STRESS: INFLUENCE ON HEALTH STATE AND IMPORTANCE OF STRESS MANAGEMENT

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1. Stress generally

The word „stress", is very commonly used, most people could understand the stress as strain (load) of the organism mental and physical; we use to say: "I am stressed", "I am under stress" etc. Conception of stress includes not only influence of outer environment (as above simplified notion) but influence and signals of inner environment (organs, tissues, pain, disease etc.), and more, the stress includes: the complex reaction of the organism to these information, signals, and changes of outer and inner environment as a complex reaction of the organism to stabilize homeostasis, balance between organism and environment. This idea is commonly accepted; more difficult is to try to define the stress. We can well define what we can feel under stress, we know what stress is, we can well define influence of load particularly of outer environment (work load, disease, disease and/or death of relatives etc.), we can well define the reactions following the stress as tremor, palpitations, sweating; but to define stress scientifically is very difficult also in scientific literature.

The first scientist who was interested in stress and first defined the stress was Austrian-Hungarian-Canadian physiologist **Hans SELYE;** his definition is: **the stress is not specific** (what means that this reaction is stereotypically same on different kinds of load) **physiological reaction of the organism on load (strain) put in the organism.** This definition is given as some general aspect on stress but does not include difference of organism reaction: for one organism the stress of (some) known intensity could be a current load, for another the same load could be extremely high stress with endangering the life functions; for untrained could be only a try to undergo marathon run direct life threatening stress, for trained it is current, of course intensive, load- its organism is **adapted** to the extreme stress of marathon run. We can see, that it is not only the intensity of stress, but that there is importance of state of organism, its health, its state of regulatory, control, and adaptation systems. There are many other stress definitions (Lazarus, Ganong), but for our practical purposes are less useful. The last ten to twenty years there are some disputations within scientific circles: some of them are defining the stress as not general and stereotypical reaction of the organism; they are defining the stress as different reactions to different signals, that the reactions on stress are specialized. These theories are mostly based on animal experiments.

For practical use is very apt, however compromise, definition by **Schreiber: stress is any influence of environment (inner, outer: physical, chemical, biological, political, labor, social, psychological) endangering health of some sensitive individuals.** That means: the most important **factor** determining health after-effects (disorders) of stress is individual **perceptiveness** of the organism to the stress. For practical purposes there is a need of some method allowing measure the stress, particularly the individual perceptiveness. Many different methods have been developed to measure stress and individual perceptiveness to stress, mostly psychological tests and questionnaires. These tests reflect the possibility of organism to cope with stress, its ability to control stress etc. The psychological methods, much as they brought progress to the problems of stress measurement, are less or more depending on subjective reactions, valuation, and answers of test person. Not-till **the heart rhythm variability analysis** came with possibility of objective evaluation of stress, activity of regulatory and adaptation systems.

2. Mechanisms of stress reactions

a) Acute stress situations.

These reactions are **alarm** reactions based on mechanisms leading to the state of stabile homeostasis: changes of inner and outer environment are causing changes inside the organism;

principally these reactions could be an inconspicuous and transitory but they can have very serious consequences to body physical and mental state. Principles of alarm reaction are **nerve and hormonal mechanisms** leading to **state of alert** that prepare the organism to very ancient reaction: **escape or fight;** this reaction is allowing the organism to **overcome** stress situations. Basically, it is the reaction of **activated sympathetic** part of autonomic nervous system (ANS) followed (after a few seconds) by activation of medullar **part of suprarenal gland** with outflow of "stress" hormones, **adrenaline and noradrenalin** - the reaction is called sympathetic-adrenal reaction: comprising increase of blood pressure and heart rhythm to secure better supply of nutrition and oxygen to the organs involved in "escape and/or fight - muscles etc., activation of glucose from the liver and activation of fat reserves as a source of higher need of energy supply. Metabolism is centered mostly to **energy activation**, so the metabolic processes are so called **katabolic, destructive -** most of all tissues could be used as a source of energy by stress. Simultaneously, vasopressin (antidiuretic hormone ADH) increases its outflow. This hormone is saving water in body lowering the urine production in kidneys, so enabling "cooling" effect of increased sweating by heat stress or caused by high physical load. The hormone vasopressin influences directly the vessels**: increase of blood pressure**, so improving the blood flow into the working organs. Another effect of this hormone is that it increases the development of **memory print (track**); that means the organism remembers the stress situation and what mechanisms was involved in successful adaptation, what is important when the same or similar stress situation appears again **(training).**

Problem of present civilized society is the fact, that these old ancient alarm stress reaction is useless: present human being **cannot react to the stress situation by escape or fight.** That is why the **stress** is becoming **a risk factor** worsening or causing so called stress diseases, as hypertension, myocardial infarction and coronary heart disease, peptic ulcer, arteriosclerosis with complications, diabetes of the 2nd type (non-insulin dependent) and complications of diabetes of both types.

b) Chronic stress reactions, adaptation syndrome

If the stress reaction is prolonged, influencing longer time, stress is becoming the chronic stress. This is united with very important reactions of nerve, hormonal, and mental reactions what enables the further **survival.**

Principle of this reaction starts with activation of adrenocorticotrophic hormone ACTH from hypophyseal gland what cause outflow of another "stress" hormone, this time from adrenal (suprarenal) gland cortex: **cortisone.** This hormone serves to long lasting energy production. ACTH is developed from precursor: **propiomelanocortine POMC,** which is precursor of other hormones, as Melanocytes Stimulating Hormone MSH and more important group of polypeptide hormones called **endorphins and encephalins**. These polypeptide hormones play very important role in processes of survival: they have very strong analgesic, anxiolytic, and euphorising properties; by stress the pain reception is reduced. This mechanism is important not only as one of necessary condition for survival but it is important **to secure the possibility of training and adaptation to stress**.

If the stress situation is lasting another time, the adrenal cortex react with hypertrophy (enlargement), what is necessary for long-term energy supply, for long-term mobilization of energy reserves to keep active defend reactions of the organism in stress. Cortisone further increases its outflow, what is absolutely necessary for activation of long-term energy and nutritional reserves, terminated in development **of adaptation syndrome**. Longtime cortisone levels comprise some unpleasant negative effects: decrease of proteins production (what could be useful as therapeutic mean to treat allergies), mostly of immune system – inhibiting the immune reactions, development of fat reserves (to secure energy reserves), and **atrophy of muscle mass** with development of **osteoporosis. Very important negative factor is that the activation of sympathetic-adrenal system is causing long-term inhibition of parasympathetic activity, responsible for anabolic (constructive) metabolic processes (regeneration of muscle mass, healing processes, restoration of destroyed cells and parts of tissues and organs).**

Further stress influences result in phase of exhaustion; if the stress lasts sufficient period of time, the all regulatory-adaptation system (esp. the suprarenal gland) is exhausted and experimental animal (and under specified extreme condition also the human) organism perishes with stress.

Selye summarized the cascade of stress reactions, what means **alarm** reaction, phase of **adaptation** reaction, and phase of **exhaustion** to the concept of **common (general) adaptation syndrome.** This simplified concept is generally accepted; it is necessary to notice that it is approved that on different stresses the organism reacts with **specific reactions** (older people who care the sick relatives suffers from low antigen production after vaccination and that they much easier suffers from infectious diseases with sub-lethal or lethal course). Generally accepted is also concept of sympathetic reaction, adrenal and suprarenal activation, production of ACTH, vasopressin, endorphins. What is not fully approved is that case of exhaustion by human organism- the human organism is dying not on long-term stress influence with exhaustion of suprarenal gland but on the diseases what caused this long lasting stress.

Some authors differentiate two types of stress: stress who is not causing any kind of health damage, called **eustress** (could strengthen the organism)**,** and stress causing some kind of health damage, called **distress.** Here is useful to notice that stress comprises also the organism reaction on load and that concept of stress evaluation is very individual: for somebody the load could be current

common load causing only light stress reaction, for somebody the same load could be extremely intensive and cause life endangering health damage. To use the concept of eustres s and distress is so too individual, speculative and no practical. More useful is to use- for practical purposes- the definition by Schreiber described above.

3. Stress influence on development and course of diseases, stress diseases

Common adaptation syndrome is, in the fact, the state in which we are living. Some sensible organisms or under some specified conditions, esp. by organism unable to defend against stress or less resistant to stress (what could be caused by many different inner and outer factors), can this adaptation syndrome change to **diseases from adaptation or stress diseases** with different damaging influence to health state:

Inhibition of immunity

It is to notice that on this research we are missing good scientific studies; to this thematic there is not enough attention present. We can operate with many of indirect but credible arguments that stress is negatively influencing on the course of immune reactions and some diseases. It is commonly known that the people easily become sick with angina or influenza after physical exhaustion and/or after staying in cold conditions. Older stressed people react to influenza vaccination with reduced production of antigens in comparison with middle aged, and more, the influenza could be for these people fatal disease. The cancer development and course of cancer disease depends on mental-emotional state of the patient. Stress management seems as hopeful method to improve immune reactions, strengthen the regulatory and adaptation systems and so to have a positive influence on courses of different diseases where the efficacy of immune system is the most important factor in healing-therapeutic process.

Coronary heart disease, myocardial infarction

It is well known that the myocardial infarction occurs very often after emotional and/or physical stress. Stress is so far the risk factor of cardiovascular diseases and MI is typical and frequent **stress disease.** The only one problem is present- stress is very difficult to measure, to quantify, and then: how to prevent the stress. Preventive means as by another risk factors, i.e. physical activity, diet and life changing matters, weight loss, quit smoking etc.: how with stress prevention? More: higher incidence of MI is within professionals with leading jobs, managers of banks and industrial enterprises, workers with high personal responsibility and workers operating very complicated systems, surgeons etc. All they suffer from so called manager's syndrome. Preventive means of risk factors are well known, not for stress, so that is why the MI after stress is not a professional disease. The question is if these preventive means are possible to apply to the above named responsible jobs without the restriction of current profession. Is it possible for surgeon, bank manager, industry enterprises company manager to quit his/her job? Then, how long time they could serve as leading professionals until they should quit: before or after they suffer from MI?

High blood pressure, hypertension

Stress is causing alarm reaction, which comprises the transient increase of blood pressure. If this stress (mental, emotional, physical) is often repeated and/or is lasting long time, then after the period of transient blood pressure increase we can detect permanent high blood pressure, **essential hypertension**, without known cause (stress only?), contrary to secondary hypertension from kidney disease, arteriosclerosis, some endocrinology diseases etc. So, the normal physiological alarm reaction could develop a disease necessary to treat with medicaments. Another problem is that we can normalize blood pressure with medicaments, we **can treat the disease but never cure it**: the patient should use the medicaments indefinitely. If there is a cause of repeated and/or long lasting stress, how to treat and eventually cure the hypertension? And if this stress is causing the disease, could the treatment of blood pressure be the efficient therapy? Present medicine is able to treat the hypertension but not to cure it. Presently, we are able to reduce the effect of different risk factors but **stress is very difficult to reduce or eliminate due to the fact that stress is standing and permanent part of present modern style of work and living.**

Peptic ulcer

Ulcerative disease of stomach and duodenum is not a typical stress disease but it is also well known that stress could worsen the course of the disease that stress could negatively influence to the peptic ulcerative disease. There is also a diagnostic unit known as stress ulcer, complication of severe burn or head trauma etc. Incidence of MI by people suffering from peptic ulcer is higher than by other population without peptic ulcer.

Stress disorders of menstruation

Very often we can see this disorder by overloaded sporting girls or young women, not caused by use of anabolic hormones; the stress here is also a cause of menstruation period disorders. In the case of overloaded sporting young girls and women the period disorders are caused by extreme

stress, physical and emotional, too. We can postulate that this reaction is normal defending reaction preventing the pregnancy of overloaded, stressed organism. This can bring some unpleasant effects: lower production of female hormones could cause lower development of bone mass, osteoporosis, what in young women could cause pre-menopausal pathological bone fractures.

Some other stress diseases

Very important disease highly negatively influenced by stress is asthma and some other allergy diseases. Stress negatively influence also ulcerous colitis and bowel irritant syndrome. The migraine depends some on stress, the attacks are more intensive and frequent under emotional and physical stress.

Stress and aging

Stress is accelerating the aging process. The main cause of this acceleration of aging process is increased production of free oxygen radicals (reactive oxygen species ROS) and insufficient supply of antioxidants, free radicals scavengers. ROS present destructive influence to many cell structures, the influence is very complex and they can cause extreme damage of different cell structures, organells, developing the chain reaction. The most sensitive to ROS damage are cell membranes and mitochondria. ROS have also positive role i.e. in immune reactions but negative influences prevalent. There are many studies about free radicals (ROS), so to know more is better to find in the literature. Detailed analysis of ROS problematic is not the matter of this article. In aging process the ROS are negatively involved mostly in cell membrane and mitochondria damage, accelerating the process of arteriosclerosis by activation of LDL-cholesterol; these processes causing reduction of functional capacity of the cells (muscle, nerve, heart and other organs).

4. Manager's syndrome and its management

Something of this syndrome is presented in previous part. This syndrome is more complicated, comprising some another factors. Principle to develop this syndrome is responsible and sedentary work. Stress (caused by this responsible job) is starting the alarm reaction-but activated energy sources are not used for muscle work and so this energy is given back as a reserve to fat formation; this results in development of obesity, higher levels of cholesterol resulting in development of arteriosclerosis and hypertension. This never ending carousel goes further: obesity further reduce physical activity, hypertension needs to be treated and this is bringing the existence problem, possibility of job loss, what is pushing the patient to be more intensive in work what causing more intensive stress. More, the manager's work is work under intensive flow of information necessary to be analyzed and as soon as possible processed. The stress is again more intensive and we are speaking about the stress from **overload of information**. The process is alone very stressful, we can see the accumulation of stress factors: keeping the dead-line terms, meetings, the problems from inner sphere, as with subordinates, work groups etc., from outer sphere, as with suppliers etc. what multiply development of stress diseases, esp. hypertension and MI. This is, of course, only brief information of manager's syndrome as a model situation.

5. Stress measurement, heart rhythm variability analysis, donosological diagnostics

One of the best of situation of influence of outer environment to the organism is stress in conditions of long lasting space flight. That is why the studies of stress during long lasting space flights are basic for the estimation of adaptation mechanisms and regulatory systems activity- esp. the tension of both parts of autonomous nervous system-of the organism. The very useful method of estimation of activity of the regulatory systems is analysis of heart rate variability. The method is exact (when measurement is provided under standardized conditions), easy, economic, and possible to repeat on demand; it is one of acceptable indicator of general health; so the space medicine has brought a new dimension of estimation of general health to conventional (mostly preventive) medicine.

The presented results of HRV analysis in preventive medicine are based on large scale studies provided in Russia within the last 20 years on different groups of industrial and rural regions as well as of different age and sex-together about 20.000 of studied persons. Examples described in following parts of this article are of use of methods of space medicine in mass preventive examinations and investigations of different groups of population: in donosological diagnostics.

Estimation of general health

One of the most difficult but most important questions in practicing to preserve good health is question of estimation of general health. Usually this problem is characterized by different statistical parameters as morbidity, mortality, birth rate etc. Mass donosological diagnostics allows take advantage of a simple method solving the problem-with help of knowledge of structure of health of different population groups. Comparable structure of health from different industrial enterprises or from different workshops of one enterprise could reflect the industrial influence on health; comparable

structure of health of population from different regions could reflect the climatologic-geographic and ecological influence on health.

Basal principles and importance of heart rate variability analysis

Basal functions the organism depends on those not (or very moderately) depending on the will- they are independent, automatically managed and controlled, as respiration, metabolism, cardiovascular system, hormonal and immune system, digestive tract etc. These systems are subject of control and regulation of **autonomic (vegetative) nervous system (ANS)** constituted from two parts: sympathetic and parasympathetic. The system comprises own hierarchy, periphery and higher vegetative centers as vasomotoric center (regulating tonus of vessels) and highest sub cortical sympathetic centers (managing hypothalamic-pituitary-suprarenal system). Certainly, the main role to control and manage plays brain cortex. The system is receiving information from outer environment (main source are senses) and inner environment-status of organs (main source are special receptors in vessels, lungs, heart and other organs, as baro-, chemo receptors etc.). The most important function of ANS is to provide **balance between environment and organism (adaptation), homeostasis.** After the information are processed first the lowest parts of ANS are activated, only when this activation is not sufficient to keep balance (adaptation), and/or the load is too high, then the higher parts of regulation are activated. Activity of each ANS part is well reflected in **heart rhythm variability.** Heart rhythm is almost never fully regular, also healthy heart has physiological, normal **arrhythmia** = rhythm irregularity known as respiratory (sinus) arrhythmia. The variability of heart rhythm refers to degree of fluctuation of the length of the heart beat intervals. Two people could have exactly the same average heart rate and yet when the variation is precisely measured in milliseconds it can be demonstrated that there is variance between individual beats and that degree of variance is different for different individuals under different conditions. This degree of variance between different beats is called **heart rate variability HRV.** Variability is the opposite of stability: as higher variability so lower stability and vice versa. Low variability (high stability) is typical for sympathetic activity responsible to manage regulatory functions of organism by load - **stress.** High variability (low stability) is typical for parasympathetic activity as we can see by sleeping and anesthesia.

For analysis of HRV there was developed by Russian, German and Czech scientists a unique device **CONVAR/Varicard/Variotact** with software **Dynacons.** The complex is recording standard ECG record recognizing R-peaks within 5 minutes measurement under standardized conditions. The record is then processed in PC. On the processed information there is possible to evaluate the load of organism, state of stress, degree of variability, activities of different parts of ANS etc. (see further).

Undoubtedly, the utilization of the complex is in different human activities where the knowledge of objective state of organism and its adaptation-regulatory systems is necessary incl. stress load and its management: as professions with high responsibility, pilots, managers, operators of complicated systems etc. as well as in sport (stress, regeneration). Certainly there is broad spectrum of use the complex in medicine.

Here is necessary to notice that the results of every measurement and analysis is strictly individual (i.e. to step up stairs to the 1st floor will be for somebody without significant increase of sympathetic activity with minimal heart rate increase = minimal variability change; for another the same load will be so high with need of significant activation of sympathetic system, increase heart rate and reduction of variability.

There are also differences of HRV by sex, body height and weight, age- the data are part of information necessary for precise estimation.

6. Principle methods of heart rhythm variability analysis

Statistical characteristics of dynamic cardio intervals row

HR **-** heart rate, characterizes running level of cardiovascular system activity at the moment of recording, depends on individual typological characters and different influences (use of medicaments, emotional status etc.): bradycardia, normocardia, and tachycardia
D **-** Dispersion
SDNN **-** standard deviation norm to norm, average second power deviation
CV - coefficient of variation

These parameters are generally accepted and broadly used and there are no basic disparities in their interpretations. D, SDNN, and CV- these parameters characterize state of regulatory systems. CV is a normalized estimation of dispersion (D). SDNN characterizes generally HR variability; reduced SDNN means increased activity of sympathetic part of autonomous nervous system (ANS); when lower than 50 msec then the risk of sudden death is increased 2-3times; when reduced lower then 35 msec then the risk of sudden death is 10times higher.

Variational pulsometry

Importance of variation pulsometry inheres in law that distribution of cardio intervals is a incidental event. For evaluation of variation pulsometry the **histogram** (variation pulsogram) is set up as a graphical picture of distribution of cardio intervals. Basic mathematical parameters of histogram are:

Mo **-** mode; the most credible parameter of cardiovascular system function; by normal distribution of cardio intervals and high stability the mode is close to **HR**

AMo - amplitude of mode; number of cardio intervals accordant with mode in % to value of recorded intervals; this parameter reflects the stabilizing effect of central control of heart rate, what corresponds to activation of sympathetic part of ANS.

AV - aggrandizement of variation; reflects the degree of variations of cardio intervals in recorded row; it specifies differences between maximal and minimal values of cardio intervals and that is why the parameter could be inappropriate by arrhythmias and/or artifacts; the parameter commonly reflects activity of parasympathetic part of ANS.

SI - stress index reflects degree of tension of regulatory systems and characterizes activity of sympathetic part of ANS.

Correlation rhythmography

Method of graphical representation of cardio intervals dynamic row in form of “cloud”- scatter-gram; every point means every beat where (in rectangular system of coordinates) in ordinate is “running” R-R interval and in abscissa “following” R-R interval. Importance of the scatter-gram inheres in the possibility to recognize and analyze effectively arrhythmias. Physiological importance of relations between consecutive R-R intervals is in the fact that characterizes the degree of central control of heart rhythm (activity of sympathetic part of ANS).

Autocorrelation analysis

The method is based on numerical representations of dynamic cardio intervals row with autocorrelation function; specifies inner structure of this row as an incidental process. Autocorrelation function represents graphically the dynamic of correlation coefficients, attained by mergence of analyzed dynamic row to one number in relation to its own row. After the first uplift the correlation coefficient is as lower than one as higher activity of respiratory (vagal) waves. If there are prevalent low frequency components of waves then the coefficient of correlation will be very close to one. Subsequent lifts successively reduce their values; the last lifts having negative correlation coefficients. Importance of autocorrelation inheres in estimation how central contour of regulation influences to autonomic contour. As higher this influence is so higher the correlation coefficient of first lift. Autocorrelation allows detect hidden periodicity of heart rhythm; so this parameter comprises qualitative character.

7. Autonomic nervous system-anatomy

	PARASYMPATHETIC	SYMPATHETIC
IRIS	N III	Th1
SALIVARY GLAND-A	N VII	Th2-3
SALIVARY GLAND-B	N IX	Th2-3
HEART	N X (VAGUS)	Th3
LUNGS	N X	Th4
STOMACH	-"-	Th5-9
DUODENUM	-"-	-"-
PANCREAS	-"-	-"-
SUPRARENAL GLANDS	N X	Th10-12
COLON	N X+S2-4	L1-3+L4-S1
URINARY BLADDER	S2-4	L4-S1
SEXUAL ORGANS	S2-4	L4-S1

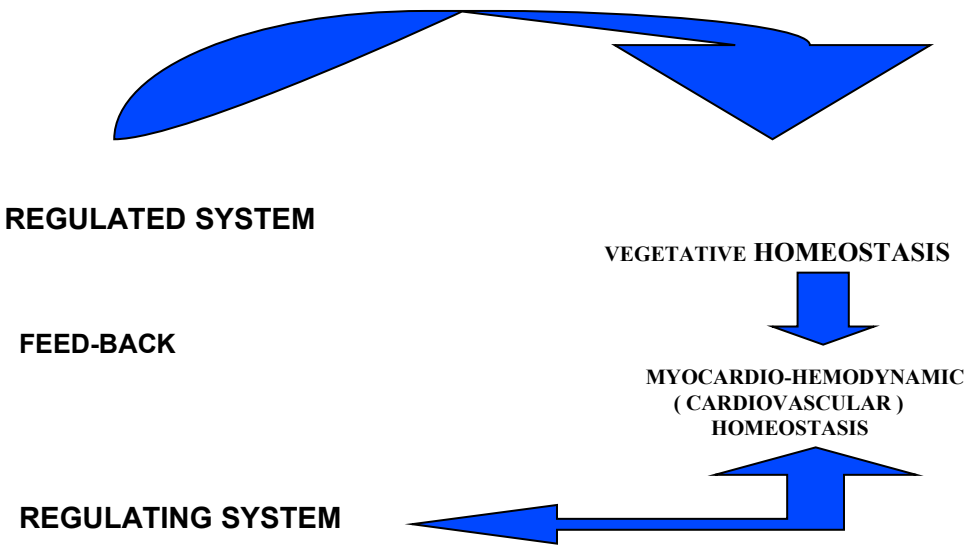
Sympathetic nerves → ganglion (acetylcholine) → ganglion (noradrenalin) → muscle, gland

Parasympathetic nerves → ganglion (acetylcholine) → muscle, gland

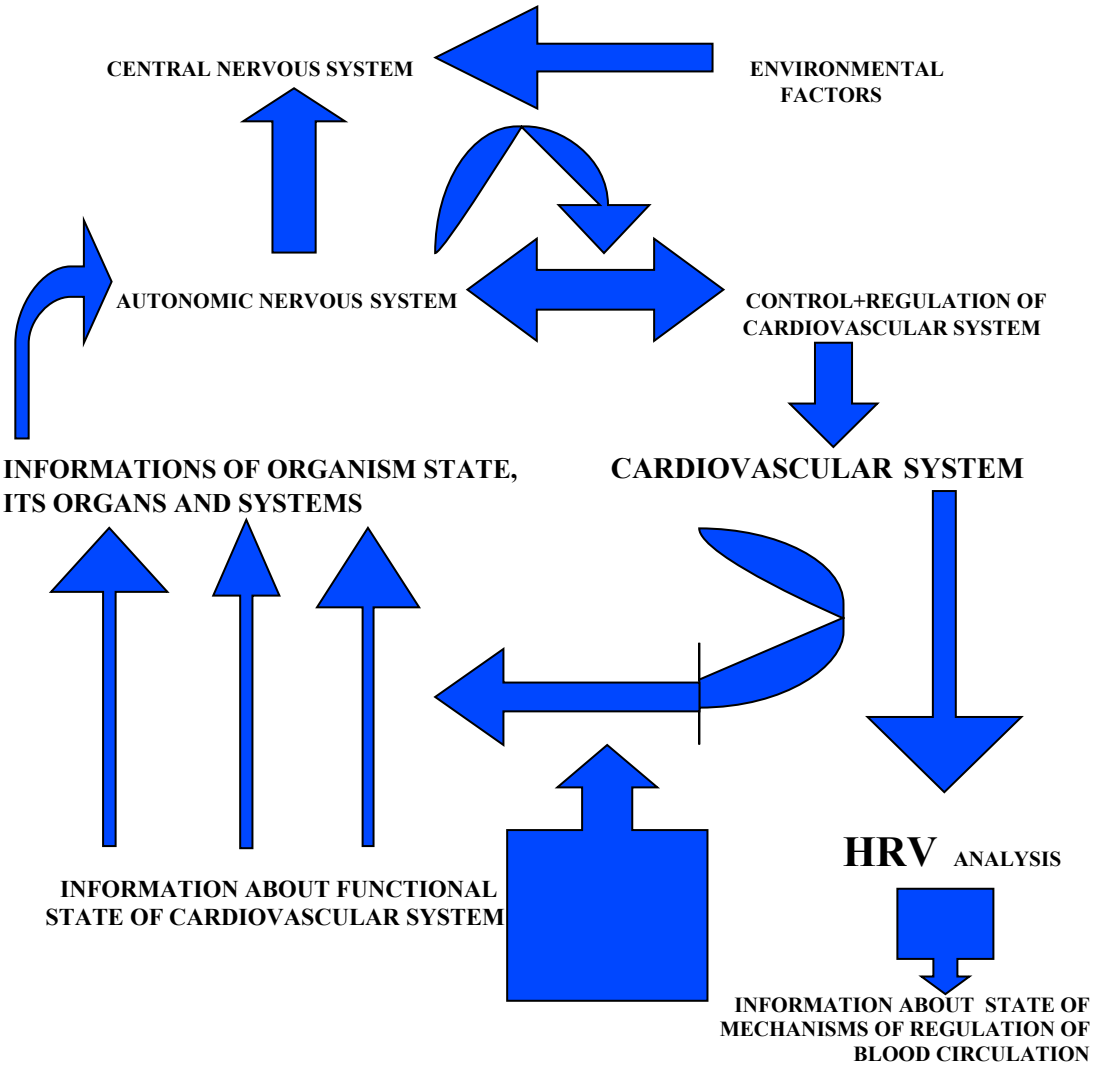
8. Autonomic nervous system - physiology

ORGAN or FUNCTION	SYMPATHETIC	PARASYMPATHETIC
Metabolism	Destructive	Constructive
Body temperature	Increase	Decrease
Liver	Glycogen disintegration	
Kidneys	Reduction of urine production	
Striped muscles	Delay of fatigue	
Unstriped muscles:		
-bronchial	Widening	Constriction
-urinary bladder		Constriction
-gall-bladder	Constriction	Relaxation
-bowels	Attenuation of contractions	Reinforcement of contractions
-pregnant uterus	Contraction	
-pupilla	Dilatation	Contraction
Glands:		
-sweat	Secretion of concentrated sweat	
-salivary	Secretion of concentrated saliva	Secretion of diluted saliva
-digestive	Secretion	
Blood circulation:		
-heart	Rate acceleration	Rate slow-down
-blood pressure	Increase	Decrease
-coronary arteries	Dilatation	Constriction
-skin and abdominal arteries	Constriction	
-brain arteries	Dilatation	Constriction
-genital organs arteries	Constriction	Dilatation

9. Biocyber model of organism and structure of vegetative and myocardial-hemodynamic homeostasis



10. Cardiovascular system as indicator of adaptation reactions of organism



11. Possibilities of strengthening the adaptation of organism, stress management, and mitochondrial medicine

Principles of mitochondrial medicine

Mitochondrial medicine has developed (within last thirty years) on the basis of living cells energy creation knowledge, recognizing intracellular biochemical reactions, knowledge of cell membrane functions, functions of cell membrane receptors, role of free radicals (better: ROS=reactive oxygen species) in physiological and pathological processes, together with enormous development of knowledge of role of Coenzyme Q-10 (Ubichinone, Ubiquinone), as well as role of some vitamins, trace elements and minerals in all the above described cell functions and biochemical reactions, physiological and pathological, esp. in the field of securing the cell energetic levels and protection against cell (and its structures) damage caused by increased development of ROS (i.e. environmental pollution, enormous mental and physical load, ageing, influence of some medicaments and medical methods etc.), and lack of ROS scavengers. The aim of mitochondrial medicine is to keep, restore (or at least partially restore) cell functions and their viability (and functions of cell's structures and organelles), in sense of prevention and as an additional method to conventional medicine; here as a means lowering side effects of some medicaments and medical methods (cancer and cardiovascular diseases etc.), and as means of increasing effects of some medicaments and medical methods (beta blockers, antidiabetics, vaccination etc.), also with possibility to decrease the dosages of these medicaments and so to reduce their side effects. Mitochondrial medicine, in any mean, does not replace (and cannot replace) therapeutic methods of modern conventional medicine, but significantly can increase efficiency of conventional medicine. Non- irrelevant fact is the direct therapeutic effect of means of mitochondrial medicine, esp. the effect of Coenzyme Q-10. Many medical studies and two international congresses on themes of Coenzyme Q-10 (and other mitochondrial medicine means) approved effective use of these means by different chronic diseases of metabolism (diabetes of both types and diabetic complications, obesity, arteriosclerosis), muscular and neurological (Parkinson's disease, Alzheimer's dis., multiple sclerosis, muscle dystrophies etc.), cardiovascular diseases (esp. coronary heart disease, hypertension, cardiomyopathies etc.), chronic degenerative and inflammatory joints and spinal diseases (osteoarthritis, osteochondropathies, spondylosis), malignant diseases (important reduction of side effects of radiotherapy and chemotherapy, acceleration of regeneration of the white and red blood cells etc.), immune system diseases (allergies, asthma etc.), dental diseases as parodontosis and many others. The very positive effect was approved in sport medicine (esp. in acceleration and improve the quality of regeneration processes after heavy training load and during sport competitions); in addition to that, the means of mitochondrial medicine are not listed as restricted doping means. Significant effect is in the field of stress management and management of stress situations, where means of mitochondrial medicine provide all processes of stress management and support development of stress reserves in systems responsible to manage the stress situations (mental and physical) - the autonomous vegetative nervous system, hypothalamic-pituitary-suprarenal system, sub cortical sympathetic centers and central nervous system, what is important for workers with very high responsibility, operators of complicated systems, and workers with high mental demand (aircraft pilots, speed-train pilots, flying navigators , bank and enterprises managers etc.).

Mitochondrial therapy: its influence to adaptation and regulatory mechanisms, measured by heart rhythm variability analysis

Mitochondrial therapy seems to be a new actual method to be able to correct health conditions with energy deficiency caused by different diseases (1; 2). The deficiency of energetic resources in healthy organism (on the cell level) is characteristic for long- term adaptation mechanism (3). Thank to this mechanism the synthesis of proteins and nucleic acids are activated what increase power of mitochondrial apparatus in the cell resulting in increase of adaptation capabilities of the organism. To keep these adaptation mechanisms functionally capable then the informational, energetic, and metabolic reserves are essential-when the reserves are inadequate, the functional insufficiency of the organism develops leading to restricted ability of the adaptation to different environmental influences, esp. under conditions of moderate or mild load.

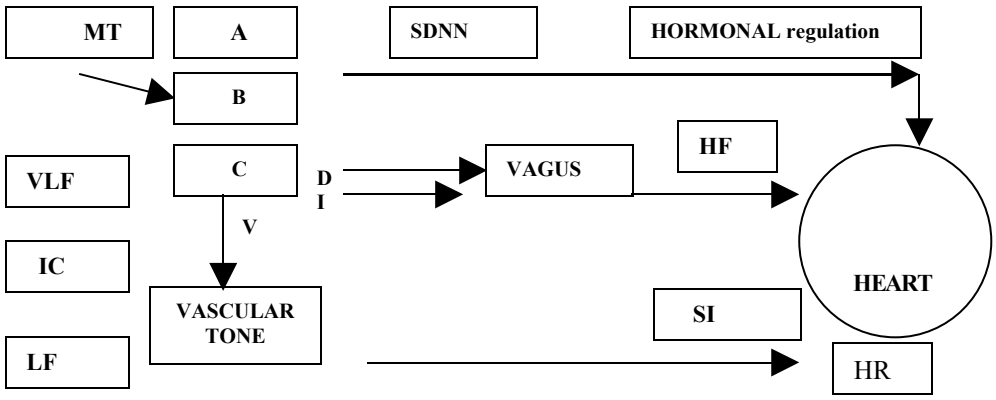
The last years there is growing importance of the methods increasing capability of cell mitochondrial apparatus with help of different natural remedies incl. Coenzyme Q-10, vitamin C, and others (antioxidants). Effectiveness of these compounds (mitochondrial therapy) was confirmed in different diseases by clinical-physiological studies (1; 2). They are available different scientific-experimental and clinical laboratory methods based on biochemical, immunologic, and radio isotopic methods which are not so advantageous for use by practical doctors-for that reason the development of methods of effectiveness of mitochondrial therapy represents important scientific and practical interest.

The method of use of heart rate variability analysis (actually very important method for estimation of functions of autonomous vegetative nervous system and of adaptation reactions of the organism) for evaluation of practical mitochondrial therapy effect is presented. The work is concentrated to study both problematic factors: evaluation of phasing of adaptation processes under mitochondrial treatment

and to process method of evaluation of effectiveness of mitochondrial therapy based on heart rate variability analysis.

The double-contour conception of heart rhythm regulation was used for estimation of HRV analysis. Principles of this concept are shown in Fig.1:
Central contour of regulation and control is schematically presented with level “A” (cortical level), “B” (higher vegetative centers, hypothalamus, pituitary gland), and “C” (sub cortical cardiovascular center). Autonomic contour is presented with vagal (parasympathetic) heart rhythm regulation, connected to respiration. Every of level of regulation can be characterized by corresponding parameters of HRV. Heart rhythm depends on triple control: accelerating and strengthening through sympathetic part of ANS, decelerating and stabilizing through parasympathetic part of ANS, and mobilizing functional reserves (operational and long lasting effect through hormonal activation). The figure shows that the effect of MT is on level “B”.

Fig.1: Model of heart rhythm regulatory system. A-level of brain regulation; B-level of high autonomous regulatory centers; C-level of sub cortical regulatory nervous centers; D, I, V-sub cortical cardiovascular center which **D**ecrease or **I**ncrease heart rate and control the **V**ascular tonus; parameters of HRV: HR, SDNN, SI, HF, LF, VLF, IC



The materials of the study are based on measurements of 65 patients of different age and sex suffering from different diseases who were treated with Coenzyme Q-10 within 2 years in Health Centers in Karlovy Vary, Czech Republic and Meissen, Germany. The study was provided within normal usual practice, what means that they begin use the Q-10 and some other natural products in recommended dosages, only: the patients use their usual medicaments without any changes; they were instructed not to change their life style etc. Coenzyme Q-10 was recommended to use in dosage: 150 mg twice daily with meals. The measurement of HRV was done-from beginning of MT-up to 15 days, up to 30 days, up to 45 days, up to 60 days, up to 90 days and last measurement after more than 90 days. Statistical significance was provided by criteria methods of ANOVA- test and STUDENT’S t-test.

MT is basically centered to increase adaptation capabilities of organism and to reduce degree of tension of regulatory systems, decrease the stress level. In this sense, the MT is adequate as the method of increase and “set up” of adaptation and defense capabilities of organism to prevent development of diseases and to successful “fight” with already developed diseases. The important fact is that the increase of adaptation capabilities of the organism is running stepwise. The 4 phases of development of adaptation reactions of organism under influence of MT were detected:

1st phase could be named as stage of functional tension and is characterized by stress reaction corresponding to first stage of general adaptation syndrome- increase of sympathetic activity. This phase is lasting not longer than 2-3 weeks.

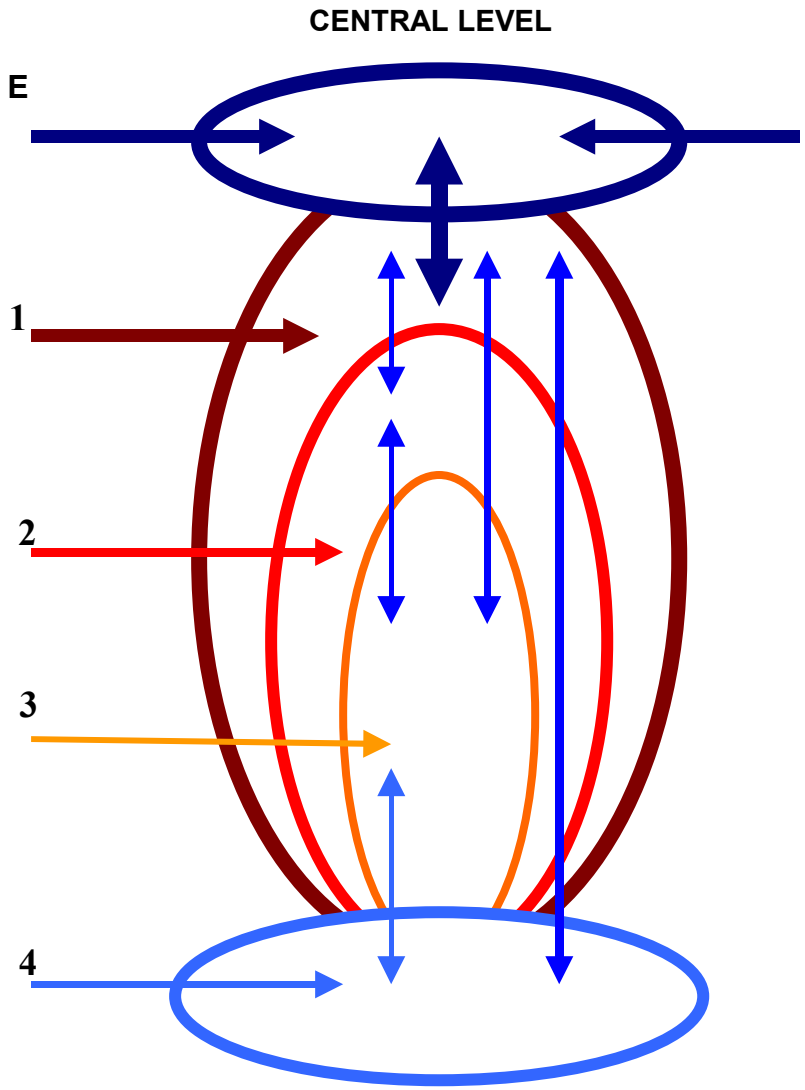
2nd phase is characterized by increase of neuro-hormonal structures responsible for energetic and metabolic processes what means increase of activities of all parts of regulation, sympathetic, parasympathetic and hormonal. This phase is lasting from 2 weeks up to 1,5 month.
3rd phase is intermediate phase between 2nd and 4th phases and is characterized as transitional phase when organism passes to new level of functioning of adaptation systems with use of hormonal regulation.

4th phase is characterized by stabilized functioning of all regulatory systems on a new level with active influence of parasympathetic part of ANS what is guaranteeing secure and stabilizing effect. 3rd and 4th phases are coming averagely after 2-3 months from beginning of MT.

The presented work of results of HRV after use of mitochondrial therapy is of preparatory character without any claim to be a real medical study. The measurements of HRV were provided under condition of routine consultation practice in both Health Centers but the results are so impressive **(threefold decrease of sympathetic activity and stress index-SI and threefold increase of SDNN-HRV variability)** that maybe this pilot observation with its results could be an inspiring tool to follow in further investigations and studies of this very actual problem. The results achieved in this observation work were-for the authors-not awaited in full extension. Basal and significant effect of MT on changes of HRV analysis stimulate authors to analyze materials of 65 patients with aim to know more about mechanisms of MT influence on adaptation capabilities of organism.

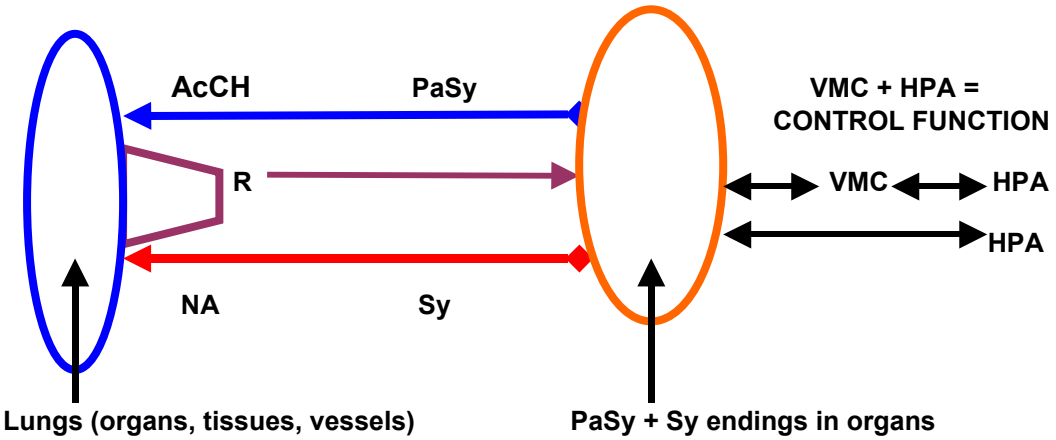
Certainly again is necessary to notice that the presented observational work is of preparatory character as well as the theoretical conclusions. The conclusions of this work need more detailed, especially prepared approval in multicentric study with more extensive samples.

FUNCTIONAL MODEL OF ANS REGULATION



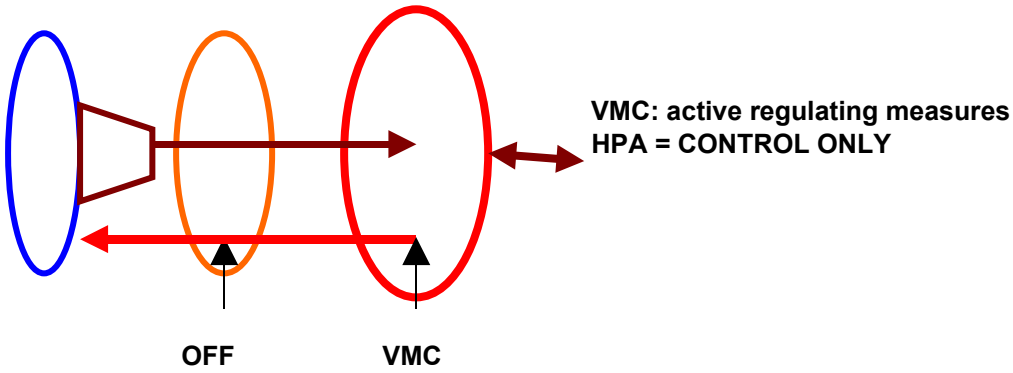
E: Environment; 1: HPA axis (hypothalamic-pituitary-adrenal axis); 2. VMC (vasomotoric centre); 3. AIL (autonomic independent level); 4: Organs, tissues, vessels

Automatic (independent) sphere: sympathetic and parasympathetic



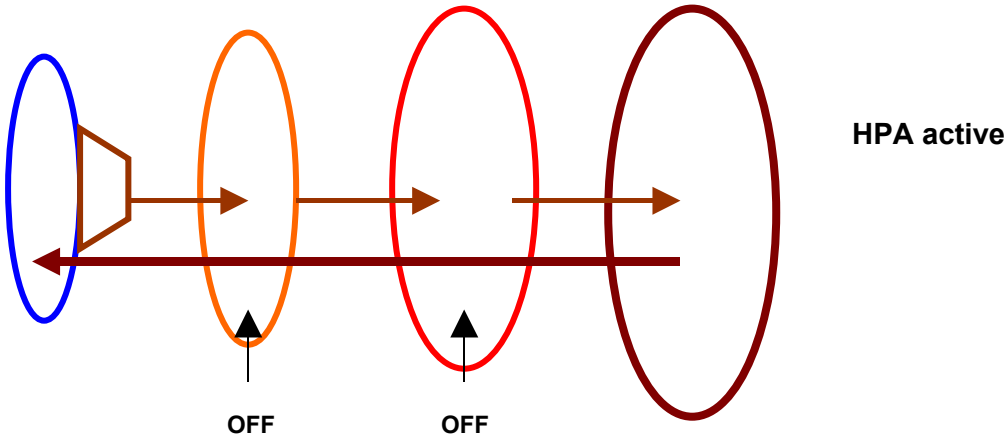
AcCH: acetylcholine; PaSy: parasympathetic; VMC: vasomotoric center; HPA: hypothalamic-pituitary-adrenal axis; R: receptor (afferent signals); NA: noradrenalin; Sy: sympathetic

2. Vasomotoric sphere: Sy only



Independent level out of control; regulating measures through activity of vasomotoric center

3. Hypothalamic-pituitary-adrenal axis: Sy only



Independent level and vasomotoric center out of control; regulating measures through HPA axis activity

AUTONOMIC REGULATION OF HEART RHYTHM AND FUNCTION

PARASYMPATHETIC:

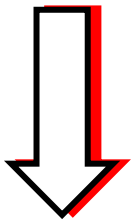
Vagal cardiac nerves:
- **right vagus to the right atrium, concentrated in sino-atrial node SA-N**
- **left vagus concentrated in atrio-ventricular node (AV-n)**

Sphere of action:
- **negative chronotropic (decrease of frequency)**
- **negative dromotropic (decrease of atrio-ventricular transfer)**
- **negative ionotropic (decrease of heart contraction power)**
- **negative bathmotropic (decrease of myocardial irritability)**

SYMPATHETIC:

Sympathetic cardiac nerves: endings symmetrically all over the heart

Sphere of action:
- **positive chronotropic (increase of frequency)**
- **positive dromotropic (increase of atrio-ventricular transfer**
- **positive ionotropic (increase of heart contraction power)**
- **positive bathmotropic (increase of myocardial irritability)**



Atrial innervations is parasympathetic and sympathetic
Ventricular innervations is mostly sympathetic

MECHANISMS OF CHRONOTROPIC ACTION

Based on speed of diastolic spontaneous depolarization.
Parasympathetic acetylcholine increases permeability of sino-atrial cells for K+ (from cells to extra cellular space) causing delay of depolarization process.

Sympathetic noradrenalin decreases permeability for K+ (from cells out), and simultaneously increases permeability for Na+ (from extra cellular space into cells) causing acceleration of depolarization process of sino-atrial cells and of Purkyne's fibers.

MECHANISMS OF INOTROPIC ACTION

Parasympathetic **mechanism similar to the above described: increase of permeability of muscle cells for K+ evocate** shortening **of time of action electrical potential of atrial-myocardium cells and** decrease of contractions power.

Sympathetic **mechanism: noradrenalin stimulate Ca+-Na+ channels what increases penetration of Ca+ into myocardial cells what evocate** increased power of contractions and shortening of contraction time.

MECHANISMS OF DROMOTROPIC ACTION

Parasympathetic influence: lowering of idle membrane potential and deceleration of Na+ channels → **slow down** of atrio-ventricular transfer (**up to** complete transfer stop=**complete atrio-ventricular block**).

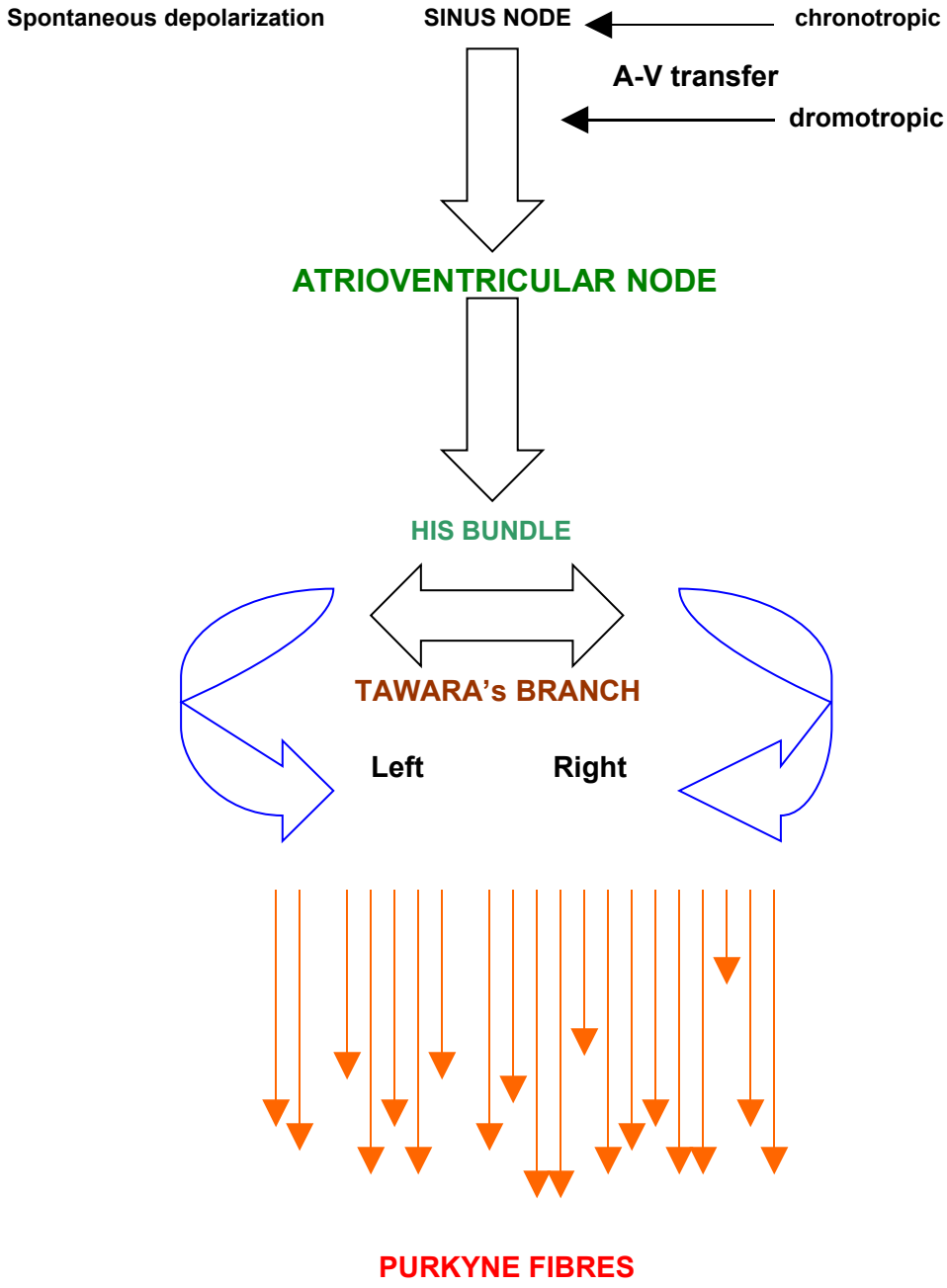
Sympathetic influence: increasing of idle membrane potential and acceleration of Na+ channels → **acceleration of atrio-ventricular transfer.**

MECHANISMS OF BATHMOTROPIC ACTION

Parasympathetic influence: enlargement of difference **between values of** idle **membrane potential and of** threshold **stimulation** potential **+**attenuation **of membrane** Na+-K+ATP-ase **activity.**

Sympathetic influence: making threshold stimulation potential close to idle **membrane potential** + increase of Na+-K+ATP-ase **activity.**

Heart conduction system-schema



Strength of contraction = inotropic

Myocardial irritability = bathmotropic

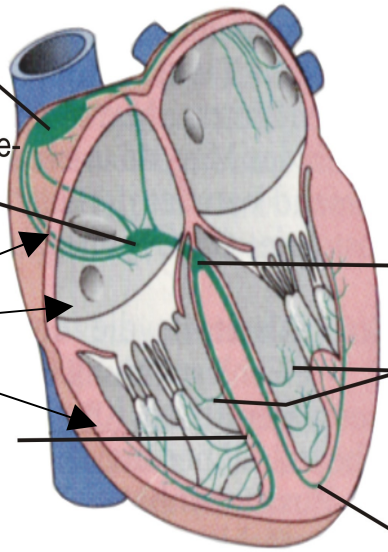
Conduction System

Parasympathetic

Right vagus → sinus node

Left vagus → vestibule-chambre-node (AV node)

Sympathetic → right branch of conduction system (TAWARA)



trunk of conduction system (HIS branch)

Purkyne fibers

left branch of conduction system

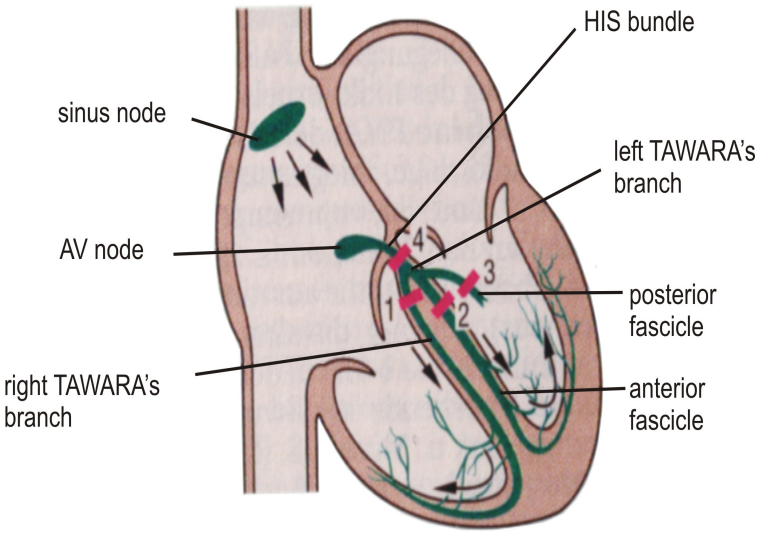
Tawara's Branch

Parasympathetic:

Negative
- **ino**
- **dromo**
- **chrono**
- **bathmo**

Sympathetic:

Positive
- **ino**
- **dromo**
- **chrono**
- **bathmo**



Humoral regulation

Adrenergic β-receptors react on noradrenalin and adrenaline. The stimulation with NA and A evokes the same response as the sympathetic stimulation.

Acetylcholine stimulates muscarinic receptors and evokes negative chronotropic and negative inotropic; by some kinds of heart cells also negative dromotropic = analogue with parasympathetic stimulation.

Cellular regulation

Fully autonomic regulation of heart performance on cellular level: Starling' law = heart work is equal to its diastolic charge – heterometric regulation of heart output.

Some another hormonal influences:

- **Glucagon – positive inotropic + chronotropic**
- **Thyroid gland hormones – positive inotropic + chronotropic**
- **Prostaglandin E_2 – positive inotropic; in cells with reduced idle potential also positive chronotropic + bathmotropic**
- **Progesteron – negative inotropic + chronotropic + bathmotropic**

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Stress – homeostasis and hormonal regulation

MUDr. Michael Kucera

(Homeostasis (by Cannon) comprises different physiological processes to restore normal system state when infringement happened)

1. **Alarm reaction:**
   - Activation of sympathetic part of autonomic nervous system with output of adrenaline and noradrenalin = increase of BP, glycogenolysis (hyperglycemia), lipolysis (securing metabolic substrates: glucose, free fatty acids) for muscle functioning = preparing "fight or escape" reactions. Simultaneously the CRH-ACTH-Cortisol system is activated as well as POMC system.
   - Increase of anti-diuretic hormone (vasopressin) output
   - Increase of prolactine output
   - Increase of aldosterone output

2. **Adaptation phase:**
   - POMC and CRH-ACTH-Cortisol systems are further activated
   - Cortisol influence: gluconeogenetic, lipolytic = securing metabolic substrate (fuel) for energy production. High output of cortisol is causing proteokatabolic reactions, immunosupression, bones demineralization

3. **Exhaustion phase: the organism's failure:**
   - If stress outstays for a prolonged period and/or is too intensive
   - If cortisol output is diminished (damage of adrenal gland)
   - Hypotension, shock, heart failure

Acts of hormones:

1. **CRH** = Corticotrophin releasing hormone
   – activates ACTH output
2. **ACTH** = Adrenocorticotropic hormone
   – stimulates cortisol and aldosterone output
3. **Cortisol**
   - In liver increases gluconeogenesis and enhances effects of glucagons, adrenalin and noradrenalin
   - Increases production of glycogen (in presence of insulin)
   - Decreases glucose input to the muscles (so sparing glucose for the brain)
   - In fatty tissues increases lipolysis
   - High output causes hyperglycemia (exhaustion of pancreatic B-cells – steroid diabetes)
   - Low output causes hypoglycemia (break of a gluconeogenesis)
   - Proteokatabolic action – inhibition of proteosynthesis and acceleration of proteolysis
   - Slowdown of healing processes
   - Skin becomes thin
   - Demineralization of bones (osteoporosis), inhibition of bone formation
   - Involution of immune system organs and tissues, reducing number of eosinophiles, leucocytes, and lymphocytes = immunosuppressive action, reduce of resistance against infections
   - Anti-inflammatory effects

4. **Aldosteron**
   - Maintains normal sodium and potassium concentrations in blood
   - Maintains volume of extra cellular fluid
   - Activity depends on angiotensin II and ACTH

5. **POMC =** Propio-melano-cortic system
    - Precursor of ACTH
    - Precursor of beta-endorphin and met-encephalin (natural pain-killers)
    - Precursor of beta- and gama-lipotropins (effect unknown)
    - Precursor of alpha-, beta-, and gamma MSH (Melanocytes Stimulating Hormone (effect unknown)

6. **Catecholamines** (dopamine, adrenalin, noradrenalin)
    - Effect on heart beta-1-receptors: increase of myocardium irritability and heart frequency, increase of heart output
    - Effect on vascular alpha-receptors: vasoconstriction, increase of BP
    - Variable effect on un-striated muscles: relaxation and/or constriction of uterus, relaxation of intestines muscles (slowdown of peristaltic), relaxation and/or constriction of urinary bladder and intestine sphincter muscles, relaxation of bronchial muscles
    - Increase of metabolism
    - Thermogenic effect
    - Liver glycogenolysis (output of glucose)
    - Lipolysis in fat tissues (output of free fatty acids and glycerole)

Mechanism of action: activation of specific membrane receptors (adrenoreceptors) of heart, liver, and other cells.
Receptors are of two kinds:

1. **Alfa-receptors** – in vessels, intestines, Langerhans islets of pancreas, skin (sweating), and in uterus.
2. **Beta-receptors** (subgroups beta-1 and beta-2) – in heart, vessels, kidneys, fat tissue, and bronchioles.

Homeostasis is (generally) stability of inner environment of organism; here, the most important factor is the stability of interstitial part of extra cellular fluid (ECF). Second part of homeostasis is blood and other organism fluids: they are in dynamic balance with interstitial fluid. Most of regulatory mechanisms (to keep stability of inner environment – composition of ECF, in particular its interstitial part) act on principle of feed back: changes from norm are detected by sensitive cell, and signal from this cell is a start for compensating reactions**.**

Homeostasis – regulated systems:

1. Osmolality
2. Acid basic balance (pH)
3. Natremia (sodium blood level)
4. Kalemia (potassium blood level)
5. Calcemia (calcium blood level)
6. Phosphate (phosphates blood level)
7. Magnesemia (magnesium blood level)
8. Cholesterolemia (cholesterol blood level)
9. Proteinemia (protein blood level)
10. Glycemia (glucose blood level)
11. Energy, metabolism and oxygen consumption
12. Thermoregulation
13. Blood pressure and heart function
14. Volume of blood, extra cellular and intracellular fluids

Homeostasis systems

System	Norm (mmol/l)	Increased by	Influence	Decreased by	Influence
Osmolality	280-300	-Sodium retention -Hyperglycemia	-High aldosteron -Low vasopresin -Low insulin	-Sodium deficiency -Water retention	-Low aldosteron -High cortison -High vasopresin
Acid-base balance	pH 7,35 - 7,45	-Respiratory acidosis -Metabolic acidosis	-CO_2 retention -Insulin deficiency -Thyreo-toxicosis -Starvation -Kidney disease	-Respiratory alkalosis -Metabolic alkalosis	-CO_2 deficiency -Diuretics -High aldosteron
Natremia	130-148	-Aldosteron -Cortisol		-Atrial natriuretic peptide -?Hypothalamic natriuretic hormon? -Osmotic diuresis -Plasma dilution	
Kalemia	3,8-5,1	-Cortisol deficiency -Aldosteron deficiency		-Aldosteron	
Calcemia	2,25-2,9 (ionisied 1,05-1,3	-Parathormon (increased bone resorption) -Calcitriol (increased calcium absorption from intestines)		-Calcitonin (increasing calcium built-in bones)	
Phosphatemia	0,65-1,62	-Calcitiol		-Parathotmon -Calcitonin	
Magnesemia	0,75-1,5	-Renal failure		-Parathormon deficiency -Calcitriol surplus	
Chole-sterolemia	4-6 (age related)	-Hypothyreosis -Diabetes mellitus	-Androgens -Gestagens	-Thyroxin -Triiodthyronin	
Proteinemia	64-82 g/l (albumin 35-55)	-Androgens (proteosynthesis generally and in target tissues) -Estrogens (bones and target tissues) -Somatotropin and other growth factors -Thyroxin in physiological concentrations (proteosynthesis increase)	-Decrease of proteosynthesis	-Thyroxin and triiodthyronin in higher concentrations -Cortisol (+immunosupression)	
Glycemia	3,9-6,7	-Glucagon -Cortisol -Adrenalin -Somatotropin -Somatoliberin (indirectly)		-Insulin	

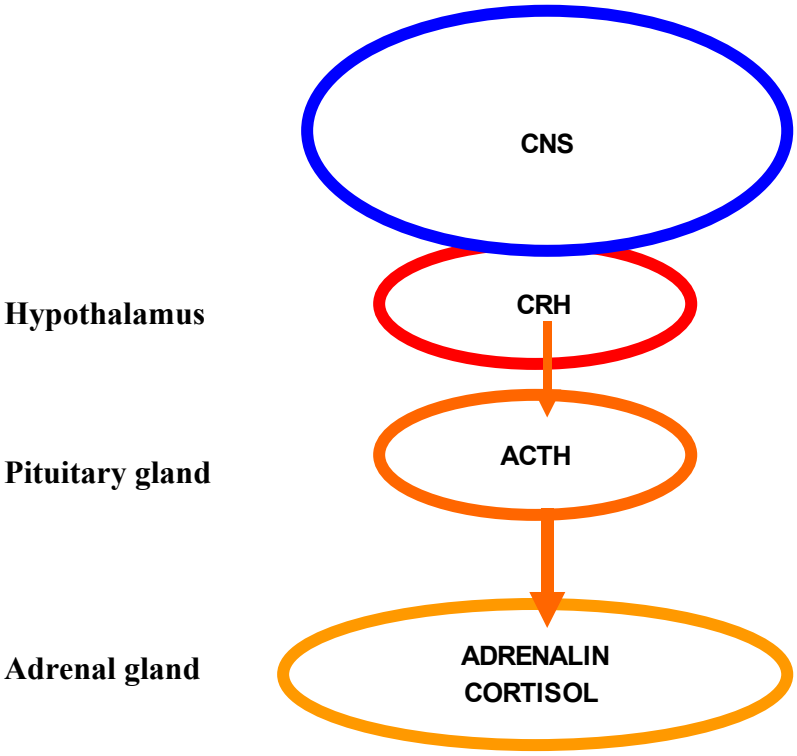
Energetic metabolism and oxygen consumption

Basal metabolism	1800 kcal/24 hours = 7600 kJ/24 hours
Increased by	-Thyroxin -Triiodthyronin (conversion of thyroxin to triiodthyronin -Adrenalin -Noradrenalin -Glucagon -Cortisol
Decreased by	-Thyroxin deficiency -Reverse triiodthyronin (biologically inactive form; development in tissues under condition of starvation and/or fever) -Insulin

Blood pressure homeostasis

Blood pressure	Norm 120/80 mmHg (limit WHO 140/90 mmHg
Increased by	-Angiotensin -Endotelin -Adrenalin -Noradrenalin -Aldosteron -Glucocorticoids
Decreased by	-ANP = atrial natriuretic factor -EDRF = endothelial relaxation factor – NO -Quinines

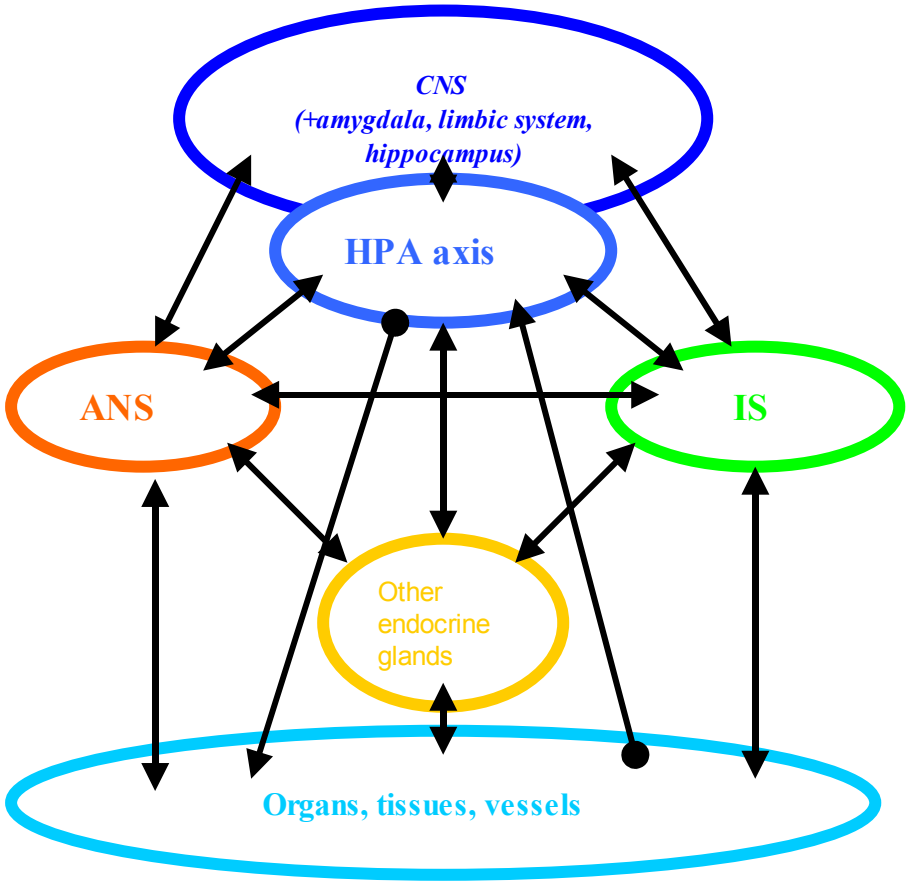
HPA axis schema



Interaction with:

- **ANS**
- **Hippocampus (memory formation, motivation, mood)**
- **Amygdala (fear reaction to danger)**
- **Limbic system (motivation, mood)**
- **Brain regions controlling body temperature, appetite, and pain**
- **Other glandular systems (reproductive hormones, growth hormones, thyroid hormones)**
- **Immune system**

Total integrated system securing homeostasis



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