their differently sized (in relative units) fragments in the samples followed by interpretation of the results by the respective classifier determining the direction and degree of manifestation (or absence) of metabolic shifts.

The statistical analysis of intergroup differences in the control recording was performed using one-way ANOVA; the intergroup differences in the changes in indices during the functional tests were estimated by repeated ANOVA measures followed by a comparison of the mean (post-hoc) values using Fisher’s test; coefficients of correlation between the indices of the cardiovascular system in the control recording and the results of laser correlation spectrometry were calculated using Pearson’s test (Statistica 6.0).

Results and Discussion

Data in literature on the effect of physical training on the indices of the cardiovascular system, in particular, the spectral indices of HR variability and BP are rather contradictive and reflect both the training process characteristics and the technical characteristics of instruments. Comparison of the indices of adolescents (16-20 years old) leading a mainly sedentary life (school and university students) with the indices of school sport team members showed no difference in the values of HR variability at rest or during the functional tests [7]. Long-term physical training with a moderate load (three to five times a week, 40-60% of the maximal oxygen consumption) is accompanied by a decrease in the absolute and relative power of the LF range in the HR variability spectrum, whereas the spectral indices of BP variability do not change significantly [8]. Training aimed at a high level of sport skills (the level of maximal oxygen consumption no less than $55 ml/kg_{-1}/min_{-1}$) results in the development of bradycardia in athletes and an increase in the absolute and relative powers of the HF range in the HR and BP variability spectra; at the same time, no changes are found in the α-index indirectly reflecting the BRS value [9]. However, other studies comparing the indices of medical students and students of the Department of Physical Education with a high sport qualification, in addition to intensification of the high-frequency components in the HR and BP variability spectra, showed a significant increase in the indices characterizing the spontaneous baroreflex value [10].

In our work, testing in the state of rest has shown no differences between the main indices of the cardiovascular system (BRS, BP) in adolescents with different levels of motor activity. However, we note the higher pBPd values in 13 to 14 year old girls from the control group as compared with boys. In the group of athletes of the same age, no gender differences were found.

Among other indices, a statistically significant increase was shown for the α-index and for BRS in the groups of young athletes of both sexes, the most marked in the youngest age subgroup (Table 1).

In addition, the adolescents aged 13-14 years attending sport classes proved to have significantly higher indices of the total power of the HR variability spectrum and the relative contribution of the LF component to the HR and pBP_d spectra. These data demonstrate the probable intensification of the functional activity of the sympathetic division of autonomic control under the conditions of regular physical activity. The results of testing of the cardiovascular system of adolescents from the youngest age subgroup in the state of rest do not coincide with the literature data on older subjects but are in agreement with the results of the estimation of the autonomic control of the cardiovascular system in young athletes [11]. In this case, one should probably take into consideration not only the presence and intensity of the training process, but also the stage of ontogenetic development.

In the older age subgroup (15-16 years), no differences were found between the indices of subjects with different levels of motor activity or between boys and girls from different groups. At the same time, the indices of adolescents from the control group “catch up” with those for young athletes, while the indices of adolescents going in for sports do not change significantly (Table 1). In addition, the control group shows an increase in the spectral power of slow-wave ranges (VLF and LF) in the HR spectrum and the indices calculated on their basis (AB and CI), which is evidence of an enhanced contribution to the HR and BP regulation of both the sympathetic division and the central control loop [3], including humoral and psychoemotional effects [12].

The findings demonstrate a relative lag of the functional development of the autonomic control of the cardiovascular system of adolescent non-athletes (13-14 years old) as compared with young athletes. This lag is compensated by the age of 15-16 years, but an adequate level of autonomic activity is attained through the activation of central regulatory mechanisms, with a relatively low contribution of the peripheral vagal and baroreflex mechanisms.

This conclusion is confirmed by assessment of the reactivity of the cardiovascular system indices in the functional test with the limitation of pulmonary ventilation used in our work. It is known that intense physical training, with an oxygen consumption of 65% of the maximum, in young people with sedimentary lifestyles, results in a significant decrease in the BP and BRS levels [13]. Our previous works showed that intensification of the respiratory system's activity (e.g., during physical training) under the limitation of pulmonary ventilation in adults does not change the main indices of the cardiovascular system (HR, stroke volume, pBP_s, pBP_d, stress index, and α-index), causing only the redistribution of the HR variability spectrum towards an intensification of the high-frequency component.

Index	13-14 years old		15-16 years old	
	Control	Athletes	Control	Athletes
	n=29	n=36	n=21	n=20
Age, years old	14.23 ± 0.08	14.04 ± 0.08	15.50 ± 0.06	15.72 ± 0.11
Heart rate, stroke/min	90.76 ± 2.20	87.39 ± 1.88	83.77 ± 1.68++	80.84 ± 2.63
Stroke volume, ml	64.11 ± 1.51	62.69 ± 1.22	65.27 ± 1.58	64.12 ± 2.26
Autonomic balance, LF_{HR}/HF_{HR}	1.81 ± 0.22	2.23 ± 0.30	2.86 ± 0.33++	2.24 ± 0.32
Centralization index, $(VLF_{HR}+LF_{HR})/HF_{HR}$	3.32 ± 0.35	3.50 ± 0.41	5.39 ± 0.63++	3.84 ± 0.57
Stress index	199.63 ± 35.49	162.45 ± 23.10	149.93 ± 20.50	119.23 ± 23.03
α-index, $(LF_{HR}/LF_{BPS})^{0/5}$	10.50 ± 0.95	15.46 ± 2.43*	17.05 ± 2.35+	19.39 ± 2.50
Baroreflex sensitivity, ms/mmHg	12.55 ± 1.15	18.99 ± 1.84**	15.61 ± 2.44	23.47 ± 3.32*
BP_S, mmHg	106.46 ± 2.17	108.09 ± 1.89	105.35 ± 1.81	111.00 ± 3.16
BP_D, mmHg	68.72 ± 2.73	68.68 ± 1.65	70.99 ± 1.96	64.67 ± 2.29
Total spectral power TP_{HR}, ms^2	2799 ± 308	4008 ± 456**	5251 ± 1048+	4383 ± 730
VLF_{HR} range power, ms^2	864 ± 118	1058 ± 159	1717 ± 337++	1168 ± 211
LF_{HR} range power, ms^2	1102 ± 124	1760 ± 238**	1971 ± 293++	1923 ± 370
HF_{HR} range power, ms^2	832 ± 134	1189 ± 160	1561 ± 474	1291 ± 312
Relative VLF_{HR} range power, %	31.49 ± 2.21	26.83 ± 2.21	34.63 ± 2.30	28.15 ± 3.07
Relative LF_{HR} range power, %	40.60 ± 2.38	44.84 ± 2.55	41.84 ± 2.29	45.65 ± 2.89
Relative HF_{HR} range power, %	27.91 ± 2.51	28.33 ± 2.19	23.53 ± 2.67	26.21 ± 2.59
Total spectral power TP_{BPS}, $mmHg^2$	41.67 ± 5.85	48.40 ± 8.10	36.41 ± 3.63	21.83 ± 4.73++**
Relative VLF_{BPS} range power, %	43.56 ± 3.43	45.13 ± 3.00	43.56 ± 3.27	41.82 ± 3.54
Relative LF_{BPS} range power, %	31.65 ± 2.34	30.79 ± 1.92	28.11 ± 2.03	36.76 ± 3.02*
Relative HF_{BPS} range power, %	20.80 ± 2.27	19.83 ± 2.08	24.77 ± 2.44	17.25 ± 1.60*
Total spectral power TP_{BPD}, $mmHg^2$	36.58 ± 5.54	37.72 ± 8.10	19.37 ± 2.35++	23.13 ± 4.03
Relative VLF_{BPD} range power, %	57.93 ± 3.53	49.59 ± 2.98*	53.92 ± 2.94	49.37 ± 4.42
Relative LF_{BPD} range power, %	24.74 ± 2.34	33.84 ± 2.44**	26.67 ± 2.00	33.91 ± 3.47
Relative HF_{BPD} range power, %	13.36 ± 1.62	13.20 ± 1.46	16.01 ± 1.62	13.03 ± 1.82

Note: differences from the control group of the same age (one-way ANOVA) are marked with asterisks: *$p<0.1$, **$p<0.05$; differences from the respective younger group (one-way ANOVA) are marked with pluses: +$p<0.1$, ++$p<0.05$.

Table 1: Indices of the cardiovascular system of examined adolescents in the control test (state of rest).

In children, the procedure of testing with the mask induces a decrease in pBP_s, an increase in HR and, according to the spectral indices of BP variability, activation of the sympathetic nervous system [5]. In this work, a decrease in the pBP_s and pBP_d during the functional test was found in adolescents aged 13–14 years from the control group (Figure 1), which is typical of primary school children [5] and absent in young athletes.

The pBP_d decrease is more marked in boys, which conforms to the well-known advanced development of girls at this age. At the same time, the HR variability spectrum (with an unchanged value of the total spectral power) shows redistribution of spectral powers, i.e., are lative decrease in the contribution of Very Low Frequencies (VLF) and an increase in the portion of High Frequencies (HF) (Figure 2) and, accordingly, a decrease in the calculated BV and CI, as well as the stress index (Figure 3).

Similar rearrangements were found in the pBP variability spectra (Figure 4). No pBP changes were observed in young athletes of the same age, although they were shown to have bradycardia (Figure 1) accompanied by an intensification of autonomic activity, which was expressed by an increase in the total power of the HR variability spectrum (Figure 2). At the same time, the decrease in the LF contribution was found in addition to redistribution of the relative power of the VLF and HF ranges described in the control group. The changes in the calculated indices were similar in both groups. Gender differences in the reactivity of the cardiovascular system were also absent. No changes in the main indices of the cardiovascular system (HR and BP) were found during the functional test in the older age subgroup, in 15-16 years old adolescents of the control group (Figure 1). However, they retained the spectral rearrangements of HR (Figure 2) and the changes in the calculated AB, CI, and stress indexes (Figure 3), with the stress index decreasing more markedly in girls. In

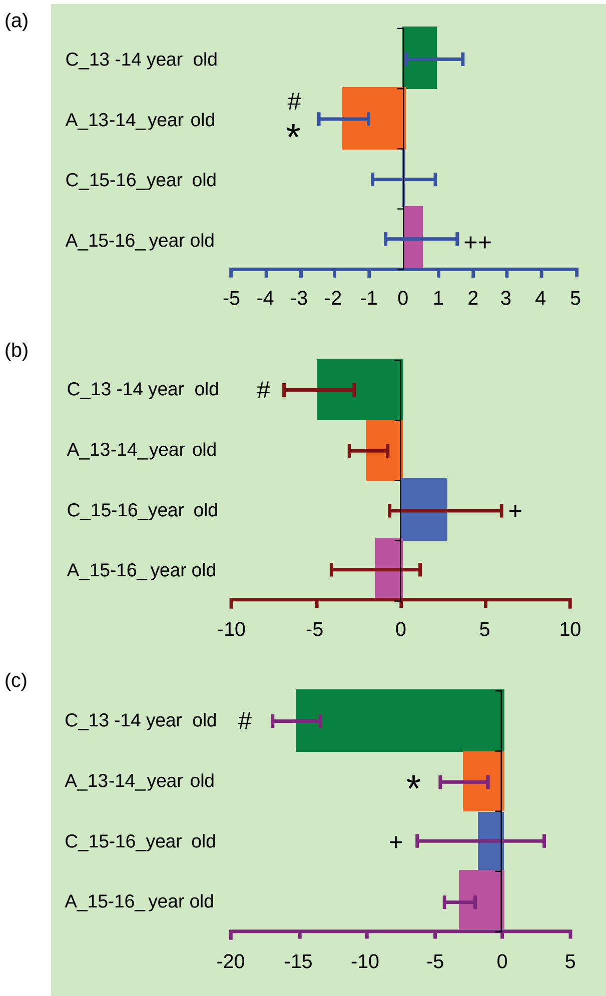

Figure 1: Changes in the main indices of the cardiovascular system during the functional test in percent of those in the control test (explanations are given in "Methods"): (a) Heart Rate; (b) Peripheral Systolic Blood Pressure (BP); (c) Peripheral Diastolic BP. Groups of adolescents: C_13-14 year old and C_15-16 year old, adolescents of the control group; A_13-14 year old and A_15-16 year old, young athletes of the respective ages. Statistical significance of the changes in the indices during the functional test (within a group): # $p< 0.05$ (one-way ANOVA). Statistical significance of intergroup differences (in the same age subgroup) during the functional test (repeated measures ANOVA): *$p<0.05$. Statistical significance of differences from the respective group in the younger subgroup (repeated measures ANOVA): +$p<0.1$; ++ $p<0.05$.

addition, the increase in the relative contribution of l LF was shown in the pBP_s variability spectrum as compared with the younger age subgroup (Figure 4).

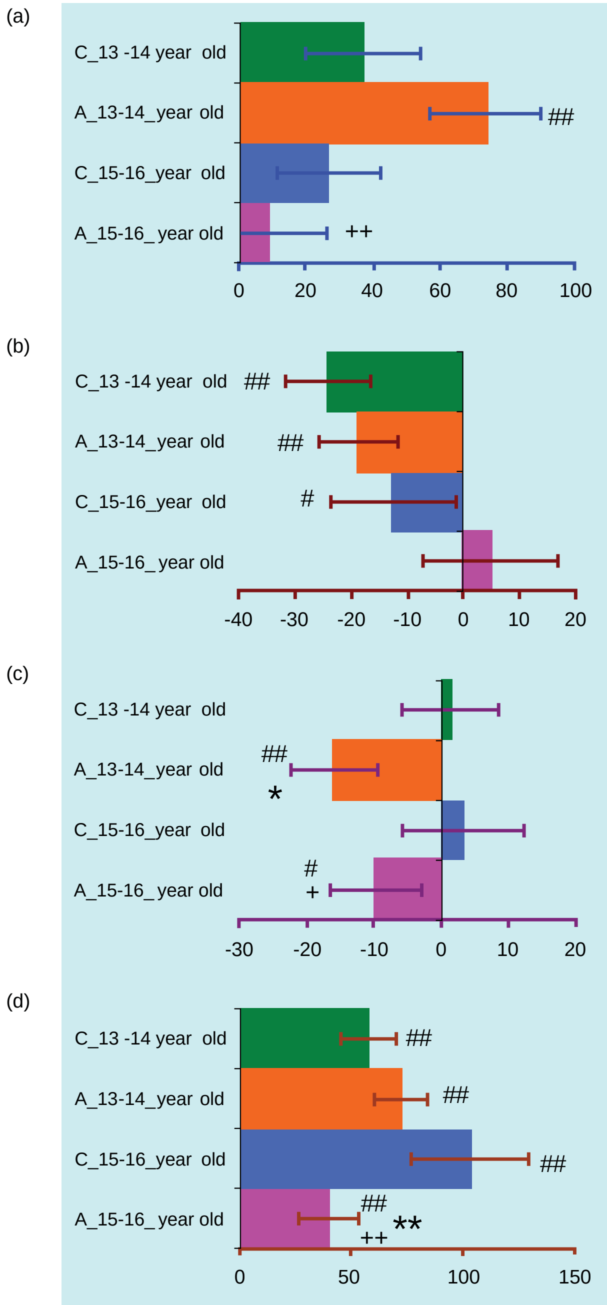

Figure 2: Changes in the spectral indices of heart rate variability during the functional test in percent of those in the control test: (a) total power of the spectrum; (b) relative power of the VLF range; (c) relative power of the LF range; (d) relative power of the HF range. Designations of the groups of adolescents, statistical significance of intergroup differences (in the same age subgroup), and differences from the respective group in the younger subgroup are the same as in (Figure 3). Statistical significance of the change of indices during the functional test (within a group): #p<0.1; ##p<0.05.

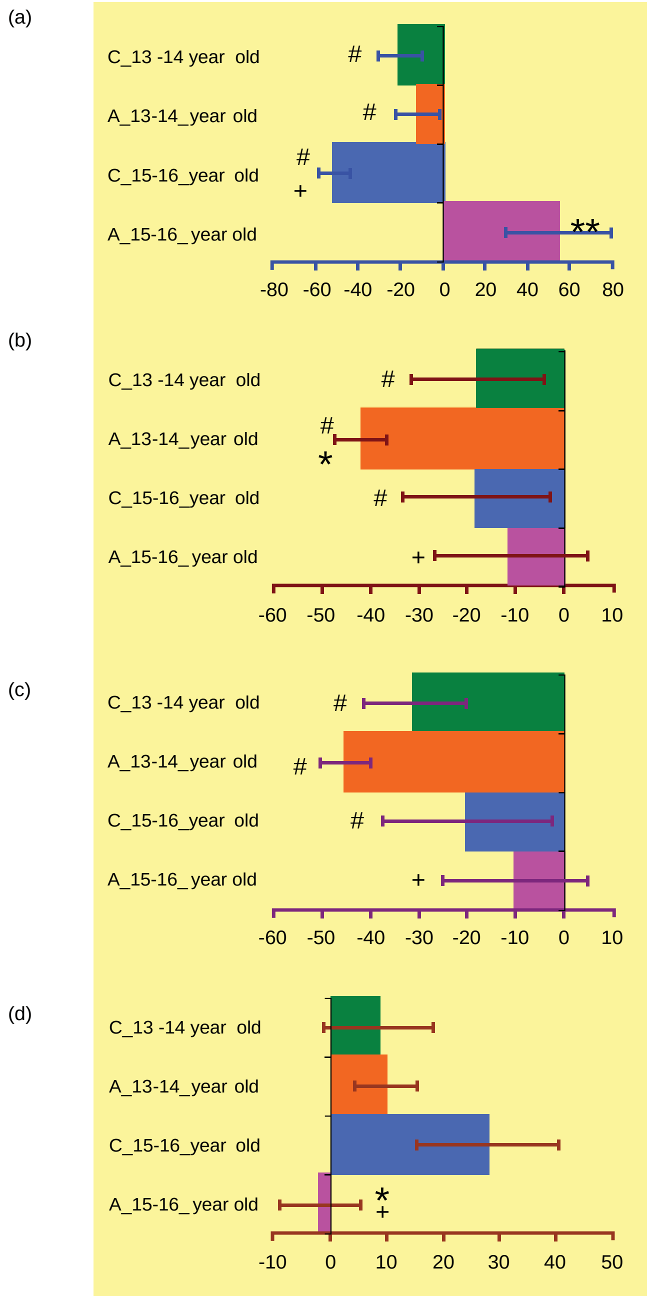

Figure 3: Changes in the calculated indices during the functional test in percent of those in the control test: (a)Stress Index; (b)Autonomic Balance; (c)Centralization Index; (d)Sensitivity of spontaneous arterial baroreflex. Designations of the groups of adolescents, statistical significance of the change of indices during the functional test (within a group), and differences from the respective group in the younger subgroup are the same as in Figure 1. Statistical significance of intergroup differences (in the same age subgroup) during the functional test: *$p< 0.1$; **$p< 0.05$.

Similar rearrangements were found in the pBP variability spectra (Figure 4). No pBP changes were observed in young athletes of the same age, although they were shown to have bradycardia (Figure 1) accompanied by an intensification of autonomic activity, which was expressed by an increase in the total power of the HR variability spectrum (Figure 2). At

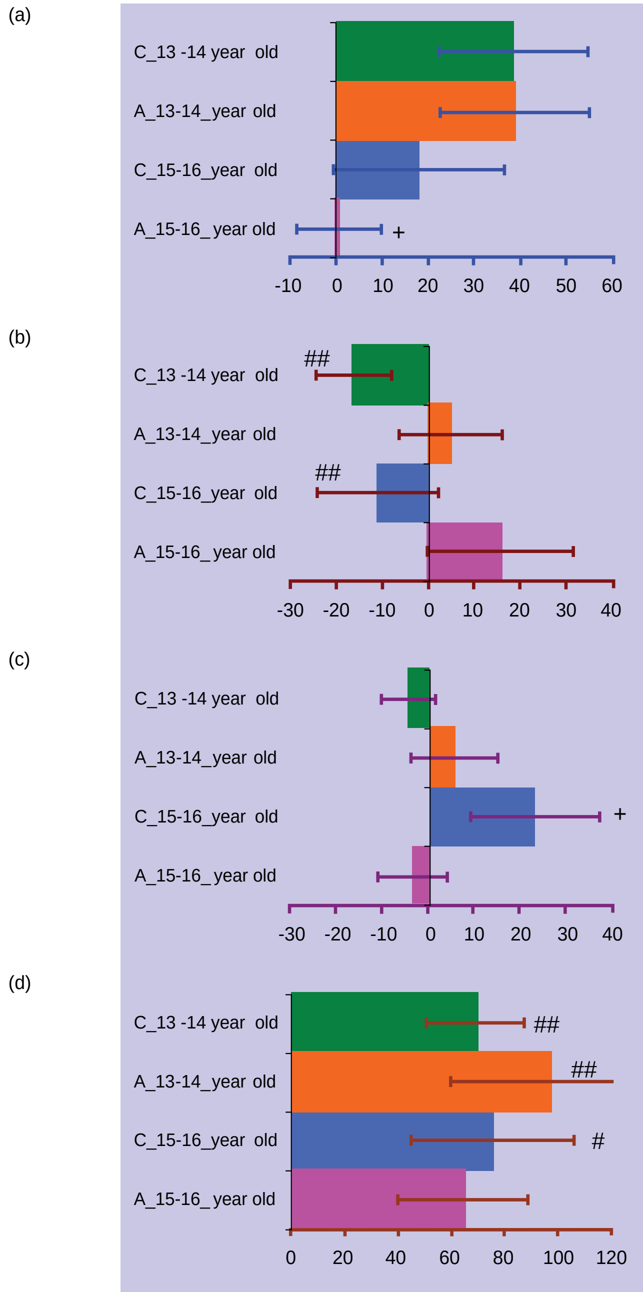

Figure 4: Changes in the spectral indices of peripheral systolic BP variability during the functional test in percent of those in the control test: (a) total power of the spectrum; (b) relative power of the VLF range; (c) relative power of the LF range; (d) relative power of the HF range. Designations of the groups of adolescents and statistical significance of the changes in the indices during the functional test (within a group) are the same as in Figure 2. Statistical significance of the differences from the respective group in the younger subgroup: +p<0.1.

the same time, the decrease in the LF contribution was found in addition to redistribution of the relative power of the VLF and HF ranges described in the control group. The changes in the calculated indices were similar in both groups. Gender differences in the reactivity of the cardiovascular system were also absent. No changes in the main indices of the cardiovascular system (HR and BP) were found during the functional test in the older age subgroup, in 15-16 years old adolescents of the control group (Figure 1). However, they retained the spectral rearrangements of HR (Figure 2) and the changes in the calculated AB, CI, and stress indexes (Figure 3), with the stress index decreasing more markedly in girls. In addition, the increase in the relative contribution of l LF was shown in the pBP_s variability spectrum as compared with the younger age subgroup (Figure 4).

These data demonstrate that the level of autonomic activity in such adolescents has reached an adequate level for the maintenance of constant HR and BP values upon respiratory system activation in the functional test due to an increase in the sympathetic regulation efficiency. Adolescents of both sexes participating in for sports, at an age of 15–16 years, were shown to have no changes in HR, BP, or the total power of the HR variability spectrum but to retain spectral rearrangements typical of a younger age, except for the absence of a decrease in the relative power of the VLF range and a lesser increase in the portion of high frequencies (Figure 2). At the same time, the calculated indices based on the values of the HR variability spectrum were unchanged, while the increase in the stress index and decrease in BRS were shown in some of the adolescents (Figure 3). The presented data demonstrate that adaptation to the functional test conditions in young athletes from this age subgroup employs mainly the peripheral mechanism of HR regulation, with preferable involvement of baroreflex effects.

Since the differences between the groups of adolescents, both in the state of rest and during the functional test, were observed also in the VLF index which is generally believed to include humoral effects [3,12], the character of metabolism in their body has been studied in this work by the method of laser correlation spectrometry [6]. It was shown that the relative quantity of particles <50nm in diameter in the samples was positively correlated with the relative power of the *HF* range of HR variability spectrum (r=0.228, p=0.049). The increase in the contribution of the finest particles to light scattering, according to the data obtained previously, accompanies catabolic processes and is observed under an enhanced physical load [6,14]. The level of relative power of the *HF* range characterizes the activity of peripheral HR control loop [3], which, according to the data in literature and our results, is higher in athletes. Consequently, our work has demonstrated a consistent increase in the functional activity of peripheral mechanisms of HR regulation in young athletes against a background of catabolic directivity of system metabolism.

In addition, we have found a correlation dependence of the relative power of a Low Frequency (LF) range of pBPs variability spectrum on the contribution of particles 400-2000nm in diameter to light scattering (r=–0.229, p=0.049) and a statistically significant tendency towards correlation of this index of the cardiovascular system with the relative quantity of particles 50-400nm in diameter (r=0.214, p=0.069). Since the relative power of the LF range in the BP variability spectrum is associated with the level of sympathetic activity in relation to vascular tone [15], and the differences according to this index have been found in our work between groups of adolescents with different levels of physical activity, it may be supposed that the delayed functional maturation of the sympathetic division of autonomic control in sedentary adolescents is caused (in addition to other factors) by biochemical characteristics. This assumption is also confirmed by the correlation of the VLF value in the pBPs variability spectrum, reflecting the humoral effects on BP variability, with the contribution to light scattering of particles 50-400nm in diameter (r=–0.235, p=0.045).

Conclusion

The data obtained in our work demonstrates a relative lag of the functional development of the autonomic control of the cardiovascular system in 13 to 14 year old non-athletes as compared with young athletes. This lag is compensated by the age of 15-16 years, but an adequate level of autonomic activity is achieved through activation of central regulatory mechanisms (sympathetic and humoral), with a relatively small contribution of the peripheral vagal and baroreflex mechanisms. The assessment of the reactivity of the cardiovascular system in the functional test with limited pulmonary ventilation has shown that the adaptive potential of adolescent non-athletes fulfilled with the involvement of the sympathetic division of autonomic control, whereas adaptation to the functional test conditions in young athletes occur mainly through peripheral mechanisms, with the predominant involvement of baroreflex effects.

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Chapter: IV

Functional Characteristics of the Cardiovascular System and General Metabolism in Adolescents with High-Normal Blood Pressure

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Introduction

Arterial hypertension is one of the most widespread noninfectious diseases. It often first manifests itself in adolescence [1], and statistical data indicate that, during the past 10 years, the "the incidence of cardiovascular pathology has doubled in children 14 years of age and increased 2.5 times in adolescents, which is probably a result of the improved diagnosing of cardiac diseases in childhood" [2].

According to the recommendations of the European Society for Hypertension and Cardiology and WHO [3], the level of arterial Blood Pressure (BP) of 140/90mmHg is assumed to be a unified criterion of hypertension for both adults and adolescents from 13 years of age. However, distinguishing the group with the above threshold BP values alone leaves out a significant proportion of adults, children, and adolescents representing the borderline cases and constituting a special group of the medically disadvantaged [4]. In recent years, this has been an urgent problem because of the rapid growth in the number of people of various ages with BP increased to the boundary levels. The new term "high-normal BP" (or "prehypertension"), referring to a BP value between the 90th and 95th percentiles has been introduced. Children and adolescents with these AD values constitute a risk group; they need to undergo regular medical checkups and receive non-pharmacological treatment.

The Expert Committee of the Russian Society of Cardiology and Association of Pediatric Cardiologists of the Russian Federation have elaborated recommendations for BP assessment in children and adolescents; these recommendations have been approved at the Russian National Congress of Cardiologists (Moscow, October 2008). The average level of systolic BP (BP_s) and/or diastolic BP (BP_d) in three visits, which exceeded or were equal to the 95th percentile for the given age, sex and height, have been viewed as essential hypertension. When this parameter was at the level of the 90th percentile or above it but below the 95th percentile for the given age, sex and height (equal to or exceeding 120/80mmHg even when the value was below the 90th percentile), the condition was assigned to high-normal BP or prehypertension. According to the tables published in 2004 in Pediatrics, the proportion of children and adolescents in a conventionally normal population, which falls within a range above the 90th percentile, should be 10%. However, screening studies performed abroad in recent years demonstrated an increase up to 20-25% in the overall proportion of adolescents with high-normal and elevated BP [5,6]. Both Russian and foreign researches demonstrate that medical monitoring of the risk groups and health testing in schools were equally effective in identifying children and adolescents with elevated BP [2,4,7-9].

In both cases, the elevated BP was found to correlate with metabolic disorders [9-11], the influence of psychoemotional and neurohumoral factors [12-14], and disturbed autonomic control of the cardiovascular system [4,15]. The objectives of this study was (1) to determine the incidence rate of elevated BP among the 8th-11th class students living in different regions of the Russian Federation and (2) to determine the parameters of the autonomic regulation of the cardiovascular system in adolescents with hypernormotension at rest and during a functional test with increasing "dead" space.

Methods

The data of health monitoring of high school students from Moscow city schools nos. 315, 548, 735, and 1357, as well as from the schools of the city of Pushkino and Pushkino raion (district) of Moscow region, the school of the Nagovo village, Novgorod region, and from the schools of the city of Maikop and the Dzherokay village, Republic of Adygea, Russia (a total of 1300 observations) were used in our study. Adolescents with BPs exceeding 120mmHg and/or BP_d exceeding 80mmHg constituted a group of subjects with elevated BP (410 individuals). Adolescents with BP higher than 140/90mmHg have not been included in the hypertension group; they underwent regular medical checkups and received the necessary treatment. Gender differences were not taken into account in this study.

The level of BP was determined by a conventional procedure using an AD Medical device, model UA 777 (Japan). Simultaneous recording of respiration parameters, peripheral BP (pBP) at the finger level (Penaz's method), and electrocardiogram (standard lead I) was performed using a Spiroarteriocardiorhythmograph (SACR) [16]. Continuous recording for 75-300s makes it possible to analyze spectral, geometrical, and statistical parameters of the Heart Rate Variability (HRV), as well as the parameters of spectrum variability of the finger (peripheral) systolic and diastolic BP (pBP_s and pBP_d). Spectral parameters were determined using the algorithm of parametric evaluation of power spectral density. Total spectral power was calculated within a range of 0-0.4Hz, the limits of individual spectral bands coincided with those generally accepted: the range of High Frequencies (HF), 0.15-0.4; the range of Low Frequencies (LF), 0.04-0.15Hz; and the range of Very Low Frequencies (VLF), 0.04-0.15Hz [17]. On the basis of the parameters of the HRV spectrum, the indices of the autonomic balance and indices of centralization were calculated: (AB=LF / HF) and IC=(VLF + LF) / HF), respectively. The α-index reflects the sensitivity of the spontaneous arterial baroreflex. It is calculated from the indices of the HRV and pBPs (the square root of ratios of the absolute power of the LF bands of HRV and pBP_s spectra [18]).

The adaptive capacity of the cardiovascular system was evaluated in the loading test in adolescents 15-16 years of age with normal BP (school no. 1357 in Moscow, n=22) and in their peers with hypertension (Moscow schools, n=36, and those of Adygea, n=45). Random breath in a spirometric mask of SACR and without a mask served as a functional test and control, respectively (only HRV and pBP were recorded). During each testing, two consecutive 2 min recordings, the control and testing ones, were performed to assess the parameters of the cardiovascular system in percent. An increase in the dead space during this testing has been previously demonstrated to be quite informative for determining the state of the cardiovascular system of healthy subjects of different ages [19].

Oropharyngeal lavage samples were taken in some of the adolescents from all the groups to determine the character of the main metabolic processes on the level of the whole body by the method of laser correlation spectrometry. Intergroup differences in the control recording were determined using discriminant analysis. The nonparametric Spearman's correlation coefficients between the BP values and indices of the cardiovascular system, which were determined on a SACR device at rest (without a mask), were calculated. The differences in the proportion of high BP in different samples were determined using the two-tailed x^2 test.

The group differences during functional testing were evaluated using repeated measurements ANOVA; comparison of the mean values was performed using Fisher's test (the Statistica 6.0 software).

Results and Discussion

Both Russian and foreign research studies suggest that high informational and psychoemotional stress, characteristic of the current learning process especially when the latter is combined with physical inactivity, serves as a risk factor of essential hypertension [1,4,8-9,12-14]. Increased attention to adolescents of this group may enhance the effectiveness of the preventive therapy of some cardiovascular diseases, especially of psychosomatic character [12-14], and serve as the basis for the prevention of severe organic cardiovascular pathology in adults [20]. In our study, the proportion of adolescents with hypertension (with a BP exceeding 140/90mmHg) was 3-7% in all age groups (Figure 1), which is in accordance with the published data [1,2,8].

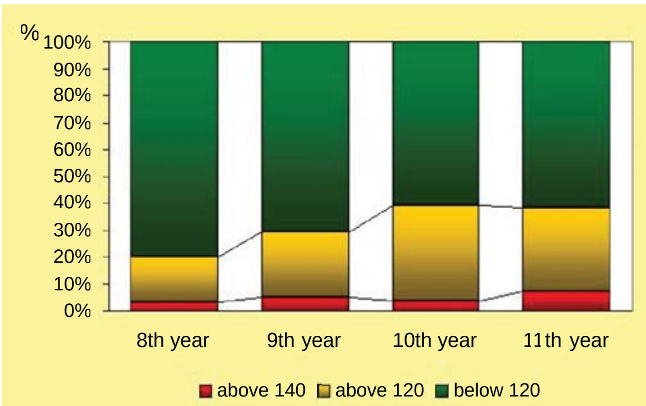

Figure 1: Dynamics of the incidence rate of elevated AD among adolescents inhabiting different regions of the Russian Federation (total examination, *n*=1300). The limits of systolic blood pressure are indicated on the right, mmHg.

When the criterion "higher than 120/80mmHg" was used for all age groups, the proportion of adolescents with elevated BP (hypertension + hypernormotension) increased during the period from the eighth to the eleventh year at school to reach 40–50% of the entire sample. In the conventionally normal populations, the proportion of these adolescents was as low as 10% (below the 90^{th} percentile).

Analysis of BP dynamics in adolescents of this group suggests that the percentage of BP elevation is the highest during their transition from the eighth to the ninth year. This was undoubtedly a consequence of ontogenetic development rather than the appearance of hypernormotension and hypertension. First, during schooling, the anthropometric parameters of the subject are increased to determine the baseline blood pressure. Second, the child's (later, teenager's) body undergoes significant changes related to functional maturation of the sympathetic autonomic control of the cardiovascular system [21]. Third, the stage of puberty in adolescents should be also taken into account, because it has a significant effect on the level of BP [8]. However, the above factors fail to explain the increase in the proportion of adolescents with BP elevated to values several times exceeding the normal ones (in a conventionally normal population).

School	Year	Total number of students examined	Number of students with elevated BP	Proportion of students with elevated BP (%)
Moscow, no. 1357	8	57	9	15.8%
	9	73	22	30.1%#*
	10	56	28	50.0%##
	11	49	24	48.9%
Moscow, no. 315	9	47	16	34.0%*
	10	48	19	39.6%
	11	45	12	26.7%
Moscow, no. 548	8	44	11	25.0%
	9	183	71	38.8%#+*
	10	122	47	38.5%
	11	50	19	38.0%
Maikop, nos. 3, 6, 9	9	48	16	33.3%*
	10	53	19	28.3%
Pushkino, Moscow region, nos. 1, 5, 9	9	150	25	20.8%
Nagovo, Novgorod region	9	31	5	16.1%

Note: Statistical significance of the intergroup differences (according to the χ^2 test): differences from the previous group of the same school (# $p < 0.1$; ## $p < 0.05$);
+differences from the parameters of Nagovo, $p < 0.05$;
*differences from the parameters of Pushkino, $p < 0.05$.

Table 1: The proportion of students with elevated blood pressure (BP, systolic BP>120 mm Hg) in schools of Moscow and other regions of the Russian Federation.

Table 1 shows the incidence of elevated BP (hypertension + hypernormotension) among high school students of various age groups and regions. It can be seen that the proportion of adolescents with elevated BP in schools of Moscow and Novgorod regions was lower than in schools of Moscow and Adygea. The proportion of adolescents with elevated BP depended also on age; it reached a stable level in the ninth and tenth years (14-16 years of age), which is in accordance with the age dynamics of BP and with the timing of juvenile hypertension. The data from the simultaneous examination of various samples were confirmed by those obtained from a five-year study of the level of BP in the same class (Table 2).

Year	Date of examination	Total number of students examined	Number of students with elevated BP	Proportion of students with elevated BP (%)
8	December 2002	35	8	22.8%
9	December 2003	37	7	18.9%
10	October 2004	49	21	42.8 %#
	April 2005	46	21	45.5%
11	October 2005	41	19	46.3%

Note: Statistical difference from the foregoing examination (according to the χ^2 test): # $p < 0.05$.

Table 2: Dynamics of changes in the proportion of students with elevated blood pressure in the same class for a four-year period (school no. 1357, Moscow, 2002-2005).

Analysis of BP_S and BP_D in adolescents with elevated BP revealed difference between the examinees living in different regions of the country by these parameters. In ninth grade pupils, the highest BP_S values were found in Moscow region (143.8 ± 2.7 mm Hg) and among Moscow schoolchildren, in pupils of general education classes of school no. 548 (133.3±1.7mmHg). In other age groups, BP_S did not depend on the region (Figure 2).

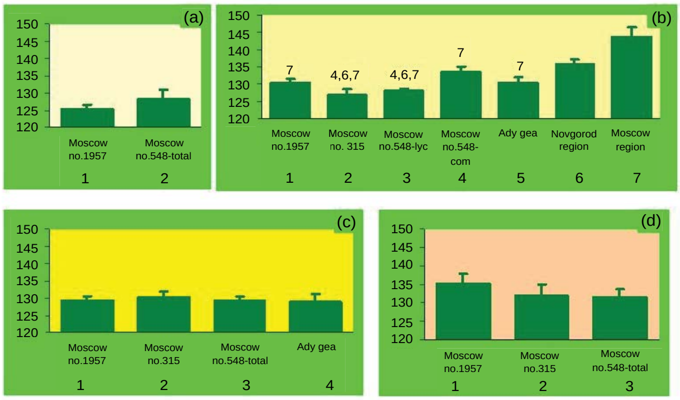

Figure 2: BP_s (mmHg) in risk group adolescents, pupils of the 8th (a), 9th (b), 10th (c), and 11th (d) grades, in different regions. Groups: Moscow no. 1957: pupils of Moscow school no. 1357; Moscow no.315: pupils of Moscow school no. 315; Moscow no. 548-lyc: pupils of lyceum classes of Moscow school no. 548; Moscow no.548-com: pupils of general education classes of Moscow school no. 548, Moscow no.548-total: all pupils of Moscow school no. 548, Adygea: schoolchildren of Republic of Adygea, Novgorod region: pupils of Nagovo village school, Novgorod region; Moscow region: schoolchildren of Pushkino town and Pushkino district of the Moscow region. Group number is shown under its title. Statistical significance of intergroup differences (p< 0.05 One way ANOVA) is designated by the number of the corresponding group.

The highest BP_D values in all age groups were observed in pupils of Moscow school no. 1357, and the lowest values were recorded in Republic of Adygea and Novgorod region (Figure 3).

Since, in children and adolescents, the autonomic regulation of the cardiovascular system varies with age, different age groups were examined separately to assess the functional state of hypernormotensive adolescents (BP_s from 120 to 139mmHg, BP_d from 80 to 89mmHg).

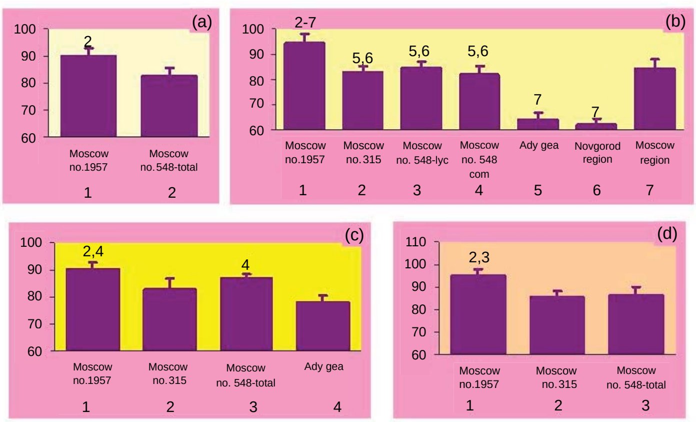

Figure 3: BP_d (mmHg) in risk group adolescents. Designations are the same as in (Figure 2).

This approach revealed statistically significant differences between the state of the cardiovascular system in normotensive and hypernormotensive eight-year students (adolescents) (the total n=101). We studied the results of the discriminant analysis for 16 parameters: the heart rate, pBP_s, pBP_d, α-index, the power of individual bands, and total spectral power of HRV, pBP_s, and pBP_d (λ_W=0.444, $F_{(16,279)}$=7.083, p=0.000). However, pBP_s was the only parameter which differed significantly in different adolescent groups. No correlations were found between the level of BP and either HRV or pBP. The ninth-year adolescent students (n=393) with different levels of BP (λ_W=0.375, $F_{(16,144)}$=19.972, p=0.000) were also characterized by statistically significant differences in only one parameter, pBP_s. In addition, the level of their BP_s was found to correlate significantly with the heart rate (r=0.144, p=0.004), relative power of LF spectral band of pBP_s variability (r=0.126, p=0.006), and α-index (r=–0.103, p=0.041). BP_d was also correlated with the heart rate (r=0.162, p=0.001) and *VLF* band power of the HRV spectrum (r=0.130, p=0.010). These results suggest that an elevated BP level in adolescents 13-14 years of age is observed against a background of a high sympathetic activity (judging by HRV spectrum) and reduced sensitivity of the arterial baroreflex. However, these correlations give no ground for suggesting a cause-effect relation between the parameters studied. Such a conclusion can only be inferred from experiments, preferably on animal models.

In tenth-year adolescents with statistically different BP levels (n=279), the discriminant analysis for 16 parameters of the cardiovascular system (λ_W=0.413, $F_{(16,279)}$=23.220, p=0.000) revealed significant intergroup differences not only for pBP_s (p=0.000) and pBP_d (p=0.021), but also for the heart rate (p=0.016), which in hypernormotensive adolescents was lower than in normotensive ones, for the α index (p=0.081), which was lower in the normotensive subjects, and for the relative power of *VLF* band of the pBP_s variability spectrum (p=0.093, the lower values in the group of hypernormotensive adolescents). In addition, the level of BP_s was correlated with the relative power of the *LF* band of the pBP_s variability spectrum (r=0.144, p=0.016), whereas the level of BP_d was correlated with the heart rate (r=0.224, p=0.000) and AB (r=0.118, p=0.048). These data indicate that, at the age of 15-16 years, the level of BP in adolescents was still correlated with the level of sympathetic activity characterized by HRV spectral parameters. However, unlike younger subjects, the increase in BP in tenth-year students was accompanied by a reduced heart rate and a higher sensitivity of the arterial baroreflex, which could be a result of disturbed autonomic regulation.

In 11th-year adolescent students, the results of discriminant analysis (λ_W=0.375, $F_{(16,144)}$=19.972, p=0.000) demonstrated that differences in BP level were accompanied by differences in pBP_s (p=0.000) and the α-index (p=0.087). Unlike in the previous group, this parameter was higher in normotensive adolescents. The level of BP_s was correlated with the power of the *HF* band of the *HRV* spectrum (r=–0.164, p=0.049) and with the relative *LF* band power of pBP_s variability spectrum (r=0.228, p=0.006), whereas no correlations were found between the level of BP_d and the parameters of both HRV and pBP variability. These data suggest that, in the oldest age group, an elevated BP was also related to insufficient vagal control along with high sympathetic activity and low sensitivity of the baroreflex. Similar results were reported in [22]: in subjects with the BP close to the upper normal limit (133 ± 0.7 mm Hg), an increase in the LF power band and reduced power of the HRV HF band were accompanied by a low α-index. This was interpreted as an impaired autonomic regulation most characteristic of young persons (16-20 years of age).

The elevated levels of BP are assumed to be caused by both environmental and metabolism-associated genetic factors [1]. Chronic psychoemotional stress caused by problems in the family, at work (in school), or others were found to lead often to hypertension [12,14]. Under these conditions, even in the absence of clinical signs of somatic diseases, BP elevation to the upper normal limit is often recorded and HRV analysis demonstrates an increase in sympathetic activity (high power of the LF band), insufficient vagus activity (HF band), and a reduced α-index [23]. In adolescents with a genetic predisposition to hypertension (who have at least one parent with this disease), the autonomic regulation of the cardiovascular system is characterized by changes in the HRV spectrum, which are similar to those in the off-spring of healthy parents [15]. Herewith metabolic shifts (lipid metabolism disturbances and impaired glucose tolerance) are more often observed in adolescents with high BP [10,11]. Analysis of health status in Moscow schoolchildren also showed the prevalence of gastrointestinal and allergic diseases in senior year students [24], which affect the parameters of metabolic processes. These data prompted us to analyze the basic type of metabolism in hypertensive adolescents.

Previous fundamental studies on various models of pathological syndromes by the method of laser correlation spectroscopy showed that the total range of light scatter spectrum of Oropharyngeal Washout Fluid (OPWF) can be divided into 4 informative zones (by the size of light scattering particles): I–0-50nm; II–51-400nm; III–400-2000nm; IV–>2000nm. Zone I primarily contains low-molecular-weight albumins and free glycolipid complexes. Zone II includes globular proteins and lipoprotein complexes. Zone III primarily contains ribonucleoprotein and deoxyribonucleoprotein particles and low-molecular-weight immune complexes. Zone IV primarily reflects the presence of medium-molecular-weight immune complexes. Changes in the relative contributions of different LC-spectrum zones reflect the increase or the decrease in the content of particles of different origin. It was found that increased content of small particles in biological fluids reflects the prevalence of biosubstrate degradation processes, while increased contribution of high-molecular-weight particles is indicative of polymerization processes. A semiotic classifier created on these principles allows differentiation of 6 different metabolic states in the organism, with 3 grades in each. It should be noted that the name of the semiotic shift reflects only general nature of the identified spectrum. For group 0 (normological group), two main directions of metabolic shifts can be identified in the oropharyngeal fluid: 1) catabolic shifts characterized by increased contribution of low and medium molecular weight subfractions into the light scatter and including intoxication, catabolic, and dystrophy like shifts; 2) anabolic shifts formed by increased contribution of high- and superhigh-molecular-weight subfractions and including allergy and autoimmune like shifts.

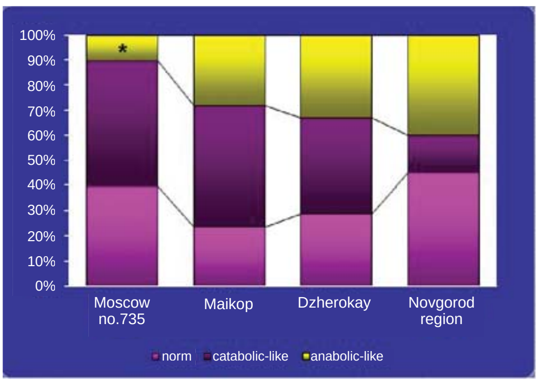

Figure 4: Metabolic shifts in the organism of schoolchildren from different regions of the Russian Federation. Groups: Moscow no 735 – students of Moscow School no. 735, Maikop – students of Maikop town schools of Adygea Republic, Dzherokay – students from Dzherokai village, Adygea Republic, Novgorod region – students from Nagovo village, Novorod region. Arrow indicates significant difference from the parameters in group Novgorod region γ^2 (p<0.05).

Analysis of LC-spectra of OPWF samples in children from Nagovo village school, Novgorod region (Figure 4), showed predominance of normological spectra (45.0%) and relatively high incidence of anabolic spectra (40.0%), the incidence of catabolic-like spectra being low (15.0%). In children from Moscow school no. 735, the incidence of anabolic-like spectra was lower ($p<0.05$) than in rural children and the incidence of catabolic-like shifts was high (50%). In children from Maikop and Dzherokay village (Republic of Adygea), the percentage of different spectra was similar to that in Moscow.

Analysis of possible correlations of pre-hypertension state with metabolic status in Moscow school children (n=91) showed that the relative content of smallest particles (zone I, <50nm) in OPWF negatively correlated with heart rate (r=–0.241, p=0.022), AB (r=–0.187, p=0.075), IC (r=–0.231, p=0.028) and relative VLF range power in the HRV spectrum (r=–0.313, p=0.003), while SBR correlated with the contribution of large particles (zone III) into light scatter (r=0.204, p=0.052). In Moscow region population (n=98) BP_d correlated with the contribution of zone I particles into the light scatter (r=–0.520, p=0.047), while the content of zone III particles correlated with integral power of HRV spectrum (r=–0.256, p=0.011), reflecting the level of autonomic activity [17]. In hypertensive adolescents, residents of Novgorod region (n=18) and Republic of Adygea (n=69) a correlation, though positive, was also found between the contribution of the smallest particles into light scatter and AB: r=0.520, p=0.027 и r=0.259, p=0.032 respectively. Moreover, the content of large zone III particles correlated with relative power of VLF range of HRV spectrum (r=0.689, p=0.002), in adolescents from Novgorod region and LF range of (r=0.266, p=0.027). These findings suggest that a correlation exists between the parameters of the autonomic regulation of the cardiovascular system and the pattern of metabolic processes in adolescents from different regions of the Russian Federation and the sign of this correlation depends on the place of residence – Moscow/Moscow region or more remote parts of the country. At the same time, the dependence of BP on peculiarities of metabolism was observed only in Moscow and Moscow region, whereas in Republic of Adygea even the correlation between LC spectrometry parameters and the power of VLF range of HRV spectrum reflecting, among other things, the influence of metabolic factors [17] was absent. These findings agree with our previous data that living conditions in a metropolis considerably modulate the mechanisms of the cardiovascular system regulation in adolescents [7] and can be considered as a possible target for more specialized biochemical and physiological studies in this field.

Our analysis of the autonomic regulation of the cardiovascular system in adolescents of a certain age (15-16 years, Moscow school no. 1357) but with different levels of BP showed no differences between these groups at rest. Probably, the fact that all students of the same school were under the same environmental and psychosocial conditions accounts for this phenomenon; adaptation to these conditions induced similar changes in the autonomic activity [23].

However, the above data obtained on a wide sample of adolescents from different regions of the country demonstrate that, at this age, an elevated BP is accompanied by changes in the parameters of autonomic regulation, which is not the case at younger or older ages. The loading test with increasing dead space allowed us to reveal regional changes in the parameters of the cardiovascular system in adolescents with different levels of BP. Testing in the spirometric mask of hypernormotensive adolescents 15-16 years of age demonstrated that the heart's acceleration and a decrease in pBPS were characteristic of subjects from both Moscow and Adygea, whereas the pBPd was reduced only in Moscow residents (Figure 5).

In adolescents with normal BP, this functional test caused no changes in the above parameters. In prehypertensive adolescents, the relative power of the LF band of the HRV spectrum was reduced (the LF band reflects the level of sympathetic influences [17]) though the total power of the spectrum remained unchanged. Changes in the LF band of the pAD_S

spectrum of variability as compared to the same parameter of normotensive adolescents were statistically significant only in Moscow residents, though their total spectral power also remained unchanged (Figure 6).

Reducing the effectiveness of the sympathetic component was described in the study [23], where subjects with borderline BP values (because of chronic psychosocial stress) were tested for their response to changes in posture: from a seated position to a standing position. The results were interpreted as adaptive reduction in sensitivity to excitatory stimuli. In the subjects with a genetic predisposition to hypertension, sympathetic activity was, on the contrary, increased [15]. Unlike the results obtained in other regions, in the adolescent Moscow residents (school no. 1357) examined under our conditions, high normal BP was not accompanied by any significant increase in parameters of sympathetic activity at rest, which is probably a result of maladaptive changes in the sympathetic component of autonomic regulation as recorded during the performance of the functional test. The functional insufficiency of this regulatory system was manifested in a reduction of pBP itself, rather than only of the relative power of the LF bands of both the HRV and pBP_s spectra. In adolescents from Adygea, these changes in the autonomic activity were less pronounced, which may be accounted for by specific psychosomatic development and psychosocial adaptation, as well as by the influence of environmental factors.

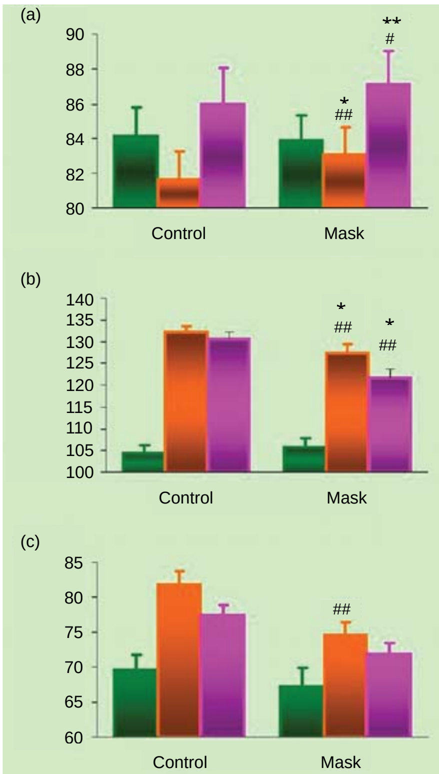

Figure 5: Changes in the parameters of the cardiovascular system during the functional testing (control–mask): (a) heart rate; (b), pBP_s; (c), pBP_d. Group designations: green columns, students with normal BP (Moscow school no. 1357); orange columns, students with hypernormotension (Moscow school no. 1357); magenta columns, students with hypernormotension from the schools of Adygea. Statistical significance of changes during functional testing (repeated measures ANONA): # – $p < 0.06$, ## – $p < 0.05$. Statistical difference from the group with normal BP (one_way ANOVA): *p<0.06, **p <0.05. Here and in Figure 4, see "Methods" for explanations of abbreviations.

We may assume that the development of hypertension in adolescents, which was the most pronounced in tenth-year students of Moscow schools, was a consequence of a combination of regular ontogenetic changes in their regulatory systems and the negative influence of ecological and school risk factors. The way out of this situation for Moscow students may be a change in lifestyle or, as an alternative, place of residence.

Conclusion

1. The results of the sanogenetic monitoring of the health of school children have demonstrated that, among high school students, the proportion of adolescents with elevated BP (hypertension + hypernormotension) has risen from 15-20% in 8th year students to 30-50% in 9th to 11th year ones, though the proportion of adolescents with hypertension is 3-7% in all age groups. The incidence of adolescents with elevated BP is different in various regions of the country; the highest BP values were recorded in Moscow.

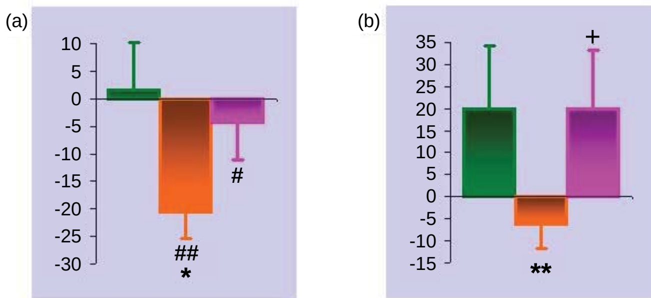

Figure 6: Changes recorded during the functional testing (in % of the control) in the relative power of the low-frequency LF band of the spectra of (a) the heart rate variability and (b) pBPs. Designations are the same as in Figure 5. Statistical differences during the functional testing and from the group with normal BP are the same as in Figure 3. Statistical difference from the students with hypernormotension (school no. 1357). (One-way ANOVA): $+p<0.06$.

2. Comparison of the BP level with the parameters of the autonomic regulation of the cardiovascular system revealed correlations between the state of hypernormotension in adolescents of 13-14 and 17-18 years of age and both a higher proportion of low frequencies in the spectrum of heart rate variability and reduced sensitivity of the arterial baroreflex. At the age of 15-16 years, a high-normal BP was accompanied by a reduced heart rate and a higher sensitivity of the arterial baroreflex; high normal BP was also correlated with a reduced power of the high-frequency band of the spectrum of heart rate variability.
3. When performing a functional test (with an increase in the dead space), hypernormotensive adolescents from Moscow 15-16 years of age were characterized, in contrast to normotensive peers, by reduced finger blood pressure and reduced relative power of the low-frequency band in the spectrum of heart rate variability, which may be related to the maladaptive functional changes in the sympathetic autonomic regulation.

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Chapter: V

Methodological Approaches to the Assessment of Health-Building Potential of New-Generation Educational Standards

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Russia started the process of the gradual transfer of the education system to the new standards. These new educational standards reflect the social order and are seen as a social compact matching the requirements imposed by the family, society, and the state to the educational system; they represent the sum of three systems of requirements: to the structure of the basic educational program, results of learning and conditions of realization providing personal and professional development of students. On the other hand, social and economic changes in our country and around the world make high demands of the quality of human capital: mentality, biological and social resources, physical and mental health of graduates. This, in turn, determines their competitiveness on the labor market, successful professional adaptation and the social welfare of the young generation in general.

Therefore, in the context of the requirements of new educational standards, the health-building approach should be one of methodological principles of the organization of educational process determining the content, organizational forms, and methods of education. This approach can be presented as follows: the interpersonal “student-teacher” interaction is based on the subject-subject relations aimed at the joint search of “healthy” solutions for various problems. In addition, the updated content of education programs provides the priority of student health, while health-protecting educational technologies contribute to the harmonious development of the physical and mental spheres, focusing on health, learning healthy life style, maintenance and development of the individual psychological and personality characteristics of the students determining their health status and social and professional adaptation. The purpose of health protection, the proportion between health protection and other activities within the educational process, a hierarchy of values and priorities, development of reflection as subjective health education, formation of personal position regarding health, etc. are the main guidelines of the educational process based on the health-building approach.

The development of specific ways of realization of the health-building approach is a complex interdisciplinary task implying the priority of health as a prerequisite for the educational process. This determines the algorithm of the formation of health-protecting educational environment, where the teachers, experts of medical centers and psychological services, students, and their parents together solve common problems related to health building and incur responsibility for the achieved results.

Practically, health-protecting activity of educational institutions includes several aspects. These are:

- Organization of rational nutrition.
- Organization of optimal regimen of physical activity.
- Due consideration of interests of children with different physical abilities.
- Specific approach in physical education classes in accordance with the group health.
- Inclusive education for disabled.
- The use of health-protecting educational technologies.
- Updating of the educational courses.
- Introduction of new progressive forms, methods, and tools of the pedagogical process (at school and in individual work).
- Adjusting of the structure and presentation of the teaching material.
- Protection of teacher's health.

These measures became the barest necessity in view of rapid development of sciences and information media and increasing volume and intensity of workload. All the tasks that without due consideration for individual characteristics of the pupils cannot be coped without potential harm to child's health. Teacher's health should not be neglected as well.

Thus, evaluation of health-protecting activity of any school is evaluation of the results of this activity, evaluation of the efficiency of health-building work. The task of educational institutions consists in fulfillment of a social order [1]: "to rise a generation of free, well-educated, creative citizens..." (principal task) and to protect the health of students and pedagogues (associated task).

Then, the main parameters of health-protecting activity of educational institutions are:

Efficiency of intellectual work (by the results of pedagogical statistics) and dynamics of intellectual working capacity (by the results of psychological tests);

"The cost" of the achieved pedagogical results:

- By the results of medical statistics.
- By the dynamics of functional state of the major systems of child's organism (nervous system and sensory systems, locomotor, cardiovascular, respiratory systems, and systems of neuroautonomic and neuroendocrine regulation).
- By the dynamics of physical capacity.

Thus, the efficiency of health-protecting work in educational institutions is a sum of the results of quantitative methods of psychological and pedagogical monitoring and quantitative methods of physiological and hygienic (sanogenetic) monitoring. The choice of methods of monitoring is determined by the material and technical equipment of the educational institution and personnel proficiency.

Let us speak about underlying potential problems complicating the interpretation of the obtained results.

First, the principal contingent of health monitoring is healthy children and healthy teachers. In case of prophylactic medical examination, the main task is the detection of sick children and evaluation of the incidence of transition from “health” to “disease”, while sanogenetic monitoring is focused on the processes within the “health” state. According to modern views, the range of “health” is not that homogeneous as the range of “disease”. There are a number of transitional states from physiological norm to adaptation failure or disease such as the stage of mobilization of functional reserves and stage of adaptation strain or pre-disease, which still fall into the category of “health”, but signal to ill-being. Hence, changes in the functional parameters of the organs and system of child’s organism induced by various educational technologies, including variants of physical education, reflect not the transition from “norm” to “pathology” and vice versa, but the formation of a new functional state within the “health” state. For evaluation of functional state of the organism within the range of “health”, methods for measuring functional reserves of the organism are used.

Second, nonexpert interpretation of the obtained results can be complicated by some methodological details. Practice of many years for evaluation of the efficiency of health-protecting activity in educational institutions and the experience of advanced training of school health-protection specialists allowed us to select some important aspects critical for correct interpretation of the obtained results.

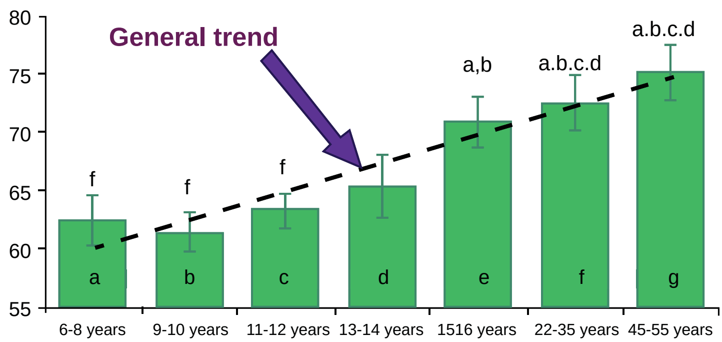

Figure 1: Age-related stroke volume dynamics. Letters on the bars denote age groups, significant differences ($p<0.05$; One Way ANOVA) are shown above the bars. Dotted line shows the general trend.

Evaluation of the efficiency of any educational technology requires two examinations: baseline and testing; moreover, the technology is applied against the background of physical, mental, and intellectual development of the child. Hence, it should be taken into account during interpretation of the obtained results that the anticipated result in terms of improvement/impairment will interfere with natural age-specific dynamics of physical and functional development of the organism. If the researcher analyses two end-points, they will always differ due to these physiological regularities. This can be illustrated by the results of myocardial function analysis (Figure 1).

Hence, the researcher should “reset” the effect of the natural biological factor to prove the efficiency of the proposed method: or at least the corresponding control groups should be formed.

Another important aspect is related to chronobiological regularities. Educational technologies are applied during the school year, usually during three seasons. In 1970-1980, researchers of Tartu University performed long-term monitoring of the cardiovascular system parameters in rats, mice, and rabbits [2-4]. The animals were kept in a vivarium at constant illumination regimen (12:12h) and standard ration. Even under these conditions, the analyzed parameters underwent seasonal variations: the minimum heart rate and blood pressure and the maximum autonomic nervous and hormonal activities are observed in the spring. Twofold examination during the school year also revealed seasonal variations in the cardiovascular system and psychomotor parameters in school children [5]. In pedagogical practice, however, the researches make erroneous conclusions from the two end-point results (in the beginning and end of the school year, i.e. in the fall and spring) on positive/negative influence of the educational medium factors on the functional state of the organism in school children. In fact, these changes are caused by natural chronobiological processes (Figure 2).

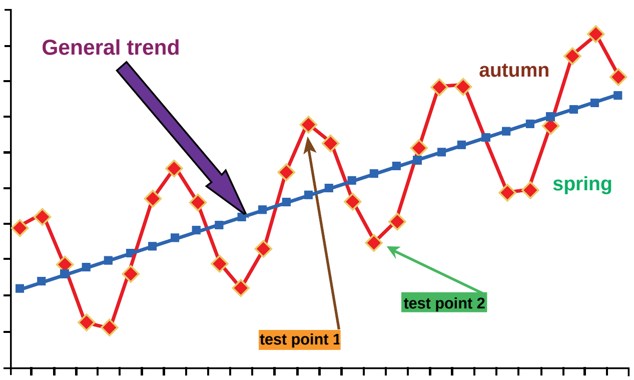

Figure 2: Seasonal dynamics of the parameters of functional state of the organism. General ontogenetic trend is shown by an arrow.

The results of monitoring are often scored by comparing the actual results with centile limits of the corresponding age and gender groups. This method of analysis is based on the comparison of the studied parameter with averaged data for a conventionally normal age- and sex-matched sample. The score is determined as follows (Figure 3):

- 0 corresponds to the population sample mode,
- –0.5 and +0.5 correspond to the limits of medium 50% interval of the parameter distribution in the population sample (balanced state),
- –1.5 and +1.5 correspond to the limits of 90% interval of the parameter distribution in the population sample (medium 50%+20% from each side; adequate state),
- –2.5 and +2.5 correspond to the range of conventionally normal sample (5% extreme values from each side, tense state).

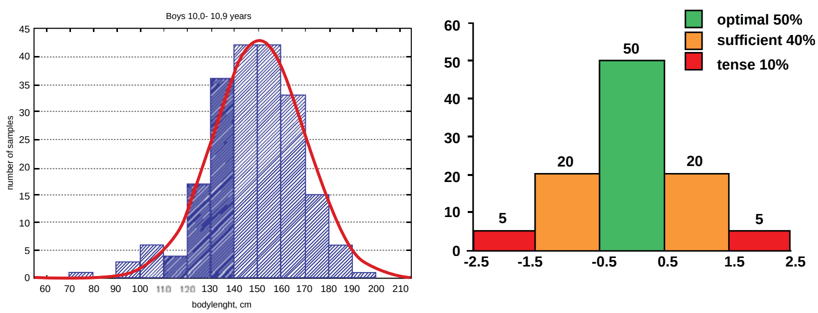

Figure 3: Left panel: distribution histogram and plotted results of the body length of 10 year old boys. Right panel: principles of scoring using the distribution histogram.

For evaluation of various systems, e.g. the state of myocardium, each parameter (duration and amplitude of six relevant intervals of ECG) is scored and score modules are summed up. The resultant values reflect deviation of the analyzed parameters from the conventional norm and the balance between the analyzed parameters describing functional state of this system. The lower is the score, the better is the result. Elevated score attests to increasing functional tension in body functions. The functional state of each body system is also ranked in terms of “balanced” – “sufficient” – “tense”, similarly to individual parameters of the corresponding system.

The integral evaluation of the functional status of the whole organism is formed from scores of several system:

“Anthropometry” includes body height (score is calculated by the regional centiles for the corresponding gender and age) and weight (score is calculated by centile tables for the corresponding gender, age, and body height).

“State of the myocardium” includes evaluation of six relevant intervals of averaged ECG (over 2 min): duration of P, PQ, QR, QRS, QT intervals and ST depression according to sex and age norms approved by Russian cardiologists.

“Heart rhythm variability” includes total TP spectral power and the power of individual spectrum ranges VLF, LF, and HF; centile tables for each parameter were composed based on our own database (tests on a spiroarteriokardiorhythmograph, >30,000 observations in 1990-2002.

“Blood pressure” includes scoring of systolic and diastolic pressure according to national centile tables.

“Blood pressure variability” includes total spectral power and the power of individual ranges for systolic and diastolic blood pressures. Similar to heart rhythm variability, centile tables for each parameter were constructed using our own database.

“Psychomotor coordination” includes scores of 5 parameters: velocity, accuracy, and smoothness of movements, movement amplitude gradient, and latency of simple sensorimotor responses to visual and acoustic stimuli. Centile tables for each parameter were formed using our database (testing on Computer Movement Meter; more than 30,000 observations in 1995-2002).

“State of the respiratory system” includes scoring of vital lung capacity and Tiffeneau index by regional centile tables for the corresponding gender, age, and height.

Thus, the values falling between 25^{th}-75^{th} centiles can be considered as balanced. The values falling from the 5^{th} to the 25^{th} and from the 75^{th} to the 95^{th} centiles characterize adequate state, and values below the 5^{th} and above the 95^{th} centiles indicate functionally tense state.

The use of these abstract integral evaluations of health status also is associated with seasonal variability (Figure 4).

Solution: For proving the efficiency of health-protecting method or for substantiation of the health hazard, control groups and at least two-factor statistical tests should be used where one factor is the effect of chronobiological regularities.

One more aspect: When evaluating long-lasting after effects of changes in the educational process we should take into account that the differences between the children from different experimental groups can be not always revealed. The same children enter the first grade of the primary school and during the first year similar processes of adaptation to school develop in them. The intensity of these processes exceeds all possible influences of various pedagogical innovations. In graduation classes, the students start to prepare for final exams, attend preparatory courses, and take preparatory unified state exams, and these troubles exceed all pedagogical features of particular educational programs [5]. Thus, the main result of pedagogical innovations is a shift of the terms of development and functional maturation of systems and organs, for instance, accelerated development of the locomotor system in response to adequate intensification of physical load [6].

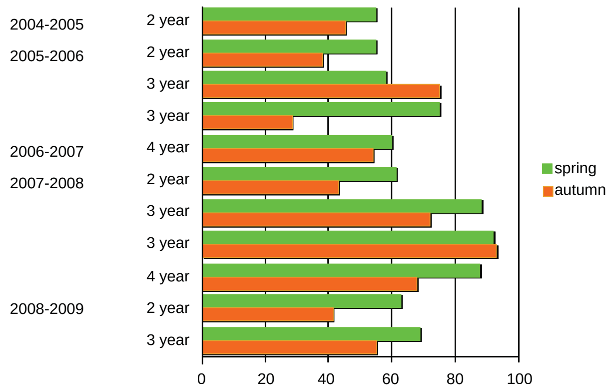

Figure 4: Monitoring of the functional state of Moscow primary school children (South Administrative District): percent of children with optimal functional status.

Neglecting these aspects can lead to false-positive or false-negative conclusions about the efficiency of the used health protecting technology, whereas due consideration of all these methodological details in practical work makes it possible to assess the health protecting potential of new generation educational standards as soon as during the first year of their application.

In 2010-2011, some Moscow schools (~180) adopted new educational standards for the primary school education. Other school functioned in usual regimen. Experts of the Center of Educational Medium and Children Health preformed repeated sanogenetic examination of first grade pupils in all schools adopting new standard and in 15 schools working in usual regimen.

It was found that in the fall (starting level), the incidences of balanced, adequate, and tense states in schools using different standards were similar and considerably differed from the corresponding parameters in conventionally normological population (Figure 5). The percent of children with balanced status decreased, while the percent of children with tense state increased in all schools. This coincides with the results of long-term observation of various researchers and reflects the processes of psychophysical tension during child adaptation to systematic school education (i.e. correspond to normal).

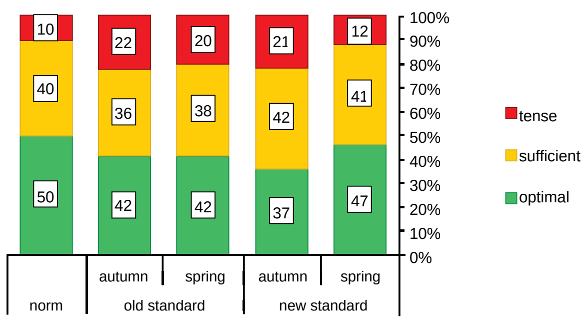

Figure 5: Incidence of various assessments of the functional state of children in schools applying different educational standards in comparison with conventionally normological population ("norm").

However, spring examination showed that the proportion of the normological population was restored, whereas in schools adhering to old standards, the percent of balanced states remained lowered against the background of increased incidence of tense states, and, as was previously reported by us, the adaptation to school was completed only in second grade children [5].

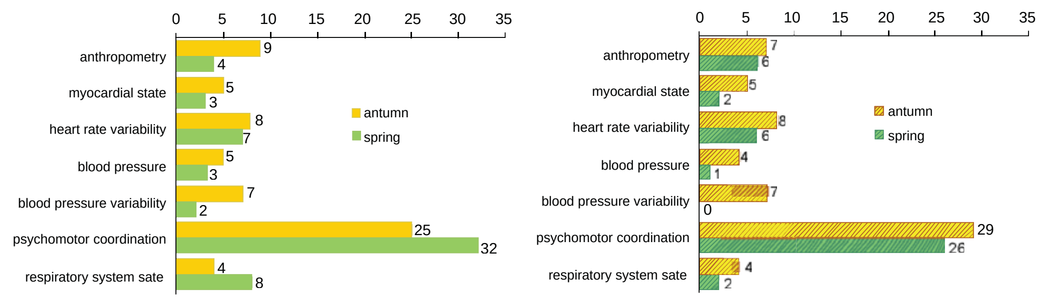

Figure 6: Percent of children with tense functional status of various systems of the organism (A) In school adhering to usual education standards and (B)In schools adopting new educational standards.

Detailed analysis showed that imbalance in the system of psychomotor regulation (the first system responsible for adaptation to school) made the major contribution to dysregulatory states (Figure 6). And this fact deserves special analysis. By the method of scoring, "tense" range comprises ~10% conventionally healthy individuals of the examined sample (the data were obtained in 1995-2002). The same values were obtained in later studies, e.g. in comparative analysis of psychomotor parameters of schoolchildren in Moscow and other regions in 2006 [7]. However, in the present study, the proportion of students with "tense" functional status of psychomotor coordination was 25-32%. Analysis of individual parameters suggests that in modern first graders, the development of speed characteristics of manual performance prevails over accuracy and smoothness of movements. This process is probably an objective law determined by widespread and early penetration of the Internet (and other information and communication technologies) in our life starting from kindergarten, where computer training begins from the age of 3 years (at least in Moscow). One can assume that "computerization" and "internetization" not only changed minds and thinking of the new generation of schoolchildren, but also led to physiological changes in the systems regulating movements. However, in the context of our study this assumption is no more than a speculation requiring serious physiological and psychological verification.

Spring examination showed that the percent of children with tense status by anthropometric (excessive or insufficient body weight) and cardiovascular function parameters (myocardial function, blood pressure, heart rhythm and blood pressure variability) decreased in all schools. Positive changes in the parameters of the respiratory system and, most important, in psychomotor system were noted only in schools adopting new educational standards. The latter attests to alleviated influence of mental stress related to adaptation to school. The dynamics of the respiratory system parameters requires more detailed analysis.

Thus, the results of sanogenetic monitoring suggest that new-generation educational standards are more adaptive to the children health than previous standards, in other words, they are characterized by higher health-protecting potential.

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Chapter: VI

The Complex Approach to a Multipurpose Estimation of a Sportsmen Condition

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Under the present circumstances training of high quality athletes is aimed to mastering the sportsmanship of an individual athlete and it depends mainly on the balanced interactivity of multiple functional systems of the body that determine the nature of his/her adaptive capabilities [1]. Meanwhile, the adaptive characteristics contain bound functional systems of hemodynamics, metabolism, immune and hemopoiesis, the general profiles of which should be within the boundaries of the static fluctuations in majority of parameters that correspond to the analogous gender and age range of the persons who do not purposefully go in for a certain kind of sport activity [2-5]. In other words, the optimal methods of high-quality athlete training is that one that allows to reach the intensive rise of sportsmanship with the maximum balance of separate parameters and integral level of the functional systems that determine the adaptive reserves of the athlete's body and in full volume follow the criteria for population of persons in the practically healthy group of population of the same age and gender. Still, the range of variability for athlete' homeostasis parameters are much wider in comparison with those for the persons who do not go in for sports, thereby rather often different parameters exceed boundary population ones and they may be interpreted as pre-pathological and pathological ones [6-9]. These changes indicate a higher adaptation capacity of an athlete's body.

Nowadays it is quite clear that diagnosis and correction of athletes' functional state should be made with taking into account the results of the integral study methods and with use of individually selected training conditions, volume and intensity of physical loads, cycles of competitions and rest which will save sport in future from those problems that the trainers and doctors face at intensification of the training process [1,10].

The actuality of the integral approach to estimation of athletes' state is confirmed with appearance of cross-disciplinary sciences of medicine, biology, physics, chemistry, etc. which assume individualization of making a diagnosis and effect of the environment on the body in the context of integral understanding of the mechanism of human's vital functions.

The functional state of a human body can be studied adequately only in the process of the advanced medical examination. All approaches with instrumental ones adopted in modern medicine included are used for the diagnosis of the functional state of the body [7].

Studying the functional state of athletes' bodies is one of the most important tasks of the sports medicine. Information about it is required for estimation of the state of health, revealing specificity of the functional state of the body related to sport training, as well as for determination of the level of physical fitness [11,12].

Fitness of the body, in its turn, determines the level of high training, which is a complex medical and pedagogical concept that characterizes athlete's fitness to achievement of high results in sports. It is developed under the effect of systematic and task-oriented sport exercises and its level depends on efficiency of the structural and functional rearrangement of the body in connection with tactical and technical and psychological physical fitness of an athlete.

Since term "high training" acquired a more universal nature in the modern sports, and then a sufficiently convenient in this sense is term "functional readiness". The level of functional readiness of the athlete's body can be really used by the trainer for the diagnosis of high training/fitness.

The study of functional fitness of an athlete is carried out by evaluation of the functional state of the body systems at rest and in taking functional tests. Deviation is more often a consequence of those functional variations which are developed in the process of sports training. Still, in some cases it may be related to fatigue, overtraining or a disease [6,13,14].

It is appropriate in sportive medicine to compare some markers of the active state of the body not with normal standards, but with values so-called proper ones for the given conditions which are determined by these or those variables. We can put down here, for instance, age, height and mass of the body examined, sports specialization, qualification, etc. But a simple comparison is not enough for a reliable evaluation of the functional fitness of an athlete [12]. The matter is that diagnosis of functional fitness is made on the basis of many parameters that often depend on each other. Therefore the characteristic of the functional state of the body systems may be considered complete enough if it takes into account the results of the functional tests taken, along with the data registered at rest [15].

The systems that determine the functional state of the body include first of all: the Autonomic Nervous System (ANS) carrying out regulation of activity of all visceral systems of the body, as well as the cardiovascular and respiratory systems [2,11,15,16].

When considering the ANS significance, it should be noted that under the effect of sports training, its functional state changes. The athletes at rest have manifested domination of the tone of the parasympathetic part. It is expressed in slowing-down of Heart Rate (HR), lowering of Blood Pressure (BP), bradypnoe, etc., which provides economization of activity of the body systems. During training or at once after it the tone of the sympathetic part prevails, which facilitates development of adaptive reactions of the body [17].

For detailed evaluation of the ANS functional state, a number of methods of testing has been used that allow to characterize the tone of sympathetic and parasympathetic innervations-dermographism, oculocardiac reflex, study of latent perspiration, thermography, etc [18,19]. For the past time instrumental methods of studying variability of functions of the cardio-respiratory and other systems are widely used for determination of ANS activity and tone [20-22].

Still, the system integral approach to estimate the results of study is difficult, which is related to different approaches to their interpretation disengaged both at the level of methods and conditions of study and units of measurement for absolute values of rates. Therefore for interpretation of the data obtained, more often quality estimates are used which are related to determination of conditional criteria. In its turn, the latter ones are sufficiently dependable on the community of the persons tested and the tasks for the researcher.

This is the fact that made us pay attention to two moments: 1) use of express approaches of study that allow to study the function of the cardio-respiratory system in the simultaneous mode of registration; 2) design of a unified model of estimation and interpretation of the results of study associated with consideration of percentile distribution deviations of the values obtained.

For solving the problem of rapidity and information capacity, the up-to-date method has been used which was designed by the "Intox, Ltd." company (St. Petersburg)–Spiroarteriocardiorhythmography (SACR) considered above. Note that it was not used before in solving the problems related to testing of the functional state of athletes.

Also note, that the percentile method for distinguishing the norm and not the norm differs from others only by the fact that the range of its applications is not limited only by normal distribution, i.e. the type of distribution is leveled at its use [23]. The method is based on percent of indicator accumulation in population. The estimation is done according to the tables of percentile type. The columns of the percentile tables show quantitative boundaries of the indicator in a certain portion or percent (percentile) of persons of the given age and gender. The intervals between the percentile columns (zones, corridors) reveal the range of a variety of the indicator values which is peculiar or makes 3% (a zone to the 3rd or from the 97 percentile) or 7% (a zone from the 3rd to 10th or from the 90th to 97th percentile) or 15% (a zone from the 10th to 25th or from the 75th to 90th percentile) or 50% of all the persons from the given age-gender group (a zone from the 25th to 75th percentile). The boundaries of the percentile groups and numbers of percentile intervals (zones) are presented in the upper lines of each table. The task for the researcher is to find to which percentile interval (zone) the obtained value comes and to estimate it with consideration of the average level range. Depending on that, the estimate is formed [23,24]:

- zone No. 1 (up to the 3rd percentile) –a "very low" level;
- zone No. 2 (from the 3rd to the 10th percentile) – a "low" level;
- zone No. 3 (from the 10th to the 25th percentile) – a "below average" level;
- zone No. 4 (from the 25th to the 75th percentile) – an "average" level;
- zone No. 5 (from the 75th to the 90th percentile) – an "above average" level;
- zone No. 6 (from the 90th to the 97th percentile) – a "high" level;
- zone No. 7 (from the 97th percentile) – a "very high" level.

Thereby, the 1st (up to threshold of 3% or to 5%) and the 7th (after 97% or after 95%) percentile corridors are "certainly abnormal" and the 3rd, 4th, 5th percentile corridors are "certainly normal".

In our researches we used the estimate on the basis of following distributions:

- zone No. 1 (up to the 5th percentile) – a "very low" level;
- zone No. 2 (from the 5th to the 25th percentile) – a "below average" level;
- zone No. 3 (from the 25th to the 75th percentile) – an "average" level;
- zone No. 4 (from the 75th to the 95th percentile) – an "above average" level;
- zone No. 5 (from the 95th percentile) – a "very high" level.

Considering the given approach to evaluation, the important circumstance was in finding the versions of functional indicators coming to the extreme ranges which evidence an expressed stress of a corresponding function. Coming to the intermediate ranges (2 and 4) characterizes the moderate stress, testifying as a rule some adaptable reorganizations of the function.

Such approach at the stage of the comparative analysis allowed to reveal differences in the functions to be studied in the uniform qualitative system of estimations taking into account well clear interpretations.

According to the technique offered, the basis for obtaining numeric scores in the uniform scale is age percentile distributions of parameters. In joint researches at the earlier stage, according to the analysis of the results of screening practically healthy persons of various ages in Odessa, St.Petersburg and Moscow, which was carried out within the period of time from 1998 to 2010, percentile tables have been elaborated for distributions of the indicators obtained in study of SACR [25,26].

We have modified the percentile tables for evaluation of the functional state of persons who go in for sports. We have examined 1,368 persons who do not have confirmed cardiologic, neurologic or other chronic pathology and who go in for different sport disciplines. Measurement of HR, BP and breathing pattern with duration of 2min. was done in the sitting position on the background of quiet breathing, in the state of relative physical and psychical rest in quiet premises by means of instrument "SACR". In addition, tests were made with 6 and 15 times Controlled Respiration (CR). The percentile distributions obtained as a result of the statistic treatment of these measurements are shown below (Tables 1-11).

Parameter	0-5	5-25	25-75	75-95	95-100
HR,1/min	<51.8	51.8-59.5	59.6-73.6	73.7-83.9	>83.9
P,s	<0.087	0.087-0.093	0.094-0.105	0.106-0.117	>0.117
PQ,s	<0.109	0.109-0.123	0.124-0.152	0.153-0.180	>0.180
QR,s	<0.025	0.025-0.030	0.031-0.034	0.035-0.039	>0.039
QRS,s	<0.077	0.077-0.082	0.083-0.095	0.096-0.102	>0.102
QT,s	<0.336	0.336-0.358	0.359-0.396	0.397-0.432	>0.432
ST,n.u.	<0.080	0.080-0.130	0.131-0.187	0.188-0.235	>0.235

Table 1: The boundaries of percentile distributions of ECG parameters in athletes.

Table 1 shows distribution of cardiointervalometry parameters at lead 1 which are obtained in the group of qualified athletes. It should be noted that as a whole, they are matched with distribution of parameters taken from almost healthy persons who do not go in for sports, except for the expected, more expressed lowering of HR and some displacement of ST above the isoline [26]. Thereby, as it is seen in Table 1, any variants of ST displacement which are lower or even on the isoline are considered as prohibitive.

In diagnosis of disturbances in the body systems control, the most important place belongs to the functional state of ANS (Partsernyak SA, Yunashkevich PI, 2002).

The static and wave characteristics of HR at rest allow to define activity of sympathetic and parasympathetic paths of control, and conducting functional tests gives a chance to obtain the most significant information on vegetative supply and vegetative reactivity [11,12,15,27]. Under the effect of different tests, the control is rearranged with formation of a new functional state which is not steady, but is specified by every minute needs [28,29].

When evaluating HRV data at all stages of functional tests, it is recommended to consider not only average values of parameters, but dynamics of their variations as well [30-32]. Lowering of LF with increase of HF is considered to be the criterion of good test tolerance [33,34].

The existing literature offers to use two standard cardiovascular tests [15] for estimation of the condition of cardio-respiratory system which allow to estimate the activity of parasympathetic (RR is 6 per minute) and sympathetic (orthostatic test) control loops [3,35-39].

The test with controlled respiration of 6/min. (further on CR_6) is aimed to find disorders in the parasympathetic control loop, since it has been ascertained that effect of respiration is spread onto HR variations defined as HF variations, and it is conditioned by the common mechanisms of controlling the cardiovascular and respiratory systems [40].

However, there is no common opinion on interpretation of test results. The analysis of numerous studies allows to speak about existence of several types of response:

- mismatches or rigidity» along the sympathetic or parasympathetic path [33];

- balance redistribution towards parasympathicotonia due to HF increase [40,41];

- balance redistribution towards sympathicotonia with increase of not only HF, but LF as well [42].

It has been shown that pathological responses to CR_6 test evidencing a vegetative dysfunction are found in 62% patients with a vegeto-vascular dystonia [19]. Thereby the HR response is considered to be determined by hypercapnia [43], a change in tidal volumes [44], functional rearrangement of cardio-respiratory neurons of the CNS [45,46].

Unfortunately, we have not found any data on use of other tests with controlled scheme of respiration in the accessible literature, and in particular with CR of 12, 15 per minute. However, one can suppose that they, as well as CR_6 test, possess a vegetotropic action the nature of which requires clarification.

Approaches to the analysis, evaluation and interpretation of variability of cardiovascular system functions are related to determination of the spectral power of function variability and they assume calculation of data in various frequency ranges that characterize, according to many authors [21,40,47,48], the activity of regulatory effect of different components of the vegetative nervous system. Within the range less than 0.04Hz (an ultralow-frequency component) we have oversegmentary effects, within the range from 0.04 to 0.15Hz (a low-frequency component) - sympathetic effects, within the range from 0.15 to 0.4Hz (a high-frequency component) - parasympathetic effects. Traditionally these data are represented in мs^2 [21] - for variability of the heart rate, in Hgmm^2 [49] - for variability of systolic and diastolic pressure and in L/min^2 - for variability of spontaneous breathing (Figures 1-3). For

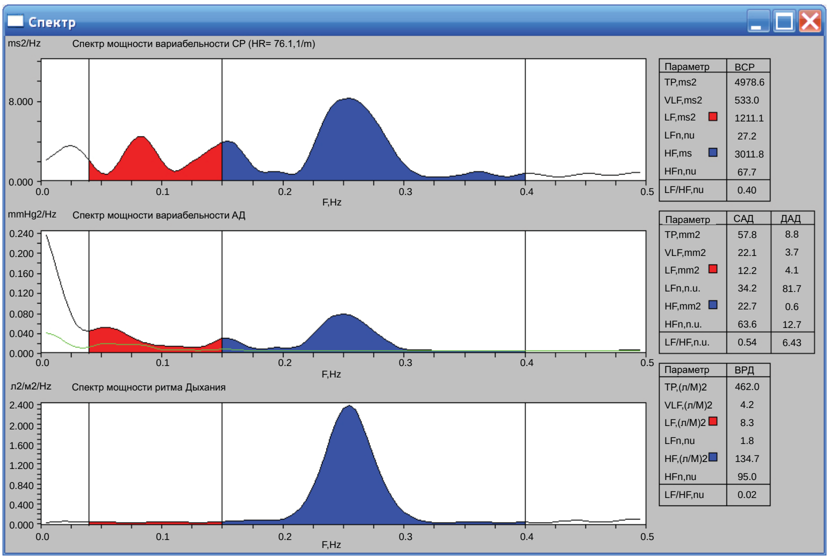

Figure 1: Graphic representation of spectral powers of HR, SBR, DBR and respiration variability for athlete K. at rest with uncontrolled respiration.

simplicity of data presentation and manipulations with smaller values we have carried out the analysis of the square root of these parameters. All the centile distributions presented hereinafter have been calculated with taking into account this specificity.

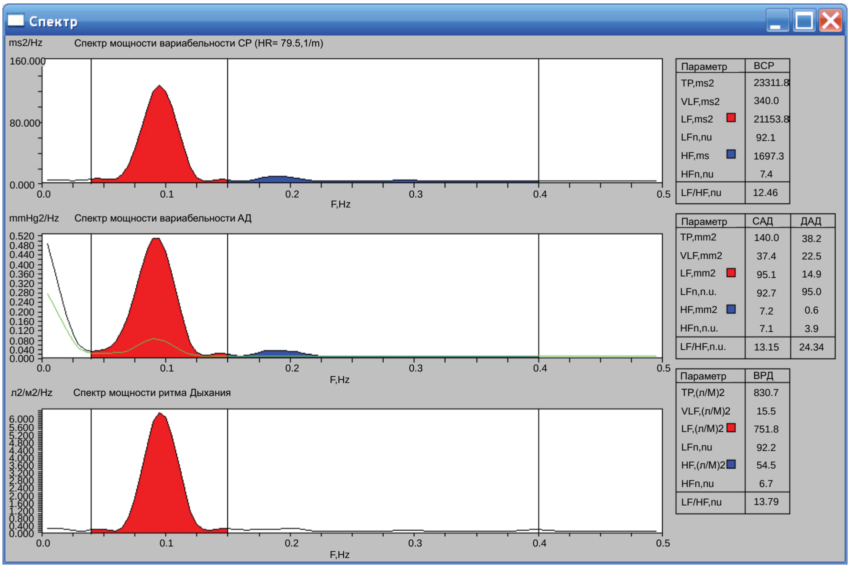

Figure 2: Graphic presentation of spectral powers of HR, SBR, DBP and respiration variability for athlete K. at rest with CR_6.

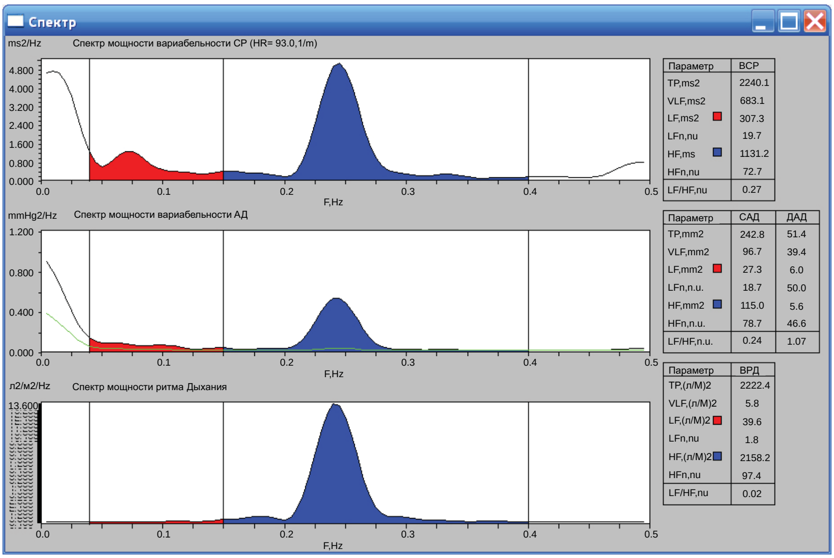

Figure 3: Graphic presentation of spectral powers of HR, SBR, DBP and respiration variability for athlete K. at rest with CR_{15}.

Long-term use of this approach has shown a high enough information capacity in estimating the functional state of the cardio-respiratory system, still, for obtaining an adequate estimation for top-level athletes, the obligatory condition is consideration of the respiratory rate [50] which makes significant effect on the spectral power of variability of cardiovascular system functions. As an example, we will show differences in Fourier transformation spectra of the functions studied which were measured for the same person tested at spontaneous respiration (Figure 1), Controlled Respiration (CR) at the rate of 6 times per minute (Figure 2) and 15 times per minute (Figure 3), further on CR_6 and CR_{15}, respectively. The choice of these rates is justified by the baroreflectory stimulation of blood circulation in the first case and evident vagotonic effect in the second one. In more previous studies we have shown that within the range from 6 to 10 breaths per minute there is an inversely proportional relationship between CR and HRV and BPV values [26] and at CR_{15} HRV and BPV are stabilized.

Even at brief glance at Figures 1-3 it is seen that effect of CR_6 and CR_{15} on variability of cardiovascular system functions differs essentially. With CR_6 the LF-component mainly prevails, and with CR_{15} - The HF component.

This is the circumstance that made us elaborate the report of examination that includes three consecutive two-minute measurements by means of the SACR instrument in accordance with the centile tables we have worked out. An important addition to the complex estimation of the functional state of the cardio-respiratory system at SACR-testing is estimation of ECG at lead 1 and the average pattern of respiration which was carried out at the same time [25,26].

Parameter	0-5	5-25	25-75	75-95	95-100
TP, ms	<31.9	31.9-49.5	49.6-85.0	85.1-125.3	>125.3
VLF, ms	<8.8	8.8-14.4	14.5-28.5	28.6-46.4	>46.4
LF, ms	<14.2	14.2-23.5	23.6-46.0	46.1-88.8	>88.8
HF, ms	<16.3	16.3-28.9	29.0-59.0	59.1-86.9	>86.9
LFHF, ms^2/ms^2	<0.13	0.13-0.37	0.38-1.47	1.48-5.53	>5.53

Table 2: Boundaries of percentile distribution of variability parameters of the heart rate in qualified athletes with spontaneous respiration.

Parameter	0-5	5-25	25-75	75-95	95-100
TP, ms	<61.1	61.1 - 97.8	97.9 - 144.7	144.8 - 176.9	>176.9
VLF, ms	<13.9	13.9 - 20.6	20.7 - 33.3	33.4 - 51.3	>51.3
LF, ms	<51.3	51.3 - 85.2	85.3 - 130.4	130.5 - 156.9	>156.9
HF, ms	<16.7	16.7 - 26.3	26.4 - 55.1	55.2 - 78.6	>78.6
LFHF, ms^2/ms^2	<2.28	2.28 - 4.20	4.21 - 12.60	12.61 - 26.53	>26.53

Table 3: Boundaries of percentile distribution of variability parameters of the heart rate in qualified athletes with CR_6.

Parameter	0-5	5-25	25-75	75-95	95-100
TP, ms	<28,2	28,2 - 43,3	43,4 - 76,5	76,6 - 106,8	>106,8
VLF, ms	<11,4	11,4 - 17,8	17,9 - 31,0	31,1 - 57,3	>57,3
LF, ms	<10,9	10,9 - 16,8	16,9 - 29,6	29,7 - 42,0	>42,0
HF, ms	<14,2	14,2 - 25,6	25,7 - 58,9	59,0 - 98,2	>98,2
LFHF, ms^2/ms^2	<0,13	0,13 - 0,20	0,21 - 0,73	0,74 - 1,45	>1,45

Table 4: Boundaries of percentile distribution of variability parameters of the heart rate in qualified athletes with CR_{15}.

Tables 2-4 show centile distributions of HRV obtained from the same tested persons (more than 1,000) in SACG testing with use of the protocol of examination given above.

As we can see in the Tables shown (2-4), the HRV parameters vary significantly in dependence on the rate of respiration.

First of all, the TP value that characterizes the total power of HRV and reflects the total state of the ANS controlling function [48] evidences a considerable enlargement and increase of the middle range in qualified athletes at rest, as compared to the population. The latter characterizes specificity of rearrangement in vegetative supply of the heart activity in case of intensive physical training, as well as a rise in its functional reserves. In the Figures 1-3 shown above, the modulating effect of the Controlled Respiration (CR) on the spectral characteristics of the total spectral power can be visualized rather clearly. Thus, with CR_6 a manifested activation of controlling effect on HR can be seen, and the median zone of the centile distribution is shifted significantly, with double increase of absolute values in practice. At the same time with CR_{15} a non-significant decrease of this value can be seen.

When analyzing changes of other HRV parameters, it is necessary to note, that the least varied one is oversegmentary (VLF) component which within the boundaries of the median values of the centile distribution is the most evident with CR_6 and the least with spontaneous respiration (in total from 14.5ms to 33.3ms). Such tendency can be seen in all the centile ranges to be tested, which allows to characterize it as significant. The high-frequency parameter of the HRV component is the least subjected to CR effect and it is stable in all variants of the test report and within 25-75 centiles it varies within 25.7ms to 59.0ms. The most variable spectral characteristic of HRV is a Low-Frequency component (LF) which is greatly increased with CR_6 (more than 3 times greater) and it is moderately decreased (1.5 times) in all the centile ranges. Respectively, the ratio of given characteristics (LF/HF) calculated in the usual way is increased by 9-11 times with CR_6 and it is twice as small with CR_{15}.

That is, carrying out tests with CR allows to clarify reactivity and depression of LF component of HRV that characterizes the sympathetic control loop for physiological functions.

In this case with joint estimation of HRV according to the data from the test report we have worked out, the objectification of reactivity and depression of sympathetic effects is possible with taking into account TP transfers between various centile ranges. For example, in case of transfer from the median range (25-75%) to the higher centile range (75-95%) when carrying out the test with CR_6, one can state the higher reactivity of the sympathetic control loop for HR, and in case of transfer to the same range when carrying out the test with CR_{15}, one can state insufficient depression of sympathetic effects, etc.

Parameters TP_{SBP} and TP_{DBP} characterize the total power of SBP and DBP variability spectrum, respectively. These parameters represent relationship between different control processes, with the autonomous nervous system in BP support included. Parameter TP_{SBP} is connected more with the variability of the pumping function of the heart ensuring SBP value, and parameter TP_{DBP} - with regulation and adjustment of the tone of vessels, their rigidity, ensuring DBP value. Distribution of this parameter in qualified athletes in comparison with almost healthy persons of the same age and gender [51,52] is worth paying attention to, it is characterized by a significant reduction of SBP variability, which in our opinion evidences a more stable and economic support of SBP under condition of higher HRV (according to parameter TP, ms). The change of TP_{SBP} and TP_{DBP} with controlled respiration is a kind of example. With CR_6 the SBP variability increases approximately by 1.5 times, as compared to the spontaneous respiration, and with CR_{15} –in 1, 7-2 times in different ranges. Thereby, DBP variability with CR_{15} is 1.5 times higher, and with CR_6 - 1.7-2 times higher in different ranges. Thus, one can state that CR_6 and CR_{15} effect the vegetative support of BP in a different way. These data are confirmed by the results shown in Figure 4-5, where the average versions of HR and SBP variability are shown within the limits of the respiratory cycle.

However, with CR_6 (Figure 5) the shift of SBP absolute value in relation to the initial level is directed mainly towards increase, and with CR_{15} towards reduction reduction. The latter circumstance allows to interpret BP variability absolutely in different ways and it evidences with CR_6 the raising reactivity of the pumping function, and with CR_{15} (Figure 6) - its decreasing reactivity. The similar changes take place with controlled respiration with DBP; therefore TP_{DBP} variability with different CR can be connected with reactivity of the vascular tone in response to a change in the heart output [53]. Presumably, the greater TP_{DBP} parameter, the more is lability of the wall of the vessel, and the less it is, the greater is its rigidity [54].

The data obtained are added with the results of the study of other components of SBPV and DBPV. The Very Low Frequency component (VLF_{SBP}) varies by analogy to TP_{SBP} (Table 6) which allows to connect increase of TP_{SBP} in case of CR_6 and CR_{15} with oversegmentary effects on the pumping function of the heart. Practically the Very Low Frequency component (VLF_{DBP}) of DBPV varies in the same way.

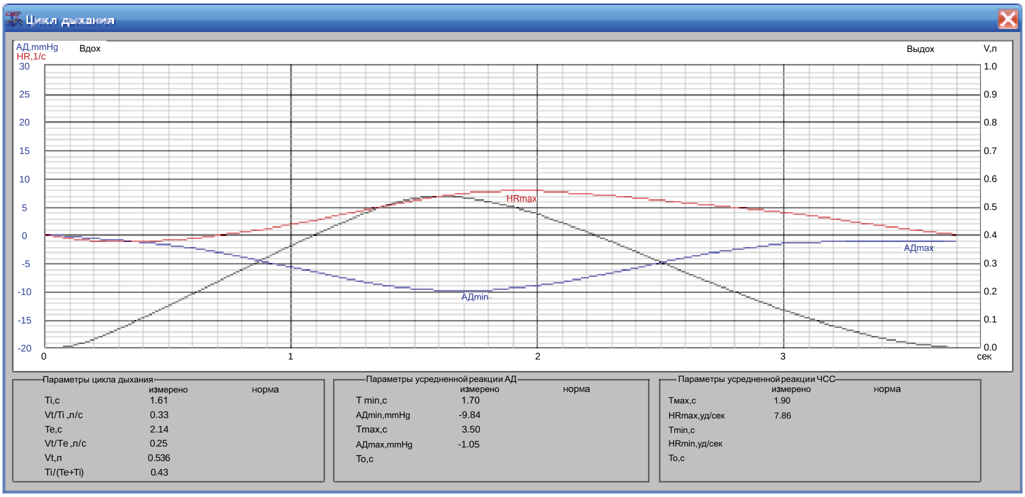

Figure 4: Variability of absolute values of HR and SBP in the respiratory cycle of athlete K. in case of spontaneous respiration.

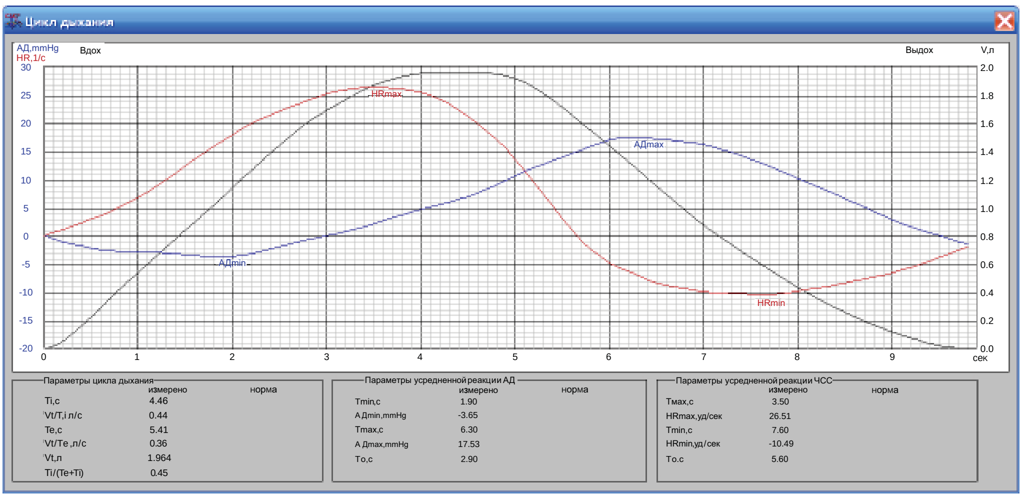

Figure 5: Variability of absolute values of HR and SBP in the respiratory cycle of athlete K. in case of CR_6.

Significant differences are observed at the analysis of Low-Frequency (LF_{SBP} and LF_{DBP}) and High-Frequency (HF_{SBP} and HF_{DBP}) components of SBPV and DBPV at various RR. The LF-component of SBP and DBP control in case of CR_6 becomes several times as much, at the same time with CR_{15} it does not vary practically in comparison with spontaneous respiration. It evidences that in the first case the sympathetic mechanisms of control are become evidently more active, and in the second one they remain intact. The HF-component of SBP and DBP control with CR_6 varies slightly – there is a trend to a small drop of effects on SBP and to the same increase of effect on DBP. With CR_{15} effects of the HF-component on SBP and DBP are connected with a relative increase of its contribution to the control both on the pumping function of myocardium and vascular tone. That is, one can suppose that CR_{15} enables activation of vagotonic mechanisms of control of the latter ones, which are often related to the HF effect.

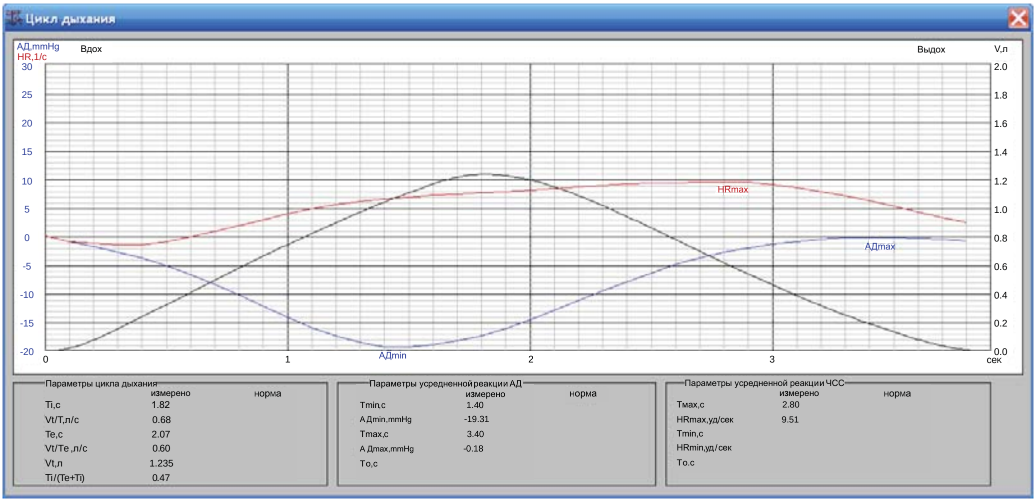

Figure 6: Variability of absolute values of HR and SBP in the respiratory cycle of athlete K. in case of CR_{15}.

Parameter BPV	0-5	5-25	25-75	75-95	95-100
$TP_{SBP,}$ mmHg	<1.7	1.7-2.5	2.6-5.0	5.1-8.4	>8.4
$TP_{DBP,}$ mmHg	<1.2	1.2-1.8	1.9-3.5	3.6-5.6	>5.6
$VLF_{SBP,}$ mmHg	<0.7	0.7-1.2	1.3-2.6	2.7-5.1	>5.1
$VLF_{DBP,}$ mmHg	<0.6	0.6-1.0	1.1-2.2	2.3-4.1	>4.1
$LF_{SBP,}$ mmHg	<0.9	0.9-1.5	1.6-3.1	3.2-5.3	>5.3
$LF_{DBP,}$ mmHg	<0.6	0.6-1.0	1.1-2.1	2.2-3.6	>3.6
$HF_{SBP,}$ mmHg	<0.9	0.9-1.4	1.5-2.6	2.7-4.5	>4.5
$HF_{DBP,}$ mmHg	<0.5	0.5-0.8	0.9-1.4	1.5-2.5	>2.5
$LFHF_{SBP,}$ $mmHg^2/mmHg^2$	<0.31	0.31-0.75	0.76-2.27	2.28-6.05	>6.05
$LFHF_{DBP,}$ $mmHg^2/mmHg^2$	<0.44	0.44-1.09	1.10-3.29	3.30-7.59	>7.59
ABR, $ms^2/mmHg^2$	<6.1	6.1-11.5	11.6-24.0	24.1-37.9	>37.9

Table 5: Boundaries of the centile distribution of parameters of the blood pressure and baroreflex variability in qualified athletes in case of uncontrolled respiration.

The analysis of the LF and HF components ratio of SBP and DBP control confirms that effect of CR_6 is significant both on SBP and on DBP and directed towards increase, and that of CR_{15} is less expressed and directed towards reduction. A similar directivity of the control activity, though less evident, is noticed from the side of Baroreceptor Sensitivity (ABR).

Thus, examination within the limits of the report offered, with estimation according to elaborated percentile tables allows to determine the level of activation of the general (TP), oversegmentary (VLF), sympathetic (LF) and parasympathetic (HF) effects on SBP and DBP in comparison with the expected ones, which significantly objectifies the state of the autonomous control of the BP support system.

Parameter BPV	0-5	5-25	25-75	75-95	95-100
$TP_{SBP,}$ mmHg	<1.7	1.7-2.5	2.6-5.0	5.1-8.4	>8.4
$TP_{DBP,}$ mmHg	<1.2	1.2-1.8	1.9-3.5	3.6-5.6	>5.6
$VLF_{SBP,}$ mmHg	<0.7	0.7-1.2	1.3-2.6	2.7-5.1	>5.1
$VLF_{DBP,}$ mmHg	<0.6	0.6-1.0	1.1-2.2	2.3-4.1	>4.1
$LF_{SBP,}$ mmHg	<0.9	0.9-1.5	1.6-3.1	3.2-5.3	>5.3
$LF_{DBP,}$ mmHg	<0.6	0.6-1.0	1.1-2.1	2.2-3.6	>3.6
$HF_{SBP,}$ mmHg	<0.9	0.9-1.4	1.5-2.6	2.7-4.5	>4.5
$HF_{DBP,}$ mmHg	<0.5	0.5-0.8	0.9-1.4	1.5-2.5	>2.5
$LFHF_{SBP,}$ $mmHg^2/mmHg^2$	<0.31	0.31-0.75	0.76-2.27	2.28-6.05	>6.05
$LFHF_{DBP,}$ $mmHg^2/mmHg^2$	<0.44	0.44-1.09	1.10-3.29	3.30-7.59	>7.59
ABR, $ms^2/mmHg^2$	<6.1	6.1-11.5	11.6-24.0	24.1-37.9	>37.9

Table 6: Boundaries of the centile distribution of parameters of the blood pressure and baroreflex variability in qualified athletes in case of uncontrolled respiration.

Parameter BPV	0-5	5-25	25-75	75-95	95-100
$TP_{SBP,}$ mmHg	<2.7	2.7 - 4.0	4.1 - 7.4	7.5 - 11.4	>11.4
$TP_{DBP,}$ mmHg	<2.7	2.7 - 3.7	3.8 - 5.8	5.9 - 8.3	>8.3
$VLF_{SBP,}$ mmHg	<1.1	1.1-1.6	1.7- 3.9	4.0- 6.8	>6.8
$VLF_{DBP,}$ mmHg	<1.1	1.1-1.4	1.5- 2.6	2.7- 4.1	>4.1
$LF_{SBP,}$ mmHg	<1.7	1.7-3.1	3.2- 5.8	5.9- 9.4	>9.4
$LF_{DBP,}$ mmHg	<1.9	1.9-2.9	3.0-4.8	4.9- 6.7	>6.7
$HF_{SBP,}$ mmHg	<0.8	0.8-1.2	1.3- 2.2	2.3- 3.8	>3.8
$HF_{DBP,}$ mmHg	<0.8	0.8-1.0	1.1- 1.7	1.8- 2.8	>2.8
$LFHF_{SBP,}$ $mmHg^2/mmHg^2$	<1.59	1.59-3.85	3.86- 11.72	11.73- 22.00	>22.00
$LFHF_{DBP,}$ $mmHg^2/mmHg^2$	<1.77	1.77-4.66	4.67- 12.52	12.53- 23.18	>23.18
ABR, $ms^2/mmHg^2$	<9.9	9.9-16.7	16.7-34.8	34.8-68.8	>68.8

Table 7: Boundaries of the centile distribution of parameters of the blood pressure and baroreflex variability in qualified athletes in case of CR_6.

Parameter BPV	0-5	5-25	25-75	75-95	95-100
TP_{SBP},mmHg	<3.6	3.6 - 5.0	5.1 - 8.9	9.0 - 15.9	>15.9
TP_{DBP},mmHg	<1.8	1.8 - 2.8	2.9 - 4.9	5.0 - 8.1	>8.1
VLF_{SBP},mmHg	<1.4	1.4 - 2.4	2.5 - 5.9	6.0 - 9.4	>9.4
VLF_{DBP},mmHg	<1.1	1.1 - 1.8	1.9 - 3.1	3.2 - 6.2	>6.2
LF_{SBP},mmHg	<1.3	1.3 - 1.8	1.9 - 3.6	3.7 - 6.6	>6.6
LF_{DBP},mmHg	<0.8	0.8 - 1.3	1.4 - 2.4	2.5 - 3.5	>3.5
HF_{SBP},mmHg	<1.6	1.6 - 2.8	2.9 - 6.1	6.2 - 10.6	>10.6
HF_{DBP},mmHg	<0.7	0.7 - 1.2	1.3 - 2.5	2.6 - 4.3	>4.3
$LFHF_{SBP}$,$mmHg^2/mmHg^2$	<0.10	0.10 - 0.17	0.18 - 0.68	0.69 - 2.78	>2.78
$LFHF_{DBP}$,$mmHg^2/mmHg^2$	<0.21	0.21 - 0.55	0.56 - 1.81	1.82 - 4.71	>4.71
ABR, $ms^2/mmHg^2$	<2.4	2.4 - 6.0	6.1 - 13.9	14.0 - 21.0	>21.0

Table 8: Boundaries of the centile distribution of parameters of the blood pressure and baroreflex variability in qualified athletes in case of CR_{15}.

Parameter RRV	0-5	5-25	25-75	75-95	95-100
TP_{RR},l/m	<9,8	9,8-17,0	17,1-25,2	25,3-33,3	>33,3
VLF_{RR},l/m	<0,7	0,7-1,1	1,2-2,2	2,3-3,7	>3,7
LF_{RR},l/m	<1,6	1,6-2,8	2,9-5,8	5,9-14,8	>14,8
HF_{RR},l/m	<7,6	7,6-14,4	14,5-23,4	23,5-30,2	>30,2
$LFHF_{RR}$,$(l/m)^2/(l/m)^2$	<0,013	0,013-0,024	0,025-0,150	0,151-1,245	>1,245

Table 9: Boundaries of the centile distribution of respiration variability parameters in qualified athletes in case of spontaneous respiration.

Parameter RRV	0-5	5-25	25-75	75-95	95-100
$TP_{RR,}$ l/m	<15,2	15,2-20,8	20,9- 32,0	32,1- 49,1	>49,1
$VLF_{RR,}$ l/m	<1,6	1,6-2,2	2,3- 3,8	3,9-5,5	>5,5
$LF_{RR,}$ l/m	<12,6	12,6-18,3	18,4- 27,6	27,7- 40,1	>40,1
$HF_{RR,}$ l/m	<6,1	6,1-7,9	8,0- 14,3	14,4- 25,1	>25,1
$LFHF_{RR,}$ $(l/m)^2/(l/m)^2$	<1,393	1,393-2,527	2,528- 7,208	7,209- 10,726	>10,726

Table 10: Boundaries of the centile distribution of respiration variability parameters in athletes in case of controlled respiration 6 times per minute.

Parameter RRV	0-5	5-25	25-75	75-95	95-100
$TP_{RR,}$ l/m	<15,1	15,1 - 23,8	23,9 - 55,1	55,2 - 92,6	>92,6
$VLF_{RR,}$ l/m	<1,2	1,2 - 1,6	1,7 - 3,7	3,8 - 5,7	>5,7
$LF_{RR,}$ l/m	<2,6	2,6 - 3,5	3,6 - 7,1	7,2 - 12,4	>12,4
$HF_{RR,}$ l/m	<14,4	14,4 - 23,5	23,4 - 54,1	54,2 - 90,2	>90,2
$LFHF_{RR,}$ $(l/m)^2/(l/m)^2$	<0,011	0,011 - 0,015	0,016 - 0,027	0,028 - 0,049	>0,049

Table 11: Boundaries of the centile distribution of respiration variability parameters in qualified athletes in case of controlled respiration 15 times per minute.

We have not found any data in references on percentile distributions of spontaneous respiration variability, therefore we have carried out before a study of short entries about spontaneous respiration cycles for stating its variability in various age groups [22,55-57], as well as in qualified athletes. It has been noticed that the significant differences in the general power of the spectrum of spontaneous respiration variability in age groups were not found, at the same time the median corridor in athletes is evidently shifted towards a drop. Differences in the spontaneous respiration variability within the VLF range were worth paying attention to, they considerably increase after 50 years and are significantly reduced in top-level athletes. In persons of young and middle age the frequency parameters within this range have intermediate values [26]. It has been shown that the spectral characteristics of the spontaneous respiration power within the HF and LF ranges are practically proportional in all age groups and they are a little bit lowered in athletes. It has been noticed apart that in LF/HF component ratio of respiration variability, the widest corridors of boundary percentile values were found in top-level athletes. Hence, the conclusion comes to mind that with considering the mechanisms of autonomous control of the cardio-respiratory system that is the variability of the spontaneous respiration that determines high results of HRV. On the other hand, that is it that provides support of stable enough parameters of SBPV and DBPV in top-level athletes due to outcardial mechanisms of hemodynamics control and that was confirmed as a whole by much higher ABR values.

Thus, considering RR as the criterion of modulating effects of the respiratory centre on the inspiration and exhalation muscles, it is necessary to notice that the known mechanisms of the breathing act control, related to irritation of CO_2 blood chemoreceptors and mechanoreceptors of the lungs and airways [4,5,43,58-62], are supplemented with a number of haemodynamic and vegetative determinants, ensuring maintenance of homeostasis and stable blood circulation [1,63]. Therefore enhancing of ventilation in case of muscle loading takes place even before a change in the blood chemism which assumes participation of the respiratory muscular system actively participating in physical work, in control of the act of breathing.

When analyzing parameters of variability of the cardiorespiratory system functions which are known to characterize the mechanisms of vegetative support, we had received before the results evidencing the effects of frequency-volume features of breathing on variability of HR and BP functions, which vary in case of muscular activity, effect of the ambient temperature, respective signals from the environment, the emotional state, etc. [17,26,32,44,47,64-70].

From these positions, the especially actual is the fact that variation of the mechanism of breath control can result in various deviations in homeostasis related to variation of metabolic and acid-base balance of the body [71], or it may be a consequence of the latter [68].

It has been noticed that the parameter of respiration variability TPRR has a linear dependence on the pulmonary Ventilation (V_e) that has been also proved by relationship between TP_{RR} and tidal Volume (V_t). From here the assumption was made about relation between TP_{RR} and economizing of the function at rest and its reserve capacity in case of the imposed rhythm of breathing.

The analysis of the ratio of the spectral power of respiration within the Low-Frequency and High-Frequency ranges (LF/HF_{RR}) has shown a close polynomial relation with the averaged V_t, thus, with V_e such relation was not found at all [26]. It has been shown apart that at V_t (ml) up to 600 ml inclusively these effects are negligible, and at its further increase there is almost linear increase of LF/HF_{RR} ratio which in total predetermines activity of the ANS sympathetic loop that makes a modulating effect on parameters of HR and BP vegetative support. Thereby the analysis of relationship in LF/HF_{RR} ratio with RR has shown a drop of controlling vegetative effects in case of tachypnea (more than 20/min) [26].

From positions of establishing an athlete's functional state, the data of the spontaneous respiration pattern [72] look as not less informative. However, we have not found ranged parameters in references. In this case the data are significant enough that evidence the fact that at physical activity the rate of transition of metabolic mechanisms to the anaerobic way completely correlates with the fatigue of the respiratory muscles. And only then follows the response of the cardiovascular system in the form of HR increase.

The mechanisms of respiratory muscles fatigue are directly connected with a decrease in volume velocities of inspiration and expiration, as well as with a ratio of inspiration and expiration phases [22,61,71,73]. It has been also shown before that in various periods of the annual training cycle of athletes there were not found significant differences in Respiration Rate (RR), the volume velocities of inspiration and expiration throughout the preparatory and precompetitive periods of time decreased and to our mind, it determined economizing of the external respiration function at rest which evidences enhancing of oxygen supply reserves of the body. Thereby all the parameters of the respiration pattern before competitions also had a tendency to decrease [72].

In the competitive period (in the microcycle) indicators of the respiration pattern varied considerably. In RR the state observed on the day of competition, to some tendency to bradypnea, has already almost reached the initial level in 15 hours after the termination of intensive physical activity, with some tendency to RR increase [72]. Upon termination of the recovery stage (in 63 hours after the intensive load) the greatest occurrence of optimum RR (64, 5% of cases) was noticed, and versions of tachypnea were most seldom met. Thereby by the fourth day of the post-loading period the greatest contribution of manifested bradypnea (19, 4%) was found. Some regularities characterizing the period of recovery and readiness of the respiratory system were observed in other parameters. Thus, after action in competitions the significant shifts were found both in the rate parameters of the pattern and in the ratio between the time characteristics of inspiration and expiration which significantly decreased, which under conditions of insignificant tachypnea evidenced fatigue of expiration muscles. On the next days (in 39 hours) the ratio of inspiration/expiration duration was increased, and RR was within the norm (in 60% of cases) which is possible only under condition of increase of rate characteristics of expiration which in this period of time were the greatest. On the third day of recovery with the optimal RR values the versions of reduction in volume velocity of inspiration and expiration were considerably predominating, which in this case evidenced economization of the external respiration functions. The further changes on the next day evidenced some delay of recovery processes in the external respiration pattern, though intensity of training was somehow increased. On the eve of the competitions the distribution of all parameters of the respiration pattern already reminded the optimal one [69].

In total, the carried out analysis has allowed to establish significant informative capacity of parameters of the spontaneous respiration pattern in determination of the functional state of the external respiration system during the training microcycle, the main task of which is the quickest optimization of the functional state of the body with maintenance of increase of the level of training capacity which is the condition for reaching the respective result in sports [10].

Parameter	0-5	5-25	25-75	75-95	95-100
Tinsp, s	<1.0	1.0-1.2	1.3-1.7	1.8-2.2	>2.2
Texp, s	<1.5	1.5-1.8	1.9-2.6	2.7-3.9	>3.9
V_t, l	<0.27	0.27-0.46	0.47-0.68	0.69-0.89	>0.89
Tinsp/Texp	<0.48	0.48-0.59	0.60-0.75	0.76-0.85	>0.85
RR,1/min	<8.3	8.3-12.3	12.4-17.8	17.9-21.8	>21.8

Table 12: Boundaries of the centile distribution of parameters of spontaneous respiration pattern in qualified athletes.

The criteria of estimation of key parameters of the respiration pattern are shown in Table 12. When analyzing the data shown for qualified athletes, one can notice that in comparison with almost healthy persons of middle age [26], the indicators of the respiration pattern differ only in V_t values which exceed within the ranges from 5 to 75 percentiles the population ones by 2 to 1.2 times.

Parameter	controlled	0-5	5-25	25-75	75-95	95-100
V_t, l	6/min	<0,86	0,86 – 1,20	1,21 – 1,92	1,93 – 2,55	>2,55
V_t, l	15/min	<0,44	0,44 – 0,66	0,67 – 1,47	1,48 – 2,69	>2,69

Table 13: Boundaries of percentile distribution of V_t parameters in case of controlled respiration in qualified athletes.

Considering specificity of carrying out the tests with controlled respiration which were carried out within the schedule of imposed respiration with a fixed duration of breathing: with CR_6 – inspiration for 5 seconds and expiration for 5 seconds, and with CR_{15} - inspiration for 2 seconds and expiration for 2 seconds, it was expedient to analyze indicator V_t only. In Table 13 percentile distributions of V_t parameters are shown when carrying out tests with CR which evidence higher values of V_t in testing CR_6, thus, within boundaries from 5 to 25 percentiles they exceed similar values for spontaneous respiration by 3 times, and for CR_{15} testing they are almost twice as much. At higher percentile values at CR the values become equal.

The generalized results of variability of the cardio-respiratory system functions in qualified athletes with controlled respiration, as compared to spontaneous respiration within the boundaries of percentile range of 25-75% are shown in Tables 14-16.

Parameter	CR_6	CR_{15}
TP, ms	↑ by 1.7 – 2.0 times	≈
VLF, ms	≈	≈
LF, ms	↑ by 2.8 – 3.6 times	↓ by 1.4 – 1.6 times
HF, ms	≈	≈
LFHF, ms^2/ms^2	↑ by 8.6 – 11.0 times	↓ by 1.8 – 2.0 times

Table 14: Direction of shifts of HRV parameters in qualified athletes within the range of 25-75% of occurrence in case of controlled respiration in comparison with spontaneous respiration.

As seen from Table 14, effect of CR_6 and CR_{15} on HRV significantly differs due to activating effect of CR_6 on a LF-component and depressing effect of CR_{15} on a LF-component which is reflected in TP indicators TP and LF/HF ratio. Thereby VLF and HF components practically do not vary.

Parameter	CR_6	CR_{15}
$TP_{SBP,}$ mmHg	↑ by 1.5 – 1.7 times	↑ by 1.8 – 2.0 times
$TP_{DBP,}$ mmHg	↑ by 1.7 – 2.0 times	↑ by 1.4 – 1.5 times
$VLF_{SBP,}$ mmHg	↑ by 1.3 – 1.5 times	↑ by 1.9 – 2.3 times
$VLF_{DBP,}$ mmHg	↑ by 1.2 – 1.4 times	↑ by 1.4 – 1.7 times
$LF_{SBP,}$ mmHg	↑ by 1.9 – 2.0 times	≈
$LF_{DBP,}$ mmHg	↑ by 2.3 – 2.8 times	≈
$HF_{SBP,}$ mmHg	↓ by 1.2 time	↑ by 1.9 – 2.3 times
$HF_{DBP,}$ mmHg	↑ by 1.2 time	↑ by 1.4 – 1.8 times
$LFHF_{SBP,}$ $mmHg^2/mmHg^2$	↑ by 5.1 – 5.2 times	↓ by 3.3 – 4.2 times
$LFHF_{DBP,}$ $mmHg^2/mmHg^2$	↑ by 3.8 – 4.2 times	↓ by 1.8 – 2.0 times
ABR, $ms^2/mmHg^2$	↑ by 1.4 – 1.5 times	↓ by 1.7 – 1.9 times

Table 15: Direction of shifts of SBPV, DBPV and ABR parameters in qualified athletes within the range of 25-75% of occurrence in case of controlled respiration in comparison with spontaneous respiration.

Parameter	CR_6	CR_{15}
$TP_{RR,}$ l/m	↑ by 1.2 – 1.3 times	↑ by 1.4 – 2.2 times
$VLF_{RR,}$ l/m	↑ by 1.7 – 1.9 times	↑ by 1.4 – 1.7 times
$LF_{RR,}$ l/m	↑ by 4.8 – 6.3 times	↑ by 1.2 time
$HF_{RR,}$ l/m	↓ by 1.6 – 1.8 times	↑ by 1.6 – 2.3 times
$LFHF_{RR,}$ $(l/m)^2/(l/m)^2$	↑ by 48.1 – 101.1 times	↓ by 1.6 – 5.5 times

Table 16: Direction of shifts of CRV parameters in qualified athletes within the range of 25-75% of occurrence in comparison with spontaneous respiration.

The analysis of variability of SBPV and DBPV shifts has shown (Table 15) that CR_6 increases TP_{DBP} and LF components of SBP and DBP control more significantly. At the same time with CR_{15} one can see more significant increase of TP_{SBP} and VLF component of SBP and DBP control, as well as practically lack of effect on LF components of SBP and DBP control. Differences in variations of HF components of SBP and DBP control are significant, which with CR_6 vary negligibly in comparison with spontaneous respiration (by 1.2 times). For SBP towards increase, for DBP towards reduction. Thereby CR_{15} promotes increase of HF components of SBP and DBP control by 1.4-2.3 times. Finally, these variations are reflected on LF/HF ratio which significantly increase at CR_6, and significantly decrease at CR_{15}, which should be taken into account at their estimation.

The latter also concerns the baroreceptor sensitivity which at CR_6 increases and at CR_{15} decreases significantly.

When analyzing CRV parameters in carrying out the tests with CR in comparison with spontaneous respiration, one can notice that CR_6 significantly raises the LF component and reduces the HF component, and CR_{15} make a slight effect on the LF component and significantly raises the HF component of the spectral power of respiration which is shown in parameters of LF and HF component ratio.

In whole, we can state that CR_6 and CR_{15} enable activation of various control links of system haemodynamics [74] at CR_6-increase of LF components of respiration control is transferred onto the LF component of HR, SBP and DBP control, and the decrease of HF-components of respiration control practically does not effect the HF components of HRV, SBPV and DBPV; at CR_{15}–insignificant increase of LF components of respiration control practically does not make any effect on LF components of SBP and DBP control and reduces the LF component of HR control, and significant increase of HF components of respiration control is transferred onto HF components of SBP and DBP control and practically does not make any effect on the HF component of HRV.

Thus, considering simplicity and rapidity of test performance, the data obtained can be used for a complex estimation of reactivity and depressive shifts of ANS sympathetic and parasympathetic part activities in cardio-respiratory system control, which are used for diagnostics of functional readiness of the body under conditions of learning and training and competitive processes.

The important element of making a diagnosis of functional fitness of the athletes' bodies is determination of the general Physical Working Capacity (PWC) the study of which under conditions of the competitive period of time is essentially difficult. That is why for the following stage of our research it was important to determine SACR-determinants of the PWC level.

One hundred qualified athletes going in for various sports have been observed. Among them there were 69 men and 31 women in age from 18 to 28 years. According to the results of the Harvard step-test, 3 groups were formed: 1 with high level of PWC (54 persons, among them 13 women and 41 men); 2 with PWC level above the average (33 persons, among them 11 women and 22 men), 3 with the average level of PWC (13 persons, among them 7 women and 6 men) (Table 17).

HSTI	f	m
high level	110.2 ± 12.4	105.0 ± 9.3
above average	86.0 ± 2.1	85.5 ± 2.0
average	75.4 ± 1.8	76.9 ± 1.4

Table 17: The average values of Harvard Step-Test Index (HSTI) in men and women with different PWC level.

In addition to the Harvard Step-Test, the examination report included conduction of anthropometrical measurements, tests with a delay of breath and Martine-Kushelevsky test. When carrying out Martinet-Kushelevsky test, measurement of HR and BP was done by a usual approach - HR calculation on the radial artery during the first and last 10 seconds of each of 3 minutes of recovery, as well as by measurement of BP according to Korotkov's method during each of three minutes.

Table 18 shows a morphometrical characteristic of the examined contingent separately for men and women. Not going into definition of significance between intergroup differences due to a small number of women athletes and a small group of men with the average PWC level, we should note that no clear relationship with the PWC level has been established in any anthropometrical parameter.

Thereby the indicators of physical development as a whole characterized specificity of sports disciplines which athletes mainly represented.

The data given in Table 19 completely confirm the well known data that the high level of PWC as compared to the above average and average PWC levels is characterized with lower values of heart rate in the initial state, lowered reactivity of heart rate in response to the dosed physical activity (20 squats) and more significant gain in PBP. The latter under condition of less evident raise of heart rate evidences a greater efficiency of the pumping function of the heart in athletes with the high PWC level.

The further analysis of group specificities of athletes assumed studying of the differences obtained in SACG-testing of cardio-respiratory system indicators at rest and in carrying out tests with CR_6 and CR_{15}. For this purpose the groups of men and women with various PWC levels have been united. Here the first group included 54 persons, the second one 33 and the third one 13 persons.

For the analysis of centile distributions of the parameters to be tested, we have selected quantity of athletes who have come with consideration of the parameters tested in some of them to the ranges of evident deviations in values: towards reduction - a range <5% and towards increase - a range >95%. Note, that the quantity of the latter should not exceed 5%. In the rest cases we can say about the degree of expressiveness of the latter: to 10% - about a tendency, from 10 to 20% - about the expressed tendency and at more than 20% - about prominent feature.

Parameter	High (H)		Above Average (AA)		Average (A)	
	f	m	f	m	f	m
	n=13	n=41	n=11	n=22	n=7	n=6
Body mass, kg	58.8 ± 5.9	75.4 ± 9.1	57.0 ± 5.7	77.8 ± 10.5	54.6 ± 6.1	70.5 ± 7.5
Body length (upright), cm	167.4 ± 6.3	171.0 ± 14.2	164.2 ± 2.6	177.7 ± 6.5	163.1 ± 4.8	178.0 ± 6.0
Body length (sitting), cm	87.9 ± 3.3	94.9 ± 3.8	87.8 ± 1.7	94.5 ± 2.3	78.1 ± 14.0	94.8 ± 3.2
Shoulder diameter, cm	35.9 ± 0.8	40.5 ± 2.1	35.5 ± 1.5	40.5 ± 1.5	35.3 ± 0.9	41.2 ± 2.2
Diameter of pelvis (front), cm	26.9 ± 0.9	28.5 ± 2.3	27.6 ± 1.6	29.4 ± 2.1	27.1 ± 2.0	28.3 ± 1.7
Diameter of pelvis (saggit), cm	19.2 ± 0.9	21.2 ± 1.9	19.2 ± 1.5	21.3 ± 1.4	18.1 ± 1.5	20.7 ± 0.8
Neck circumference, cm	30.7 ± 1.5	36.9 ± 2.5	30.5 ± 1.0	36.8 ± 2.4	30.7 ± 1.8	36.5 ± 1.3
Abdominal circumference, cm	72.1 ± 4.8	80.4 ± 6.6	73.5 ± 4.9	83.6 ± 7.9	69.1 ± 5.1	72.8 ± 15.3
Chest circumference, cm	84.3 ± 2.4	95.3 ± 7.6	85.4 ± 3.8	95.5 ± 8.0	84.3 ± 4.0	93.3 ± 3.0
Thorax mobility, cm	7.5 ± 1.3	9.1 ± 3.4	6.8 ± 1.9	8.2 ± 1.4	8.7 ± 1.8	8.7 ± 1.1
Mid-arm muscle circumference (relaxed), cm	24.0 ± 1.1	28.9 ± 2.3	24.4 ± 2.0	28.7 ± 2.5	23.9 ± 1.6	28.7 ± 1.0
Mid-arm muscle circumference (tense), cm	26.3 ± 1.5	33.0 ± 2.5	26.6 ± 2.6	32.5 ± 3.1	25.6 ± 2.2	31.4 ± 1.1
Forearm circumference, cm	22.1 ± 1.1	26.2 ± 2.4	21.9 ± 0.9	26.1 ± 2.0	21.9 ± 1.1	26.5 ± 0.8
Hip circumference, cm	53.2 ± 3.4	53.7 ± 4.0	52.2 ± 2.8	53.9 ± 4.3	50.9 ± 4.1	52.7 ± 3.8
Tibia circumference, cm	34.8 ± 1.9	36.3 ± 2.4	33.3 ± 1.4	36.5 ± 1.9	32.9 ± 1.3	36.0 ± 2.3
Rigth hand dynamometry, kg	30.2 ± 4.6	48.7 ± 8.6	26.4 ± 4.5	47.5 ± 8.0	28.1 ± 4.5	53.3 ± 4.7
Left hand dynamometry, kg	24.2 ± 4.9	44.5 ± 9.4	25.0 ± 5.6	48.1 ± 6.9	25.4 ± 6.0	47.8 ± 2.6
Back muscles dynamometry, kg	80.7 ± 15.3	142.7 ± 20.0	70.3 ± 7.1	147.0 ± 22.5	76.3 ± 13.8	144.2 ± 9.4
Lungs vital capacity, l	3.6 ± 0.3	4.9 ± 0.6	3.6 ± 0.3	5.0 ± 0.7	3.5 ± 0.6	5.1 ± 0.7
Fat,%	25.4 ± 2.4	16.5 ± 5.0	27.8 ± 4.6	17.6 ± 4.7	24.5 ± 3.6	12.4 ± 3.8
BMI, kg/m^2	21.4 ± 1.7	23.9 ± 2.2	21.1 ± 1.6	24.1 ± 1.8	21.9 ± 2.5	22.1 ± 1.5

Table 18: Morphometrical characteristic of the examined contingent of athletes.

First of all, it was expedient to follow the differences in parameters obtained with application of the SACR-testing of parameters at rest.

According to data of cardiointervalometry, it is possible to draw the following conclusions: athletes of group 1 (H) are characterized with evident bradycardia, elongation of atrioventricular conduction with evident tendency to increase of the preload to the heart, to shortage of time of ventricle depolarization and elongation of the electrical systole [75]. Athletes in group 2 (AA) are characterized with the evident increase of the preload to the heart and shortage of time of ventricle depolarization with evident tendency to bradycardia, elongation of AV-conduction and electrical systole of ventricles. And tendency to retardation of the intraventricular conduction has been found rather often. Group 3 (A) is characterized with evident tendency to bradycardia and elongation of AV-conduction, thereby a part of athletes have tendency to infringement of ventricle repolarization. That is, the distinctive feature of high PWC level is evident bradycardia at rest with a moderate tendency to increase of preload to the heart and to acceleration of ventricle which in total provides efficiency of the pumping function of the heart under conditions of physical activities. From the data presented one can suppose that the limiting factor with the PWC level above the average is inadequacy of preload increase to the heart which is significantly increased in 30% of athletes and inadequacy of ventricle repolarization which is evidently accelerated in a part of athletes (almost ¼) and retarded in another part. At the average PWC level the evident tendency towards bradycardia is followed by moderate disorders in ventricle repolarization.

Parameter	High (H)		Above Average (AA)		Average (A)	
	f	m	f	m	f	m
	n=13	n=41	n=11	n=22	n=7	n=6
HRrest, 1/m	65.1 ± 5.5	65.1 ± 6.1	67.6 ± 5.4	71.5 ± 7.1	70.3 ± 8.8	76.0 ± 6.0
SBPrest, mmHg	107.1 ± 7.0	120.6 ± 9.8	106.8 ± 6.8	125.2 ± 10.6	110.9 ± 5.2	122.5 ± 8.3
DBPrest, mmHg	68.8 ± 5.9	77.2 ± 7.9	68.6 ± 7.9	76.1 ± 6.9	72.0 ± 6.3	76.7 ± 8.9
PBPrest, mmHg	38.3 ± 6.7	42.9 ± 7.7	37.3 ± 7.9	49.0 ± 10.7	38.9 ± 7.3	45.8 ± 4.2
HRrestitution (0`00``), 1/m	97.4 ± 13.3	101.3 ± 9.3	106.7 ± 10.0	108.4 ± 10.2	113.1 ± 13.2	103.0 ± 5.3
HR restitution(0`50``), 1/m	71.1 ± 5.8	76.4 ± 8.2	79.1 ± 8.4	79.9 ± 8.8	84.9 ± 9.8	79.0 ± 5.0
SBP restitution (1`), mmHg	120.5 ± 10.9	138.8 ± 12.3	122.7 ± 8.4	144.1 ± 13.9	122.6 ± 8.5	133.3 ± 10.0
DBP restitution (1`), mmHg	62.3 ± 6.3	68.4 ± 9.2	64.5 ± 7.8	72.0 ± 8.2	61.4 ± 10.2	68.3 ± 5.6
PBP restitution (1`), mmHg	58.2 ± 11.8	70.4 ± 13.3	58.2 ± 11.1	67.5 ± 14.7	61.1 ± 7.9	65.0 ± 6.7
HR restitution (1`00``), 1/m	65.5 ± 4.3	71.6 ± 7.0	72.0 ± 6.5	74.2 ± 8.9	81.4 ± 11.8	79.0 ± 1.7
HR restitution (1`50``), 1/m	64.6 ± 4.5	66.7 ± 8.5	68.2 ± 6.0	72.8 ± 6.9	76.3 ± 8.8	79.0 ± 3.7
SBP restitution (2`), mmHg	112.9 ± 9.2	129.7 ± 10.9	112.5 ± 9.6	136.4 ± 14.2	112.6 ± 7.1	131.7 ± 8.9
DBP restitution (2`), mmHg	66.6 ± 4.7	73.4 ± 8.7	64.5 ± 8.8	73.6 ± 6.3	66.6 ± 6.8	70.0 ± 6.7
PBP restitution (2`), mmHg	46.5 ± 8.3	55.9 ± 10.5	48.0 ± 9.8	62.3 ± 12.8	46.3 ± 5.6	61.7 ± 5.6
HR restitution (2`00``), 1/m	64.2 ± 4.1	66.0 ± 5.5	67.6 ± 7.2	72.5 ± 7.2	73.7 ± 8.8	78.0 ± 2.0
HR restitution (2`50``), 1/m	64.2 ± 4.8	65.5 ± 5.9	68.5 ± 8.2	71.2 ± 8.1	73.7 ± 7.1	76.0 ± 4.7
SBP restitution (3`), mmHg	109.5 ± 6.8	125.0 ± 11.3	111.4 ± 5.6	129.3 ± 13.1	108.0 ± 7.4	125.2 ± 10.2
DBP restitution (3`), mmHg	64.2 ± 6.7	75.1 ± 8.3	65.0 ± 7.3	72.9 ± 8.1	65.1 ± 7.3	73.3 ± 7.8
PBP restitution (3`), mmHg	46.2 ± 9.7	49.9 ± 8.4	44.5 ± 6.8	56.5 ± 13.1	42.9 ± 5.0	51.8 ± 7.4
Fat,%	25.4 ± 2.4	16.5 ± 5.0	27.8 ± 4.6	17.6 ± 4.7	24.5 ± 3.6	12.4 ± 3.8
BMI, kg/m^2	21.4 ± 1.7	23.9 ± 2.2	21.1 ± 1.6	24.1 ± 1.8	21.9 ± 2.5	22.1 ± 1.5

Table 19: Averaged parameters of heart rate and arterial blood pressure in athletes from the groups tested when conducting the Martinet-Kushelevsky test.

According to data of cardiointervalometry, it is possible to draw the following conclusions: athletes of group 1 (H) are characterized with evident bradycardia, elongation of atrioventricular conduction with evident tendency to increase of the preload to the heart, to shortage of time of ventricle depolarization and elongation of the electrical systole [75]. Athletes in group 2 (AA) are characterized with the evident increase of the preload to the heart and shortage of time of ventricle depolarization with evident tendency to bradycardia, elongation of AV-conduction and electrical systole of ventricles. And tendency to retardation of the intraventricular conduction has been found rather often. Group 3 (A) is characterized with evident tendency to bradycardia and elongation of AV-conduction, thereby a part of athletes have tendency to infringement of ventricle repolarization. That is, the distinctive feature of high PWC level is evident bradycardia at rest with a moderate tendency to increase

of preload to the heart and to acceleration of ventricle which in total provides efficiency of the pumping function of the heart under conditions of physical activities. From the data presented one can suppose that the limiting factor with the PWC level above the average is inadequacy of preload increase to the heart which is significantly increased in 30% of athletes and inadequacy of ventricle repolarization which is evidently accelerated in a part of athletes (almost ¼) and retarded in another part. At the average PWC level the evident tendency towards bradycardia is followed by moderate disorders in ventricle repolarization.

Parameter	High (H)		Above Average (AA)		Average (A)	
	<5	>95	<5	>95	<5	>95
HR,1/m	**28.3**	0.0	**20.7**	3.4	**18.2**	0.0
P, s	0.0	**15.2**	0.0	**30.0**	**9.1**	**9.1**
PQ, s	0.0	**28.3**	0.0	**16.7**	0.0	**18.2**
QR, s	**15.2**	0.0	**23.3**	**6.7**	0.0	0.0
QRS, s	0.0	4.3	3.3	**6.7**	0.0	0.0
QT, s	0.0	**15.2**	3.3	**10.0**	0.0	0.0
ST, n.u.	2.2	4.3	0.0	3.3	**9.1**	0.0

Table 20: Versions of boundary deviation occurrence in cardiointervalometry at rest in the groups tested.

Parameter	High (H)		Above Average (AA)		Average (A)	
	<5	>95	<5	>95	<5	>95
TP, ms	2.2	**19.6**	6.7	**16.7**	**0.0**	**27.3**
VLF, ms	2.2	2.2	**10.0**	**10.0**	**18.2**	**9.1**
LF, ms	4.3	**34.8**	0.0	**13.3**	0.0	**36.4**
HF, ms	2.2	**23.9**	**0.0**	**20.0**	0.0	**36.4**
LFHF, ms^2/ms^2	**8.7**	**13.0**	**13.3**	**10.0**	**27.3**	0.0

Table 21: Versions of occurrence of boundary deviations of BCP parameters at rest in the groups tested.

When analyzing HRV data in the groups tested at rest it is necessary to notice that at a high PWC level the most balanced level is the oversegmentary (VLF component) level of HR control, thereby athletes from group 2 (AA) and group 3 (A) have significant deviations of this parameter both towards decrease and increase (Table 21). Increase of total HRV power (TP) is a feature of all the groups, though out of any connection with PWC level, in spite of the fact that this parameter is more often may be connected to increase of adaptable capabilities. Increase of contributions of sympathetic (LF component) and parasympathetic (HF component) components is significant which is noticed at the evidently increased level. At the same time, when evaluating their contribution separately, one can notice that at the high level the LF component prevails, at the level above average - the HF component, at the average level - both components are increased equally. To some extent the noticed parameters are supplemented with ratio of LF and HF components. And at the average PWC level the evident tendency to parasymptathicotonia (27.3%) is found, and at the PWC levels above the average and at a high level - moderate tendencies to symptathicotonia and to parasymptathicotonia.

That is, when analyzing HRV parameters, one can notice, that increase of TP due to increase of LF and HF components is specific for the high PWC level. At lower PWC levels contribution of the VLF component into TP increase is increased, and LF and HF ratio which is associated with prevailing of ANS tone is not informative with respect to the PWC level.

Analyzing the data shown in Table 22, it is necessary to note that at rest TP_{SBP} in athletes from groups 1 (H) and 2 (AA) variations in excess of the boundary deviations have not been observed. In group 3 (A) the moderate tendency towards TP_{SBP} reduction and increase has been observed. The insignificant tendency to reduction and increase of the VLF-component in group 1, lack of such changes in group 2 (AA) and a tendency to VLF-component increase in group 3 (A) is worth paying attention to. An evident tendency to decrease of the HF component of control is significant at high PWC level under condition of an insignificant tendency to increase of LF component of SBP. The latter characterizes the evident tendency to prevalence of sympathicotonic effects on SBP. In groups 2 (AA) and 3 (A) the evident tendencies in deviation of SBPV has not been observed. Some disregulation of SBPV frequency effect has been observed in group AA which is characterized by moderate tendencies to decrease of the LF component at moderate tendencies to increase and decrease of the HF component, the ratio of which in 13.3% of cases evidences prevalence of sympathicotonic (LF) effects. In group 3 (A) moderate tendencies to LF-component increase have been observed at moderate tendencies to increase and decrease of the HF component, the ratio of which has a slight tendency to evident parasympathicotonia.

Thus, the regulatory effects on SBP at the high PWC level are clearly differentiated by lack of variations of the evident decrease and increase of TP_{SBP} under condition of the evident tendency to decrease of the HF component and increase of LF/HF ratio that evidences prevalence of sympathicotonia. The factors limiting PWC at its level above the average should include mismatch of LF and HF effects, at the average PWC level - instability of the pumping function of the heart that ensures TP_{SBP}.

Parameter	High (H)		Above Average (AA)		Average (A)	
	<5	>95	<5	>95	<5	>95
$TP_{SBP,}$ mmHg	4.3	2.2	3.3	3.3	**10.0**	**10.0**
$VLF_{SBP,}$ mmHg	**8.7**	**6.5**	3.3	3.3	0.0	**10.0**
$LF_{SBP,}$ mmHg	2.2	**8.7**	**13.3**	3.3	0.0	**10.0**
$HF_{SBP,}$ mmHg	**19.6**	0.0	**13.3**	**10.0**	**10.0**	**10.0**
$LFHF_{SBP,}$ $mmHg^2/mmHg^2$	4.3	**21.3**	6.7	**13.3**	**9.1**	0.0

Table 22: Versions of occurrence of boundary deviations of SBPV parameters at rest in the groups tested.

Parameter	High (H)		Above Average (AA)		Average (A)	
	<5	>95	<5	>95	<5	>95
$TP_{DBP,}$ mmHg	0.0	2.2	0.0	0.0	0.0	0.0
$VLF_{DBP,}$ mmHg	4.3	2.2	**10.0**	0.0	**20.0**	0.0
$LF_{DBP,}$ mmHg	0.0	4.3	3.3	3.3	0.0	0.0
$HF_{DBP,}$ mmHg	**10.9**	2.2	**13.3**	6.7	**20.0**	0.0
$LFHF_{DBP,}$ $mmHg^2/mmHg^2$	**8.7**	**63.0**	**20.0**	**46.7**	**9.1**	**54.5**

Table 23: Versions of occurrence of boundary deviations of DBPV parameters at rest in the groups tested.

When analyzing the data shown in Table 23 one should note that the significant boundary deviations of DBPV parameters in the groups tested are differentiated only by the level of decrease of the VLF component of DBP regulation and that is even insignificant: in group 1 such variations are absent, in group 2 - there is an insignificant tendency, and in group 3 - the evident tendency. As for the level of a drop in the HF components of DBP regulation, in all the groups a moderately evident tendency has been observed. Also in all the groups a prevailing mismatch of effects of sympathetic and parasympathetic parts of BHC has been observed, both towards the evident prevalence of LF components and towards the evident prevalence of HF components. In total, such effects in group 1 have been met in 71.7% of cases, in group 2 - in 66.7% of cases and in group 3 - in 63.6% of cases.

Thus, a specific feature of DBP regulation in athletes is a mismatch of autonomous effects with prevalence of sympathicotonia within 46.7-63% of cases, a tendency to a decrease in HF component. Groups with various PWC level are differentiated only by a degree of a drop of the oversegmentary component (VLF components) of DBP regulation which at high PWC level is balanced in the maximum.

The RRV data were full enough of information and they evidenced a manifested tendency towards the drop of TP_{RR} and VLF_{RR} components in all the groups of athletes. The HF_{RR} component in all the groups also had a tendency towards dropping, however the most significant drop almost for every third athlete (31.1%) was in group 1 (H). In all the groups the insignificant and moderate tendency to a drop of the LF_{RR} components of spontaneous respiration control has been also observed, however in group 1 (H) the moderate tendency to a raise of LF components (in 15.6% of cases) has been observed. Finally, according to increase of the LF/HF_{RR} ratio (35.6% of cases) the group with a high PWC level is differentiated from group 2 (AA) and group 3 (A) in which only an insignificant tendency to increase of this relation (in 9.1% and 10% of cases) has been observed (Table 24).

Thus, in variability of the spontaneous respiration the group of athletes with a high PWC level is clearly differentiated in tendency to increase of LF component control, to more evident decrease of HF_{RR} components, which is characterized also by the evident increase of the LF/HF_{RR} ratio. Groups with the PWC level above the average and average in RRV parameters are not differentiated among themselves.

Parameter	High (H)		Above Average (AA)		Average (A)	
	<5	>95	<5	>95	<5	>95
$TP_{RR,}$ l/m	**28.9**	0.0	**30.0**	0.0	**27.3**	0.0
$VLF_{RR,}$ l/m	**24.4**	0.0	**26.7**	3.3	**18.2**	0.0
$LF_{RR,}$ l/m	**8.9**	**15.6**	**13.3**	3.3	**9.1**	0.0
$HF_{RR,}$ l/m	**31.1**	0.0	**16.7**	0.0	**18.2**	0.0
$LFHF_{RR,}$ $(l/m)^2/(l/m)^2$	2.2	**35.6**	6.7	**10.0**	0.0	**9.1**

Table 24: Versions of occurrence of boundary deviations of RRV parameters at rest in the groups tested.

Differences in the spontaneous respiration pattern at rest which characterized a high PWC level were significant too. First of all, in RR data (evident bradypnea in 32.6% of cases) and V_t, having the evident tendency to increase (in 17.8% of cases) which were followed by a moderate tendency to a drop of Tinsp/Texp ratio (in 13.3% of cases). The evident bradypnea in other groups was not followed by observed volume and phase characteristics of spontaneous respiration (Table 25). Thereby, there is a necessity to state that in group 3 (A) the manifested bradypnea has been characterized by absence of versions of increased V_t at more than by 2.5 times frequently expressed elongation of inspiration in comparison with expiration.

Parameter	High (H)		Above Average (AA)		Average (A)	
	<5	>95	<5	>95	<5	>95
Tinsp, s	0.0	**28.9**	3.3	**10.0**	0.0	**27.3**
Texp, s	0.0	**37.8**	0.0	10.0	0.0	**9.1**
Vt, l	**6.7**	**17.8**	**6.7**	3.3	**9.1**	0.0
Tinsp/Texp	**13.3**	**6.7**	**6.7**	0.0	0.0	0.0
RR,1/min	**32.6**	0.0	**10.0**	3.3	**18.2**	0.0

Table 25: Versions of occurrence of boundary deviations in respiration patterns at rest in the groups tested.

Thus, the complex study of variability of functions of the cardio-respiratory system together with the analysis of the cardiointervalometry and a pattern of spontaneous respiration has allowed to reveal sufficiently distinctive SACR-determinants of the high PWC level which can be described as follows:

- According to data of cardiointervalometry – an evident bradycardia at rest with moderate increase of preload onto the heart and acceleration of repolarization of ventricles;

- According to data of HRV – a moderately evident increase of TP due to increase of LF and HF components;

- According to data of SBPV – absence of version of evident decrease and increase of TP_{SBP} component and evident increase of the LF/HF_{SBP} ratio.

- According to data of DBPV – a maximally balanced VLF_{DBP} component;

- According to data of RRV – increase of the LF_{RR} component, evident decrease of HF_{RR} component, as well as evident increase of the LF/HF_{RR} ratio;

- According to data of the respiration pattern – evident bradypnea on the background of V_t increase and moderate decrease of ratio Tinsp/Texp.

During the following stage of our researches it was important to establish specificity of reactivity of the cardio-respiratory system in response to the tests with CR_6 and CR_{15}. Table 26 shows versions of variability of boundary deviations of HRV data in athletes with various PWC levels in carrying out tests with RB, taking into account the centile tables we have elaborated for evaluation of HRV parameters for CR_6 and CR_{15} (Table 2-4).

Parameter	High (H)		Above Average (AA)		Average (A)	
	Rest CR_{15} CR_6	Rest CR_{15} CR_6	Rest CR_{15} CR_6	Rest CR_{15} CR_6	Rest CR_{15} CR_6	Rest CR_{15} CR_6
	<5	>95	<5	>95	<5	>95
TP, ms	2.2→0.0→2.2	**19.6**→6.7→0.0	6.7→**13.3**→0.0	**16.7**→3.3→0.0	0.0→**9.1**→0.0	**27.3**→**9.1**→0.0
VLF, ms	2.2→4.4→0.0	2.2→**8.9**→0.0	**10.0**→6.7→0.0	**10.0**→3.3→0.0	**18.2**→0.0→0.0	**9.1**→0.0→0.0
LF, ms	4.3→2.2→2.2	**34.8**→6.7→4.3	0.0→**10.0**→0.0	**13.3**→3.3→**13.3**	0.0→**9.1**→0.0	**36.4**→0.0→0.0
HF, ms	2.2→0.0→2.2	**23.9**→6.7→0.0	0.0→**16.7**→6.7	**20.0**→3.3→0.0	0.0→0.0→0.0	**36.4**→**9.1**→0.0
LFHF, ms^2/ms^2	**8.7**→**22.2**→0.0	**13.0**→4.4→15.2	**13.3**→**10.0**→0.0	**10.0**→6.7→3.3	**27.3**→**18.2**→0.0	0.0→0.0→**27.3**

Table 26: Variation of percentage contributions to the boundary zones of percentile distributions of HRV values in carrying out tests with controlled respiration (CR_{15} and CR_6) in comparison with spontaneous respiration (rest).

When analyzing in turn a variability of boundary deviations of HRV values, it is necessary to state that in TP data in case of a high PWC level the evident decrease versions in response to CR have not been observed, thus the initially increased values of TP at CR_6 and CR_{15} become normalized, at PWC level above the average and average the CR_{15} significantly increases contribution of lowered versions of TP, and as well as at a high PWC level, drop of versions of evident TP raise in response to CR_6 is observed. The VLF component value at a high PWC level has an insignificant tendency to increase with CR_{15} while at above average and average levels of PWC when carrying out the tests with CR, contribution of VLF components decreases. Sufficiently informative was variability of LF and HF components which in athletes with a high PWC level significantly decrease at performance of the both tests. Athletes with the average PWC level have a similar dynamics of LF and HF components, except for a tendency to insignificant increase of lowered versions of LF with CR_{15}. Rather often at the PWC level above the average a depressing effect of CR_{15} on LF and HF components is observed and absence of effect on the raised LF component when carrying out the test with CR_6.

Variability of LF/HF value was the most informative which significantly decreases in athletes with a high PWC level in carrying out the test with CR_{15}, and in carrying out the test with CR_6 it practically does not vary. The athletes with a PWC level above the average have a practically unchanged LF/HF ratio in test with CR_{15}. At the same time athletes with an average PWC level have a decreased contribution of reduced versions of this parameter in carrying out the test with CR_{15} and a significantly increased contribution of evidently increased versions (27.3%) which evidences a higher reactance of the sympathetic loop of HR control.

Parameter	High (H)		Above Average (AA)		Average (A)	
	Rest CR_{15} CR_6	Rest CR_{15} CR_6	Rest CR_{15} CR_6	Rest CR_{15} CR_6	Rest CR_{15} CR_6	Rest CR_{15} CR_6
	<5	>95	<5	>95	<5	>95
TP_{SBP}, mmHg	4.3→0.0→0.0	2.2→4.5→4.3	3.3→**13.3**→3.3	3.3→6.7→**10.0**	**10.0**→**22.2**→0.0	**10.0**→0.0→0.0
VLF_{SBP}, mmHg	**8.7**→0.0→0.0	6.5→2.3→4.3	3.3→6.7→3.3	3.3→6.7→3.3	0.0→**11.1**→0.0	**10.0**→0.0→0.0
LF_{SBP}, mmHg	2.2→6.8→0.0	**8.7**→6.8→8.7	**13.3**→6.7→0.0	3.3→6.7→**10.0**	0.0→**11.1**→0.0	**10.0**→0.0→**10.0**
HF_{SBP}, mmHg	**19.6**→0.0→0.0	0.0→9.1→0.0	**13.3**→**13.3**→0.0	**10.0**→3.3→0.0	**10.0**→**11.1**→0.0	**10.0**→0.0→0.0
$LFHF_{SBP}$, $mmHg^2/mmHg^2$	4.3→4.4→0.0	**21.3**→2.2→**23.9**	6.7→**10.0**→0.0	**13.3**→**13.3**→0.0	**9.1**→0.0→**9.1**	0.0→0.0→**18.2**

Table 27: Variation of percentage contributions to the boundary zones of percentile distributions of SBPV values in carrying out tests with controlled respiration (CR_{15} and CR_6) in comparison with spontaneous respiration (rest).

When analyzing SBPV values, it is necessary to notice that TP_{SBP} is the most balanced one in group 1 both at rest and in carrying out respiratory tests, at the same time in group 2 CR_{15} results in a drop, and CR_6 in increase of TP_{SBP} (Table 27). The reactivity of TP in group 3 is differentiated in the same way in which CR_{15} results in increase of contribution of the lowered versions, and CR_6 - in optimization of the pumping function regulation. The VLF_{SBP} component is least variable in carrying out the test with CR, except for optimization at the high PWC level and some drop of reactivity in group 3 in carrying out the test with CR_{15}. The dynamics of the HF component in SBP control is significant. Being reduced in group 1, it becomes normalized in carrying out the tests with CR, and moderately increases in carrying out the tests with CR_{15}, which has not been observed either in group 2 or in group 3. On the other hand, the initially reduced level of the HF_{SBP} component in groups 2 and 3 remains the same in carrying out the tests with CR_{15}. The most significant is the dynamics of the LF/HF_{SBP} value, which does not vary in athletes from group 1 in percentiles of the evident reduction in carrying out the tests with CR, and in percentiles of the evident increase it becomes normalized in carrying out the tests with CR_{15} and remains unchanged in test with CR_6. In group 2 the initially increased versions of LF/HF_{SBP} with CR_6 do not vary, and with CR_6 disappear which evidences inadequacy of adjustment of controlling the pumping function of the heart. At the same time in group 3 the initially reduced versions of LF/HF_{SBP} remain at the same level in test with CR_6, within the evident increase range the initially adequate versions increase significantly in test with CR_6 in every 5th athlete, which evidence a sympathicotonic reaction of the pumping function of the heart in response to more rare respiration.

Thus, variation of SBPV data in response to the tests with CR has allowed to differentiate reactivity of the pumping function of the hearts of athletes with various PWC levels. Among the data analyzed, the dynamics of variations of the HF_{SBP} component LF/HF_{SBP} ratio was the most informative, which has allowed to conclude that in athletes with a high PWC level, having initially a low level of the HF_{SBP} component, CR_{15} and CR_6 result in a significant raise of activity of the parasympathetic path of ANS, and with PWC levels above the average and average the raise is found only at CR_6.

The dynamics of DBPV variations in response to the tests with CR has shown that in majority of DBPV data no significant transitions were found. The only exception was a LF/HF_{DBP} ratio which has been differentiated as follows: in athletes from group 1 in carrying out the test with CR_6 the contribution of evidently increased versions has decreased by 5 times, in group 2 - by 2.3 times, in group 3 - by 2 times; carrying out the test with CR_{15} in group 1 of athletes did not change the ratio within the limits of evidently reduced percentiles, and in groups 2 and 3- the ratio has been increasing (Table 28).

That is, in athletes with a high PWC level in carrying out the test with CR_6 a more significant reduction of sympathycotonic versions of DBP regulation has been found, in comparison with athletes with the PWC levels above the average and with an average level. Thereby, the test with CR_{15} in athletes with a high PWC level does not affect the parasympathicotonic versions of regulation, while in athletes from the other groups a reduction of parasympathicotonia versions has been observed at CR_{15}.

Parameter	High (H)		Above Average (AA)		Average (A)	
	Rest CR_{15} CR_6	Rest CR_{15} CR_6	Rest CR_{15} CR_6	Rest CR_{15} CR_6	Rest CR_{15} CR_6	Rest CR_{15} CR_6
	<5	>95	<5	>95	<5	>95
$TP_{DBP,}$mmHg	0.0→4.5→0.0	2.2→0.0→2.2	0.0→**10.0**→0.0	0.0→3.3→0.0	0.0→0.0→0.0	0.0→**11.1**→0.0
$VLF_{DBP,}$mmHg	4.3→**9.1**→0.0	2.2→2.3→2.2	**10.0**→**10.0**→6.7	0.0→3.3→0.0	**20.0**→0.0→0.0	0.0→**11.1**→0.0
$LF_{DBP,}$mmHg	0.0→6.8→0.0	4.3→0.0→0.0	3.3→6.7→0.0	3.3→3.3→3.3	0.0→0.0→0.0	0.0→**11.1**→0.0
$HF_{DBP,}$mmHg	**10.9**→4.5→4.3	2.2→2.3→0.0	**13.3**→**10.0**→3.3	6.7→6.7→0.0	**20.0**→0.0→0.0	0.0→**11.1**→0.0
$LFHF_{DBP,}$mmHg²/ mmHg²	**8.7**→**8.9**→0.0	**63.0**→4.4→**13.0**	**20.0**→3.3→0.0	**46.7**→6.7→**20.0**	**9.1**→0.0→0.0	**54.5**→**9.1**→**27.3**

Table 28: Variation of percentage contributions to the boundary zones of percentile distributions of DBPV values in carrying out tests with controlled respiration (CR_{15} and CR_6) in comparison with spontaneous respiration (rest).

When analyzing data on RR variability, first of all it is necessary to state that the controlled respiration within 6 and 15 times/min. in athletes from all the groups should equalize the spectral characteristics, however, variations of RRV data differ significantly (Table 29). Let us remember that in the initial condition athletes with a high PWC level had some increase of LF_{RR} components, more evident reduction of HF_{RR} components, as well as evident increase of LF/HF_{RR} ratio. It is worth paying attention that in carrying out tests with CR these indicators are differentiated rather clearly. For athletes in group 1 (H) performance of the test with CR_{15} optimizes LF and HF components of RRV and the most significantly in their ratio. The distinctive specificity in carrying out the test with CR_{15} in group 2 (A) is optimization on the background of the moderate tendency to increase of the higher version contribution, while in group 3 (A) the test with CR_{15} promotes the evident reduction of the LF component (increase by 2 times of boundary deviations within the range less than 5%), which is not followed by significant variations within the range exceeding 95%.

Parameter	High (H)		Above Average (AA)		Average (A)	
	Rest CR_{15} CR_6	Rest CR_{15} CR_6	Rest CR_{15} CR_6	Rest CR_{15} CR_6	Rest CR_{15} CR_6	Rest CR_{15} CR_6
	<5	>95	<5	>95	<5	>95
$TP_{RR,}$l/m	**28.9**→6.7→**17.4**	0.0→4.4→**8.7**	**30.0**→0.0→**16.7**	0.0→**10.0**→**16.7**	**27.3**→**9.1**→**27.3**	0.0→0.0→0.0
$VLF_{RR,}$l/m	**24.4**→6.7→**8.7**	0.0→4.4→**17.4**	**26.7**→**10.0**→**10.0**	3.3→**10.0**→**13.3**	**18.2**→**9.1**→**27.3**	0.0→0.0→**18.2**
$LF_{RR,}$l/m	**8.9**→6.7→4.3	**15.6**→4.4→**13.0**	**13.3**→6.7→6.7	3.3→**10.0**→**16.7**	**9.1**→**18.2**→**9.1**	0.0→0.0→0.0
$HF_{RR,}$ l/m	**31.1**→6.7→**19.6**	0.0→2.2→2.2	**16.7**→0.0→**16.7**	0.0→**13.3**→0.0	**18.2**→**9.1**→**18.2**	0.0→0.0→0.0
L $LFHF_{RR,}$(l/m)²/ l/m)²	2.2→6.7→0.0	**35.6**→4.4→6.5	6.7→3.3→0.0	**10.0**→3.3→**10.0**	0.0→**9.1**→0.0	**9.1**→0.0→**9.1**

Table 29: Variation of percentage contributions to the boundary zones of percentile distributions of RRV values in carrying out tests with controlled respiration (CR_{15} and CR_6) in comparison with spontaneous respiration (rest).

Carrying out the test with CR_6 in group 1 (H) results in raise of activity in initially reduced versions of LF and HF component contribution without changing their ratio, and practically not affecting the initially increased versions of LF and HF component contribution, it significantly optimizes their ratio. In athletes from group 2 (AA) carrying out the test with CR_6 optimizes the lowered versions of LF components and does not affect the reduced versions of HF component, while contribution of the LF component within the increased range is increased (more than by 5 times). Group 2 (AA) is characterized by the fact that LF and HF component ratio in test with CR_6 does not vary LF and HF component contribution within the boundary ranges of percentile distributions.

Thus, the distinctive specificity of RRV in carrying out tests with CR in athletes with a high PWC level is optimization of LF and a HF component ratio under condition of a raise of possible initially lowered versions of LF and HF components.

When characterizing variability of components of the cardio-respiratory system function variability in carrying out tests with CR in athletes with different PWC levels, we should state that the distinctive specificity of the high PWC level is the following:

For HRV: TP optimization with a tendency to a raise of the VLF components contribution (with CR_{15}) and drop of LF and HF components that is followed by a significant decrease of LF/HF ratio with CR_{15} and stability of LF/HF with CR_6;

For SBPV: expressed raise of the HF component in carrying out tests with CR_6 and CR_{15};

For DBPV: optimization of initially raised relation LF/HF;

For RRV: optimization of initially raised LF/HF ratio.

As a whole, the researches conducted have allowed to define SACG-determinants of the high PWC level at rest and in carrying out the tests with CR. The latter is important for a complex express-estimation of the level of physical working capacity as one of the components of the functional state of athletes' bodies in carrying out step-wise and current control under conditions of the training process.

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Chapter: VII

Evaluation of Cardiovascular System's Functional Reserves in Young Figure Skaters

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Introduction

Modern sport imposes high requirements on human body and puts forward the problems of studying functional status of various systems of the body and instant level of physical performance and timely diagnosis of prepathological and pathological conditions arising from inappropriate organization of the training process. Medical support of elite athletes first implies comprehensive medical examination that through analysis of clinical markers allows evaluation of the degree of prepathological or pathological conditions that occur in the body of the athlete as the long-term compensatory or adaptive response to strain of functional systems providing athletic activities. The possibility of achieving top scores depends on appropriate medical support in the dynamics of the training process in the form of step-by-step, continuous, or casual control of the health condition of athletes providing adequate training organization with due consideration for changes in their physical fitness and functional state of the body.

Elite sport makes maximum demands of athlete's organism that can exceed its actual possibilities. This is most typical of sports, where the athletes demonstrate their best results at the young age and main training loads occur in childhood. This mismatch results in severe functional disorders that can prevent the young athlete to continue exercising and even lead to disability. This fully applies to figure skating, where the children make the first steps at the age of 3-4 years and the decision on the prospects for further work with the child should be made by the age of 9-10 years.

The health status of athletes, including children, is closely monitored by medical staff, as at rest and during exercise (functional tests). In young skaters, monitoring the functional state is a part of biological and pedagogical control [1], including the cases of graded physical activity [2].

However, the minimal standard set of parameters (heart rate and blood pressure) can be insufficient for accurate assessment of functional reserve of the body. Heart rhythm variability and blood pressure variability, especially if they are evaluated simultaneously (polysystemic studies), provide valuable information for both the coach and doctor about the state of not only the cardiovascular system, but also autonomic regulation, which is of crucial importance for prediction of physical capacity of the athlete in the dynamics of the training and competitive periods. Moreover, heterogeneity of the state of the body defined as “health” dictates the need in quantitative evaluation of functional activity of the various systems of the body within the corresponding range. To this end, various functional tests are used.

In recent years, introduction of complex express methods of polyfunctional sanogenetic monitoring, e.g. spiroarteiocardiorhythmography, into practice of elite sport medicine has allowed objectivization of changes in the functional state of the body during both training and competition periods, which helps to optimize the adaptive capacity of athletes.

The aim of this work was validation of the method of Spiroarteiocardiorhythmography (SACR) for long-term monitoring of the functional status of young athletes. Apart from basic hemodynamic parameters (heart rate and blood pressure), this method allows evaluation of cardiac performance (stroke volume and cardiac output) and a set of parameters characterizing the state of the autonomic regulation systems (heart rate variability, blood pressure variability, and arterial baroreflex sensitivity) with the corresponding calculated indices.

Methods

We used the health monitoring data of 28 young skaters (20 girls and 8 boys) aged between 8 and 14 years, “Candidate Master” or “Master of Sports” qualification degree. One of the authors, Evgeniya Bogdanova, master of sport in figure skating and international referee for many years is a member an complex research group accompanying training of skaters (she supervises medical and biological issues of training). We carried out a long-term monitoring of children trained by Evgeniya Bogdanova. In accordance with Articles 5, 6 and 7, all tests were carried out only with the consent of the children and their parents (or legal representatives). Collection of personal data was performed in accordance with the requirements of the Federal Law “On Personal Data”, No. 152-FZ (July 27, 2006) with amendments (No. 261-FZ of July 25, 2011). Instrumental testing was performed in accordance with Methodology Recommendations “Evaluation of adaptive reserves of the human body in the system of physiological and hygienic standards of various types of activities” (approved and recommended by the Department of State Sanitary and Epidemiological Surveillance of the Ministry of Health of the Russian Federation, No. 11-1/282-09, November 22, 2001).

The study was performed in 2010-2012, a total of 5 surveys were carried out (3 in the spring, in the first half of May and 2 in the fall, in the second half of September), 194 recordings were made in three functional states (some children participated in not all these tests). All the children were healthy and had no medical problems.

The study was performed on a SACR complex. The device allows simultaneous recording of breathing air flows, continuous digital Blood Pressure (BP) measuring on unload artery (Penaz technique), and electrocardiogram in standard lead I with calculation of spectral heart rate variability parameters. The following parameters of the cardiovascular system were evaluated: Heart Rate (HR), range of intervals between the systoles (RR), End-Systolic (ESV), End-Diastolic (EDV), and Stroke Volumes (SV), Cardiac Output (CO), HR variability parameters (Total Spectral Power TP, the absolute and relative power of High-Frequency (HF), Low-Frequency (LF), and Very Low Frequency (VLF ranges), calculated indices of Autonomic Balance AB = LF / HF and Centralization (CI = (VLF + LF) / HF), and stress index. In addition, we evaluated the mean, minimum, and maximum parameters, the range of systolic and diastolic BP variations (BP_S and BP_D), and Baroreflex Sensitivity (BRS). The examiner saw four real-time curves on the monitor: volume parameters of inhaled and exhaled air (spirometric mask was on, but this was an optional condition), continuous duration of beat-to-beat (RR) intervals (in the form of heart rate in the current ECG), and continuous blood pressure values, from which BP_S and BP_D are derived. Other parameters are calculated by the software after the record is completed and can be viewed in special dialog boxes.

In our study, functional capacities of the cardiovascular system were evaluated by the degree of changes (reactivity) in various parameters after short program (lasting for 2min 30sec±10sec with the same set of required elements) in comparison with testing before it (after warm up). This test is close to the sub maximum exercise test, but can be done during training, which facilitates organization aspects. The duration of both records was 2 minutes because of some limitations for using SACR at low temperatures (see explanations below).

The experimental protocol included the following stages:

- Warming up (exercises) in the gym – 50-60min;

- Baseline recording of cardiovascular system parameters on a SACR instrument (in 10-15 min after warming up; record duration 2min);

- Warming up on the skating ring (10-20min depending on phonogram order);

- Program performance (2.5min);

- SACR recording immediately after program performance (20sec for getting the examiner table and 40-60sec for instrument adjustment; record duration 2min);

- Off-line analysis of the obtained data.

Statistical analysis was performed by nonparametric methods and analysis of variance using algorithms for repeated measurements.

Results and Discussion

Before describing the obtained results, we should discuss some methodical issues.

Methodical peculiarities of spiroarteriocardiorhythmography method

The study was performed on a SACR device, which determined nonstandard duration of recording: 2min instead of recommended 5min [3]. It should be noted that SACR simultaneously records HR and digital BP and both the shape and amplitude of BP signal quickly starts changing at low temperature (skating-rink) due to technical features of Penase's method [4] that is used in the SACR device. To adjust the level of digital blood pressure in devices continuously recording this parameter (Finometer Pro, Portapres etc.), the readings from the digital sensor were periodically corrected for BP measured by the auscultatory method on the arm. Recent modifications of the device are equipped with a double finger cuff and digital BP is measured alternately on different fingers with periodic adjustment to BP measured on the arm. This is impossible on SACR device, because this device is intended for screening surveys of large samples and the primary requirement is maximum simplicity of the measurement procedure. Not to lose the data on BP variability, we reduced the time of recording to 2min, no doubt losing in reliability of VLF range assessment in the HR spectrum and in BP_S and BP_D spectra. This is the limiting factor for using SACR.

Second, the measurements were actually started in 60-80sec after program performance (some time is needed for approaching to the device and its adjustment). The duration of record was 2 minutes, i.e. we evaluated the cardiovascular system parameters not immediately, but in 2-3min after the program was performed. In highly skilled athletes, this time is enough for partial recovery: HR considerably decreased (from 195-210 to 120-140stroke/min), which was demonstrated by using portable pulsometer followed by SACR recording) and BP also decreased. In our study, BP_S usually returned to near-normal level by the end of recording (Figure 1). Mush less often we observed not only BP_S decrease, but also a tendency towards BP_D elevation (this parameter recovers more slowly) (Figure 1).

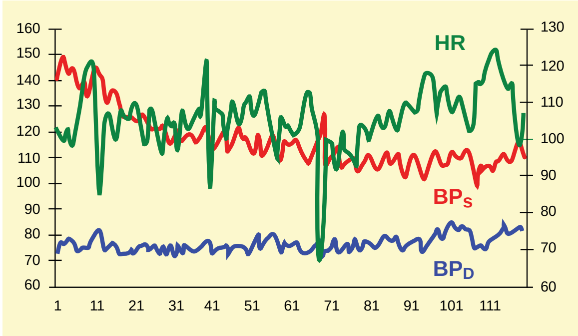

Figure 1: Parameters of the cardiovascular system after short program performance recorded by SACR.

Green curve – HR (right ordinate, stroke/min), Red curve – BP_S (left ordinate, mmHg), Blue curve – BP_D (left ordinate, mmHg). Abscissa: time, sec.

Despite these shortcomings, SACR provides useful information about the dynamics of cardiovascular system parameters that cannot be assessed using many other instrumental complex. In particular, it allows evaluation of BRS in direct measurement at HR and BP coherence. BRS, together with HR variability parameters, characterizes the state of autonomic regulation. Moreover, the device allows evaluation of SV and CO.

Comparative analysis of SV values measured by SACR and other non-invasive methods at rest

The classical methods of SV measurement are based on Fick's principle (1870), according to which cardiac output is proportional to the arterio-venous oxygen content difference [5]. This principle can be applied to not only oxygen, but also carbon dioxide (which provided the basis of carbon dioxide rebreathing method) or any other gas [6]. Noninvasive methods of SV measurements are more preferable for children, e.g. the method based on Kubicek's formula for impedance cardiography [7] allowing evaluation of SV from the pulse wave parameters. This approach was continued in new noninvasive methods of SV measurements based on continuous BP recording using Finometer-type pressure devices [8,9]. Another approach is SV calculation by two-dimensional reconstruction from the parameters of averaged electrocardiogram [10]. The latter algorithm is realized in SACR. However, SV calculation from BP values is still widely used [11,12].

We have previously demonstrated that SV measured by SACR technique well correlated with the values obtained by measurement using Finometer Pro device [13]. Here we compared SV values measured by SACR and indirectly calculated from BP in a cohort of children of different age and adults (control group for additional verification of the results) with different fitness levels (Table 1 and 2). We used Starr formula [12] modified for 8-14 year old children (1) and adults (2) [14]:

(1) $SV = 80.00 + (0.50 \cdot (BP_S - BP_D)) - (0.60 \cdot BP_D) - (2 \cdot age)$

(2) $SV = 90.97 + (0.54 \cdot (BP_S - BP_D)) - (0.57 \cdot BP_D) - (0.61 \cdot age)$

In addition, SV was determined by the indirect method of Lilje-Strander and Zander (cited by [11]):

$SV = (BP_S - BP_D) / ((BP_S + BP_D) / 2) \cdot 100$

It found that SV values measured by different noninvasive methods significantly differed in all groups of examinees. It should be noted that the values recorded by SACR in children (Table 1) were maximally close to echocardiography data obtained by Russian researchers [15] and to the results obtained by foreign researchers using various noninvasive methods [16,17].

	n	SV measured by SACR method ml	SV calculation after Vein [11], ml	SV calculation by Starr formula [14], ml
Untrained children (8-14 years)	73	62.54 ± 0.93	53.17 ± 1.69 *	43.37 ± 1.60 *+
Children athletes (sport games and martial arts) (11-14 years)	48	61.49 ± 1.03	53.53 ± 1.50 *	33.48 ± 1.63 *+
Young figure skaters (8-14 years)	69	53.02 ± 0.97	53.35 ± 2.62	43.15 ± 1.78 +

Table 1: Comparison of SV values obtained by different methods in the same examinees in children. Significance of differences (evaluated by Wilcoxon's test): *–p<0.05 in comparison with SACR data, +–p<0.05 in comparison with Vein method [11].

In adults (Table 2), SV measured by SACR corresponded to our findings in adult athletes obtained by carbon dioxide rebreathing method: 74.0 ± 1.2 ml in untrained individuals (n=28) and 90.0 ± 2.6 ml in athletes (athletics, modern pentathlon, water polo, swimming, figure skating; n=32); the differences are significant at p<0.05; One-way ANOVA).

	n	SV measured by SACR method ml	SV calculation after Vein [11], ml	SV calculation by Starr formula [14], ml
Untrained adults	43	71.23 ± 1.35	44.04 ± 1.30 *	42.12 ± 1.93 *
Adult athletes (rugby)	14	75.61 ± 3.50	42.42 ± 4.03 *	57.92 ± 2.80 *+

Table 2: Comparison of SV values obtained by different methods in the same examinees in adults. Significance of differences (evaluated by Wilcoxon's test): *–p<0.05 in comparison with SACR data, +–p<0.05 in comparison with Vein method [11].

Results of SV evaluation during physical exercise

In children, the increase in CO after short program performance was detected by all methods (Figure 2b), but different results were obtained for SV: SACR detected a decrease by 8-9%, while calculations showed an increase in this parameter (Figure 2a).

Reactivity of the heart performance parameters used in the monitoring of young figure skaters was also tested in a group of untrained adults (n=43, 22 men and 21 women) during squat stand test (20 squats over 30sec). In adults, both SV and CO increased after

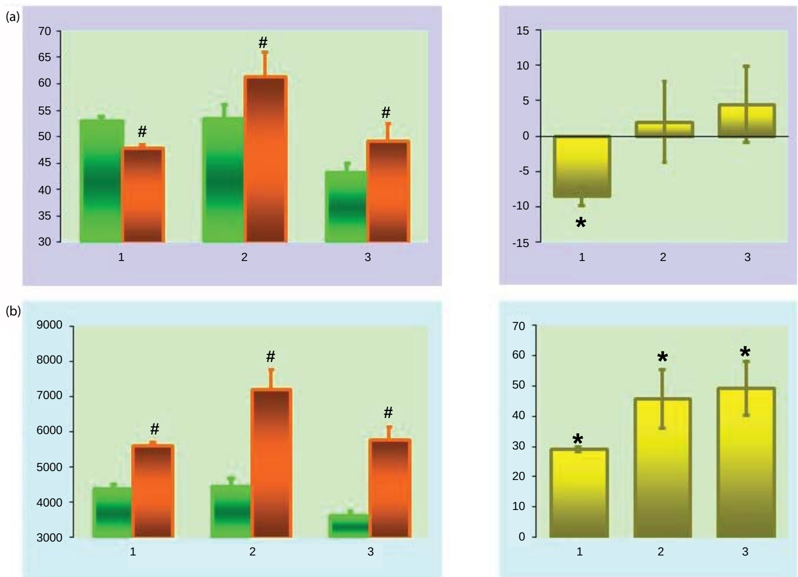

Figure 2: Changes in parameters of cardiac productivity after physical exercise. SV (a) and CO (b) in young skaters after short program performance. Abscissa: method of evaluation: 1 – SACR, 2 – calculation after Vein [11], 3 – calculation by Starr's formula for the corresponding age group [14]. Left histograms show values before (green bars) and after exercise (orange bars); #: significant differences by Repeated measures ANOVA (p<0.05). Right histograms show changes of the parameter in %; *: significant differences by One way ANOVA (p<0.05).

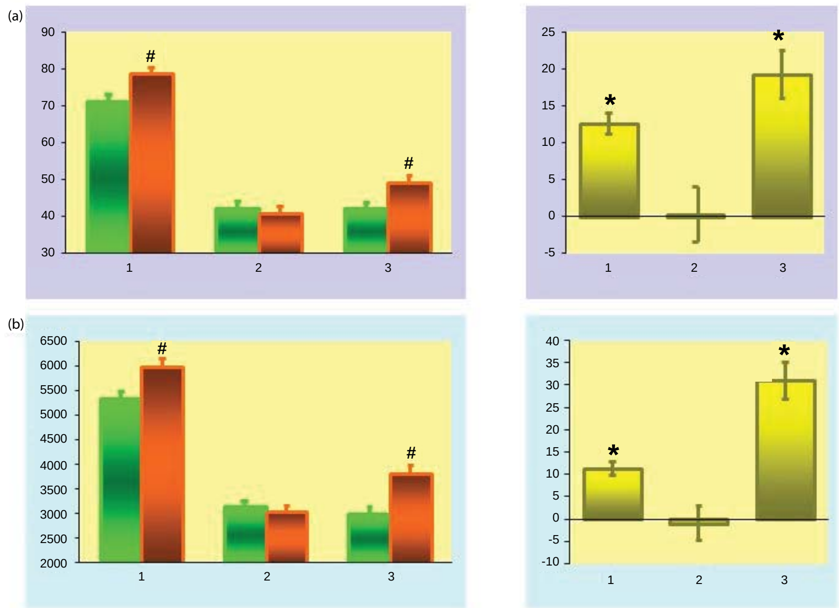

Figure 3: Changes in parameters of cardiac productivity after physical exercise. SV (a) and CO (b) in untrained adults after 20 squatting over 30 sec. Abscissa: method of evaluation: 1 – SACR, 2 – calculation after Vein [11], 3 – calculation by Starr's formula for the corresponding age group [14]. Left histograms show values before (green bars) and after exercise (orange bars); #: significant differences by Repeated measures ANOVA (p<0.05). Right histograms show changes of the parameter in %; *: significant differences by One-way ANOVA (p<0.05).

exercise, but these changes were detected only by SACR or by calculations using Starr formula (Figure 3a and 3b).

It has been previously postulated that SV increases during physical exercise to ~40% maximum oxygen consumption and than attained a plateau [18]. However, resent studies have demonstrated different changes in the parameters of cardiac performance during physical exercise depending on the work power, sex and age of athletes [19], and probably on the method SV and CO measurements. Measurement of SV by inert gas rebreathing method and by SACR yielded similar results. It should be noted that in 8-17 year old athletes SV decreased below the resting values (91%) during sub maximum and maximum physical exercise, which agreed with our observations [17]. Similar regularities were previously found in adults [20]. It was hypothesized that exercise-related increase in CO in young athletes is primarily determined by HR acceleration, which leads to shortening of the cardiac cycle and systole duration and therefore reduces SV [19]. The methods of SV measurements based on pulse wave and cardiac cycle assessment algorithms are more sensitive to these changes (in particular, SACR, as was demonstrated in out study).

Method of evaluation of physical status of the organism in young skaters and prediction of exercise intensification results

Analysis of our functional monitoring results in young skaters by a set of cardiovascular parameters and their reactivity during exercise made it possible to choose the indicators that were most sensitive to the state of the child's organism; these were geometrical and spectral parameters of HR variability, spectral parameters of BP variability, and BRS. We determined two extreme types of the organism reaction corresponding to favorable and unfavorable prognosis for intensification of physical exercises (and proficiency improvement). The results are presented in Table 3.

Gender, age	f, 10 years			f, 10 years		
prognosis	positive			negative		
	before	after	Δ (%)	before	after	Δ (%)
Heart rate, stroke/min	84.39	92.45	9.55	91.05	133.60	46.74
End-systolic volume, ml	27.9	32.0	14.70	22.7	32.9	44.93
End-diastolic volume, ml	86.8	88.7	2.19	74.4	78.1	4.97
Stroke volume, ml	58.9	56.7	–3.74	52.0	48.2	–7.31
Minute volume, l/min	5.0	5.2	4.00	4.7	6.0	27.66
RR range, ms	383	463	20.89	410	67	–83.66
Total Spectral Power $TP_{HR,}$ ms^2	8074	9745	20.69	6585	219	–96.67
VLF_{HR} range power, ms^2	795	1268	59.43	938	144	–84.67
Relative VLF_{HR} range power, %	9.85	13.01	32.10	14.25	65.68	360.91
LF_{HR} range power, ms^2	1960	1500	–23.48	1289	60	–95.38
Relative LF_{HR} range power, %	24.28	15.39	–36.60	19.58	27.20	38.95
HF_{HR} range power, ms^2	5319	6978	31.18	4358	16	–99.64
Relative HF_{HR} range power, %	65.88	71.60	8.69	66.17	7.12	–89.24
Autonomic balance, LF_{HR}/HF_{HR}	0.37	0.21	–41.67	0.30	3.82	1191.46
Centralization index, $(VLF_{HR}+LF_{HR})/HF_{HR}$	0.52	0.40	–23.43	0.51	13.04	2452.01
Stress index	52.3	39.61	–24.26	46.83	1121.33	2294.47
BP_S, mmHg	99.74	108.34	8.62	122.45	116.00	–5.27
BP_S max, mmHg.	122	137	12.30	135	130	–3.70
BP_S min, mmHg	82	91	10.98	114	101	–11.40
BP_S range, mmHg	40	46	15.00	21	29	38.10
BP_D, mmHg	66.31	78.19	17.92	64.87	75.00	15.62
BP_D max, mmHg	76	89	17.11	77	85	10.39
BP_D min, mmHg	58	64	10.34	59	69	16.95
BP_D range, mmHg	18	25	38.89	18	16	–11.11
Pulse pressure, mmHg	33.43	30.15	–9.81	57.58	41.00	–28.80
Baroreflex sensitivity, ms/mmHg	20.1	31.5	56.72	28.7	5.1	–82.23

Table 3: Parameters of the cardiovascular system in 2 examinees of the same gender and age with different exercise intensification prognosis: before and after short program performance and changes in the parameters in %.

As is seen, HR increased after program performance in all children, but this increase was more pronounced in children with limited functional capacities. In both cases, the changes in functional parameters of the myocardium were close by ESV, EDV, and SV. The increase in calculated CO was more pronounced in case of unfavorable prognosis, due to more pronounced HR acceleration. The R-R variation range in case of favorable prognosis increased by 20% and in unfavorable it decreased by 8-9 times; TPHR underwent the corresponding changes. In the favorable prognosis, the power of all frequency bands (VLF_{HR}, LF_{HR}, HF_{HR}) increased, which was accompanied by spectrum redistribution towards higher frequencies (decrease in AB and CI). On the contrary, a sharp decrease in the power of all HR spectral bands and redistribution of some frequency bands towards manifold increase in AB and CI were observed in unfavorable prognosis. Similarly, stress index in favorable prognosis somewhat decreased, while in unfavorable prognosis it increased to critical values: (stress index>1200arb.units attests to high risk of myocardial infarction [21]). In children, this parameter after program performance sometimes attained 2500arb.units.

Changes in BP parameters were the follows: BP_S increased after exercise in skaters with favorable prognosis and somewhat decreased in children with unfavorable prognosis; BP_S variability increased in both cases. On the contrary, a decrease in BP_D by 20-15% (by 10-15mmHg) and a decrease in its variability (a decrease in BP_D variation range) were the indicators of unfavorable state. Moreover, a sharp decrease in BRS attesting to functional insufficiency of systems adjusting BP and HR values is considered as an unfavorable sign.

Our findings coincided with the results of clinical assessment of health status of young figure skaters and observations and comments of their coachers as well as with the data of other authorities [22-24]. It seems that the conclusions on exercise intensification/easing should be made on the basis of the key indicators of autonomic regulation, for instance, excessive decrease in the contribution of HF and LF ranges into HR spectrum leading to an increase in the relative power of VLF range attests to poor prognosis. However, the dynamics of stress index is a more reliable parameter because of short duration of our records.

Results of functional status monitoring in young figure skaters

Analysis of the dynamics of the test parameters over 24 months (from May 2010 to May 2011) showed that at rest (after warming-up before program performance) only age-related changes in the cardiovascular system parameters can be detected in young athletes: decrease in HR (and CO), increase in TP_{HR} and all ranges of the spectrum (without changes in their relative contribution), increase in BP_S (and pulse BP), and decrease in stress index. During the training and competition season (May-October), BP_S elevation and BP_D decrease were noted in the same children (and the corresponding increase in TP_{HR}) and all spectral ranges also decreased (without changes in their relative contribution); these shifts were partially compensated during the summer holidays. An increase in TP_{BPC} и TP_{BPD} with anticipatory increase in the relative HF range power were also observed during the training and competition season. The latter can be explained by the effects of long-term adaptation to intensive physical exercise [25-28].

Assessment of the reactivity of cardiovascular parameters after program performance showed that scheduling the third workout (after summer 2010) led to an increase in reactivity of stress index, HR, and SV (Figure 4) as well as relative VLF_{HR} power and BRS in young skaters. In parallel, episodes of heart rhythm disturbances were noted in the majority of skaters (most often after program performance). These changes were attributed to the overtraining, which required urgent correction of the training regimen and thorough medical examination of young athletes. Further tests showed that the parameters returned to normal.

The dynamics of reactivity of BP_D variation range deserves special attention. As stated above, BP_D at rest (after warming-up) decreased and TP_{BPD} (i.e. BP_D variability) increased gradually during the training and competition season with subsequent partial recovery during summer holidays. Hence, the increase in reactivity of BP_D variation range recorded during each spring testing (in comparison with autumn) with partial recovery after summer rest reflects interference of ontogenetic processes and the influence of the training process on the hemodynamic parameters in young figure skaters. This is most clearly demonstrated by the analysis of individual tracks (Figure 4a).

The dynamics of SV reactivity (Figure 4d), in particular, the decrease in this parameter after program performance in comparison with the control (in %) probably reflects the process of ontogenetic maturation of the cardiovascular system of our examinees that got older by 2 years over the survey period.

The use of discriminant analysis for evaluation of functional status monitoring results in young figure skaters

The results of monitoring are now typically presented as the dynamics of individual indicators. However, a long list of indicators used for the analysis is difficult to apprehend, on the one hand, but on the other, multiparameter estimation of a single system of the body allows applying multivariate statistical methods for the calculation of a single integrated indicator. In particular, it refers to the capacity of the discriminant analysis, allowing calculation of coordinates for a point corresponding to subject condition in the phase plane based on a number of indicators. In this case, significant parameters are selected by the method of step-by-step analysis and the corresponding regression equation coefficients are calculated. In our view, wide use of this method is hampered by difficulty in interpreting coordinates X (Root 1) and Y (Root 2), calculation which includes all analyzed parameters, but with different coefficients.

In light of this, of particular interest is the model proposed and tested by Baevsky RM and Chernikova AG [29] that is based on evaluation of the status of conventionally healthy individuals and those with prenosological conditions and compensated chronic diseases. According to this model, the functional state of an individual can be estimated by the results of discriminant analysis of a variety of HR variability parameters. The first canonical variable (Root 1) is an indicator of the mobilizing function of regulatory mechanisms (stress index and HR have the maximum weight in it), therefore it is viewed as an indicator of functional reserves. The second variable (Root 2) related to the parameters of parasympathetic activity (pNN50, absolute HF_{HR} power – TP) reflects the protective function of regulatory mechanisms and autonomic balance and is believed to characterize the regulatory system tension. The values Root 1and Root 2 are considered as the coordinates of the phase plane forming the space of functional states that consists of four sectors: physiological norm (Root 1>0; Root 2<0), prenosological states (Root 1>0; Root 2>0), premorbid states (Root 1<0; Root 2>0), and pathological conditions (Root 1<0; Root 2<0).

This method has been tested for evaluation of the dynamics of individual functional state of cosmonauts and participants of the “Mars-500” project [30].

We used this model in our study for single evaluation of the functional state of 14 skaters in spring 2011 [31]. Three 2-min records were made for each examinee: baseline (after warming up), in spirometric mask on (“in mask”), and after short program performance. Testing in a spirometric mask on a SACR device is a functional load test modeling light hypercapnia [13]. The application of Chernikovoy AG model for our subjects showed that the state of skaters at baseline (Root 1 = 0.93 ± 0.23, Root 2 = 0.06 ± 0.05) and in mask (Root 1 = 1.05 ± 0.17, Root 2 = 0.13 ± 0.03) corresponded to the “prenosological state” segment, while the status after short program performance corresponded to “pathology” (Root 1= -4.76 ± 1.16, Root 2 = -0.98 ± 0.25).

Taking into account the specific features of SACR measurements and young age of the examinees, we analyzed HR variability parameters and digital BP readings in three states (Table 4). The results were close to the values predicted by Chernikova AG’s model: HR and stress index still were critical for Root 1 variable, while Root 2 became critically dependent on the relative power of LF ranges of HR и BP_D spectra (LF_{HR}% and LF_{BPD}%). We have previously demonstrated that these ranges are informative for SACR assessment of functional maturation of the cardiovascular system in humans during ontogeny [32].

	n = 42 (2011, spring)		*n* = 194 (5 trials, 2010-2012)	
	Root 1	Root 2	Root 1	Root 2
Heart rate, stroke/min	**–0.493**	–0.018	**–0.733**	–0.059
Total spectral power TP_{HR}, ms^2	0.133	0.165	0.214	**0.354**
Relative LF_{HR} range power, %	0.117	**–0.326**	0.232	–0.093
Relative HF_{HR} range power, %	0.282	0.226	**0.398**	0.236
Total spectral power TP_{BPS} mmHg^2	–0.266	0.059	–0.152	–0.028
Relative LF_{BPS} range power, %	0.092	0.018	0.237	0.042
Total spectral power TP_{BPD} mmHg^2	–0.162	–0.049	–0.160	–0.042
Relative LF_{BPD} range power, %	0.214	**–0.348**	0.262	–0.276
Baroreflex sensitivity, ms/mmHg	0.183	–0.192	0.263	**–0.439**
Stress index	**–0.313**	–0.199	**–0.370**	–0.150

Table 4: Factor structure of discriminant analysis matrix for two models plotted according to the results of single examination and monitoring of the functional state of the cardiovascular system in young skaters by SACR.

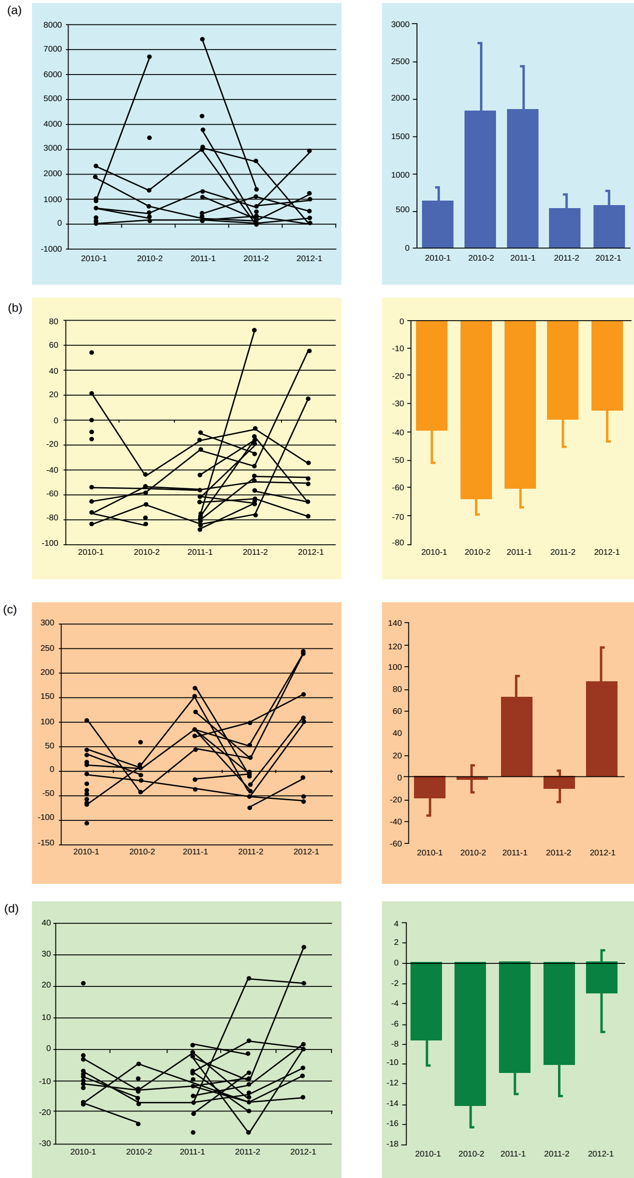

Figure 4: Dynamics of cardiovascular system parameter reactivity (changed after short program performance compared to baseline) in young skaters during monitoring. (a) Stress index, (b) R-R duration range, (c) BPD variation range (d) SV. Abscissa: year and season (1- spring; 2- autumn) of examination. Left panels: individual tracks of examinees; histograms: averaged data.

In the present study, we developed an extended model that included the data of all five examinations (a total of 194 observations). This extended sampling yielded the following results: Root 1 at rest=1.51374, Root 2 at rest=–0.351334; Root 1 “in mask”=1.22302,Root 2 “in mask”=0.593351; Root 1 after program performance=–2.77867, Root 1 after program performance=–0.030964. The individual values of these variables are presented in figure 5 as is seen, the general distribution pattern for individual results coincided with both Chernikova’s model and our model based on the results of single examination.

At the same time, analysis of factor structure of the extended model showed that apart from the determinant role of HR and stress index, the relative power of HF_{HR} also became crucial for Root 1 variable. For Root 2 variable, TPHR and BRS became more valuable, while the contribution of LF_{HR}% and LF_{BPD}% was still high. Thus, the coefficients for calculation of variable in terms of the extended model are the follows: Root 1 = – 0.073040 . HR(stroke/min) – 0.000043 . TP_{HR}(ms2) + 0.036066 . LF_{HR}(%) + 0.030592 . HF_{HR}(%) – 0.000688 . TP_{BPS}(mmHg^2) + 0.024010 . LF_{BPS}(%) + 0.000055 . TP_{BPD}(mmHg^2) + 0.017655 . LF_{BPD}(%) – 0.000551 . BRS(ms/mmHg) – 0.000062 . stress index (arb.units) + 3.985176; Root 2 = 0.004583 . HR(stroke/min) + 0.000140 . TP_{HR}(ms2) + 0.003493 . LF_{HR}(%) + 0.025395 . HF_{HR}(%) – 0.000633 . TP_{BPS}(mmHg^2) – 0.003743 . LF_{BPS}(%) – 0.000486 . TP_{BPD}(mmHg^2) – 0.016948 .LF_{BPD}(%) – 0.000140 . BRS(ms/mmHg) – 0.000140 . stress index (arb.units) + 0.008959.

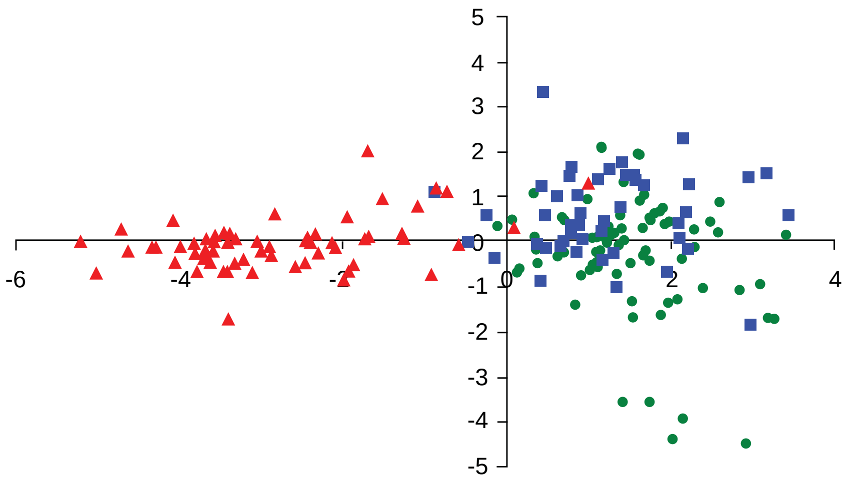

Figure 5: Individual results of young skaters in phase plane constructed by the results of discriminant analysis. Abscissa – Root 1; ordinate – Root 2. Green circles: results after warming up; blue squares: “in mask” test; red triangles: after short program performance.

These formulae can be used in other studies for monitoring of the functional state of the cardiovascular system in young athletes if HR and BP variability assessment is technically possible. BRS can be calculated as alpha-index=$(LF_{HR} / LF_{BPS})^{1/2}$: Interpretation of the results using the principles proposed elsewhere [29] will make them available not only for physiologists and sports medicine experts, but also for coachers. On application of other technical resources, the potential of discriminant analysis can be used for creation of a model, when the phase plane is built on the basis of a sufficient set of parameters characterizing three obviously different functional states.

Conclusions

1. SACR allows evaluation of both the cardiovascular system status and parameters of autonomic regulation by the spectral parameters of HR and BP variability and BRS values. Parameters of cardiac productivity recorded by SACR are close to the values obtained using Fick’s principle and pulse wave analysis.

2. Functional monitoring of young skaters is effective if assessment of the major hemodynamic parameters is combined with evaluation of autonomic regulation parameters. Analysis of parameter reactivity (magnitude of changes) upon dosed special sub maximum physical exercise (in our case, short program performance) is most informative.

3. The results of functional monitoring of young skaters can be easily presented as a point on the phase plane; the coordinates for this point can be calculated by discriminant analysis of three different states characterized by a large set of parameters.

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Chapter: VIII

Polysystemic Investigation of Children, Living in a Megalopolis: Environmental Aspect

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Abstract

The paper presents description of the concept and practical applications of modern diagnostic methods in monitoring of health and environmental safety of population in megalopolises. The main methods used are multielement analysis and laser correlation spectroscopy of biological samples. Application examples include investigations conducted in different regions of the former USSR with different climate, environmental conditions and life standards. Children and pregnant women being highly susceptible to unfavourable external influence are suggested to be most indicative groups for the monitoring. It is shown that trace elements measurements in soil, drinking water and hair samples demonstrate high correlation between environmental contamination (or natural geochemical peculiarities) of the territory and elemental disorders found in biological samples of individuals. A model of trace element monitoring using indicatory biological samples is suggested for systemic medical prophylaxis in combination with non-specific diagnostic methods like laser correlation spectroscopy. Correction of trace elements imbalances (microelementoses) revealed by multielement and laser correlation assays can significantly decrease the risk of trace element related diseases and general morbidity in populations.

Introduction

Absolute majority of diseases of adult people forms in childhood. It is admitted that children are a special part of the population, which especial peculiarity is vulnerability and sensitivity. During active growth, the organism intensely accumulates different substances including environmental pollutants. Age related differences in sensitivity to influence of industrial contaminants may be connected with lower intensity of detoxication processes in growing organism. State of child's organism not only determines health condition at the moment, but also influence on further development of the organism and its future health.

Stability of chemical composition is one of the most important and essential conditions of organism's normal functioning. Deviations in chemical elements concentration, caused by ecological, climatogeographical factors, or diseases lead to different disturbances of children's health, respectively [1]. It should be also pointed out that many metals, abundant in the environment, belong to trace elements, necessary for normal functioning of human organism. Trace elements play a great role in formation of many important adaptive mechanisms including functioning of all vital systems of the organism. That is why sufficient content of essential elements in the organism and minimal concentration of toxic and relatively toxic elements, not threatening frustration of adaptive mechanisms, is one of the most important requirement of modern human [2].

Studies on biological role of major and Trace Elements (TE) are of special interest today from the point of view of their synthesizing aspects. According to Avtsyn AP, Zhavoronkov AA [3], there is a sufficient evidence to suggest existence of a common biological system of TE homeostasis, which consists from: (1) entry routes; (2) metabolic (utilization) routes; (3) elimination routes; (4) regulatory influences of these biological systems.

The concept of microelementoses (a synthetic approach in modern medical elementology), proposed by Avtsyn AP and co-workers [3], was used as the theoretical basis of our study. Its common epidemiological classification is present in Figure 1. According to the proposed classification, the following main groups of microelementoses have been defined:

• Natural endogenous (congenital and inherited);

• Natural exogenous (endemic);

• Technogenic (occupational, neighborourgh, transagressive) and finally Iatrogenic

The diseases are generally divided into hypo(micro)elementoses, hyper(micro)elementoses and (trace) element imbalances.

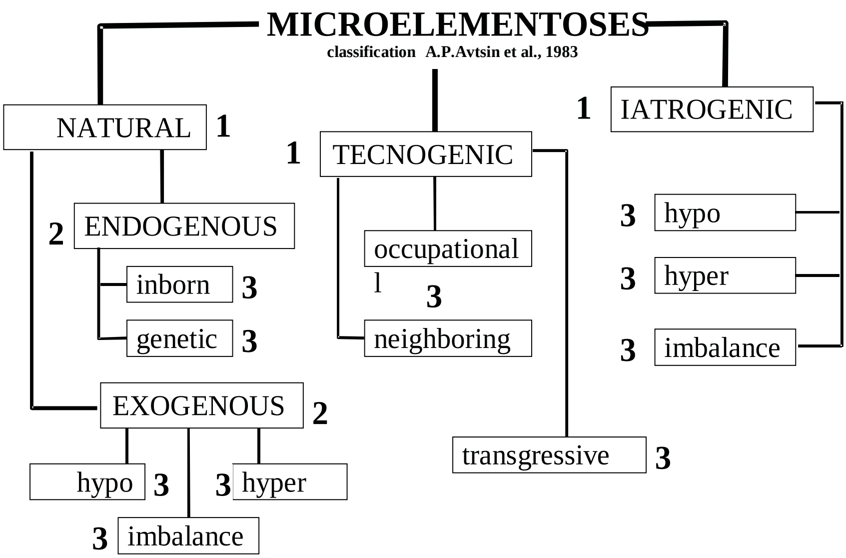

Figure 1: Human microelementoses.

Naturally, in the cases of multi-elemental investigations the absolute majority of diseases is due to the element imbalances because of the numerous specific interelemental interactions, physiological, nutritional and ecological reasons, and increased liability of main biochemical processes and sensibility of pregnant women, newborns and children to toxicants. Numerous scientific data suggest the opinion that human hair is one of the best indicative biosubstrates for the estimation of trace-elemental status of an organism [4-7] (Table 1), and it is widely used in biomonitoring researches [8].

Substance	Blood	Urine	Hair
Arsenic	+	+	+
Aluminum			+
Barium			+
Boron			+
Cadmium	+	+	+
Calcium	+	+	+
Chromium	+	+	
Cobalt	+		
Copper	+	+	+
Iron			+
Lead	+		+
Magnesium			+
Mercury	+	+	
Phosphorus			+
Selenium	+		
Silver	+		
Strontium			+
Thallium	+		
Zinc	+		+

Source: German BGA-Umweltsurvey and European Program on Trace Element Reference Values in Human Tissues.

Table 1: Substances, for which the frequency distributions of their concentrations in various biological matrices have been established by recent biomonitoring surveys (for occupationally unexposed populations in Europe).

Last time one give particular attention to correlations between concentration of toxic substances, including metal compounds, in blood, urine, hair and other human tissues on the one hand and rate of their negative influence on human organism on the other hand. At that, concentration of a substance in human tissues or excretions is used as indicator of both its influence on the organism and its concentration in the environment. Hair is a biosubstance, which adequately reflects elemental balance in the organism [9]. Multielement hair analysis allows to determine reliably enough the risk groups of hyper- and hypoelementoses for their further investigation and forehanded prophylaxis.

In our formerly reports [2,10-12] the data on exceeding of the biologically allowable hair levels of toxic elements and low hair levels of essential elements in Russian children were presented. In a lot of epidemiological studies the dependence of children's hair elements content on some ecological, socio-economical and climato-geographical peculiarities was found.

According to the obviously presented data the importance of major and trace elements supplementation and toxic elements elimination in Russian children is evident. It can help to decrease the relatively high children morbidity and mortality, numerous endemic, technogenous, genetic, nutritional factors, influencing on their health.

As shown in Figure 2, the concentrations of trace elements in children's hair reflect the environmental situation. According to our data, obtained within the present study from kindergartens situated at the distance of 0.5, 1.0 and 5.0km from the Zlatoust metallurgic plant (South Ural), the Pb, As and Ni concentrations in children's hair are positively correlated with its levels in both soil and drinking water; the Zn, Cu, B, Mo, Cr hair concentrations reflect soil levels of these elements. Strict correlation between cadmium presence in hair and drinking water has been found.

Methods

In order to develop the rapid multielemental analysis of various biological and environmental samples, the analytical laboratory was founded in the Centre for Biotic Medicine, Moscow, Russia. The main applied analytical method was spectrometry with Inductively Coupled Plasma (ICP). Last years atomic emission spectrometry and mass-spectrometry with inductively coupled plasma (ICP-AES and ICP-MS methods accordingly), as well as complex of these two methods, are used for estimation of chemical elements content in biological samples more and more often. The main type of samples to be analyzed in the laboratory was human hair. Hair has drawn attention as a good indicator of trace elements metabolism. The hair also can mark a toxic excess or insufficiency of individual elements in the body [13]. It was shown that the level of trace element abundances reflects the net trace element status of an organism and thus the hair sample can serve as an integral index of the mineral metabolism. It is important to emphasize some advantages in the use of hair as the biochemical index and as a sample:

• Easiness of the sampling and storing;

• Relatively high levels of normally occurred concentrations, in comparison with other sample types (blood, urine);

• Combination of the excretive and accumulative functions in the hair; this makes possible a retrospective analysis and advanced prognosis of the elemental balance.

In addition there should be noted some drawbacks of hair sampling:

• The elemental composition of hair can be affected by various biological factors - sex, age, natural color, etc.;

• Hair features high biological variability;

• The washing and degreasing procedures before digestion can change an initial elemental composition of a sample.

Simplicity of sampling and storing of hair samples provides the ability to control the dynamics of the elemental homeostasis in a long-term period. In conjunction with environmental monitoring this research can draw out the sources and ways of trace element intake in organisms.

In order to carry out ICP measurements of a hair sample, a weighting of hair should be quantitatively digested (mineralized) to make a final sample solution. The existing procedures of digestion imply wet ashing with mixes of hydrogen peroxide and strong acids: nitric, perchloric, muriatic, sulphuric in various combinations with heating in open or closed vessels [14]. The simplified procedure developed in this study requires the use of only nitric acid and heating in open vessels to make the rapid quantitative extraction of the elements to be measured into solution.

Initially, the sample digestion procedure was as follows. A hair sample (ca. 100mg) was rinsed in acetone and dried. Then the weighting was transported to a fluoroethylene tube, a 1mL of concentrated HNO_3 was added and tube was sealed with inert film. The batch of tubes was transported to a hot plate, preheated to 115°C. No cutting of hair was required, since droplets of condensed nitric acid effectively rinsed and dissolved the rests of sample. The time of digestion was about one hour. Digested sample appears as clear yellow solution without any particles. After digestion samples were quantitatively transported to graduated tubes and diluted to the final volume of 10ml with deionized water that results in dilution factor of 100. The blank samples were added to every batch and treated with all preparation steps. During the development of the method we recognized that some of the tubes after digestion contain traces of unoxidized organics appeared as small white lipoid droplets in bottoms of the tubes. These droplets can readily be swiped out by the mechanic washing with detergent or slowly dissolve in hot nitric acid. In order to validate such a digestion treatment for quantitative analysis, the series of tubes with these droplets were subjected to secondary heating on the hotplate with strong nitric acid at 120°C until the total digestion was achieved approximately 3-4hours. The comparison of the measured sample composition with that of the lipoid droplets supports that microelements are totally transferred to the sample solution during one-hour preparation procedure.

Later we changed the hotplate digestion to microwave digestion as described below for blood. Now this technique is used for all biological samples including hair [15].

Besides hair, determination of chemical elements in body fluids like blood or urine is also informative for estimation of body elemental status. However, the use of body fluids has certain peculiarities. The main of them is that content of chemical elements in blood (also serum, plasma) is subjected to strong homeostatic regulation. This complicates detection of light deviations in mineral exchange, making these fluids useful only in acute cases. As for urine, this fluid is informative for a very limited number of elements. Another common disadvantage of using liquid body fluids is low concentration of most chemical elements in them comparing hair that imposes additional requirements on instruments and methodology.

Nevertheless, in appropriate cases, chemical elements in liquid body fluids can be determined. Through experience [16] it has been found that determination of 10-15 most significant essential and toxic elements by ICP-AES/MS complex requires duplicated weighting of 100mg blood or urine.

For the analysis, samples were placed into PFA liners with nitric acid and decomposed in a laboratory microwave oven using the following heating mode: 5min temperature rising up to 200°C, 5min retention interval at this temperature, then chilling down to 45°C. The chilled autoclave container was shaken to mix up its content and the cover was half-opened to balance the pressure. Then the solutions were transferred into 15mL test-tubes; after that the liners and the tops were rinsed thrice by deionized water with the rinses being consequently transferred into the correspondent test-tubes. Then the solutions were filled up to 15mL with deionized water and thoroughly mixed up by shaking in the closed test-tubes. For analysis, 1mL of the solution was selected by automatic proportioner and filled up to 10mL with 0.5% nitric acid.

The instruments used for determination was: microwave oven Multiwave 3000 (PerkinElmer – Paar A, Graz, Austria); electric distiller with combined membrane set DVS-M/1HA-1(2)-L (Mediana-Filter, Moscow, Russia), ICP-AES spectrometers Optima 2000 DV (Perkin-Elmer, USA) and ICAP-9000 (Thermo Jarrell Ash, USA), ICP-MS spectrometer ELAN 9000 (PerkinElmer – Sciex, Concord, Ontario, Canada). Working regimens and spectral corrections of the both spectrometers followed recommendations of the manufacturers.

Graduation of the instruments was carried out using multielement standard solutions, which were combined from monoelement Perkin-Elmer reference solutions of the series “Essentials”, mixed in corresponding proportions. Plotting of the graduation characteristic, processing and storage of the graduation results was provided by embedded software of the spectrometers.

In all experiments, for check-up of analytical measurements, corresponding certified reference materials (human hair, blood, urine, etc.) was used.

General metabolic changes were evaluated by the method of laser correlation spectroscopy [17]. This method allows evaluation of the percent contribution of particles with different size into light scattering in biological fluids.

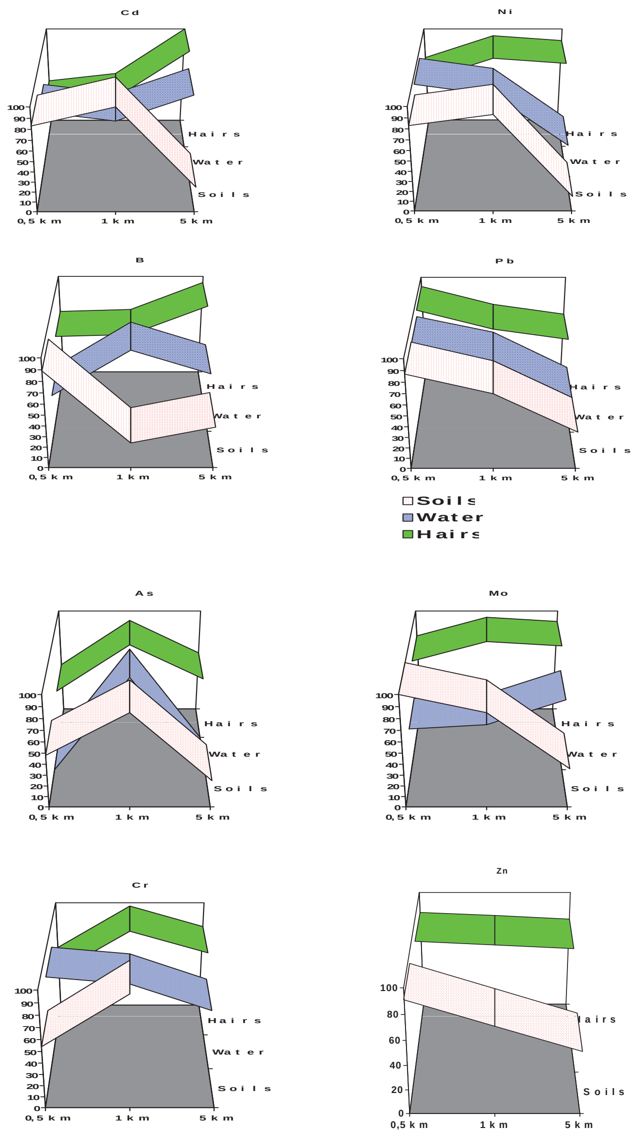

Figure 2: Correlation between trace element concentration in soil, drinking water and children's hair (distance of 0.5, 1 and 5km from a steelworks (Zlatoust, Chelyabinsk region, 1992).

Results

Investigation of macro and trace element balance in newborns and their mothers

Naturally, multielement investigations reveal that the absolute majority of diseases are connected with element imbalance because of numerous specific physiological, nutritional, ecological reasons, the increased lability of main biochemical processes and sensibility to toxicants. This is fully actual for newborns and their mothers (so called "mother-placenta-fetus" system). For example, formerly we [18-19] found a direct correlation between the placental, fetal cord blood TE contents and risk of pre-term deliveries which were very similar to the TE alterations in "mother-placenta-fetus" system, typical for ecologically polluted regions.

On another hand, the "feto-placental system" and "mother-newborn pair" are very important objects (models) for investigation of TE homeostasis, interelemental relationships, for simultaneous comparison of the clinical importance of different biosubstrates (hair, fetal cord blood, placental tissue, mother's milk, etc.).

It is known that children and pregnant women comprise the group, most susceptible to trace elements deficiencies or excesses; their homeostatic and adaptive mechanisms may be affected by different factors (stress, pollutants, malnutrition, etc.). This is why in our investigation we paid the special attention to both these groups of population. 250 newborns and their mothers were clinically examined during the years 1992-1999, and their hair samples were analyzed. Besides hair, placenta samples were also investigated. The mothers were residents of the following cities: Moscow, Electrostal (Moscow region), Elista North Caucasus-Kalmykia, Nukus, Mujnak Central Asia-Aral sea region, Ufa (Ural region), Salekhard, Yar-Salee (Polar region, Yamal peninsula). Among them Moscow is a megalopolis with more than 10 million inhabitants, high population density and moderate ecological problems typical for large urban areas without distinct city-forming enterprises. Salekhard, Yar-Salee are cities inside the Arctic Circle with uncomfortable climatic conditions and predomination of gas and oil industry. Ufa is a big city in Urals with large chemical, machine building plants and high level of industrial pollution. Electrostal is a town with highly concentrated metallurgic and machine building enterprises including in particular aluminium processing and nuclear fuel producing plants. Elista, Nukus and Mujnak are localities with generally weak industry but serious ecological problems arisen from climato-geographical peculiarities and agrochemical abuse. The Moscow and Yamal inhabitants had the highest income and life standards while those of Elista, Nukus and Mujnak were the lowest.

The results obtained in this investigation have shown that hair elemental content of newborns and mothers adequately reflects the geochemical (natural, exogenous elementoses) and industrial (technogenic, neighbouring elementoses) influence. In comparison with Moscow, which is the most comfortable locality in this study in social and ecological aspects, subjects from other regions considerably differ by elemental profile (Table 2, Figures 3 and 4). The infants from Yamal had almost eightfold exceeding of hair Mn level that corresponds to more than tenfold exceeding of maximal allowable Mn concentration in drinking water in the Polar region. In economically depressed regions with low incomes, such as Central Asia (Aral Sea region) and North Caucasus (Kalmykia), the malnutrition, undeveloped hygienic habits, hot climate and geochemical properties of the regions are accompanied with frequent pregnancies that can lead to high rate of trace element deficiencies. Also, low levels of trace elements (Cu, Zn) in hair of the subjects from Aral Sea region and Kalmykia possibly reflect low concentrations of the elements in soil and foodstuffs. Thus, in hair of more than 50% mothers from Nukus, Mujnak, and Elista considerable insufficiency of Zn, Cu was found. In the same cases there was detected an excess of Cd, which is an antagonist of Zn, Cu. Infants from these regions in 80% and 95%, respectively, also demonstrated signs of Zn deficiency (Zn concentration in hair<120mg/kg) on the background of supernormal Cd level.

Region Element	Moscow n=89		Yamal (Polar region) (n=25)		Ufa (Ural region) (n=30)	
	min-max	M ± m	min-max	M ± m	min-max	M ± m
Ca	65-2393	831.0 ± 69.0	250-2852	1147.4 ± 159.4	562-1854	1230 ± 114
Mg	70-422	144.0 ± 11.2	29.9-255.2	85.4 ± 10.0	93-151	120 ± 7.2
Fe	39-103	54.9 ± 5.7	24.2-136.1	45.2 ± 5.2	20.1-49.0	31.4 ± 3.0
Zn	206-344	272.0 ± 11.0	87.0-545.0	216.1 ± 28.6	184-1583	280 ± 64
Cu	3.5-14.5	7.20 ± 0.4	1.3-10.1	5.4 ± 1.4	6.4-21.2	17.2 ± 1.2
Mn	0.1-7.5	1.6 ± 0.2	1.6-40.0	12.5 ± 3.5	0.4-75.9	9.0 ± 3.0
Pb	0.7-42.0	2.8 ± 0.5	ND-4.3	1.8 ± 0.4	ND-26.1	19.9 ± 2.2
Cd	ND-1.2	0.4 ± 0.2	ND-0.7	0.3 ± 0.1	ND-0.7	0.2 ± 0.1

Table 2: Content of chemical elements (µg/g) in newborns' hair in different regions of Russian Federation.

Environmental contamination in Ural region leads to increase of Pb hair level, to decrease of Fe hair level in newborns and their mothers, and to deviations in Zn, Mn, Cu data. The similar situation was observed in Elektrostal city (excess of Cu, Pb, Mn, Ni). In mothers from Elektrostal, on the background of high aluminiumin in hair, relatively low Mn, Fe (40% cases) and Se (20%) was detected; in newborns biologically allowable levels of Al, Cu, Mn, Ni was exceeded in 50% cases.

Investigation of preschool children

In another our investigation [20] data on content of major and trace elements in hair of 2806 2-6 y/o children (apparently healthy, approximately 1:1 boys/girls ratio), constantly living in Moscow (control group) were compared to 56 2-6 y.o. children, suffering from secondary Immunodeficiency (ID group) and undergoing medical treatment in sanatorium (33 cases), hospital (10 cases), special kindergarden (13 cases). During the examinations the special medical documentation, including questionnary, were filled and hair samples were collected.

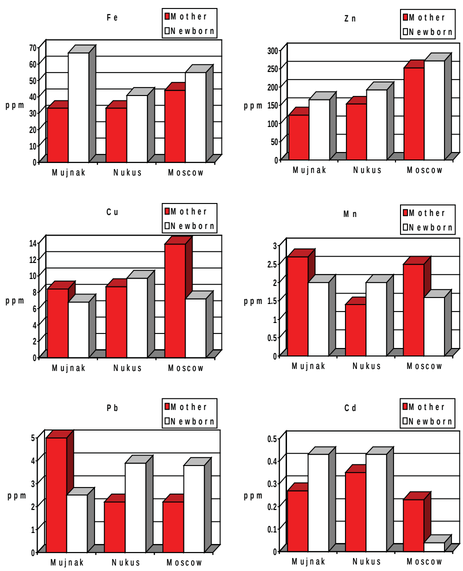

Figure 3: Content of trace elements in hair of newborns and their mothers from Aral Sea region and Moscow city.

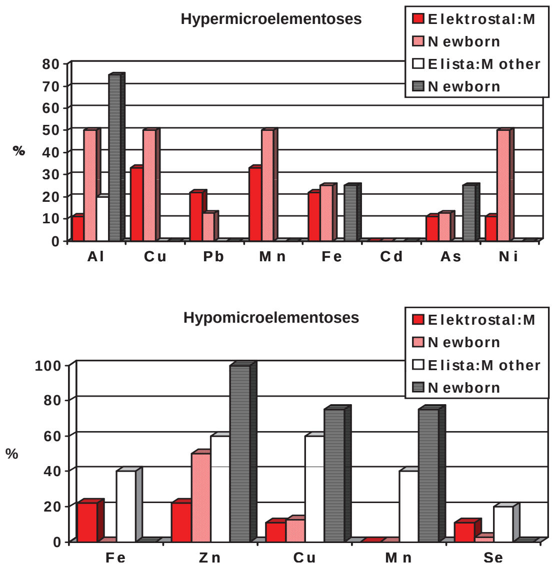

Figure 4: Prevalence of hypo- and hyperelementoses in newborns and their mothers living in different localities.

As a result of this study the data, suggested the serious differences in mineral metabolism of ID children as compared to controls, were obtained. The ID group has dramatically low Mg, Zn, Cu hair levels ($p<0.001$). Also, the hair Ca, P and Mn concentrations were significantly ($p<0.001$) decreased. The hair Si level was lower than control, but in less extent ($p<0.05$). In the case of Fe and Cr data only the tendency to decreasing its hair levels in comparison to control group was revealed.

Besides the absolute values, the percent of the essential elements deficiencies estimated by multielement hair analysis were also informative. According to these data, the frequency of decreased Mg and Zn, Cu was approximately 3 times higher in ID group in comparison to control (92.3%, 85.7 and 78.6 versus 30%, 29% and 24.8% respectively). Also, the Mn and P deficiencies can be widespread in ID children (every second case in contrary to few percents in control group). The low hair Ca in 54% of ID cases (30% in control group) was observed. Generally, excesses of essential elements in hair were relatively rare in this age group (except the K, Na elevated data in ID group). At the same time, data on distribution of potentially dangerous elements exceeding in children hair demonstrate that ID children were less contaminated by toxic metals than controls (Table 3).

Element	Control	ID
Cd	8.60%	5.36%
Pb	3.74%	1.79%
Al	4.49%	7.14%
As	2.99%	0.00%
Ni	1.31%	0.00%
Sn	14.21%	16.07%

Table 3: Prevalence of excesses in levels of potentially toxic elements in hair of children.

The low hair Mg, Zn, Cu, Ca, Mn, P levels in ID patients found in this study is supported by numerous literature data [5,11,20,21]. Such hair analysis data usually reflect deficiency of the essential major and trace elements in the organism. These hypo(hyper) elementoses can lead to derangement of immunocompetent tissues and to a decrease in cellular and humoral immunity, depression of antioxidant mechanisms (Zn, Mn, Cu, Mg), host defense resistance (Zn, Ca, Si), to derangement (or insufficiency) of protein synthesis and low niveau of energy metabolism.

It is important to highlight such an interesting fact, observed in our previous [11] investigation and supported in the presented study, that the immunodeficient children (with the frequent, more than 8 times per year, infections and inflammatory morbidity) have the lower concentration of toxic elements than relatively healthy (with rare morbidity) children. In our study the hair Pb, Cd, Sn (but not As) concentrations were significantly lower in ID group. Possibly, these facts reflect the depressed metabolic processes, differences in nutrition and private hygiene (it is well known, that nutrition and habits of ill children are under more serious control of adults), effects of medicines (some of them can chelate the toxic metals), and reduced contacts with environmental pollutants (restricted possibility for outside playing, walking in open air, etc.).

According to the clinical data and obtained hair analysis results, additionally to routine therapy (vitamins, thymus preparations, physiotherapy, etc.), the individual correction by major and trace element containing biologically active food supplements was administered to the children.

The absolute majority of additionally supplemented ID children demonstrated significant (84.2%) or moderate (10.5%) improvement of general health conditions (as reported by mothers and other relatives, physicians) with adverse effects observed only in 2 cases from 38 ones. The main result in controls was the absence of any changes (77% of cases). First of all, in ID children the improvement manifested itself in reduction of viral or bacterial infections, allergic and psychoneurological (hyperactivity) symptoms. In 2 cases of physical retardation the most evident beneficial effects were obtained.

The excellent result of individualized (based on multielement hair test) correction of major and trace elements metabolic deviations suggest the possibility to increase effectiveness of rehabilitation and additional therapy of immunodeficient children, suffering from suboptimal intake of such nutrients as minerals and vitamins. Our opinion (suggested in this study) was that the using of monopreparates or simple combinations of essential major and trace elements after the hair analysis can provide the individual approach to the correction and reveal the sufficient clinical effects through the restoration of internal needs on essential elements. The simple preparations can be preferable in children with chronic asthenic; immunodeficient conditions that not to overload the main metabolic routes or organs, to diminish the risk of interelemental antagonistic interactions and side effects, hyperelementoses, hypervitaminoses etc.

In our next investigation during the years 2000-2002 an observation of 1312 children up to 7 years old, living in Russia, mostly in Moscow, was made. The investigation included questioning, medical examination and determination of 24 chemical elements in hair (Al, As, Be, Ca, Cd, Co, Cr, Cu, Fe, Hg, K, Li, Mg, Mn, Na, Ni, P, Pb, Se, Si, Sn, Ti, V, Zn).

All investigated children were divided into four health groups depending on functional condition of the organism. Data of children's diseases were taken from physician's examination and case records present in medical cards of Center for Biotic Medicine. The group I consisted in healthy children with normal rate of physical and mental development, having no malformations, injuries or functional deviations. The group II contained children having no chronic diseases, but being characterized by some functional and morphological deviations. The group III included children having chronic diseases in state of compensation with undisturbed functional capabilities. The group IV consisted of children having chronic diseases in state of subcompensation or decompensation with disturbed functional capabilities.

The obtained results revealed considerable differences in concentration of chemical elements in hair of preschool children depending on their health condition. Generally, the highest concentration of toxic chemical elements such as Al, Hg, Pb, Ni were found in hair of children of the health group IV, As and Cd in children of the health group I. The group II was found to be the most peculiar among the others. It was characterized by significantly lower concentration of 30% of determined elements though without signs of Zn deficiency, which was characteristic of the groups III and IV.

Comparison of analytical data obtained from different health groups showed statistically significant difference in concentration of some chemical elements in hair of preschool children. Generally, hair of somatically weak children (groups II, III, IV) differs from that of healthy preschoolers (group I) by higher level of Se, Co ($p<0.01$), Sn ($p<0.05$) and lower level of Fe, Ca, Pb, Ti ($p<0.01$), Cd, Mg, and Zn ($p<0.05$).

According to the data obtained, children of the group I were characterized by high occurrence of decreased hair level of Ca (42% of children), Co (84%), Mg (64%), Se (43%), Zn (68%) and the increased one of Si (20%) and K (22%). Absence of manifested deviations in health condition does not exclude presence of hidden pathogenic agents or functional deviations, having intermediate character in children during intensive development and growth.

Children of the group II were featured by high occurrence of decreased Ca (46%), Fe (23%), Mg (67,5%), Mn (54%), P (32%), Se (37%), Zn (67%) levels and increased concentration of K (23% of children). These data evidence significant disturbances in mineral metabolism and high risk of pathologic deviations in children's health condition.

The group III was characterized by high occurrence of low concentrations of Fe, P (26% and 29%, respectively), Se (36%), Ca (44%), Mn (55%), Mg (66%), Zn (73%) and Co (79% of cases).

Children of the group IV were featured by high occurrence of decreased concentrations of Co (84%), Zn (71%), Mn (56%), Mg (59%), Se and Ca (40% each) in hair; risk of Al, Cd, Cr, Pb, Ti excess is relatively abundant (from 10% till 15% of children).

Correlation analysis of children's hair elemental content in different health groups detected interrelations between levels of many elements, which generally coincide with current knowledge about interactions of chemical elements in human organism. Thus, in virtually all investigated groups of children, despite sharp distinctions in organism functional condition, close correlation in levels of Ca and Mg, K and Na, Ca and P was found, as well as similarity of proportions of these elements (Ca/Mg, K/Na, Ca/P, Zn/Cu), which are claimed to be biochemical constants of human organism.

It is notable that number of the detected interelemental correlations was found to be dependent on health condition. Generally, the worse the health condition, the less the number of correlations. Thus, 63 pairwise correlations were detected in the group I, just 24 in the group II, 55 in the group III, and 38 in the group IV. In the group I the closest positive correlation was observed for hair levels of the following combinations of chemical elements: Al/Fe ($r = 0.51$), Ca/Mn-Mg ($r = 0.66$), Ca/Fe ($r = 0.5$), K/Na ($r = 0.69$), Fe/Mn ($r = 0.69$), Fe/P-Ti ($r = 0.57$), Mn/Ti ($r = 0.57$), P/Ti ($r = 0.68$), Cr/Ni ($r = 0.56$). Significant, though moderate enough, negative correlation was detected in the pair Be/Sn ($r = -0.32$). In the group II significant positive correlations were found only for two pairs: K/Na ($r = 0.63$) and Ca/Mg ($r = 0.53$). Significant negative correlation was observed only between Sn and Ti ($r = -0.29$). In the group III correlations Al/Cr ($r = 0.56$), Al/Fe ($r = 0.64$), Ca/Fe-Mg ($r = 0.54$), Ca/P ($r = 0.59$), Cr/Fe-P ($r = 0.53$) were found. In the group IV – Ca/Mn ($r = 0.85$), Ca/Mn ($r = 0.58$), Fe/Ni ($r = 0.5$), Mg/P ($r = 0.56$), Ni/P ($r = 0.68$), and negative correlation between K and Zn ($r = -0.3$). Thus, in organisms of somatically weak children, the interelemental metabolic relations typical for healthy organism with normal physiological functions are partly disrupted or impaired. At the same time, in some cases another new "pathologic" relations can be formed, that may cause further disturbance of various physiological processes in human organism (regulation of water-salt exchange, neuromuscular conduction, muscles traction etc.), which needs coordinated action of different chemical elements for their regulation.

In general, it may be pointed out that, according to our data, the characteristic of all observed children was imbalance of essential major and trace elements, which was conditioned by inadequate intake of nutrients on the one hand and antagonistic relations between some toxic and essential elements on the other hand, that leads to various disturbances of health condition.

So, the general conclusion is that chronically ill children have the specific "elemental portrait" [22], reflected by hair macro and trace elements content. Among main features of their elemental status are, in the first place, the widespread deficiencies of Co, Mn, Mn, Se, Ca, Fe, P and, especially, Zn. These data are corresponding to classical investigations [23-26]. Multielement hair analysis may be included in complex of mass health examination as an additional test for estimation of children's immunobiological resistance, especially in cases when combined influence of negative environmental factors takes place. Results of multielement hair analysis can be used to arrange adjusted correction of elements imbalance by means of biologically active supplements that may have a benefit effect in case of some diseases.

Investigation of adolescents

In another study hair samples of 3980 relatively healthy teenagers (1676 boys, 2212 girls) of 10-14 years old, residing in different regions of Russia, were analyzed by ICP-AES method. Concentration of Al, As, Be, Ca, Cd, Co, Cr, Cu, Fe, Hg, K, Li, Mg, Mn, Na, Ni, P, Pb, Se, Si, Sn, Ti, V, Zn was determined. The aim of the study was to reveal relations of sex and age with content of major and trace elements in hair of adolescents, as well as general influence of ecological conditions.

Among the subjects, several groups of people residing in large industrial Russian cities (Moscow, Saint Petersburg, Novosibirsk, Irkutsk, Tula) and a control group of people living in rural areas of the Moscow region were additionally separated in order to estimate an influence of ecological factors on hair mineral content.

The obtained results of multielement hair analysis (Table 4) show that hair elemental content in teenagers of each sex considerably differs. Thus, girls as a whole are characterized by higher concentration of Ca, Cu, Mg, Mn, Ni, Si, Zn and lower concentration of Cd, Cr, Fe, Hg, K, Li, Na, P, Pb, Ti as compared with boys.

The most distinct sex-dependent differences are observed in concentration of major elements. Relative excess of Ca, Mg in girls as compared to boys is found to be 1.77 fold and 1.74 fold respectively. This proportion is observed through all the age range from 10 to 14 years, and so is the Ca/Mg ratio, which is practically stable and equal in both sexes through years, being about 12:1 (Figure 5a). At the same time, Ca/P ratio is found to be very different in different sexes: 6:1 in girls and about 3:1 in boys (Figure 5b).

Such a high level of phosphorus may be due to potentially more intensive energy exchange in boys, connected with use of energetic phosphates like ATP or GTP. It is also known that in processes of absorption phosphate is closely connected with sodium [27], which is more abundant in boys. Age dependent dynamics of phosphorus level is poorly expressed. But there is a tendency towards increase of hair P concentration with age with statistically significant ($p<0.001$) peaks in girls of 12 y.o. and boys of 14 y.o. that possibly coincides with the end of growth spurt in corresponding sex. Absolute values of Ca, Mg concentrations increases with age in both girls and boys with the changes being more profound in boys (Figure 6).

Quite other determinations were observed for sodium and potassium. Hair concentrations of K, Na decreases with age. The decrease is more significant in girls, where level of these electrolytes turns nearly halved along the period from 10 to 14 y.o. (Figure 7). On the contrary to Ca, Mg, boys have about two-fold more Na, K than girls. This proportion is also observed in all the age range, though not so strict as in case of Ca, Mg: it varies from 1.8 to 2.4 for sodium and from 1.8 to 2.6 for potassium. The K/Na balance is also very similar in both sexes, but, unlike Ca/Mg, it is not constant in time. There is a gradual change of K/Na ratio with age observed: its value decreases from 0.8 in the age of 10 years to 0.6 in 14 years. It is noteworthy that this decrease is observed not only in teenagers, but also in children of more early age, however in children of 1-6 years old concentration of K in hair exceeds that of Na [28] with the inversion happening in the age of 7 years.

Chemical element	Girls (n = 2212), mg/kg (M ± m)	Boys (n = 1676), mg/kg (M ± m)	Significance of difference
Al	21.5 ± 0.36	21.95 ± 0.39	Not significant
As	0.293 ± 0.024	0.292 ± 0.01	Not significant
Be	0.008 ± 0.001	0.008 ± 0.001	Not significant
Ca	924.1 ± 16.5	521.6 ± 11.1	p<0.001
Cd	0.165 ± 0.008	0.191 ± 0.006	p<0.05
Co	0.166 ± 0.004	0.176 ± 0.007	Not significant
Cr	0.786 ± 0.019	0.861 ± 0.02	p<0.05
Cu	11.81 ± 0.17	11.26 ± 0.34	p<0.05
Fe	21.96 ± 0.43	24.68 ± 0.52	p<0.01
Hg	0.202 ± 0.012	0.283 ± 0.029	p<0.05
K	185.4 ± 8.7	414.2 ± 14.4	p<0.001
Li	0.052 ± 0.002	0.07 ± 0.005	p<0.05
Mg	74.09 ± 1.8	42.57 ± 1.4	p<0.001
Mn	1.132 ± 0.039	0.889 ± 0.023	p<0.01
Na	284 ± 9.5	608.9 ± 21.1	p<0.001
Ni	0.624 ± 0.034	0.461 ± 0.019	p<0.01
P	152.7 ± 0.9	158.9 ± 1.2	p<0.05
Pb	1.162 ± 0.079	2.279 ± 0.096	p<0.01
Se	1.396 ± 0.029	1.375 ± 0.035	Not significant
Si	27.96 ± 0.76	23.86 ± 0.68	p<0.01
Sn	1.079 ± 0.023	1.105 ± 0.028	Not significant
Ti	0.501 ± 0.013	0.569 ± 0.016	p<0.05
V	0.136 ± 0.006	0.152 ± 0.008	Not significant
Zn	189.5 ± 1.2	167.0 ± 1.2	p<0.001

Table 4: Average concentration of some chemical elements in hair of teenagers aged of 10-14 years depending on sex.

Boys are characterized by higher concentration of toxic heavy metals: Cd, Pb, Hg (Figure 8). It is especially distinct for Pb, where the difference is more than two-fold. This phenomenon was repeatedly pointed out earlier for different ages. The reasons of it are considered to be mainly of metabolic nature, because higher concentrations of toxic metals are observed in completely healthy persons living in non-polluted areas such as Caucasian villages [29], and in infants where no sex dependent difference in environmental contacts supposed [28-30]. Probably, the phenomenon may be connected with lower level of Ca, Mg and Zn, known as antagonists of these metals, in boys. However, as young children as adult people have less difference in concentration of these metals in hair between sexes than teenagers. At the same time, absolute values of the Pb, Cd concentrations in young children is higher then those in teenagers while in adults they lower than in teenagers, becoming relatively stable after the age of 15-20 years at the low level. Considering the suggestions of essentiality of Pb for some vital functions and relative essentiality of Pb, Cd, Hg as DNA protectors [30], one may probably explain the increased gap in toxic metal levels between sexes by earlier physiological development of girls as compared with boys. More rapid development can result in earlier change of metabolism from “infant” pattern with high level of Pb, Cd, Hg to the “adult” one with low level of metals in girls while in boys the “infant” pattern keeps longer.

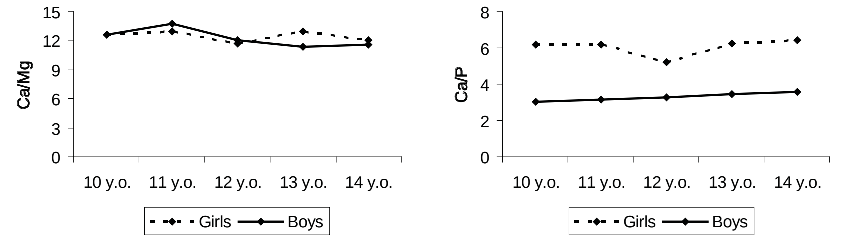

Figure 5: Change of Ca, Mg and P ratio in hair of teenagers depending on sex and age.

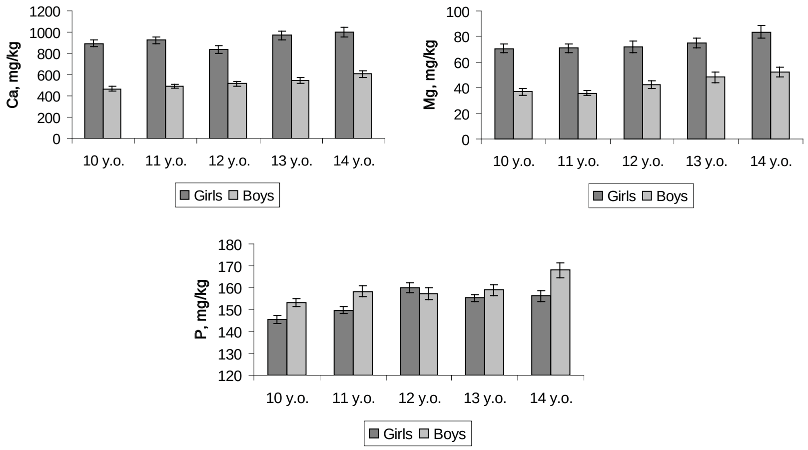

Figure 6: Change of Ca, Mg and P ratio in hair of teenagers depending on sex and age.

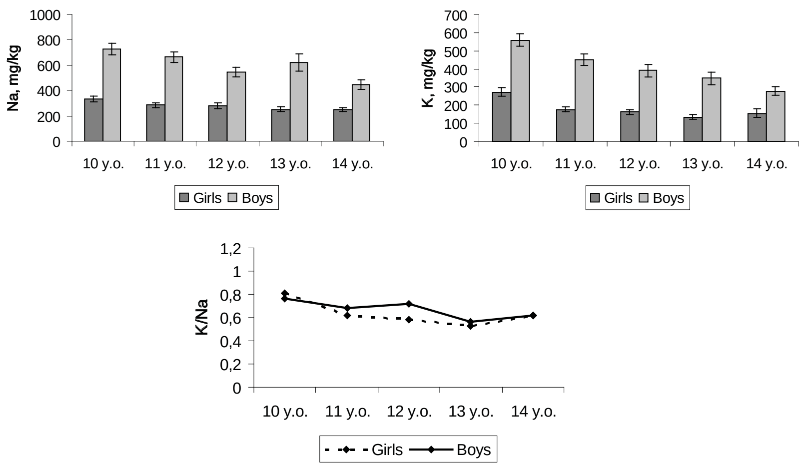

Figure 7: Change of Na, K concentration in hair of teenagers depending on sex and age.

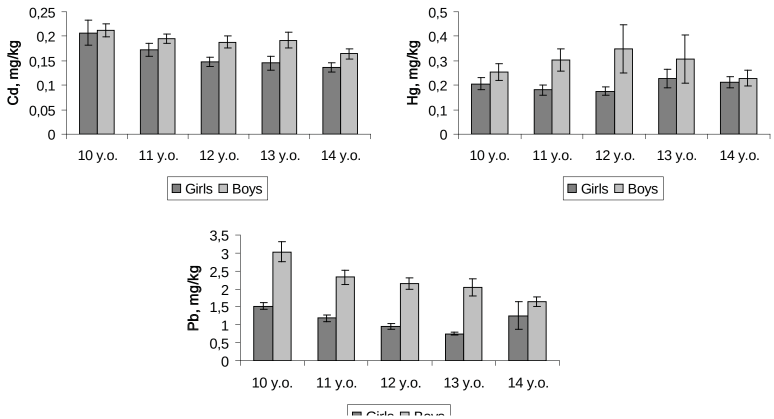

Figure 8: Change of Cd, Pb and Hg concentration in hair of teenagers depending on sex and age.

Higher levels of copper, manganese and zinc are observed in girls through all the investigated age period (Figure 9). The only exception is the age group of 12 years where mean concentration of copper in boys exceeds that of girls, however extremely high dispersion of copper concentration values in this group of boys makes the difference insignificant. Such an increased level of these trace elements can be partly due to biochemical interaction with lead and cadmium, which are known to be antagonists of zinc and copper. Besides this, Zn is intensively used during processes of body growth, especially of skeletal mass increase, and directly participates in male sexual function. These factors can also cause decrease of zinc mobile pool in boys, resulting in low hair concentration of the element. Investigation of infants' hair [28] did not show significantly increased levels of Cu, Mn, Zn in females of 1-6 years old. Thus, increased levels of copper and manganese in females are seems also typical for humans after beginning of sexual maturation [30] and can be connected with direct participation of these elements in metabolism of female sexual hormones.

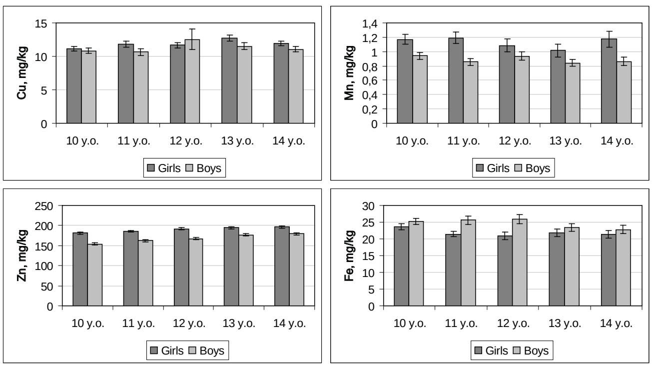

Figure 9: Change of Cu, Zn, Mn and Fe concentration in hair of teenagers depending on sex and age.

Female teenagers are found to have 1.1-1.3 times lower concentration of iron than males (Figure 9). The difference is the most significant in the age of 11-12 years coinciding with typical period of growth spurt in girls before menarche. It happens mostly due to decrease of iron level in girls on the background of practically stable level in boys. It is noticeable that after the age of 12 years the situation inverts: iron level declines in boys being about constant in girls. Considering the fact that age of 13-14 years is a typical period of intensive growth in boys, it can be supposed that iron level dynamics is connected with this processes possibly being due to changes in effective blood volume. In addition, regular menstrual blood loss in females after menarche and generally lower level of hemoglobin as compared to males may determine relatively low hair iron concentration in girls above 13 years of age.

There is no distinct sex dependent differences in level of Al, however there is a tendency to decrease of its hair concentration with age. The same is also true for Be (Figure 10). Neither age nor sex dependent differences found for Co, Se, As, Sn, V.

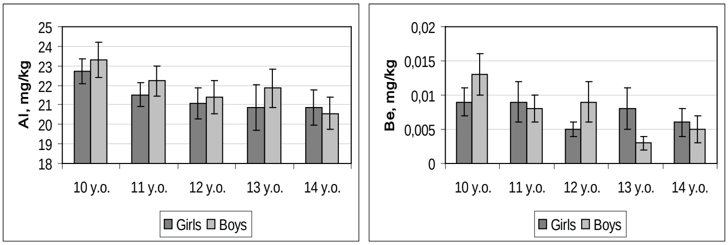

Figure 10: Change of Al, Be concentration in hair of teenagers depending on sex and age.

Comparison of the data about elemental hair content of teenagers living in large cities with those of residents of rural areas of Moscow Region, having no considerable industry or energetic plants and known as unpolluted, did not reveal any systematic differences in elemental status of these categories of people including concentration of toxic metals. Only residents of Novosibirsk have significantly higher level of metal pollutants as lead, cadmium and beryllium with the difference being more distinct in girls ($p < 0.01$). High concentration of Pb in hair is also observed in male residents of Tula; however it is not characteristic of female inhabitants. Among essential elements lower level of zinc in females is observed in all the investigated cities except Moscow. Notice may be also taken of difference in concentration of calcium, which differs from control in both boys and girls of virtually all cities, being usually lower than control. However, on the contrary, girls of Tula and Novosibirsk have significantly higher Ca concentration as compared with the Moscow region.

Generally, number of elements, which level significantly differs from control, increases with distance from the Moscow region. It allows supposing that biogeochemical and nutritional peculiarities have much more influence on elemental status of teenagers than technogenous load do. As it may be seen in Tables 5-6, boys are characterized by higher number of differences than girls. Besides other factors, it may be due to lower biochemical and physiological constancy, characteristic for mail organism in comparison to the female one.

Combination of multielement and laser correlation assays

Laboratory diagnostics allow not only obtaining specific results for each individual, but also combining basically different methods for more precise evaluation of the functional state of various body systems. This approach implies evaluation of combination and reciprocal influence of various parameters, their relationships with clinical symptoms and correlations with other indexes, rather than simple accumulation of laboratory data.

We present data obtained during combined use of standard trace element assay protocol in individuals with different content of some chemical elements (Hg, As, Mn, etc.) and laser correlation spectroscopy of blood serum, urine and OPWF. We analyzed biological samples obtained from 18 individuals conceivably exposed to toxicants: Hg and As.

Element	Concentration, mg/kg (M ± m)					
	Moscow Region (control) n = 43	Moscow City n = 913	St.Petersburg n = 57	Tula n = 59	Novosibirsk n = 304	Irkutsk n = 38
Al	21.79 ± 2.28	22.42 ± 0.61	20.08 ± 1.9	20.21 ± 2.42	22.35 ± 0.81	19.62 ± 1.62
As	0.251 ± 0.049	0.333 ± 0.056	0.341 ± 0.053	0.32 ± 0.041	0.303 ± 0.019	0.191 ± 0.039
Be	0.005 ± 0.003	0.007 ± 0.001	0.002 ± 0.001	0.002 ± 0.001	**0.012 ± 0.003****	0.012 ± 0.007
Ca	700.2 ± 57.7	811.9 ± 21.4	**466.8 ± 41.8*****	**1116.9 ± 104.2*****	**1303.2 ± 51.4*****	**543.9 ± 60.4***
Cd	0.122 ± 0.019	0.134 ± 0.007	0.114 ± 0.019	0.169 ± 0.019	**0.289 ± 0.042*****	0.12 ± 0.02
Co	0.219 ± 0.031	0.158 ± 0.005	**0.126 ± 0.016***	0.154 ± 0.027	0.218 ± 0.012	0.176 ± 0.027
Cr	0.711 ± 0.074	0.82 ± 0.039	0.735 ± 0.064	0.719 ± 0.055	0.811 ± 0.027	0.806 ± 0.085
Cu	10.47 ± 0.58	**12.86 ± 0.31*****	11.86 ± 0.97	**12.31 ± 0.73***	11.21 ± 0.5	8.43 ± 0.53
Fe	26.35 ± 4.37	19.26 ± 0.65	28.39 ± 3.18	29.52 ± 3.67	22.97 ± 0.89	25.29 ± 4.86
K	221.5 ± 51.6	180.3 ± 14.6	168.6 ± 37.7	313.5 ± 84.2	181.7 ± 27.5	144.7 ± 44.8
Li	0.076 ± 0.016	0.055 ± 0.004	**0.025 ± 0.004*****	0.056 ± 0.008	0.05 ± 0.004	0.044 ± 0.011
Mg	77.54 ± 10.08	71.39 ± 3.04	**47.48 ± 7.68****	82.93 ± 15.82	76.08 ± 3.16	**40.59 ± 7.73****
Mn	0.784 ± 0.114	0.703 ± 0.025	0.904 ± 0.099	1.231 ± 0.178	**1.596 ± 0.115*****	0.816 ± 0.133
Na	473 ± 143.7	271.2 ± 13.9	240.8 ± 41.6	491.1 ± 119.8	251.7 ± 28.8	239.5 ± 77.4
Ni	0.436 ± 0.068	0.497 ± 0.035	0.501 ± 0.11	1.221 ± 0.543	**0.599 ± 0.05***	0.341 ± 0.06
P	151.2 ± 4	155.2 ± 1.3	152.4 ± 5	158.3 ± 4.2	**139.4 ± 2.4***	147.9 ± 4.8
Pb	1.04 ± 0.192	0.825 ± 0.042	0.898 ± 0.147	1.474 ± 0.322	**1.707 ± 0.123****	1.224 ± 0.311
Se	1.532 ± 0.27	1.384 ± 0.034	1.368 ± 0.17	1.112 ± 0.112	1.548 ± 0.084	1.148 ± 0.154
Si	23.44 ± 3.99	26.61 ± 1.12	35.16 ± 5.61	19.96 ± 3.24	29.64 ± 1.9	22.88 ± 4.31
Sn	1.307 ± 0.337	1.066 ± 0.033	1.113 ± 0.151	1.035 ± 0.126	1.237 ± 0.065	0.96 ± 0.128
Ti	0.438 ± 0.058	0.468 ± 0.019	0.55 ± 0.098	0.406 ± 0.054	0.518 ± 0.031	0.427 ± 0.066
V	0.123 ± 0.022	0.129 ± 0.005	0.131 ± 0.016	0.135 ± 0.017	0.127 ± 0.008	0.111 ± 0.021
Zn	190.4 ± 8.1	199.1 ± 2	**174.3 ± 5.8****	**176.4 ± 6.6***	**176.6 ± 3.2***	**153.8 ± 9.9*****

Note: Bold font indicates significant difference with control: *–p<0.05; **–p<0.01; ***–p<0.001

Table 5: Concentration of some chemical elements in hair of girls of 10-14 years old living in large cities in comparison with rural control area, (M ± m).

Examination of biomaterials obtained from individuals exposed to mercury and arsenic showed that the incidence of some shifts significantly correlated with the content of these elements.

Biological samples for the analysis of trace elements were obtained twice with a 3-day interval; samples for LCS were taken once (during the second examination).

ICP-MS measurements showed that the percent of individuals with normal mercury content considerably increased by the second measurement, which attests to toxicant elimination from the body. Similar tendency was observed during the analysis of arsenic content in the urine (Figure 11).

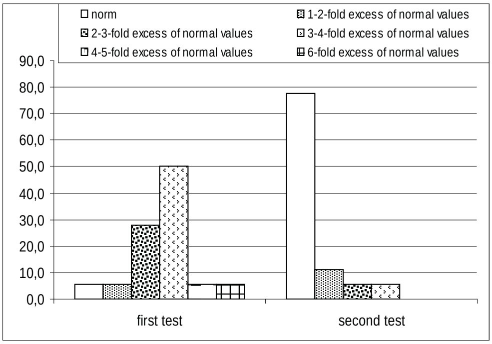

Figure 11: Percent of individuals with normal and enhanced arsenic content.

The LCS analysis of serum revealed predominance of spectra, where small particles make the major contribution into light scatter. Intoxication-like and catabolic shifts prevailed, while dystrophic shifts were infrequent, which was a result of predominance of hydrolysis and catabolism.

LC-histograms of the urine and oropharyngeal washout fluids reflect the processes of epithelium destruction. In this sample, primarily normological and anabolic shifts were observed in the gastrointestinal system and upper airways, whereas in the excretory system normological, catabolic, and anabolic shifts were detected. Although we cannot prove the fact of intoxication or determine its degree, we revealed significant correlations between the results of LCS study and standard toxicological examination (Figure12).

Element	Concentration. mg/kg (M ± m)					
	Moscow Region (control) n = 40	Moscow City n = 708	St.Petersburg n = 36	Tula n = 40	Novosibirsk n = 251	Irkutsk n = 42
Al	32.81 ± 4.27	**21.47 ± 0.55***	24.52 ± 2.72	23.94 ± 3.55	23.9 ± 1.05	23.02 ± 2.61
As	0.383 ± 0.111	0.299 ± 0.016	0.507 ± 0.099	0.314 ± 0.05	0.324 ± 0.023	**0.172 ± 0.052***
Be	0.007 ± 0.004	0.009 ± 0.002	0.002 ± 0.001	0.016 ± 0.02	**0.009 ± 0.002***	0.003 ± 0.002
Ca	728.3 ± 88.2	**524.9 ± 19.3***	**326.6 ± 36.4*****	719.4 ± 128.7	**464.9 ± 16.7***	**418.1 ± 35****
Cd	0.261 ± 0.044	0.164 ± 0.008	0.136 ± 0.024	0.244 ± 0.044	0.259 ± 0.018	**0.131 ± 0.021***
Co	0.225 ± 0.033	0.174 ± 0.015	0.106 ± 0.016	0.133 ± 0.025	0.205 ± 0.012	0.214 ± 0.026
Cr	1.35 ± 0.238	**0.781 ± 0.021***	0.815 ± 0.102	0.906 ± 0.106	0.918 ± 0.044	1.204 ± 0.131
Cu	10.8 ± 0.87	12.99 ± 0.77	10.34 ± 1.1	10.17 ± 0.54	9.72 ± 0.23	**8.42 ± 0.4****
Fe	45.53 ± 7.47	**20.97 ± 0.66***	25.52 ± 2.09	25.76 ± 2.68	24.25 ± 1.08*	29.69 ± 5.06
K	746.5 ± 140.6	379.6 ± 21	343.2 ± 82.9	567.2 ± 103.4	501.1 ± 39.6	441.3 ± 92.1
Li	0.084 ± 0.013	0.057 ± 0.004	**0.04 ± 0.007****	0.083 ± 0.013	0.057 ± 0.004	0.047 ± 0.01*
Mg	59.67 ± 8.11	44.86 ± 2.54	**24.1 ± 2.63*****	55.18 ± 14.83	27.8 ± 1.24***	29.53 ± 3.66**
Mn	1.542 ± 0.283	**0.704 ± 0.027***	**0.645 ± 0.104***	1.16 ± 0.191	0.902 ± 0.047	0.932 ± 0.164
Na	1227.9 ± 266.7	**535.7 ± 26.4***	771.2 ± 216.8	1001.7 ± 334.5	**647.9 ± 45***	**596.9 ± 128.3****
Ni	1.004 ± 0.307	0.431 ± 0.035	0.36 ± 0.068	0.556 ± 0.122	**0.353 ± 0.028***	**0.371 ± 0.06***
P	194.4 ± 16.7	159.4 ± 1.8	154.4 ± 5.7	184.3 ± 12.4	**147.4 ± 1.7***	**146.1 ± 3.8***
Pb	2.193 ± 0.343	1.625 ± 0.116	1.736 ± 0.241	**4.38 ± 1.396***	**2.851 ± 0.252***	3.305 ± 0.959
Se	1.494 ± 0.333	1.468 ± 0.061	1.258 ± 0.19	1.163 ± 0.128	**1.471 ± 0.081*****	1.189 ± 0.173
Si	30.2 ± 3.93	24.59 ± 1.2	21.25 ± 3.66	22.04 ± 3.77	22.9 ± 1.6	**18.4 ± 2.05***
Sn	1.309 ± 0.17	1.113 ± 0.05	0.916 ± 0.12	0.975 ± 0.108	1.151 ± 0.051	0.959 ± 0.152
Ti	0.84 ± 0.135	0.544 ± 0.025	0.781 ± 0.132	**0.404 ± 0.054***	0.553 ± 0.028	0.712 ± 0.161
V	0.177 ± 0.029	0.146 ± 0.007	0.142 ± 0.036	0.161 ± 0.053	0.137 ± 0.008	0.144 ± 0.032
Zn	154.7 ± 8.3	172.2 ± 2	157.6 ± 7.9	153.1 ± 9.4	152.4 ± 3.2	152 ± 11.1

Note: Bold font indicates significant difference with control: *-p<0.05; **-p<0.01; ***-p<0.001;

Table 6: Concentration of some chemical elements in hair of boys of 10-14 years old living in large cities in comparison with rural control area, (M ± m).

Analysis also revealed a negative correlation between the shifts in OPWF and arsenic concentration in the urine: the higher was the urinary concentration of metals, the greater was the contribution of small particles into light scatter.

The lower was the arsenic concentration in urine, the higher was the contribution of large particles into light scattering in OPWF ($r=-0.75$, $p<0.05$). We revealed two tendencies related to mercury concentration: in the urine ($r=0.06$, $p<0.05$) and in hair samples ($r=0.074$, $p<0.05$), which indicated that in samples with low metal concentrations the contribution of large particles into light scattering was higher.

Significant correlations between shifts in the blood serum and metal concentration in the urine were found for samples taken during the second examination: mercury ($r=0.50$, $p<0.05$) and arsenic ($r=0.82$, $p<0.05$)

Analysis of the relationship between metal concentration and the contribution of certain particles into light scattering revealed a correlation between the presence of arsenic in urine and accumulation of the first-zone particles (0-10 nm) ($r=0.53$, $p<0.05$) in blood serum. An increase in arsenic content in the urine correlated with an increase in the contribution of second-zone particles (51-400nm) ($r=0.76$, $p<0.05$) and a decrease in the contribution of the third-zone particles (401-2000nm) ($r=-0.79$, $p<0.05$) in OPWF samples; the increase in arsenic content in hair samples correlated ($r=0,58$, $p<0,05$) with an increase in the contribution of first-zone particles (0-50nm).

Thus, LCS analysis of biological fluids from individuals with elevated metal content revealed increased contribution of small particles into light scatter.

All these changes in the content of toxic elements did not exceed the biologically permissible levels and should not induce pathology development. It is known that elevated content of toxic elements by itself does not indicate the development of pathology. Moreover, individual peculiarities of sanogenetic systems of the organism determine various consequences for health in individuals exposed to equal low doses of potentially harmful factors [30]. Nevertheless, their correlation with the contributions of particles of a certain size in biological fluids to light scatter suggests that changes in trace element composition are related to metabolic shifts.

It is known that mercury in low concentrations activates Lipid Peroxidation (LPO) and initially increases, but then decreases activity of antioxidant enzymes. In this case, accumulation of LPO products (malonic dialdehyde and β-microglobulin, protein in the urine) can be expected. Indeed, positive correlations were revealed between the content of toxic elements and relative content of small particles in the examined fluids. Moreover, the contribution of the fraction containing immunoglobulins into light scatter in the serum tended to decrease with increasing arsenic concentration in the urine. Previous studies showed that the intensity of light scatter by this fraction correlates with immunoglobulin content determined by routine laboratory methods.

The maximum number of correlations was found for shifts in the urine and oropharyngeal fluid. This is most likely related to initial stages of renal dysfunction and presumably peroral intoxication route.

The observed changes in the direction of metabolic shifts are stochastic and reflect either adaptive or disadaptive responses of the organism to low doses of toxic compounds. More numerous sample and broader range of effective concentrations are required for deciphering of the real significance of the detected relationships [31].

Metabolic deviations, measured by LCS, are due to different external influences including effects of such typical ecopollutants as mercury and arsenic. Thus we can suppose the LCS can be an integrative method, useful for experimental and clinical bioelementological research, what was demonstrated in the experimental study described below.

Laser correlation spectroscopy was applied for the analysis of oropharyngeal washout fluid samples from children and adolescents living in Novgorod region, Adygei (ecologically clean regions), St.Petersburg, and Moscow (ecologically unfavorable regions). Blood samples were obtained only from examinees living in megalopolises.

None “normal” spectra were recorded in oropharyngeal washout fluids from St. Petersburg and Moscow, while the percent of “normal” spectra in other regions was similar (about 30%). Catabolic processes predominated in St.Petersburg resident (63%), in Moscow and Adydei they were less prevalent (about 40%), and the lowest incidence was observed in Novgorod region (16%). Anabolic shifts predominated in ecologically clean regions (on average 36%) and were less prevalent (30%) in St.Petersburg, while the lowest incidence was found in Moscow (9%). Mixed shifts were observed only in megalopolises (on average 8%) (Figure 13).

In serum samples, normal spectra constituted 4% in Moscow and were absent in St. Petersburg. In Moscow, no significant differences between the metabolic shifts were seen, but a trend to increasing incidence from mixed to catabolic and then to anabolic shifts were revealed (26, 30, and 40%, respectively). The highest percentage of catabolic shifts was observed in St.Petersburg (80%), the percent of anabolic shifts was considerably lower than in Moscow (by 22%), while the percent of mixed shifts did not differ from that in Moscow residents (16%) (Figure 14).

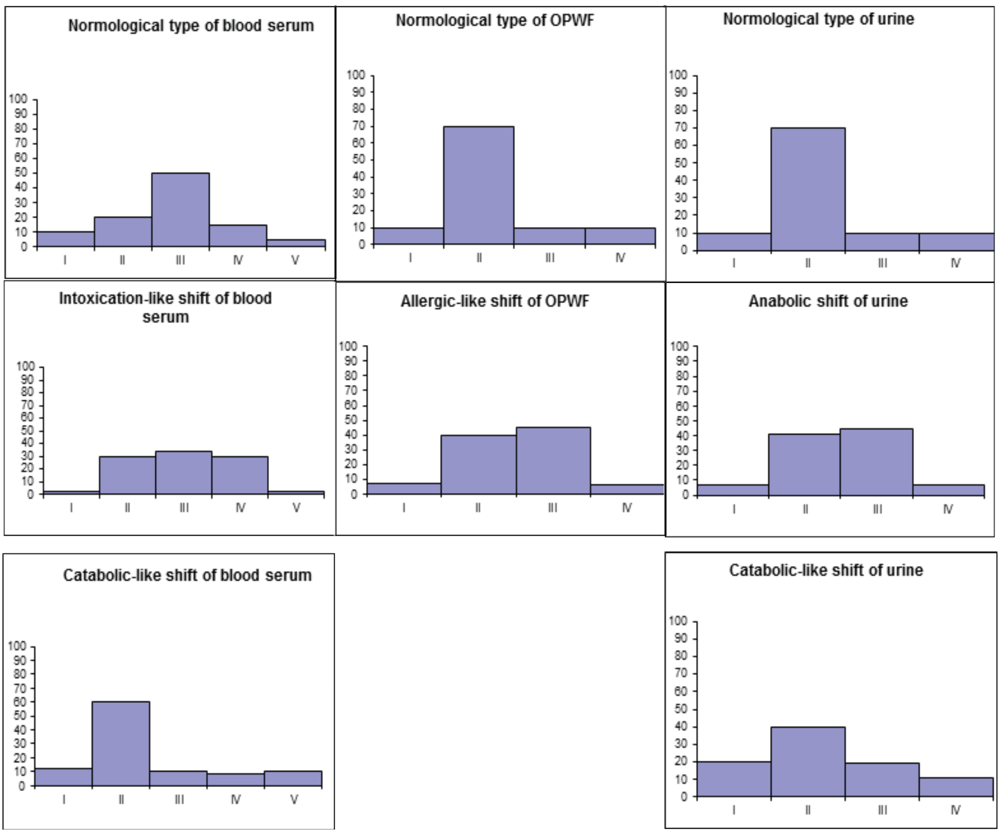

Figure 12: Histograms of size distribution of particles in different biological fluids corresponding to different types of metabolic processes. Abscissa - informative zones of the spectrum, ordinate – contribution of particles of the corresponding zone into light scattering (%).

Thus, anabolic shifts and normal spectra were more often observed in Novgorod region, while in Adygei all shifts were equally presented. Considerably increased percentage of catabolic shifts was found in St.Petersburg, while in Moscow, the incidence of these shifts tended to increase in comparison with Adygei and especially with Novgorod region. The lowest incidence of anabolic shifts was found in Moscow; mixed shifts were detected only in St. Petersburg and Moscow. In St. Petersburg, catabolic shifts predominated in both serum and oropharyngeal fluid samples, while "normal" was absent.

Analysis of these results led us to a conclusion, that Novgorod region is the most favorable region and Adygei (Dzherakay) ranks second. The megalopolises are least favorable; the situation in St. Petersburg is even worse than in Moscow.

Discussion

The evaluated trace elements concentrations in some economically depressed regions of Russia were found to be in high correlation with the environmental situation and, in particular link, with excessive or deficient entering of trace elements from drinking water and foodstuff. As, Pb, Cd, Zn, Mn and Cu contents were found to be in high positive correlation with concentration of these elements in soil, drinking water and hair samples, obtained from inhabitants of those contaminated zones. Children and pregnant women were found to represent a group of people, most susceptible to trace element alterations.

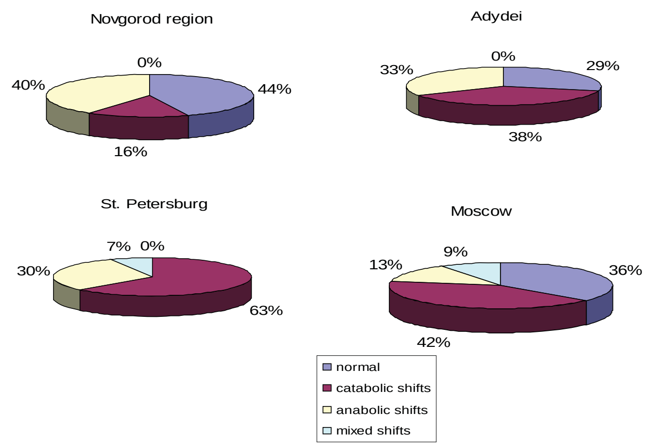

Figure 13: Metabolic shifts in oropharyngeal fluids from individuals living in different regions.

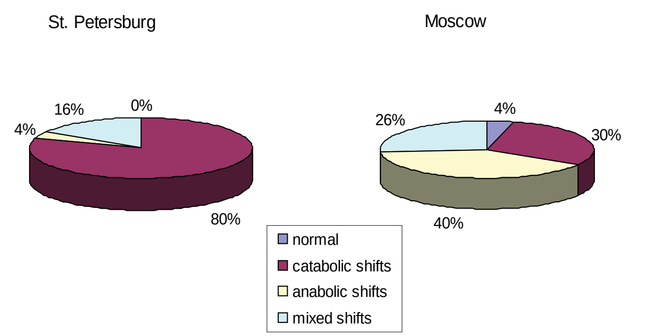

Figure 14: Metabolic shifts in serum samples from individuals living in different regions.

The chronic deficiency of the essential trace elements in organism is certainly evidenced in a pathology, accompanied by considerable metabolic disturbances and distinct clinical and morphological changes. Possible pathogenetic ways of hypomicroelementose development can be illustrated as a scheme (Figure 15). The chronic trace elements deficiency can cause two separate types of changes: different metabolic disturbances on the one hand, and distinct immune disturbances, accompanied by decrease of general immune resistance, on the other hand. Both processes result in endocrinopathies, inflammations and neoplastic diseases.

The immune system is the main target for the influence of trace elements imbalance and various ecological pathogens (xenobiotics, allergens, etc.).

Thus, in present-day conditions the decrease of organism resistance to infective and non-infective factors is probably related to rapid reduction of phylogenetic elements-based mechanisms of the resistance, in conjunction with slow formation of new mechanisms. Even non-specific increase of general intake of major and trace elements into the human organism, especially in the regions with low life standards, characterized by relatively low elemental hair content, is capable to significantly increase the population health.

According to Abdulla and coworkers [33], the one approach in identifying and treating marginal deficiencies of trace elements lies in therapeutic trials, what is supporting by the own studies [30,32]. Our opinion is that the multielement hair analysis is an adequate screening test for the hygienic diagnostics of trace elements related diseases and population providing with major and trace elements, and this test is available for routine use for detection of trace element deficiencies at an early stage, the strategies for supplementation programs and fortification of staple foods with the trace elements in question ought to be recommended for risk groups (children, fertile women) in TWC and Russia.

The approach designed in present study to monitor population disturbances of trace elements by means of hair analysis may be a probabilistic model for TWC due to the following reasons:

• Simplicity and non-invasiveness of study (observations);

• Comparatively low-cost study (4-5 US $ per individual);

• Multipurpose application in medical, nutritional and environmental practice, socio-economical management;

The complex of studies required to assess the population malnutrition problems is represented in Figure 16. As it shows, the measurement of trace elements level in hair provides a scientifically and economically advantageous tool for environmental assessment followed by correction of trace element homeostasis and malnutrition by means of wide administration of the relatively low-cost trace element supplements.

In order to optimize the trace elements balance, three-stage arrangements complex can be recommended (Figure 17).

Conclusion

1. Trace elements measurements in soil, drinking water and hair samples, obtained from territory of the former USSR demonstrate the high correlation between the environmental contamination (or natural presence) and elemental disorders found in hair samples of individuals;

2. Children and pregnant women represent a most indicative group found to be highly susceptible to environmental trace element disorders – more than other groups of population;

3. A model of trace element monitoring by means of measurements in hair samples is suggested for systemic medical prophylaxis in combination with non-specific diagnostic methods like laser correlation spectroscopy;

4. The correction of trace elements imbalances (microelementoses) revealed by multielement hair analysis can significantly decreases the risk of trace element related diseases.

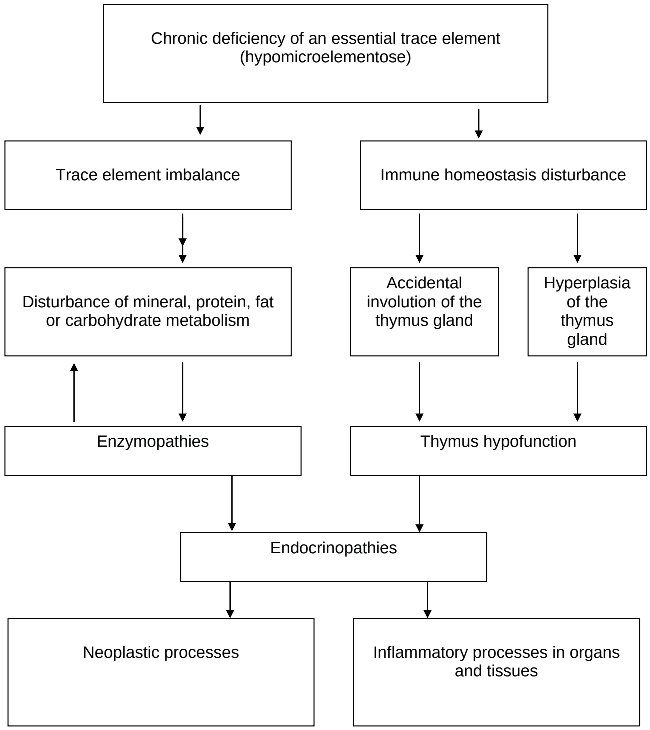

Figure 15: Main pathogenetical ways of hypomicroelementose development.

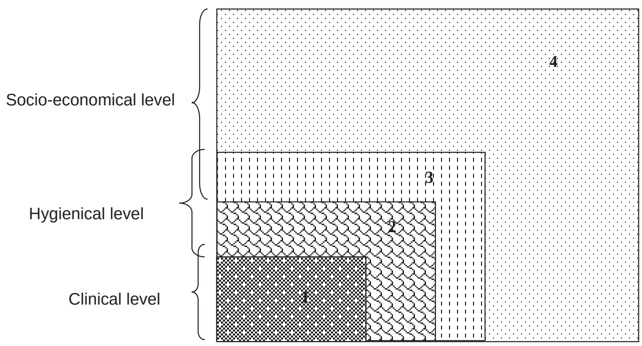

Figure 16: A probabilistic model of human trace element states monitoring. 1 – Profound biochemical and clinical investigations of trace element status by means of laboratory analyses: determination of major and trace elements content in whole blood, blood serum and urine (clinical diagnostics, 0.001-0.01% of population); 2 – Hygienical (prenosological) diagnostics and quantitative determination of the elemental status (instrumental multielemental hair analyses (0.01-0.1% of population) with risk groups formation); 3 – Non-instrumental (calculation method) estimation of population providing with major and trace elements (surveys, questionnaires, biomathemathical modeling; up to 0.5–1% of population); determination of risk contingents; sanitary and prophylactic measures within large territories; 4 – Correction and mass prophylaxis of microelement related diseases within regions (with respect to regional peculiarities of population elemental status) – supplementation, feeding.

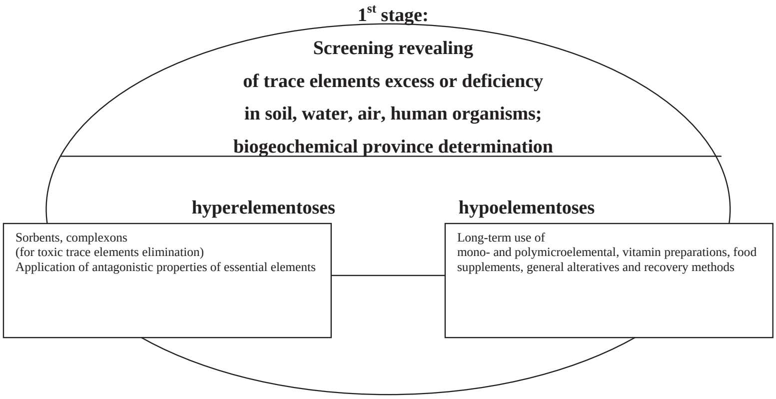

Figure 17: Arrangements for reduction of the trace elementoses occurrence.

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Chapter: IX

Multielement Analysis of Indigenous Peoples, Living in Russian North

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Abstract

Based on reference and our obtained data, the analysis of the element status (hair, blood) taken from aborigines of the North was carried out. It was found that ecological and genetic factors influence the mineral metabolism in the northern populations.

Keywords: Adaptive Processes; Native Scanity Peoples; North; Trace Elements

Introduction

As shown by many anthropologists, the phenotypes adapted to certain climatic-geographical factors can be observed among a human population. Formation of the North-related adaptive phenotype takes long time exceeding individual's life and lasts for several generations. It is considered that morphofunctional characteristics of the North aborigines have been adequate to the natural conditions. However, most climatic and geochemical factors of the northern regions are unfavourable for the health of humans who has known appeared on the planet in favourable climate areas.

It was found that the state of human mineral metabolism is determined, on the one hand, by biogeochemical environment, thus reflecting the integral impact of natural-ecological and social factors. On the other hand, mineral metabolism peculiarities (assimilation of macro- and trace elements and their involvement in biochemical reactions) can be genetically determined.

In this regard it is of scientific and practical interest to study microelement physiological systems in aborigines of the North – the most ancient ethnic population of Russia [1].

In the Russian Federation there are 40 aboriginal populations – native scanty peoples of the North, Siberia and the Far East [2]. These populations are genetically adapted to the regions' environmental factors, and this determines the natives' specific health state: delayed formation of basic systems of the body (endocrine, immune), fastened exhaustion of physiological functions at mature and old age, shortening of reproductive period, early ageing, relatively short average life length [3].

Currently the medico-social state of aboriginal populations has been one of the urgent problems in Russia's north. Due to the progressing morbidity level and high assimilation with non-aborigines the threatening demography situation has formed: the fact is the North native peoples are degenerating [4-6].

In order to overcome the depopulation of the aborigines it is necessary to account the reasons of the health disorders and, first of all, to get know the initial health state parameters of the North natives (morphological, biochemical, functional etc.) which had been formed for many centuries [7].

The significant factors that cause health problems in the North aborigines are environmental pollution, misbalance in nutrition structure and quality, and lack of vitamins and trace elements.

Very few studies have been carried as regards mineral metabolism of the North aborigines and, besides, the studies are fragmental and mainly cover Russia's Siberia and Northeast [8-25].

Having made the analysis and classification of the aboriginal element status as compared to those of newcomers, we'll be able to answer the following questions:

1. Are there any specific characters in trace element profiles of the certain ethnic groups?

2. Is there any differentiation of the element status between ethnic groups residing within the same biogeochemical area?

3. Are there common features of the element status in the North aborigines residing in different biogeochemical areas?

The answers to these questions will allow determining the priority of environmental or genetic factors in providing mineral metabolism in the North aborigines.

The studies of the North natives' element status will give the key to diagnosing and correcting the disorders in mineral metabolism and serve as a methodological tool in solving fundamental issues of medical ecology and north-related anthropology.

Problems of Terminology: Methodical Notes

The population of the North residents is heterogeneous in social-demographic aspect and is differently adapted to the North conditions. The habitants of the North are native scanty peoples, north born people and newcomers who differ from each other depending upon the length of residing in the North.

As regards the names of the northern populations mentioned in mass media, scientific papers etc. there is confusion between "aboriginal", "native" and "indigenous" [26].

In medico-biological studies the terms "aboriginal" and "indigenous" are not equal at all despite in scientific papers there is a sign of equality between them. Pursuing from this "aborigines" (from Latin "ab origine" from beginning) is considered to be scanty ethnic populations having resided in the certain territory for many centuries [22].

Those people who were born in the North from newcomers (who came to the North from regions with more favourable natural conditions) can be named neither "natives" nor "indigenous" so they actually have no proper name.

In fact beginning from the 1960s the aboriginal population has been strongly assimilated with either other ethnic groups or with newcomers. After some authors now there are up to 80-90% of the aborigines whose fathers (more seldom mothers) can be referred to neither "natives" nor "indigenous" [1,27]. In the meantime in the process of evolution the northern populations have had some mineral metabolism characteristics that are good for the population. In mixed marriages the certain adaptation signs can be inherited and fixed in metis people.

So the metis people who reside in national districts can be keepers of genetic information of the ancient ethnos. That's why they should be the object of the study equal to ethnically pure representatives of the North populations.

The accuracy of the data resulting from the aboriginal element status study can be reached if the following terms are faced: common methodical (laboratory) approach, analysis of aboriginal residents including metis people compared to newcomers accounting for their length of residing in the North, as well as the historic time of the north ethnos residing in the certain territory.

The analysis of the element status observed in the hair and blood samples taken from the Russia's north aboriginals was carried based on our own and reference data.

Results and Discussion

Khanty–Mansi Autonomous District (KMAD)

The only deficient element observed in the aborigines (Khanty) was Iodine (I) Besides, low values of iodine shown by Khanty children were more pronounced compared to those of nonindigenous residents, 50% of them demonstrated such values [18,19,21].

96% of the examined aborigines demonstrated 4 times elevated Hg values that correlated to the high Hg contents revealed in fish [19]. The concentration of Hg in hair of the aboriginal residents can be explained by the traditional eating fish which accumulates methylmercury in its muscles.

Besides that, the aborigines demonstrated the excess in Pb, Cd and Fe. Apparently, Khanty people are more sensitive to human-caused heavy metal and toxic element exposures as compared to the newcomers.

Thus, the aborigine residents of KMAD demonstrate Fe, Hg, Pb, and Cd accumulation in their hair vs the reference values what is explained with those elements high levels in drinking water and fish. If heavy metal contents in hair can be the index of excretion so it should indicate adaptation directed to removing the element toxic doses excess. In case the element contents in the hair correlates to the element level in the body (blood), the processes of dysadaptation in mineral metabolism are obvious typical for the aborigines of KMAD.

Yamalo-Nenets Autonomous District (YNAD)

As it turned out no Pb and Cd accumulation was revealed in the aborigines of YNAD (Nenets, Khanty, and Zyrian peoples). Moreover, these elements in the hair proved to be lowered as compared to the newcomers [13,25].

The common characteristic of the element status observed in the aborigines of KMAD and YNAD is the elevated Fe and Mn in the hair samples. It is a rather known peculiarity of the trace element profile typical for the residents who use drinking water rich in iron and manganese salts.

At the same time accounting for the lowered water hardness, nonindigenous people of KMAD demonstrated higher Mg levels in hair samples while the aborigines of YNAD showed excess in Ca. The misbalance of Ca/Mg observed in northern residents (the region of Tyumen) is apparently an ethnic characteristic of the mineral metabolism.

In spite of biogeochemical equality of the territories of KMAD and YNAD (zonal biogeochemistry of North Taiga and Forest Tundra) the element profiles of the residents in those areas differ from each other.

It can be clearly seen in heavy metal pollution (Hg, Pb and Cd). In particular, Hg accumulation was revealed only in KMAD residents.

The data on Pb and Cd levels are also principally different. The aborigines of KMAD showed higher Pb and Cd values vs. the reference values. In the aborigines of YNAD those values proved to be lower comparing with the newcomers.

Accounting for the unified analytical base of the element analysis as well as the common time period of the carried studies, it should be established that the profiles of Pb and Cd contents testify to heavy metal pollution occurring in the territory of KMAD.

Taimyr Autonomous District

In blood erythrocyte samples taken from the healthy people of Taimyr (Dolgan and Nganasan peoples) the reliably higher toxic Pb and lower essential Cu were revealed compared to the newcomers [8,9]. The concentration of Zn in blood plasma was lower in aborigines than in the newcomers while copper and nickel concentration was higher. The higher blood plasma copper as well as the higher erythrocyte lead correlate to high contents of these elements in the environment (moss, mushrooms). Based on this fact the author associates the revealed blood element disorders with the human-caused environmental impact.

However, in literature there can be found the information about high contents of Cu, Zn, Se, Pb, Cd and Hg in blood samples of Inuits in the Greenland [28]. It is worthy of note that the blood lead concentration demonstrated by Taimyr aborigines, was much higher than the similar parameter shown by Inuits what is really can be explained by human-caused impacts. Anyway the metal misbalance observed in the North aborigines can induce metabolism disorders and further initiate pathology.

Chukotka Autonomous District

The element status of Chukotka aborigines (Chukchi, Eskimo peoples) is characterized by lower contents of a series of elements - Co, Cu, Cr, Mg, Zn, Ca, I and Se [15,24].

The special feature of the element profile typical for the indigene girls of Anadyr town was sufficient Fe supply: 62% of the girls demonstrated even higher Fe levels in hair samples vs. the basic, while in newcomer children it is mostly in deficit [24].

Of note were lower contents of Si. The lowered silicon concentration vs. the reference values was observed in most (69%) Chukchi and Eskimo subjects. Earlier publications considered Magadan region as a silicon province [29] where 100 % of the residents demonstrated statistically elevated hair Si vs. the reference values. The lower hair Si observed in Chukotka residents compared to Magadan region ones, can be explained by low Si levels in Tundra ecosystems.

The blood samples of Chukchi reindeer breeders (Tundra area) proved to have low Fe and Zn levels but contained Hg and Pb [16,10].

The coastal area aborigines showed elevated blood K, Cu and Se compared to the tundra ones [17,11]. This apparently can be associated with the prevailing sea food rich in those elements.

Of note is that the Tundra aboriginal residents, regardless of the geography of inhabiting (Chukotka, Yamal) and ecological conditions, demonstrate the similar blood element composition. In particular, Chukotka residents (Chukchi reindeer breeders; ecologically clean region) and Yamal residents (Dolgans, Nganasans; technogenic province) proved to have higher Pb and lower Zn in blood samples. As the researchers noted the toxic doses of lead and mercury can induce the decreasing in Zn and the further disorders in immune system what is the very characteristic of the North residents [3].

While the elevated lead in Yamal residents is explained by human-caused effects, such "elevated" lead in Chukotka reindeer breeders cannot be induced by local technogenous pollution. The explanation of the phenomenon can be in the fact that lead is accumulated in reindeer moss. It is known the Arctic is an accumulator of heavy metals which are "produced" either in Polar Regions or in moderate latitudes of the Northern hemisphere [6]. The metals including lead and mercury can get into the bodies of Chukotka reindeer breeders through the nutrition chains "moss-reindeer-man", and "fish-man". The supposition is confirmed by high mercury and lead contents in fish from the examined region [17]. But yet, the ways of heavy metal transition to the bodies of the aborigines are still unclear. After Dudarev AA [6] the contents of mercury and lead in the traditional food products (fish, venison) of Chukotka's aborigines are very low.

Severo-Evensky District of the Magadan Region

The data on Severo-Evensky District are similar to those on Chukotka what is caused by biogeochemical equality of Severo-Evensky District (forest tundra) and Chukotka (tundra, forest tundra).

In the hair samples of Severo-Evensky District aborigines (Evens, Koryaks), as it was in Chukotka's aborigines, the lower Co, Cu, Mg, Zn, Cr, Se and I contents were observed [24]. The fundamental difference from Chukchee and Eskimos is the Koryaks' and Evens' increased Si level being close to that of Magadan region residents.

In some groups of the Evens, Koryaks, and metis people residing in the Magadan town there can be observed the increased Pb, Cd and Al vs. the newcomers [20]. The accumulation of the toxic metals can be a response of the aboriginal body to polluted environment of Magadan.

Besides, the aborigines of Severo-Evensky District who reside in the Magadan town demonstrate a decrease in Ca and Mg with the latter being more pronounced. Such Ca, Mg status is typical for Magadan residents. This testifies to the elemental changes occurred in the aborigines in the new ecological environment.

Practically all the examined Evens, Koryaks and metis people residing in Magadan demonstrated the decreased Na and K. This is typical for neither Magadan residents, nor the aborigines of Severo-Evensky District. Apparently, in the process of adaptation to the new ecological environment the elemental changes that concerns the "neutral" macroelements are developing.

Conclusion

The comparative analysis of the element status shown by Russia's north aborigines established that no uniform mineral profile was found in the aborigine hair samples. Moreover the obtained values clash with each other. In particular, in the territory of Tyumen north the aboriginal residents demonstrated contradictory indices of Pb and Cd-high values in KMAD and low ones in YNAD. Such contradiction can be due to some reasons: local technogenic pressure, biogeochemical profiles of the regions, and genetically determined specific mineral metabolism of each ethnos.

Aboriginal residents of the northern territories remote from each other demonstrate contradictory tactics of mineral metabolism: the elevated contents of many elements in KMAD aborigines and low in residents of Chukotka. However the deficit and accumulation can be observed for different elements. This reflects both ethnic specificity of mineral metabolism and peculiarities of zonal biogeochemistry of Chukotka and KMAD.

The Fe status has been specific for the aboriginal populations. Despite the area of residing, no low Fe values were registered in aborigines' hair samples though it has been typical for the newcomers. Some aboriginal groups (Chukchi, Evens) even showed the exceeded Fe values vs. the basic norms [24]. On our opinion, it can be explained by the diet rich in iron (meat of the reindeer and sea animals).

However it should not be excluded that the elevated Fe in the hair samples (excretory organ) can result in formation of its endogen deficit. According to Zhuravskaya E Ya and her colleagues [10], in blood samples of Chukchi subjects the Fe deficit was revealed. And besides, there are data of the common latent Fe deficit states as well as Fe deficit anemia observed in residents of Chukotka [30].

Our analysis has established that the elemental profile of blood - a dynamic biosubstrate is proved to be more stable than hair. The North ethnic populations of different areas (Taimyr, Chukotka and Greenland) showed misbalance in identical group of indicator elements in blood: Cu, Zn and Pb. It is the common feature in the aborigine's elemental status which can testify to the common mechanisms of mineral metabolism.

Thus, the question of the priority role of either ecological or genetic factors influencing the mineral metabolism is still open. We believe that genetic mechanisms "work" in isolated ethnic units - the natural areas of northern peoples' residing. Under conditions of urbanization, aborigines' assimilation, destruction of the national life style (nutrition), and environmental pollution the social-ecological surroundings become the main factor for the mineral metabolism. Peculiarities of mineral profile in indigenous residents of Russian North.

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Chapter: X

Spinal Deformities and Environmental Factors

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Abstract

Here we discuss the correlation of idiopathic scoliosis development with the degree and directionality of metabolic shifts in children. Comparative analysis included the data obtained during examination of children with idiopathic scoliosis and kyphosis and pupils of Moscow general education schools. We studied the relationship between cytogenetic abnormalities in buccal epithelial cells and metabolic shifts in children with scoliosis and kyphosis. The incidence of nucleus abnormalities and the corresponding metabolic shifts were found to depend on the presence of spine deformities and ecological factors. The problem of formation of risk groups for spine deformities in ecologically unfavorable regions is discussed.

Keywords: Buccal Epithelial Cells; Kyphosis; Laser Correlation Spectroscopy; Nuclear Abnormalities; Oropharyngeal Washout Fluid; Scoliosis

Introduction

In the growing body, the spine is the most loaded structure by its functional, adaptive, and compensatory role, therefore spine pathologies are among the earliest environmentally and technologically induced pathologies (fluorosis, Urov disease, etc.).

Kuvina et al., has demonstrated reduced functional capacities of the musculoskeletal system formation in children exposed to adverse environmental factors. For instance, in 20 years after start-up of industrial projects in 4 towns in the Irkutsk region, the number of healthy children decreased by 6.6%, while the number of children with subclinical and mild forms of orthopedic pathology increased by 31.5% and the number of children with severe orthopedic pathology increased by 35%. The prevalence of all pathologies of the Locomotor System (LMS) increased with time, with displastic type pathologies prevailing over congenital and systemic pathologies of other genesis.

Early detection of deforming spine and joint diseases (at an early age before the onset of vertical static load) is highly desirable. Unfortunately, the initial manifestations of degenerative changes often remain unrecognized, although this is the stage when conservative treatment can be really successful and follow-up until the end of bone growth can consolidate the positive effect of therapy. The early stages of LMS pathologies are under diagnosed in 80% cases. According to the report of the Ministry of Health and Social Development of the Russian Federation for 2001, the number of orthopedically disabled children increases with age. In most cases, the first manifestations of scoliosis appear in preschool children and then the disease progresses through different age periods.

Developmental abnormalities of the spine are referred to embryopathies, i.e. pathologies formed during a period from day 16 to the end of the 8th week after fertilization. This period includes the blasemal, cartilaginous, and early osseous stage of the spine development. The causes of these abnormalities are unknown. Numerous physical, chemical, and biological agents acting on the mother and fetus during the spine development can cause abnormalities of individual vertebrae and the vertebral column. The incidence of spine abnormalities in the population is difficult to evaluate (although such attempts are undertaken) because of the absence of typical clinical manifestations, while radiographs of the whole spine for their detection is unjustified. Vertebral pathology includes degenerative, dysplastic, metabolic, neoplastic, infl ammatory and autoimmune diseases, with degenerative and dysplastic diseases being most prevalent. Each of these pathologies has specific nosological forms. Scoliosis, a dysplastic state of the skeleton, is one of the most prevalent and socially significant pathologies often leading to disability.

Although hereditary bases of idiopathic scoliosis are proven [1,2], the etiology at large remains unclear. The toxic effect of chemical agents widely used in industry and agriculture on the bone tissue has been reported. There are published data on early degenerative processes induced by toxicants acting indirectly via the blood stream by violating barrier functions of the matrix, causing chronic intoxication of the connective tissue cells. Experiments on albino rats showed that chronic exposure to a toxicant in doses exceeding maximum permissible concentration accelerates genetically determined spine deformity and aggravated scoliosis [3].

Systemic pathologies, in particular, systemic connective tissue disease, develop successively stage-by-stage and in combinations, according to the age-related peculiarities of the child body. By the time of entering the school, the child has at least six symptoms of orthopedic pathology that are considered in clinical practice as independent diseases. The most rapid progress of spine deformities is observed during puberty stages 2 and 3 (in 11-14 year old adolescents). Scoliosis progresses against the background of hormone imbalance that is more pronounced in girls than in boys. Opposite influences of anabolic (androgens) and catabolic (cortisol) hormones can aggravate the metabolic changes in the connective tissue in this pathology and determine more severe course of the disease.

Numerous attempts were undertaken at detecting the influence of potentially hazardous environmental factors on the body (in particular, on children) at the preclinical stage, but the problem is far from being solved. Early detection of negative aftereffects of anthropogenic influences on human organism (body) is complicated by poor choice of methods suitable for this purpose. The objectives of the present study were:

1. To determine prevailing directionality of metabolism in children with idiopathic scoliosis and kyphosis of different degree, and to determine metabolic shifts severity for each of these pathologies;

2. To determine risk groups for the development of spine deformities under conditions of ecological hazard.

Methodology

A total of 745 children aged 7-16 years were examined twice a year in a hospital and once a year in schools. Inclusion criteria for children with spinal deformities were verified scoliosis or kyphosis and for the control group no verified diagnosis. Exclusion criteria were acute respiratory infections at the time of the survey. In the examined sample, 258 children (847 measurements) had scoliosis of different degree (I-IV) and 167 children (620 measurements) had kyphosis of different degree. Biological fluids from each child with spinal deformities were analyzed 3-4 times over 2 years. The control group comprised 320 healthy schoolchildren living in the same region (320 measurements; biological fluid from each child of control group was analyzed once). All groups were subdivided into young (7-10 years), medium (11-13 years) and elder (14-16 years) age subgroups.

We used the method of Laser Correlation Spectroscopy (LCS) providing information on the relationships between subcellular components of various biological fluids - blood serum, urine and Oropharyngeal Washout Fluid (OPWF). On the basis of the data on changes in the subfraction composition of these fluids in different pathologies in comparison with normological spectra of healthy people we developed a semiotic classifier of LC spectra. Basing on the increase (or decrease) in the percent contribution of particles of a certain fraction into light scattering, a semiotic classification of LCS spectra was proposed including identification of 8 types of shifts in homeostasis and humoral immunity and 1 normological type [4]. This approach allows evaluation of prevailing directionality of the metabolism, which can be very effective for monitoring of metabolic disorders, in particular, in musculoskeletal pathologies, e.g. scoliosis. In the present study, we analyzed OPWF obtained from fasting individuals 20-30 min after tooth brushing.

Anthropometric indexes (body weight and length) were monitored twice a year between two successive OPWF analyses.

Results

Analysis of the experimental data showed that:

1. Irrespective of the age and pathology, all 9 types (including 1 normological) of metabolic shifts were present in all examined groups, though to a different degree. The only exception was medium-age children with III-IV degree scoliosis; the number of directions of metabolic shifts decreased 2-fold (Figure 1).

2. Irrespective of the age, the incidence of autoimmune-like shifts considerably increased in III-IV degree scoliosis against the background of high incidence of intoxication-like shifts and low number of cases with normological type of metabolism (Figure 2).

3. In elder children with kyphosis, the contribution of autoimmune-like shifts increased against the background of low number of cases with normological type of metabolism and reduced incidence of intoxication-like shifts (Figure 2).

4. Intoxication-like shifts were more often found in children of all age groups with kyphosis and early stages of scoliosis compared to healthy children, but their contribution tended to decrease with age.

5. Allergic-like metabolic shifts were found in younger children with kyphosis and early stages of scoliosis.

6. In all children with dystrophic- and catabolic-like shifts, a slight decrease in body weight and height was found for both scoliosis and kyphosis groups.

7. Comparative analysis of the distribution of the examined children by height, weight, and weight/height index revealed no significant differences between kyphosis and scoliosis groups.

Similar to other biological substrates, OPWF provides integral information on various processes in the body, which determines variability of this parameter. We previously showed that changes in the subfraction composition of OPWF correlate with shifts in the urine and blood serum [4].

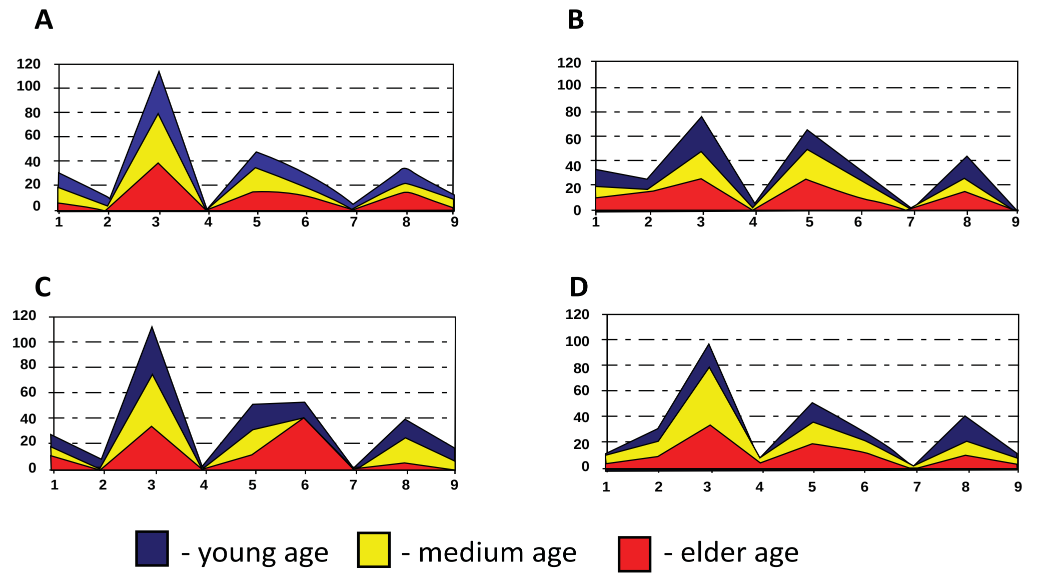


Figure 1: Prevailing types of metabolic shifts in comparison with normological type of metabolism in children with scoliosis and kyphosis of different degree. A-scoliosis, 1 degree; B-scoliosis, 2 degree; C-scoliosis, 3-4 degree; D-kyphosis.

X-axis – type of metabolic shifts: 1 – dystrophic-like shifts, 2 – catabolic-like shifts, 3 – intoxication-like shifts, 4 – intoxication-allergic-like shifts, 5 – normological type of metabolism, 6 – allergic-intoxication-like shifts, 7 - allergic-like shifts, 8 – allergic-autoimmune-like shifts, 9 – auto-immune-like shifts. Y-axis – relative incidence of metabolic shifts in children of different age.

A special experimental series was carried out to evaluate variability of LC spectra of OPWF (OPWF samples were collected with 1-2 day intervals) and to study local dynamics of the observed metabolic shifts. The experimental group comprised 16 children with I-II degree scoliosis and 5 children with kyphosis. It was found that in children with normological type of metabolism, the type of metabolic shifts was stable. In the majority of the examined patients, we observed catabolic shifts of varying degree (from dystrophic- to intoxication-like shifts). In 5 cases, the anabolic type of metabolism was replaced with the catabolic one. It should be noted that these drastic changes in the type of metabolism were observed in children with severe scoliosis (Cobb angle 20-30°) in combination with kyphosis. It can be hypothesized that these drastic changes in metabolic parameters reflect active processes of scoliosis formation.

Similar LCS studies were carried out in a summer camp. We examined 81 children aged 10-13 years. LCS analysis of OPWF revealed 27 children with catabolic type of metabolism. Subsequent medical examination revealed scoliotic spine in 23 children (85%).

These data suggest that LCS method can be used for dynamic monitoring of scoliotic patients and for identification of high-risk group among healthy children.

In the second part of the study we examined 9-12 year old children in three schools: general education school (25 pupils), Moscow boarding school for children with scoliosis and kyphosis (73 pupils), and country school in ecologically clean Novgorod region (23 pupils).

Analysis of the spectra with consideration for the predominant type of metabolic processes (Figure 3) showed that in children from country school, normal spectra and anabolic spectra were most prevalent (44.0 and 40.0%, respectively), while the incidence of catabolic spectra was low (16.0%) (Figure 4).

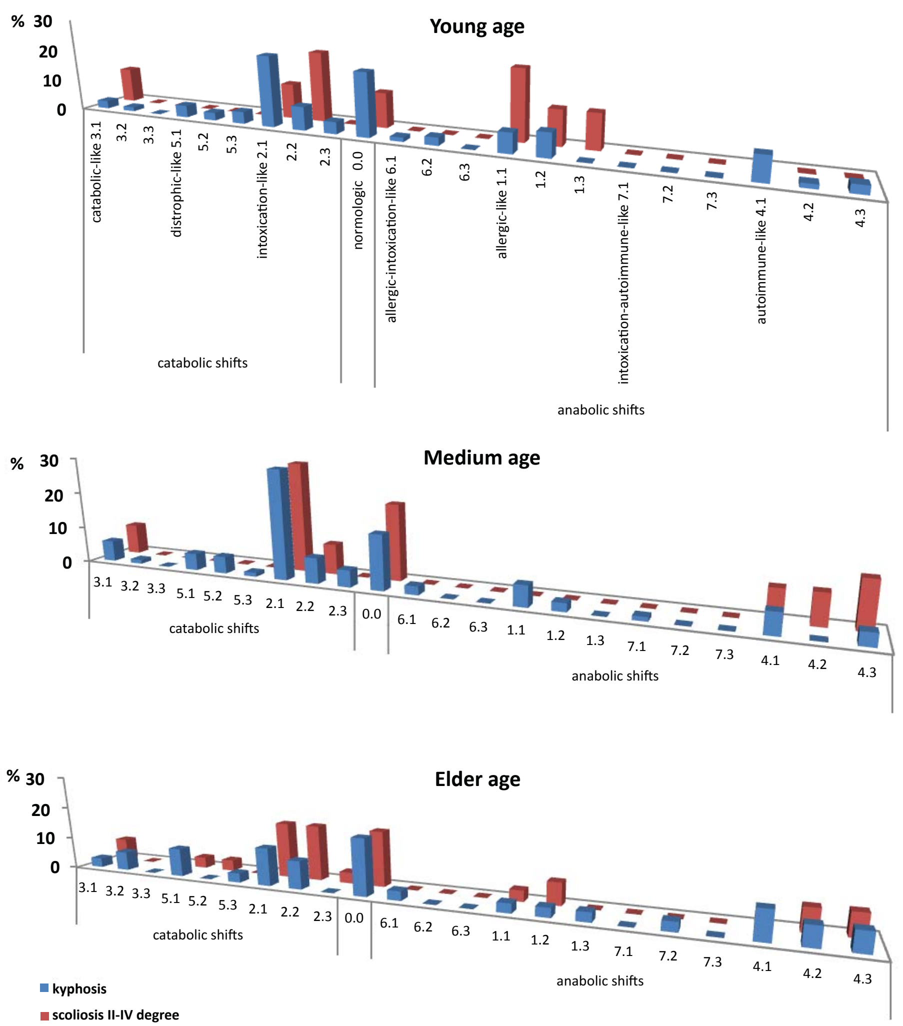


Figure 2: Distribution of metabolic shifts in children of different age groups with kyphosis and II-IV degree scoliosis. X-axis – Types of metabolic shifts used in semiotic classifier and their digital codes, where the first and the second figures denote the type of the shift and its severity (initial, moderate, and pronounced), respectively. For example, 2.2 – intoxication-like shift, moderate degree. Y-axis - incidence of different types of metabolic shifts, %.

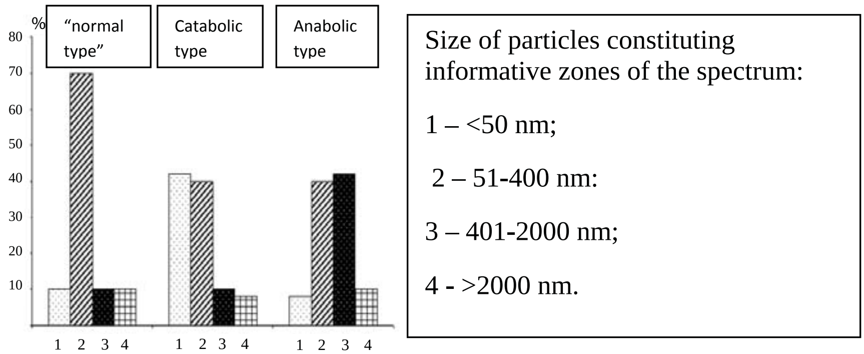
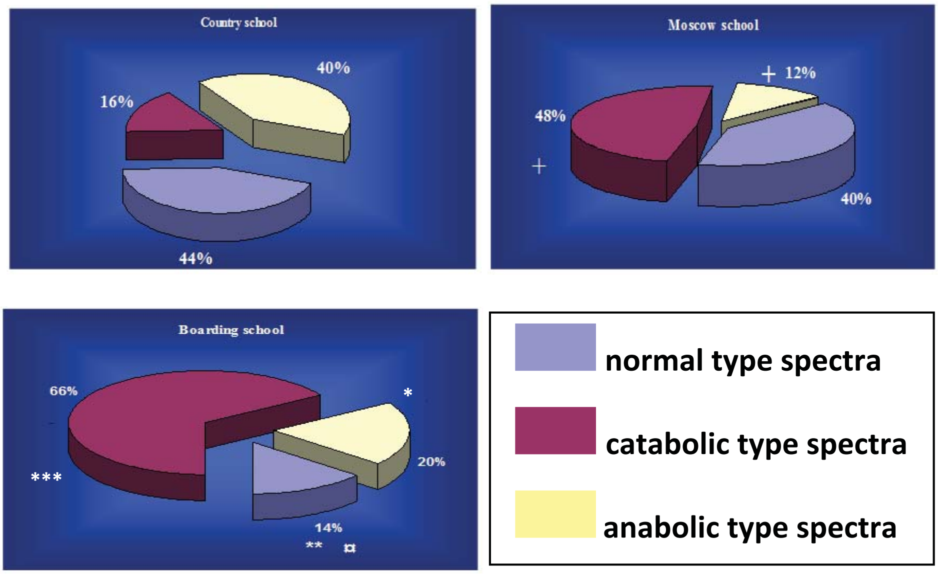


Figure 3: Size distribution histograms of oropharyngeal washout fluid particles corresponding to different types of metabolic processes. Y-axis – contribution of particles of the corresponding zone into light scattering (%).



*, **, *** – P<0.05; 0.005; and 0.0001, respectively, compared to country school; ¤ – P<0.02 compared to Moscow school; + – P<0.02 compared to country school (two-way Fisher exact test).

Figure 4: Incidence of spectra characterizing metabolic processes of different directionalities.

In children from Moscow school, the percentage of anabolic spectra decreased compared to the corresponding parameter in children from country school (P<0.05), which led to an increase in the percentage of catabolic spectra (P<0.05). In children with musculoskeletal disorders, catabolic spectra were even more prevalent (66.1%), while the percentage of normal spectra was reliably lower than in the group of country school children (P<0.001). All three examined groups differed by the distribution of predominant direction of metabolism (P<0.001). The most drastic differences were demonstrated for the contribution of catabolic shifts. In our previous work [5,6] it was shown that the mean incidence of buccal cells with karyorhexis was minimum in children from country school in ecologically clean region and maximum in Moscow school children (higher by ~13 times). In children from boarding school, the incidence of cells with karyorhexis was intermediate. These three groups also differed by the incidence of cells with karyolysis: this parameter was minimum in Moscow schoolchildren, significantly higher in children from Novgorod region, and maximum in children with musculoskeletal disorders. Data correlation analysis of the total sampling of the examined children (N=110) revealed a relationship between the direction of metabolic process and the incidence of some nuclear abnormalities. In children with catabolic LC spectra, the maximum number of cells with karyorhexis (($r=0.33$, $P<0.0001$ Spearman test) and karyolysis ($r=0.2$, $P<0.05$) were found. It can be hypothesized that the release of degraded nuclear material from cells and cell lysis increased the contribution low molecular weight subfraction into light scattering, which is typical of catabolic processes. Being a polygenic disease, scoliosis is characterized by genetic defects at various levels. According to the hypothesis proposed by Burwell RG, Dangerfield PH [7], cells with X-chromosome mosaicism or microchimerism should be present in tissues of patients with scoliosis.

Discussion

The data produced by the above two methods were in good correlation. It was found that musculoskeletal diseases and living under ecologically unfavorable conditions are accompanied by similar genetic and metabolic shifts. It is well established that the incidence of musculoskeletal diseases directly correlates with the degree of environmental pollution [8]. The combination of cytogenetic analysis of buccal epithelial cells as peripheral marker of damage to the genetic apparatus and LCS can help to determine risk groups for the development of spine deformities under conditions of ecological hazard.

The metabolic shifts detected in children with pathologies of the locomotor system considerably differ depending on patient's age and stage of the disease. Catabolic shifts are typical of the initial stage of the disease, while anabolic shifts (mainly autoimmune-like) appear at later stages. Catabolic shifts can be related to activation of metalloproteinases under conditions of intervertebral disk compression [9], while anabolic shifts can be determined by the immune system response to the release of matrix degradation products. However, it remains unclear what is the primary factor - asymmetric disk compression or matrix degradation leading to spine deformity.

The role of the genetic component in the scoliosis development is generally accepted [10]. It was demonstrated that certain loci of chromosomes 6, 9, 16 and 17 are linked with scoliosis pathogenesis [11]. Contradictory data on the role of melatonin receptor 1A and γ1-syntrophin genes in scoliosis development were obtained [12,13]. A correlation was found between estrogen receptor-α gene polymorphism and curve severity in scoliosis [14]. X bal gene polymorphism is thought to affect the severity of the disease [15].

Published reports suggest that, even in families with high prevalence of scoliosis, this disease of uncertain etiology is not always inherited. It was hypothesized that environmental factors affect its manifestation in genetically predisposed individuals [16]. This assumption was confirmed by our data on similar influence of unfavorable ecological conditions (Moscow school) and locomotor system pathologies (specialized boarding school) on the rate of karyorrhexis and karyolysis in buccal epithelial cells and the correlation of these parameters with catabolic type of metabolism. It is known that not only permanent residence in regions of ecological concern (Kuvin et al., 2005), but even short-term exposure to chemical toxicants (e.g. chlorinating agents in the swimming pool) [17] increased the incidence of spinal deformities. Interestingly, this regularity is not unique to humans, because spine deformities in fish can be caused by chemical substances present in water [18].

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Chapter: XI

Subcellular Content of Blood Serum and Urine at Asthma: Animal Model, Clinic and Monitoring Data

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Abstract

We reproduced mouse model of bronchial asthma, evaluated metabolic shifts of serum homeostasis during disease development, and compared these results with the data on metabolic shifts in bronchial asthma patients. In experimental mice pronounced pathological changes in the lungs, considerable lymphocytosis and decrease in neutrophil count were detected. Metabolic shifts were studied using method of Laser Correlation Spectroscopy (LCS) of blood serum and urine. Method of LCS allows determining the dispersion composition of the studied fluid by the relative contribution of particle components into light scattering. The relative content of particles of different size characterizes the direction of metabolic shifts in the organism. Similar patterns of particle distribution in biological fluids of experimental animals and patients suggest that LCS can be used as an additional method for evaluation of the severity of the disease and efficiency of therapy.

Introduction

Allergic Bronchial Asthma (BA) is successfully modeled in mice, rats, guinea pigs, sheep, rabbits, dogs, cats, and primates. In each species, a specific spectrum of asthma symptoms can be reproduced. The use of large animals is limited by high cost, duration and complexity of experiments. Therefore, mouse model of BA is most balanced and most often used model [4].

BA modeling on experimental animals has a number of significant advantages. Uniqueness of mouse asthma is determined by combination of the following factors. First, this model ensures high correspondence of the key histological, immune, and functional signs of experimental pathology to human asthma. The technology of breeding transgene and knockout mouse strains is well developed. Mice are convenient experimental animals due to low material and labor costs for their maintenance and feeding and due to short reproductive cycle.

The effect of heredity on pathological manifestations associated with BA in humans is difficult to evaluate because the study cannot be performed on genetically identical groups of individuals. In fact, experiments evaluating the effects of external factors against the uniform genetic background can be performed only on inbred animals.

Due to insufficient understanding of the mechanisms of asthma development, we have to reproduce only individual morphogenetic and functional changes typical of this pathology, but not the disease in whole.

Here we reproduced mouse model of BA [3], evaluated metabolic shifts of serum homeostasis during disease development, and compared these results with the data on metabolic shifts in BA patients.

Materials and Methods

Experimental model

Experiments were performed on C57Bl mice (30 males and 21 females) weighing 18-20g. During the experiments the animals were kept under standard vivarium conditions.

Short-term adjuvant-free IgE-dependent bronchial asthma model was reproduced on laboratory mice using timothy grass (*Phleum pratense*) pollen [3]. Experimental animals (10 males and 9 females) were intraperitoneally immunized with timothy grass pollen (Mikrogen, "Stavropol") in a dose of 220μg/mouse (7 injections every other day). In 3 weeks after the last injection, the allergen was daily intranasally administered in a dose of 500 μg/mouse (8 times). The control group was divided into two subgroups. They received sham-immunization and provocation: intraperitoneal and intranasal administration of physiological saline (group 1, 10 males and 7 females) or pollen solvent (group 2, 10 males and 7 females) according to the same protocol. After completion of the experimental protocol (5 weeks) the animals were decapitated.

Differential leukocyte count was determined. The blood serum was assayed by Laser Correlation Spectroscopy (LCS) [1]. For pathophysiological study, the lungs of each mouse were isolated and fixed in 10% aqueous solution of neutral formalin. Lung fragments were embedded into paraffin, histological sections (5-7μ) were routinely prepared on a MNS-2 microtome and stained with Mayer hematoxylin and eosin, and the mucus was additionally stained with alcian blue, so that cell nuclei were stained red and the mucus was stained blue-green. Mast cells were stained with toluidine blue, so that they looked violet or purple-red cells against the blue background. In preparations stained after Pearls for Fe (III) compounds, cell nuclei were stained red and structures containing Fe (III) looked dark blue.

Laser correlation spectroscopy

Method of LCS allows determining the dispersion composition of the studied fluid by the relative contribution of particle components into light scattering. The size distribution of particles presented after mathematical processing in the form of a histogram allows characterization of dispersion composition of a certain biological fluid and classification of the distribution according to chosen informative zones of the spectrum. The relative content of particles of different size characterizes the direction of metabolic shifts in the organism [1].

Results and Discussion

Morphological analysis of the lungs from control animals receiving physiological saline demonstrated the absence of pathological changes. The alveolar wall was well developed and presented by medium-size alveolocytes; the lumens were evenly round and not enlarged.

Bronchial epithelial cells had prismatic shape with well-developed brush border on the apical surface. Alcian blue staining detected thin layer of the mucus on the surface of the bronchial mucosa. Solitary mast cells were rarely seen.

In controls receiving pollen solvent, the lung parenchyma looked different in different parts of the section. The alveoli varied in size and shape, most of them had usual structure: the alveolar wall was well developed and presented by medium-size alveolocytes, the lumens were equally round and not enlarged. Some groups of alveoli located close to bronchi had thickened walls due to minor edema of the alveolar septa. Small marginal atelectases looking like dilatation of the alveoli with thinning of their walls, rupture of alveolar septa and fusion of alveolar lumens were seen at the periphery of histological sections of the lungs. On sections, large, medium and small bronchi without signs of bronchial wall sclerosis were observed. The epithelial cells in large bronchi had prismatic shape with well-developed brush border on the apical surface. In some small and medium bronchi, moderate desquamation of the epithelium was found. Alcian blue staining revealed low amount of mucus on the mucosa surface. Toluidine blue staining revealed solitary mast cells located primarily in the peribronchial connective tissue of medium and small bronchi. No mucus plugs were found.

In experimental mice, pronounced pathological changes in the lungs were detected. In large bronchi, the mucosa was thickened and plicated, which attested to bronchospasm. The bronchial epithelium was lined with elongated finger-shaped cells, apical part of ciliary epithelial cells was often destructed and desquamated into the bronchial lumen, and the apical brush border was poorly developed. The bronchial mucosa was covered with abundant granular protein mass positively stained with alcian blue for mucus (Figure 1). Numerous goblet cells were found in the mucosa epithelium. The basement membrane of bronchial epithelium was thickened. Moderate leukocytic infiltration was seen around the bronchi. Toluidine blue staining revealed numerous mast cells in the foci of peribronchial leukocytic infiltration.

In small bronchi, spasm and destruction of the mucosa epithelium were less pronounced, but intensive mucus formation and epithelium desquamation led to bronchus obstruction and formation of a mucus plug. However, this was a rare phenomenon. Accumulation of the granular mass in the bronchus lumen is a result of mucous degeneration of the bronchial epithelium and its desquamation and the formation of the mucus plug (Figure 2).

The mice can be referred to organisms with lymphocytic profile of the blood (similarly to rats, rabbits and humans). Analysis of leukocyte composition of the blood revealed considerable lymphocytosis in the experimental group and a decrease in neutrophil count to the lower boundary of the normal (Figure 3).

In neutropenia the cells are eliminated more rapidly than produced; this is observed in some bacterial infections, allergic and autoimmune diseases and under the effect of some drugs.

However, no appreciable changes in eosinophil count in blood smears were noted. Authors of the model also observed no increase in relative eosinophil content in the blood. It is well known that some strains are predisposed to IgE hyperproduction, others to the development of inflammatory changes, and others to the development of lung fibrosis. Apart from evaluation of pathology markers, complex functional changes in animal organism should be taken into account.

Changes in cell composition of the blood and tissues led to shifts in blood serum composition. LCS shows the contribution of particles with different hydrodynamic radius into light scatter in biological fluids, including the blood and urine. Comparison of LC-histograms of mouse blood revealed reduced contribution of 37 and 91nm particles and a trend to increased contribution of 122-165 nm particles into light scatter in the experimental group in comparison with the control (Figure 4).

In experimental mice with modeled BA, we observed great number of mixed shifts characterized by considerable contribution of small (<10 nm) and large (71-150nm) particles into light scatter (Figure 5).

Increased contribution of 71-150nm particles is typical of allergic processes, while increased contribution of small particles (<10nm) is a result of accumulation of small proteins (α1-, α2- and β-globulins) and indicates acute inflammation.

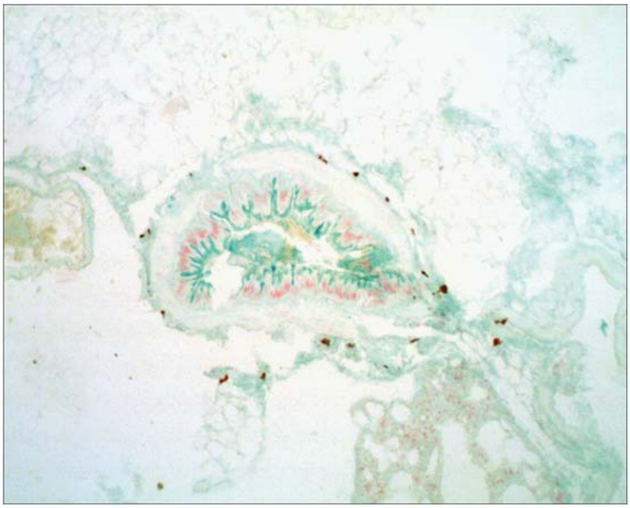

Figure 1: Mucus in a bronchus of an experimental mouse (immunization with timothy grass pollen), alcian blue staining. Mucus is stained deep blue a mucus plug is seen in the lumen. Magnification 10×10.

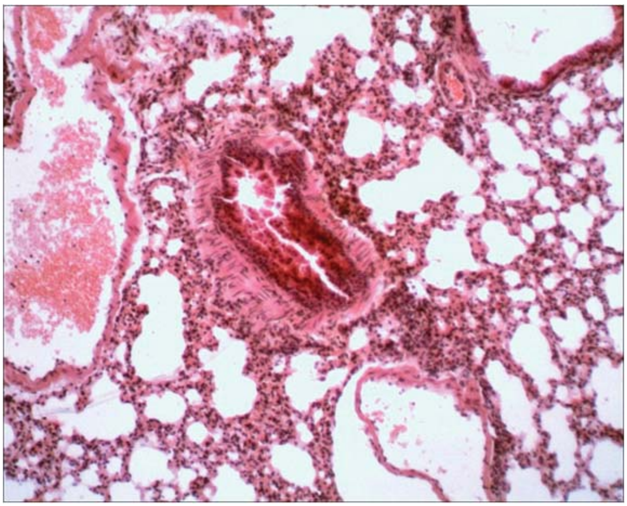

Figure 2: Structure of a bronchus of an experimental mouse (immunization with timothy grass pollen). A granular mass in the bronchus lumen (dark red), mucus plug. Hematoxylin and eosin staining. Magnification 10×10.

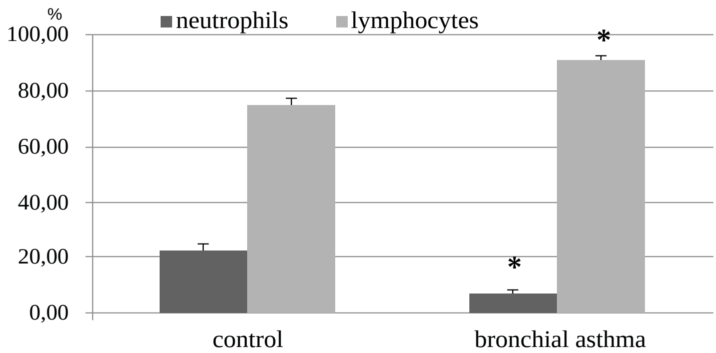

Figure 3: Relative count of neutrophils and lymphocytes (%) in control and experimental mice with modeled BA. *p<0.05 (Mann-Whitney test).

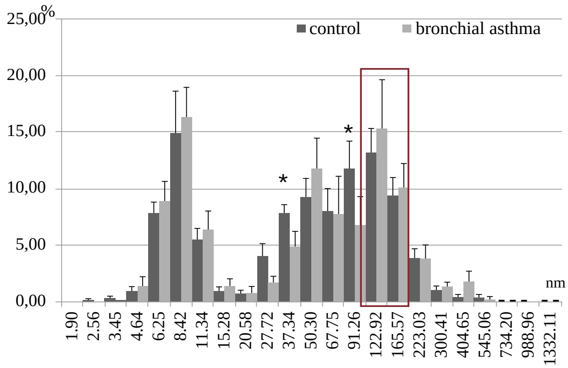

Figure 4: LCS histogram of blood serum from mice with modeled BA. Abscissa: particle size, nm; ordinate: contribution into light scatter, %.

The data accumulated in numerous experiments exploring LCS analysis of biological fluids from humans allowed division of abscissa axis (particle size) into larger intervals, so-called informative zones. Informative zones for blood serum (hydrodynamic radius of particles in nm) were: I - 0-10nm; II - 11-30nm; III - 31-70nm; IV - 71-150nm; V - >150nm; and for urine I -<75nm, II - 76-220nm; II I- 221-1500 nm; IV - >1500nm. Ordinate showed the contribution of particles into light scatter, %.

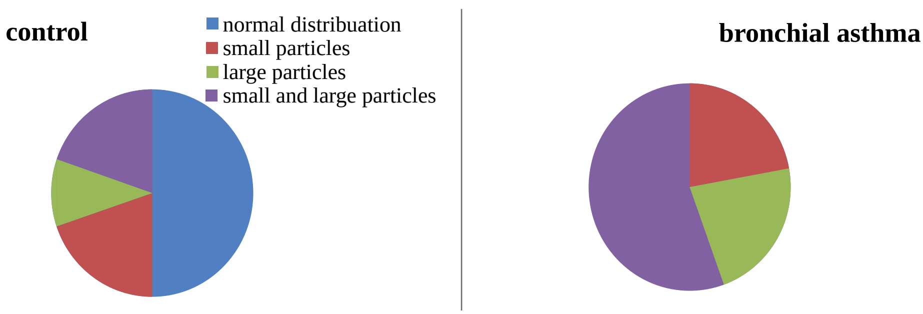

Figure 5: Incidence of different metabolic shifts in mice with modeled BA, %.

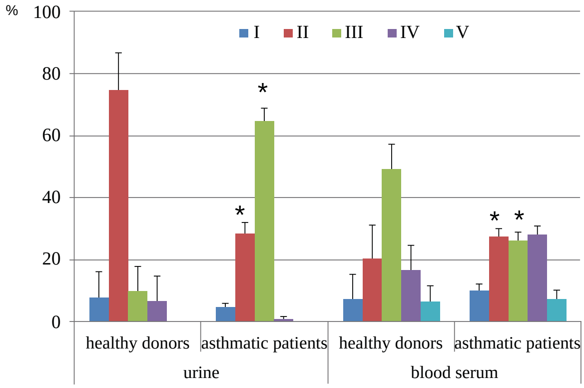

Figure 6: Averaged histograms of LC-spectra of urine and blood serum from healthy individuals and patients with allergic diseases of the bronchopulmonary system. Abscissa: hydrodynamic radius of particles in informative zones (in nm): - <75nm, II - 76-220nm; III – 221-1500nm; IV – >1500nm for urine and I - 0-10nm; II - 11-30nm; III - 31-70nm; IV - 71-150nm; V - >150nm for blood serum Ordinate: contribution of particles into light scatter, %. *p<0.05 (Mann-Whitney test).

The data obtained on healthy individuals (without verified diagnosis) were used for construction of averaged histograms of particle size distribution for the blood and urine, i.e. normal spectra (Figure 6). Analysis of analogous histograms of patients with allergic BA revealed predominance of large particles (221-1500nm, zone III) in urine samples in comparison with normal spectra. According to semiotic classifier, this shift in spectral parameters can be interpreted as allergy-like shift [2]. The main idea of the “semiotic classifier” is based on the fact that formation of the pathological trace in human organism depends not only on concrete disease nature but also on the interaction between the organism sanogenetic mechanisms, which impede of the fixation of the pathological trace defying by the ethyopathogenesis. In LC-spectra of serum samples, the contribution of small particles increased, which attested to enhanced degradation of molecules typical of states accompanied by intoxication of the organism (intoxication-like shifts).

For evaluation of the contribution of pathologies accompanying BA into metabolic homeostasis we performed LC analysis of urine and blood samples from patients with BA alone and patients with concomitant Perennial Allergic Rhinitis (PAR). No significant changes in the distribution of light-scattering particles were revealed (Figure 7) and therefore these groups were combined and the whole cohort of BA patients was analyzed.

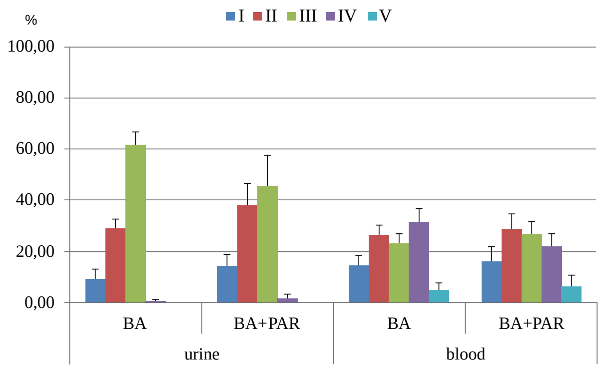

Figure 7: Averaged histograms of LC-spectra of urine and blood serum from patients with BA alone and BA with Perennial Allergic Rhinitis (PAR). Axes (Figure 6).

All the patients were divided into 3 subgroups. Patients of the first subgroup irrespective of the severity of allergic syndrome rapidly responded to basic therapy and attained remission after minimum volume of detoxification and immunological treatment. In this group, the best results in reducing the doses of basic preparations were attained.

In the second group, laboratory parameters showed apparent wellbeing despite pronounced clinical picture. Further observations drove us to a conclusion on compensatory failure of the detoxification function of the urinary system (parameters of common urine analysis were normal). This is a transition group and it will advance to the third group with endotoxicosis augmentation. These patients require greater volume of detoxification measures and immunological treatment for attaining remission. Reduction of the doses of basic therapy resulted in destabilization and the patients returned to higher doses.

In patients of the third group with severe endotoxicosis we observed a decrease in total complement activity as a manifestation of compensatory failure in the immune system. Stabilization in this group was attained after the longest period of basic anti-inflammatory therapy with maximum immunological support. The reduction of basic treatment doses in this group took the longest time.

LC-spectra of the urine in all examined groups demonstrated similar size distribution of particles: large particles (220-1500nm) made the greatest contribution into light scatter (Figure 8). The appearance of these large particles probably indicated allergization processes in the body.

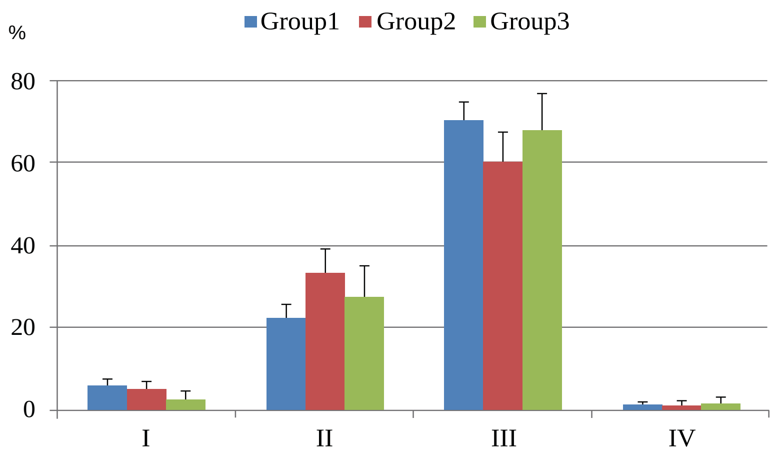

Figure 8: Distribution of light scattering particles in urine samples from patients with different degree of disturbances in organism's defense systems. Abscissa: hydrodynamic radius of particles in informative zones (in nm): I - <75 nm; II - 76-220nm; III - 221-1500nm; IV - >1500nm. Ordinate: contribution of particles into light scatter, %.

Analysis of LC-spectra of blood serum revealed considerable changes in the distribution of light scattering particles in the three examined subgroups (Figure 9). In the first group, zone IV particles (71-100nm) made the greatest contribution into light scatter. In the second and third groups, the contribution of zone IV particles decreased and the contribution of zone II particles increased in comparison with the first group ($p<0.05$; Mann-Whitney test). The pattern of light scattering particles distribution indicates predominance of anabolic shifts of serum homeostasis in the first group of patients. It is well known that allergic disorders are associated with activation of Th2 cells and enhanced production of cytokines

IL-4, IL-5 and IL-13 [5,7]. IL-5 promotes maturation and activation of eosinophils. IL-4/IL-13 induce synthesis of IgE in B-cells [6]. Hence, from immunological point of view the allergic process at the initial stage of the disease is associated with the appearance of large molecular complexes in the blood.

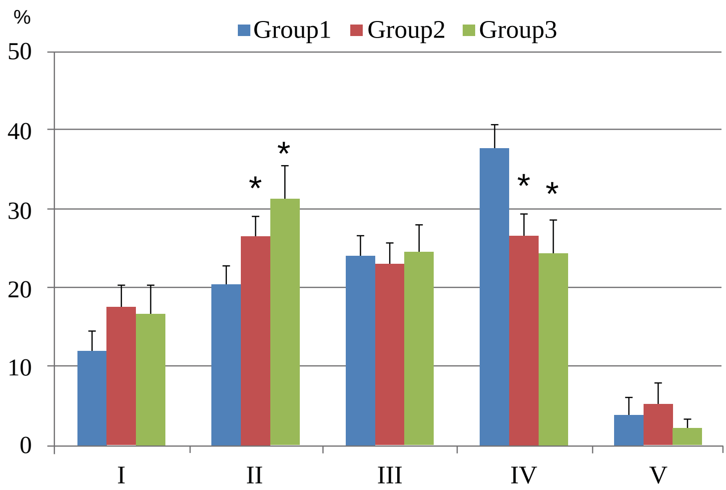

Figure 9: Distribution of light scattering particles in serum samples from patients with different degree of disturbances in the organism's defense systems (see text). Abscissa: hydrodynamic radius of particles in informative zones (in nm): I-0-10nm; II-11-30nm; III-31-70nm; IV-71-150nm; V-150nm. Ordinate: contribution of particles into light scatter, %. *p<0.05 in comparison with the first group (Mann-Whitney test).

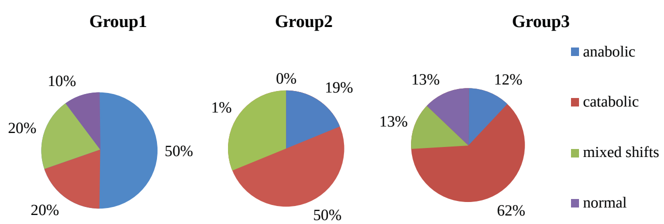

Figure 10: Incidence of different types of LC spectra in groups of patients with different degree of disturbances in the organism's defense systems. Description in the test.

Patients with catabolic shifts in the first, second, and third groups constitute 20, 50 and 62%, respectively (Figure 10). Thus, the percent of patients with endogenous intoxication in the second and third groups is considerably higher than in the first group ($p<0.05$; two-way Fisher test).

Empirical conclusions made on the basis of clinical observations and explaining the distribution of the patients into the three groups were confirmed by LCS of the urine and blood serum. The predominance of intoxication-like shifts in LC-spectra of patients in the second and third groups drove us to a conclusion on mixed character of the inflammatory process in these patients. We believe that allergic inflammation in not the sole pathology in these groups: it is aggravated by infectious inflammation after compensatory failure of the urinary and then immune systems.

BA modeling on mice with histologically verified pathology allowed identification of the type of the basic pathological processes in blood serum and demonstrated similar patterns of LC-histograms in immunized mice and patients with BA. In mice with experimental BA, a clear-cut tendency to increased contribution of 122-165nm serum particles into light scatter was noted. In patients with different BA severity, a similar increase was noted for 71-150nm particles (Figure 6) due to drastically reduced contribution of 30-70nm particles into light scatter. The maximum increase in this range was observed in the first subgroup (Figure 9) zone IV, i.e. at the initial stage of the disease (irrespective of the severity of BA symptoms).

During experimental modeling of this or that pathology, the stage of the disease reproduced and used in further experiments should be taken into account. In this case, the initial stage of the disease was reproduced. Similar patterns of particle distribution in biological fluids of experimental animals and patients suggest that LCS can be used as an additional method for evaluation of the severity of the disease and efficiency of therapy.

For creation of adequate approaches to screening studies, the current methods should be modified. Knowledge gained in long-term toxicological and epidemiological studies allows us only to outline a rather broad range of potentially hazardous environmental factors.

Direct evaluation of metabolic shifts in 130 dockside workers in the Far North performed by us using the method of LCS of body fluids yielded more arguments for discussing this problem.

By the degree of contact with potential hazard sources (physical, chemical), the examined population was divided into 3 groups: 1 (minimum contact)-storekeepers,, cloakroom attendants, cleaners, and engineers and technical workers (n=24); 2 (indirect workers)-crane drivers, painters, electricians, strappers, maintenance men, and vessel trolley-transporter men (n=53); 3 (direct contact)-welders, burners, riveters, fitters, cleaners, and engineers and other technical workers (n=53).

As is seen from (Figure 11) allergy-like metabolic shifts in the urine predominated in the examined contingent. It can be hypothesized that chemicals released into the air during ship repair and recycling equally affect all the three groups and this determines similar frequency of allergy-like shifts. Workers of the third group directly contact with substances that might induce these effects (rubber coating, wires, plastic, etc.). Neglecting the requirements on the use of personal protection equipment can lead to inhalation of aerosols, their accumulation in the body, and increased incidence of allergy-like shifts in the excretory system.

Screening of workers of the potentially hazardous plant using LCS analysis of blood serum and urine and standard clinical blood testing for eosinophil count detected a risk group for allergic diseases (5 women and 8 men). This group included individuals with moderate or pronounced allergic shifts and mixed shifts with the allergic component.

Examination of various professional groups potentially exposed to chemical, radiation and non-radiation factors showed that the risk groups by the sensitivity to the studied factors are formed on the basis of adjustment of the main regulatory systems (the cardiovascular, respiratory, and neuromuscular systems) to the primarily recorded shifts in the plasma homeostasis. Since the target was detection of the risk group by the brochopulmonary pathologies, further functional testing was performed on a Spiroarteriocardiorhythmograph hardware-software complex. It revealed reduced vital lung capacity in 5 examinees. Tiffeneau index was reduced in 4 individuals; this parameter is more important for evaluation of allegric bronchopulmonary pathologies (Table 1). In 2 examinees, reduced Tiffeneau index was associated with increased relative content of eosinophils.

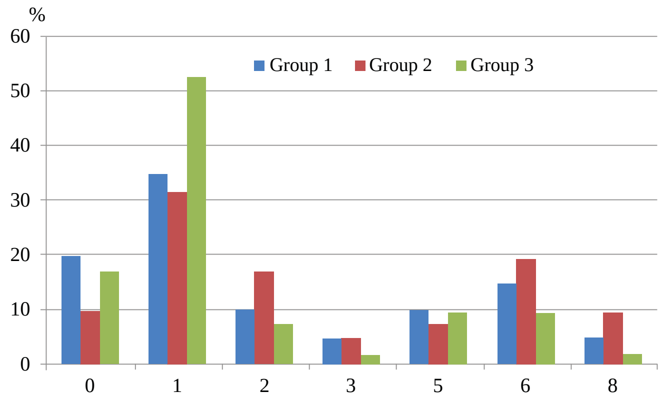

Figure 11: The incidence of predominant metabolic shifts in the excretory system of workers of different groups by the results of LCS analysis of urine samples. Abscissa: shift pattern (0 – normological; 1 – allergy-like; 2 – intoxication like; 4 – autoimmune type; 5 – dystrophic like; 6 – allergic-intoxication-like; 8 – allergic-dystrophic-like); ordinate: percent of examined individuals with the specified metabolic shift, %.

No	Gender	Age	LC spectrum of blood serum	LC spectrum of urine	Volume capacity (VC), l	Tiffeneau index	Eosinophil count in the blood, %
1	male	50	1,3	1,3	3,6	0,47	5
2	female	56	6,2	1,3	1,2	0,56	0
3	male	26	6,2	3,3	3,8	0,56	7
4	male	41	8,2	2,3	5,6	0,69	0
5	male	21	1,3	6,3	5,9	0,71	0
6	male	41	6,2	1,3	4,7	0,8	3
7	female	45	8,2	6,3	2,6	0,82	2
8	male	34	6,2	3,3	4,3	0,83	3
9	male	23	1,3	1,3	5,3	0,88	0
10	male	35	1,3	1,3	4,2	0,9	4
11	female	60	6,2	6,3	2,5	0,9	6
12	female	35	6,2	2,3	2,6	0,94	2
13	female	40	1,3	6,3	2,3	1	2

Table 1: Tiffeneau index and Eosinophil count in the blood.

Eosinophilia is observed in allergic diseases, e.g. in bronchial asthma (especially, in the beginning of attacks and between them), pollinosis, urticaria and serum sickness. Therefore, eosinophilia can be used for distinguishing between bronchial and cardiac asthma and bronchitis with asthmatic fits mimicking bronchial asthma.

Conclusion

Based on the above, the algorithm of evaluation of chronic radiation, chemical, and combined risks should include the following steps:

1. On the basis of the detected shifts in the system regulating metabolism and immunity (LCS of biological fluids), reference groups for differentiation significant shifts are formed.
2. In the corresponding reference groups, variants related to functional tension in the major physiological systems are detected.
3. On the basis of systemic analysis of the tensest states in the major physiological

systems, risk groups for the corresponding pathologies are formed within the selected reference groups.

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