MITOCHONDRIAL THERAPY: SOME QUESTIONS of AUTONOMIC REGULATION MECHANISMS with USE of HEART RATE VARIABILITY

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Foreword

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 is 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. Effectiveness of these compounds (mitochondrial therapy) was confirmed in different diseases by clinical-physiological studies (1; 2). Further development (and practical introduction) of this perspective therapeutical method is limited by two factors. Firstly, exact knowledge of mechanisms of mitochondrial therapy influence on the organism and, esp., **phasing** of the influence and its concrete **signs**. It means (for attending doctor) to know how to evaluate adequateness of the mitochondrial therapy by different diseases and evaluation of the effect of mitochondrial therapy by different stages of diseases. Secondly, need of availability of simple, easy accessible, and adequate methods of estimation of the mitochondrial treatment. They are available different scientific-experimental and clinical laboratory methods based on biochemical, immunological, and radioisotopic 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.

In this work 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.

METHODOLOGY AND MATERIAL.

Analysis of heart rate variability (HRV) – it is actual methodology and technology of evaluation of the states of regulatory systems of organism, particularly of functional states of different parts of autonomous (vegetative) nervous system (ANS). Important studies of HRV begun with break of 1960 in Russia (U.S.S.R.) (4), esp. on studies of development of HRV in space medicine (3; 5). That times different studies of use of HRV in cardiology, surgery, occupational physiology, sport medicine, and experimental physiology were carried on in a large scale; thanks to them the very important new knowledge of indicators and parameters of HRV were received to estimation of not only vegetative balance but also the evaluation of non-specific adaptation reactions. All the results are summarized in "Mathematical Analysis of Changes of Heart Rhythm by Stress" (3), further worked out by studies of problems of **donosological** diagnostics (6; 7) – the diagnostics of health conditions prior the symptoms of disease has developed.

At present time, the methods (and importance) of HRV analysis are generally accepted and every year is bringing new knowledge with broader use of HRV by different medical professionals (8; 9). Further development of HRV is linked with stormy development of computer technologies. One of the most important studies of HRV analysis is related with 20 years lasting study of 20.000 different people groups: the reason of the study was to detect different stages of adaptation reactions of the organism to different influences of outer environment ("estimation of adaptation capabilities of the organism and risk of development of diseases") (7).

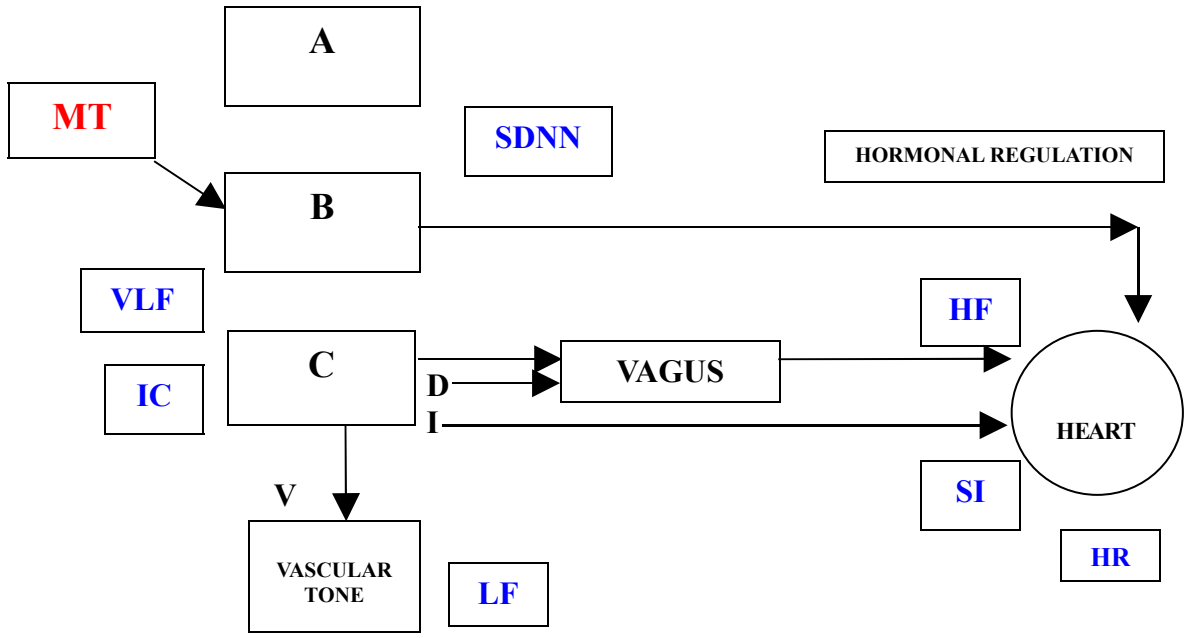
Leading factor of diseases development is reduce of adaptation capabilities of the organism what is possible to detect by degree of tension of regulatory systems. As lower functional reserves of organism, so higher should be tension of regulatory mechanisms to secure adequate energetic and metabolic functioning of systems and organs. To measure the degree of regulatory systems tension (activity) the method of HRV analysis is to be used with benefit. For evaluation of adaptation capabilities of organism, degree of activity (tension) of regulatory systems, level of stress the complex

hardware-software "Varicard" was used. All measurements were realized under standard conditions in quiet room with standard temperature in sitting position; the recording time was 5 minutes.

Table 1: List of parameters of HRV included into study of MT (Mitochondrial Therapy)

HRV parameter	Short name	Physiological interpretation
Heart rate	HR	Mean level of cardiovascular function
Standard deviation	SDNN	Total activity of regulatory systems
Stress index	SI	Activity of sympathetic system
High frequency spectrum of HRV	HF, %	Activity of parasympathetic system
Low frequency spectrum of HRV	LF, %	Activity of vasomotoric center
Very low frequency spectrum of HRV	VLF, %	Activity of energetic and metabolic levels of regulatory system, central regulation
Index of centralization	IC	Prevalence of activities of central levels of regulatory systems
Index of activities of regulatory systems	IARS	Summary of the activities of all regulatory systems

The double-contour conception of heart rhythm regulation was used for estimation of HRV analysis (10). 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, hypophysis), and "C" (subcortical cardiovascular center). Autonomous 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 autonomic regulatory centers; C-level of subcortical regulatory nervous centers; D,I,V-subcortical cardiovascular center which decrease (**D**) or increase (**I**) heart rate and control the vascular (**V**) 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 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 b.i.d. 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.

RESULTS of MEASUREMENTS.

The table 2 demonstrates statistical results of measurements in time phases after beginning of MT with changes of different HRV parameters. Heart rate **HR** increases for about 7-10 beats/min after 1 month of MT and persists higher another 3 months and later**. SDNN** within first 15 days decreases but at the end of first month increases and within 4th month of MT reaches double value. Stress index **SI** increases within first 2-2,5 months to double value but the 4th month is decreased on 1/3 of starting value. The other parameters are statistically significant only after 1,5-2 months of MT: increase of **HF** power and decrease of **LF** power, the values are lasting up to 4 months of MT. The VLF power decreases only in 4th month of MT**. IC** decreases within first two weeks of MT but after 1,5-2 months of MT significantly increases and within 4th month again significantly decreases on lower values to default ones. Integral parameter of activities of regulatory systems **IARS** regularly decreases within all 4 months of MT.

Table 2

Average days of MT	0	13	25	43	52	73	103
HR	75,7	73,8	**82,3***	76,5	**84,2****	79,4	**82,2***
SDNN	43,0	**33,1***	**68,9***	56,1	59,6	66,7	**115,8****
SI	571,6	**623,5***	**852,3****	**987,6***	504,5	**857,5***	**193,7****
HF, %	44,9	45,3	42,6	**55,5***	39,7	47,9	**60,5***
LF, %	32,4	29,2	29,7	**26,6***	31,6	30,6	**25***
VLF, %	22,6	25,4	27,5	21,2	28,6	21,4	**14,4***
IC	2,55	**2,09***	2,13	**1,43****	**4,02***	2,97	**1,26****
IARS	4,83	4,9	4,81	**4,33***	4,75	5,33	**4,0***

**- Statistical significance high (p<0,05)

* - Statistical significance moderate (p<0,10)

Fig.2 demonstrates changes of HRV parameters after the 3 months course of MT. There is demonstrated that under influence of MT the significant increase of summary regulation activity what shows up the threefold increase of general HRV corresponding to SDNN together with 1,3fold increase of parasympathetic activity-HF, %, and threefold decrease of sympathetic activity-SI. Twofold decrease of IC is caused by decrease of activities of low frequencies of 1st and 2nd order (LF, %; VLF, %). It is necessary to notice the very small change in IARS what corresponds to individual different types of vegetative regulation. Moderate increase of HR under condition of increase of parasympathetic activity and decrease of sympathetic activity corresponds to the activation of hormonal and energetic-metabolic processes in the organism necessary to increase the activity of cardiovascular system responsible for transport of oxygen and nutrition.

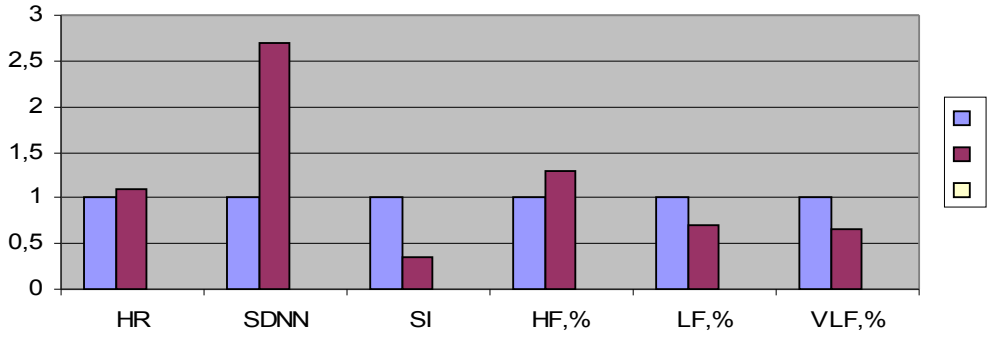


Fig.2

Hypothesis of serious role of hormonal system in regulatory processes and its influence on changes of vegetative balance during MT should be demonstrated by analysis of HRV parameters changes: Table 1 data shows that first 2 weeks of MT the sympathetic activity is increasing (reduced SDNN and increased SI), with decreased IC. However, the power of respiratory frequencies is not decreased (HF,%), it is possible to suppose the hormonal component of sympathotonic reaction. Following phase of MT (M=25) is characterized by strong rise of SI together with increase of SDNN and HR what is possible to explain as the influence of higher regulatory-control centers of ANS. Plausibility of the explanation is well-marked by the fact that after 1,5 month (M=45) of MT we can detect increase of activities of both parts of ANS; SI is doubled and HF, % 1,5fold higher in comparison with values at the beginning.

Within 2 months course of MT the "comeback" of HRV parameters to the entering values is present but with significant increase of HR and IC. IC value increase means that the higher activity of cardiovascular system is of central origin: bound to changes of vegetative balance based on humoral-hormonal influence. This effect is not fixed as it is seen in further course of MT (M=73): the new increase of sympathetic activity is present (most probably of hormonal origin). The fixed, permanent effect of MT is demonstrated on results of HRV analysis after 3 months of MT course (M=103), as shown in Table 2 and Figure 2: the data of parameters of HRV are presented with fixed moderate increase of HR together with regular increase of parasympathetic activity (permanent growth of HF, %) and significant decrease of SI. Further, there is the significant decrease of IC and significant increase of SDNN but although HR is not decreasing but increasing, then the growth of parasympathetic activity can be explained only by humoral-hormonal influence originated in higher vegetative centers which regulate energetic and metabolic processes of organism (10; 11; 12). Figure 3 demonstrates schematic influence of MT to processes of vegetative regulation in different phases.

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. We have detected 4 phases of development of adaptation reactions of organism under influence of MT:

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.

SUMMARY.

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

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