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Department of Functional Diagnostics and Rehabilitation

PROCEEDINGS

SYMPOSIUM

**CHRONOBIOLOGY AND NON-INVASIVE METHODS  
IN CARDIOLOGY**

Dedicated to the 80th Anniversary of Masaryk University Foundation

Edited by: Halberg F., Kenner T., Fišer B., Siegelová J.

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## Masaryk University 80<sup>th</sup> ANNIVERSARY

The history of Masaryk University closely reflects the history of the Czech nation. The independent Czechoslovak Republic was founded in October 1918. The second Czech university in the country was established with the aim to promote the scientific and cultural development and to create a centre of academic life in Moravia. The university was named after T.G. Masaryk, the first Czechoslovak president, whose continuous and strong support had played a decisive role in the establishment of the university.

In 1919, the Faculty of Law and the Faculty of Medicine started their teaching programmes, in 1921 followed by the Faculty of Arts and Faculty of Science. In the first republic (1919-1939), the university achieved high pedagogic and scientific recognition in many areas, in medicine in the fields of physiology, anatomy, histology, surgery and internal medicine. During the second world war, the Masaryk University was closed and many personalities of the university staff and students were prisoned and lost their lives.

In 1945, teachers and students resumed work immediately. The political development in Czechoslovakia after 1948 caused the change of the name of the University. The University bore the name of J.E.Purkyně, a famous Czech physiologist, between the years 1960-1989.

The revolution in November 1989 marked a landmark in the life of the country. The university in Brno resumed its original name Masaryk University in 1990.

At the end of the 20<sup>th</sup> century the Masaryk University became a modern institution promoting the advanced teaching in the fields of medicine, philosophy, law, natural science, economics and administration, education and informatics, and providing research in all the above mentioned fields. The Masaryk University contributed to the cultural and scientific development of the Czech Republic.

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# **CHRONOBIOLOGY**

**Prof. Dr. Franz Halberg**  
80 years of age

As we all are aware, Prof. Halberg has dedicated almost 50 years of his life to chronobiological research. His studies represent a new original Minnesotan branch of science based upon resolving the chronome and its mapping from womb to tomb. Womb -to- tomb chronome initiative consists in extension of a unique existing data archive and reference standard bank on variables of biomedical interests: heart rate, blood pressure, body temperature, a host of chemical determinations on blood, saliva and urine.

Every biologic variable is characterized by chronomes, describing the structure of rhythms and trends in its physiological and pathophysiological range of variations. The chronome provides new endpoints for ruling in health or recognizing increased disease risk before the occurrence of overt illness. Prof. Halberg 's long lasting basic scientific work is directed, at the beginning of the new century, to chronobiometry (physiological and statistical evaluation of the genetically anchored and cosmically influenced time structures), chronobioengineering (collecting physiological data by means of sophisticated equipment), chronobiological diagnosis of disease risk syndromes, and the chronotherapy, improvement of prognosis and treatment in different fields of medicine, and last but not least, chronoastrobiology focusing on rhythms and broader chronomes to explore the origins of life.

Needless to say, not only those researchers who are deeply interested in this field, but also others who are less interested, have all been strongly impressed by such incomparable records of work achieved by Prof. Halberg. In recent years he has been strenuously promoting chronobiological research further in the field of clinical medicine on the worldwide scale. We feel honored to have had the possibility of cooperation with Prof. Halberg since 1980s. At the beginning of the next century Prof. Halberg is full of energy directed to discovering new laws of chronobiology. Ad multos annos!

## WHAT CHRONOBIOASTROBIOLOGY COULD DO ON EARTH AND IN SPACE

Halberg F., Cornélissen G., Schwartzkopff O.

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Chronobiological studies enable diagnosis and testing of treatments for disease risk syndromes, such as circadian hyper-amplitude-tension (CHAT), that precedes or complicates the occurrence of high blood pressure or other overt vascular disease. As an indicator of the risk of stroke, CHAT, that is circadian blood pressure overswinging, exceeds other factors in terms of its association with subsequent catastrophic disease. Herein, we also invite participation in a project on "The BIOSphere and the COSmos"(BIOCOS). BIOCOS aims at creating a system of physical and physiological monitoring and archival organization that serves immediately for disease risk syndrome detection, while it also provides new insights into functional integration and adaptation in health and disease.

The world of Johannes Kepler, a Praguian from 1600, when he became the assistant in Tycho Brahe's observatory, was extended repeatedly by physicists, first by those in radio- and rocket astronomy and then by those in X-ray and gamma-ray astronomy. The new astronomies revealed previously unimaginable ways to the stars (*Friedman, 1997*). In the footsteps of the physician William Gilbert, who published a classical treatise on magnetism (*Gilbert, 1900*) in the same year Kepler joined Brahe, biomedicine may again serve physics and inquire, in previously equally unimaginable ways, through ontogeny and phylogeny, not only about where we are and perhaps about what we are, but also about where we were in the distant past (*Halberg et al., 1991*). Thereby, we may also learn about the chronomes of past environments. We ourselves are also ever-changing structures in time (chronomes). We are learning more and more about the chronome's three major elements, multifrequency rhythms, chaotically appearing changes and trends in the characteristics of both rhythms and chaos (*Otsuka et al., 1997 and Otsuka et al., 1997*).

An International Womb-to-Tomb Chronome Initiative (IWTCI), coordinated by one of us (*Cornélissen & Halberg, 1994 and Halberg et al., 1995 and Halberg, 1997*), is ongoing worldwide, albeit on a back burner.

As a first goal, the tools now offered for the diabetic should be equally developed into a system recommended by the health care profession for a chronodiagnosis and chronotherapy sui generis of vascular disease risk syndromes. These new clinical entities involve blood pressure, heart rate and their variabilities. The long term data recording requirement (for the span of a week or longer), two companies not only reach but surpass it by producing at this time at least an ambulatorily functioning monitor, providing a record for 14 days. One of the devices is simple to use, involving no more than the pressing of

a button to start it, and the daily charging of the instrument costs only electricity and can perhaps be done during the time spent in the bathroom each morning. In the case of a diagnose elevation of the 24-hour rhythm-adjusted blood pressure mean (MESOR), i.e., MESOR-hypertension, the continued monitoring to assess the effects of treatment can be checked via a control chart (*Halberg et al., 1995 and Siegelová et al., 1996*). The use of this approach has been documented from Brno in cooperation with the local pharmaceutical company Lachema (*Siegelová et al., 1996*). Thus, Brno continues to provide leads in the change from an expensive since ineffective, single sample medicine based on snapshots of a roller coaster to the longitudinal chronobiologic life-strand analysis in the 1990s, just as it led in the past with Gregor Johann Mendel in genetics and Kurt Goedel in mathematics.

Eventually, the mathematical task to assess the genetically anchored chronomes may be carried out fully automatically and linked to monitors of physical variables. The disease risk assessing tools may well follow the precedent of wristwatches and computers by becoming household items. Here lies the industrial challenge. The development and provision in Brno by Jan Penaz of instrumentation for the stationary beat-to-beat monitoring of human blood pressure has been followed by implanted devices that have performed the same beat-to-beat monitoring on ambulatory humans for a span of 15 months on the right side of the circulation (*Bennett, 1997*), still awaiting its counterpart on the left side, another challenge to industry. With such tools available, drug effects come to the fore, such as a variance transposition in which a prominent circadian chronome component is replaced by one of about 3.5 days. The latter cannot be assessed, of course, by the 6-hour (*Sheps & Canzanello, 1994*) and the 24-hour monitoring schedules whose limitations in record length must be overcome.

Medtronic's REVEAL, an implanted electrocardiograph, serves to determine retrospectively the precedents of a syncope. At any time, it keeps the last 44 minutes of an electrocardiogram in its memory. This approach should be extended by appropriate software for windowing to derive rhythm and chaos parameters, thereby compacting the data and recycling them (*Halberg et al., 1994 and Halberg et al., 1997*) for the interpretation of alterations in windows prepared concomitantly in different spectral regions, including windows at lower and lower frequencies, including the resolution of about 11-year cycles, once the record length permits this endeavor. Thus, one could diagnose symptomatically silent disease risk syndromes and, when need be, close the loop to treatment by an automatic drug or electrical treatment device. Furthermore, the same device may communicate with physical monitoring; it may be prompted by the latter to save original beat-to-beat data, for instance, in the case of magnetic storms in the interplanetary space and beyond, and, if indicated, to initiate countermeasures (see below). There are several reasons for this seemingly far-fetched suggestion. First, the same approximate half-week is seen during 267 days in human isolation, in both the human heart rate and in the planetary



geomagnetic disturbance index, Kp, providing a suggestive physiological association (*Halberg et al., 1996*). The physiological finding, e.g., of a biological free-running half-week thus leads to the finding of a rhythm with the same frequency in Kp. A near-weekly component had been found in our physiology in health; it differed with statistical significance from the societal week (*Halberg et al., 1965 and Halberg et al., 1996*). This finding had eventually prompted us to seek and detect a component with a similar frequency in Kp (*Halberg et al., 1991*). Within the ensuing years, the presence of this component was confirmed by physicists (*Roederer, 1995 and Vladimirskii et al., 1995*). There is also a stunning precedent for an association between physical events on earth and in interplanetary space on the one hand, and human pathology on the other hand detected first by cross-spectral coherence (*Halberg et al., 1992*) and confirmed thereafter by the method of superposed epochs (*Halberg et al., 1991 and Cornélissen et al., 1994*) and otherwise (*Roederer, 1995*). The association demonstrated by cross-spectral coherence between MI and Kp, and between MI and Bz occurs at the same frequency to nearly the second decimal, at one cycle in 3.16 and 3.17 days, respectively. A concomitant interactive physical and physiological monitoring would provide an opportunity for instituting countermeasures against undesirable triggering effects of storms in space before a catastrophic event such as a MI occurs. The detection of disease risk syndromes by a monitoring system would by far exceed the value of the black box in the cockpit of an airplane, which is consulted after the fact of a disaster.

Some changes associated with disease risk are seen first in the about-yearly component of the chronomes of endocrine variables (*Halberg et al., 1981*). The biological half-year and the biological half-week (on occasion both merely a description of the yearly or weekly waveform, respectively) can also have an importance in their own right. While all other pathologies studied had a yearly component much more prominent than the half-year (*Halberg et al., 1991*), over 50,000 cases of epileptic emergencies show a principal half-yearly component (*Halberg et al., 1991*) suggesting the search for an equivalent physical "rhythm". In our Kp spectra, the half-year can be prominent. Armin Grafe has described an about-half-yearly pattern in solar flares (*Grafe, 1958*). Before postulating any physical effect upon the central nervous system, more than the finding of similar frequencies is needed (*Halberg et al., 1991 and Halberg et al., 1996*).

One may further speculate whether, at the latitude of Florence (43.47 degrees N), circulating human melatonin is apparently geomagnetically synchronized by night, while the about-yearly component predominates at that latitude in melatonin values of blood obtained during the daily light span (*Tarquini et al., 1997*). When circulating human melatonin is studied at 65 degrees N in Oulu, Finland, where the sun's energy is received at a low angle and may take second seat to the there perhaps most prominent geomagnetics, the half-year predominates in the melatonin of blood samples drawn at noon (*Tarquini et al., 1997 and Martikainen et al., 1985*).

Magnetic storms reduce the standard deviation of heart rate of cosmonauts in space (*Baevsky et al., 1997*) and their association with MIs on earth (*Halberg et al., 1991*) is now confirmed and extended, at least at the latitudes of 55.45 degrees N (Moscow) and 59.55 degrees N (St. Petersburg) (*Villoresi et al., 1994 and Villoresi et al., 1994 and Roederer, 1995*).

The implementation of streamlined physical and physiological monitoring in BIOCOS serves for shifting emphasis in health care from a dichotomy of assumed wellness (with attention to risk factors) vs. overt illness, to a trichotomy of chronobiologically validated wellness, disease risk syndromes, and overt illness, with a share of the resources switched from the care of overt disease to developing a system for disease risk syndrome detection and treatment, and thus for arriving at a health care that achieves more for less.

There is the need for reference data bases for disease risk syndrome detection and for ascertaining the efficacy of treatment when needed (*Cornelissen & Halberg, 1994 and Halberg et al., 1995 and Siegelová et al., 1996, 1997 and Cornelissen & Halberg, 1996 and Otsuka et al., 1996 and Otsuka et al., 1997*).

Diagnosing overswinging, CHAT, which is particularly risky for stroke when the 24-hour average of blood pressure is below 130/80 mmHg (systolic/diastolic), is a must simply because the alternative is a no-win situation. There is the opportunity to develop a system for collecting and interpreting serial blood pressure measurements to facilitate for every woman and every man to do what leaders in medicine have done by setting an example, just as did Johannes Evangelista von Purkinje, who advocated self-study and whose name for a while adorned Brno's university. The disease risk syndromes start but do not stop at blood pressure overswinging. Chronome alterations of heart rate variability involving the recognition of rhythm alterations in endpoints of chaos (*Otsuka et al., 1997 and Otsuka et al., 1997*) also represent a challenge in the country of Purkinje and in the city of Jan Penaz. The proper study of human beings is the human being. Each of us can self-measure, preferably with continuously improved systems of integrated physiological and physical monitoring, a great opportunity for device and pharmaceutical manufacturers to provide increasingly denser and longer assessments of the chronomes of interest in health care, until reliance on the medical history can be integrated into a continuous self-measurement and self-interpretation of the data in a population characterized by chronobiologic literacy.

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Dedicated to the memory of Otto H. Schmitt (+ 1998), professor of biophysics and electrical engineering at the University of Minnesota, "Mr. Biophysics" worldwide; inventor of the Schmitt-trigger (a key switching device in much of today as electrical equipment); advocate of life strand analyses, an aim of chronomedicine for the quantification of health and the earliest possible detection of disease risk syndromes; a genius with a special personality who was greatly contributory to chronobiologic endeavors, realizing that the "circa" in "circa-rhythms" related variability as well as to

free-running, who accordingly coined the terms "episodic time" and "rubbery time". All who listened, learned from him. By the many of us whom he taught and stimulated, in Minnesota and on many travels around the world, Otto will be missed for as long as we are around. His legacies, ranging broadly from vector electrocardiography to radar, will withstand.

## DYNAMICS OF BAROREFLEX SENSITIVITY

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### ABSTRACT

Baroreflex sensitivity can be assessed non-invasively by means of spectral analysis without the intravenous administration of pharmacological agents such as phenylephrine. The availability of relatively cost-effective instrumentation for the beat-to-beat non-invasive monitoring of blood pressure and R-R intervals enables the large-scale clinical assessment of short-term changes in baroreflex sensitivity in response to different stimuli (such as a change in blood pressure brought about by the administration of phenylephrine), opening the door to new cardiological applications.

### INTRODUCTION

Baroreflex sensitivity (BRS), an index of autonomic nervous function, reportedly predicts survival in cardiovascular disease (*Billman et al., 1982*). Clinical applications are broadened when BRS is assessed by spectral analysis of blood pressure (BP) values and R-R intervals (*Robbe et al., 1987*) (BRS-1), allowing continuous observation. BRS-1 is here validated by comparison with the traditional infusion of phenylephrine (BRS-2), and used to study BRS dynamics (BRS-3) associated with an increase in BP.

### SUBJECTS AND METHODS

A Holter electrocardiographic record (Fukuda Denshi, SCM280) was started at 14:00 on 10 healthy 19-47-year-old volunteers and a catheter placed while the subject was resting supine. Non-invasively (JENTOW-7000; Colin Medical, Komaki, Japan;) (*Sato et al., 1993*), the arterial BP waveform was recorded continuously for at least 80 sec after phenylephrine was injected intravenously. Using the JENTOW-7000 software, a target systolic (S) BP elevation of 40 mmHg served to calculate BRS-2. BP and R-R variability was analyzed by MEM spectral analysis using MemCalc software (Suwa-Trust, Tokyo) (*Saito et al., 1994*). BRS-1 was calculated as the square root of the ratio between the ~10.5-sec (0.04-0.15 Hz; "LF") power of R-R and that of BP (*Robbe et al., 1987, Siegelová et al., 1997*). Dynamic changes in BRS were assessed

longitudinally (BRS-3, in msec/mmHg; 2) over 30-sec spans progressively displaced by 5 sec throughout the time series of SBP, diastolic (D) BP and R-R intervals obtained during the about-80-sec pressor response to phenylephrine, yielding 10 sequential records.

## RESULTS

BRS-2, conventionally determined by the slope of the line regressing R-R intervals to SBP during an intravenous bolus injection of phenylephrine, is illustrated in Figure 1 (upper left). This estimate of BRS, BRS-2, correlates positively with the spectral estimate of BRS, denoted as BRS-1 ( $r=0.75$ ;  $P<0.02$ ). BRS-1 is thus validated against an old method (BRS-2), the latter limited by drawbacks discussed below. Figure 1 (bottom) shows the time course of SBP, R-R and BRS-3, estimated at 5-sec intervals during the about 80-sec intravenous phenylephrine injection (left). The correlation between R-R or BRS-3 (y-axes) and SBP (x-axis) is displayed in Figure 1 (bottom; right). While BRS-3 fluctuates around 13 msec/mmHg for  $SBP < 135$  mmHg, it abruptly increases for  $SBP > 138$  mmHg, suggesting the presence of a threshold (around 138 mmHg in this particular instance). Similar results are obtained for DBP and mean arterial BP of this subject and for dynamic changes in BRS-3 of the other 9 volunteers, inter- and intra-individual differences in the threshold BP value notwithstanding.

## DISCUSSION

Higher BRS values during sleep and progressively lower BRS values with increasing mental arousal (reading and arithmetic tasks) have been reported, as well as age- and circadian-stage-dependent effects of BRS (*Fišer et al., 1993, Siegelová et al., 1997, Kawano et al., 1995, Di Rienzo et al., 1997*). Such studies had to rely on the pharmacologic approach involving intravenous phenylephrine administration until 1987 when Robbe et al (*1987*) introduced a new spectral method to assess BRS non-invasively from the changes in BP and R-R intervals. The validation in 1993 of the accuracy of the JENTOW-7000 (*Sato et al., 1993*) facilitated the assessment of BRS in the clinic. The new computerized method provides a dynamic description of fast BRS modulations that could not be obtained by using traditional laboratory tests. The latter usually require at least 5-10 min for a single measurement (involving the application of the external stimulus, the observation of the hemodynamic effect, and the recovery span). Moreover, the assessment can only be repeated a few times in view of side effects associated with repeated artificial stimulation (*Kawano et al., 1995*). The non-invasive continuous monitoring of BP and R-R intervals by arterial tonometry thus allows BRS evaluation over very short spans, rendering possible the detailed study of changes in response to different stimuli, opening the door to new clinical applications.

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Legend to Figure:

Spectral vs traditional assessment of the baroreflex sensitivity (BRS).

Top: BRS conventionally determined by the slope of the line regressing R-R intervals to SBP during an intravenous bolus injection of phenylephrine (left). This estimate of BRS correlates positively with the spectral estimate of BRS. While all data are displayed (left), the regression lines are computed by considering data collected only during the ascending (A) or descending (B) time courses of SBP and R-R intervals (right).

Bottom: Time course of SBP, R-R interval and BRS, estimated at 5-sec intervals during the about-80-sec intravenous phenylephrine injection (left). A plot of BRS (y-axis) vs SBP (x-axis) (right) indicates that BRS abruptly increases above a threshold BP value (for SBP >138 mm Hg in this instance), determined objectively by the use of a self-starting cumulative sum control chart.

# CIRCADIAN CARDIOVASCULAR CHANGES IN CONVENTIONALLY ACCEPTABLE AND ELEVATED BLOOD PRESSURE

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## INTRODUCTION

Using a 3-timepoint approach, Panza et al. (1991) reported a circadian rhythm in vascular tone and its relation to  $\alpha$ -sympathetic vasoconstrictor activity in clinically healthy volunteers. Herein (*and elsewhere; Otsuka et al., 1997*), these authors' results in health are corroborated with an 8-timepoint design. The scope of the present investigation is extended to include results on patients with an elevated blood pressure.

## SUBJECTS AND METHODS

Vascular resistance (VR), blood flow, total (TPR) and specific (SPR) peripheral resistance, stroke (SV) and minute (MV) volume were assessed together with blood pressure (BP) and heart rate (HR) every 3 hours for 24 hours in 55 clinically healthy subjects after a 3-day standardization in the hospital. Similarly, three groups of 40 patients with WHO Stage II "hypertension" were examined at 4-hour intervals. Methods include, with venous occlusion plethysmography, the tetrapolar variant of rheography for the determination of stroke volume (*Kubicek et al., 1974*). Each data series was analyzed by single cosinor and results were summarized by population-mean cosinor (*Cornélissen et al., 1998*).

## RESULTS

As apparent from Table 1, on a group basis, a circadian rhythm is demonstrated in health ( $P < 0.05$ ) for almost all variables. Acrophases occurred in the afternoon between 14:30 and 16:00, except for VR and TPR, which "peaked" at night around 03:00. The circadian variation in VR and blood flow was not statistically significant in the patients, except for the VR of patients with a relatively low cardiac index (averaging  $3.1 \text{ l/min/m}^2$ ). In these patients, VR was greatly reduced by comparison with their value in health (18.7 vs. 29.7 mm Hg/ml/min/100 ml forearm volume), and "peaked" around 10:00. A circadian rhythm was found for all 3 groups of MESOR-hypertensive patients in the case of TPR with acrophases at night between 23:50 and 01:40, and for HR, "peaking" in the afternoon as it did in clinical health. Blood flow was increase

in the patients, averaging 7.4, 6.9 and 5.9 vs. 3.2 ml/100 cm<sup>3</sup>/min in health. Predictably, patients also had an elevated MV averaging 8.7, 7.2 and 5.5 vs. 5.1 l/min in health.

## DISCUSSION AND CONCLUSION

Rhythmic changes characterize many aspects of the circulation as part of a broader time structure, the chronome, which includes with multifrequency rhythms also chaotically appearing changes and trends in characteristics of both rhythms and chaos (*Macey, 1994*). Treatment effects are also drastically time-dependent, as demonstrated for different antihypertensive drugs (*Gullner et al., 1979, Little et al., 1990, Halberg et al., 1995, Cornélissen et al., 1994*) as well as for the anti-hypertensive (*Siegelová et al., 1995*) and anti-clotting (*Cornélissen et al., 1991*) properties of daily low doses of aspirin. Elsewhere (*Zaslavskaja, 1993, 1994*), the response of blood flow to treatment with nitrosorbide (10 mg sublingually) or captopril (25 mg orally) in patients with ischemic heart disease and cardiac failure (stage II WHO) was also shown to depend on the time of drug administration. These results complement a difference in the extent of vasodilation (phentolamine-associated decrease in peripheral resistance) reported by Panza et al. (1991). Such findings should prompt the further scrutiny of reactive as well as spontaneous responses to treatment as a function of the stages of all assessable components of the chronomes of pertinent variables. The scope of the present investigation is extended to include results on patients with an elevated blood pressure. The circadian variation of vascular resistance and blood flow is assessed in clinically healthy subjects and in MESOR-hypertensive (WHO stage II) patients.

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**Table 1: Circadian cardiovascular changes in health and hypertension (WHO stage II)†**

Variable (unit)	MESOR		Amplitude		Acrophase		
	-----		-----		-----		
	95% confidence limits						
<i>Clinical health: 27 men, 28 women, sampled every 3 h for 24 h</i>							
VR	29.7	—	3.1	—	03:14	—	
Flow (ml/100 cm <sup>3</sup> /min)	3.2	(2.9, 3.5)	0.4	(0.2, 0.6)	15:06	(13:06, 17:00)	
TPR (din·sec·cm <sup>-5</sup> )	1647.5	(1516.0, 1779.0)	273.0	(224.8, 321.2)	02:36	(01:48, 03:24)	
SBP (mm Hg)	116.7	(114.2, 119.2)	3.0	(2.0, 4.0)	15:54	(14:30, 17:12)	
MAP (mm Hg)	94.5	(92.6, 96.4)	2.1	(1.2, 3.0)	14:24	(12:18, 16:36)	
HR (beats/min)	68.1	(65.6, 70.6)	4.3	(3.1, 5.5)	15:24	(14:24, 16:18)	
SV (ml)	74.8	(68.8, 80.8)	8.6	(7.0, 10.2)	14.42	(13:36, 15:36)	
MV (l/min)	5.1	(4.7, 5.5)	0.9	(0.7, 1.1)	15:00	(14:12, 15:42)	
<i>40 "hyperkinetic" MESOR-hypertensives sampled every 4 h for 24 h</i>							
VR	25.8	(19.1, 32.5)	—	—	—	—	
Flow	7.4	(5.1, 9.7)	—	—	—	—	
TPR	1317.6	(1038.0, 1597.3)	151.3	(35.6, 266.9)	23:54	(20:42, 02:06)	
SPR (din·sec·cm <sup>-5</sup> /m <sup>2</sup> )	750.6	(577.8, 923.5)	88.4	(23.0, 153.8)	23:54	(20:42, 02:06)	
SBP	152.2	(138.4, 166.0)	4.4	(0.1, 8.7)	18:48	(14:24, 00:30)	
HR	67.4	(62.8, 72.0)	2.1	(0.8, 3.3)	13:42	(10:54, 18:06)	
MV	8.7	(7.1, 10.3)	0.7	(0.2, 1.2)	12:42	(10:48, 14:54)	
CI (l/min/m <sup>2</sup> )	4.9	(4.0, 5.8)	0.4	(0.8, 0.7)	12:42	(10:48, 14:54)	
<i>40 "eukinetic" MESOR-hypertensives sampled every 4 h for 24 h</i>							
VR	25.2	(20.6, 29.9)	—	—	—	—	
Flow	6.9	(5.6, 8.2)	—	—	—	—	
TPR	1732.3	(1373.2, 2091.5)	151.0	(10.7, 291.2)	00:05	(19:00, 05:00)	
SPR	978.7	(775.8, 1181.6)	85.3	(6.0, 164.5)	00:05	(19:00, 05:00)	
SBP	171.0	(168.7, 183.4)	—	—	—	—	
HR	69.6	(64.1, 75.1)	3.5	(1.4, 5.7)	11:48	(09:30, 15:06)	
MV	7.2	(5.8, 8.6)	0.6	(0.1, 1.0)	12:07	(10:01, 16:08)	
CI	4.0	(3.2, 4.8)	0.3	(0.1, 0.5)	12:07	(10:01, 16:08)	
<i>40 "hypokinetic" MESOR-hypertensives sampled every 4 h for 24 h</i>							
VR	18.7	(13.2, 24.3)	4.8	(0.5, 9.2)	10:00	(06:48, 13:00)	
Flow	5.9	(3.2, 8.4)	—	—	—	—	
TPR	2042.6	(1787.8, 2297.3)	135.1	(29.8, 240.4)	01:35	(22:03, 06:09)	
SPR	1157.5	(1006.0, 1309.1)	76.9	(16.2, 137.5)	01:24	(22:00, 06:06)	
SBP	170.0	(154.7, 185.2)	—	—	—	—	
HR	65.4	(61.8, 69.1)	1.7	(0.02, 3.5)	14:18	(08:03, 19:18)	
MV	5.5	(4.9, 6.0)	—	—	—	—	
CI	3.1	(2.7, 3.4)	—	—	—	—	

†Summary by population-mean cosinor analysis of results obtained on each individual data series from the least-squares fit of a 24-hour cosine curve: MESOR=midline-estimating statistic of rhythm, a rhythm-adjusted mean; amplitude=one-half of the extent of change within a day as predicted from the fit of a single 24-hour cosine curve to the data; acrophase=time of overall high values in relation to local midnight.

VR=vascular resistance (in mm Hg/ml/min/100 ml forearm volume); TPR=total peripheral resistance; SBP=systolic blood pressure; MAP=mean arterial pressure; HR=heart rate; SV=stroke volume; MV=minute volume; SPR=specific peripheral resistance; CI=cardiac index. Methods include, with venous occlusion plethysmography, tetrapolar variant of rheography for the determination of stroke volume.

For classification as to "kinesis" see Zaslavskaya R.M. Chronodiagnosis and chronotherapy of cardiovascular diseases. 2nd ed. Translation into English from Russian. Moscow: Medicina, 1993, 397 pp.

## THE CIRCADIAN RHYTHM IN CENTRAL TEMPERATURE IN FASTING SUBJECTS IN HOT CLIMATE (SENEGAL)

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### INTRODUCTION

Human beings are characterized by a stable average core temperature with limited and regular fluctuations over 24 hours. Consequently, both core and skin temperatures are not constant as function of time. The circadian rhythm in core temperature appears to be mainly generated by periodic variations in heat production and heat loss. Within some limits, the period amplitude and phase of circadian rhythms can be influenced by cyclic variations of multiple environmental factors. There are the alternation of day and night, changes in environmental temperature and reactions to various external stimuli like noise and silence (*Houdas et al., 1971*). For human beings regular daily activities linked to hours of work and rest, or activities related to participation in social life exert influence upon circadian rhythms also. All these influences are interconnected. First, physiological response to an increase in ambient temperature does not occur with the same speed and intensity when exposure occurs during the day as compared to night (*Houdas et al., 1971*). On the other hand, the continuous exposition to high ambient temperatures will almost regularly induce an appreciable increase in core temperature (*Halberg et al., 1967*). In effect in hot climate during the hottest hours on day (ambient temperature higher than 35°C), core temperatures are found to be higher than those observed in temperate climates, even in subjects highly adapted to hot climates. The metabolic state of the organism seems to be closely linked to the heat production and it is known that metabolic heat production increases after feeding in both animals and humans. This metabolic response, referred to a post prandial thermogenesis (specific dynamic action of nutrients or diet induced thermogenesis), is thought ascribable to the energy cost of digesting and assimilating the dietary nutrients (*Kleitman et al., 1951*). Food intake does not appear to influence mainly the temperature circadian rhythm: circadian rhythms of the core temperature were shown to persist in subjects who for 3 weeks were on a very restricted diet (*Reinberg et al., 1973*). In experimental setting of underground isolation the rhythm persisted even when changes of period and/or acrophase would be imposed in the conditions of deprivation of light and other indexes necessary to orientation in time. Nevertheless in these circumstances, the circadian difference of rectal temperatures between fasting and non-fasting periods were still found to be different (*Houdas et al., 1971*). However, the exact influence of food intake on core temperature in hot environments and in

subjects highly adapted to high environmental temperatures has not been described.

The aim of the present study was to determine the influence of the fasting and usual alimentary intake on circadian variability of central body temperature and heart rate in healthy subjects highly adapted to hot climate.

## MATERIAL AND METHODS

### Environmental conditions

The experimentation was carried out in a tropical area in eastern Senegal, in the rural zone of Kedougou situated near 12°40 North latitude and 14°11 West longitude, during a warm period of the year, the month of February. During the time of experiments environmental temperatures in this part of the sub-sahelian zone ranged from 21.2°C at 6.00 AM to 35.0°C at 6.00 PM. Simultaneously relative humidity ranged from 36% to 7%

### Subjects

22 healthy young men participated in this study, mean age  $23.36 \pm 3.49$  years, height  $176 \pm 6$  cm. and body weight  $64.87 \pm 5.53$  kg. All subjects came from Senegalese army and were well-trained in physical activities. All of them were born and lived in Senegal. Before the experiment, they had been staying in eastern Senegal for six months at least. Consequently they were naturally adapted to local warm or hot climate.

They were fully informed of all aspects of the study, gave their voluntary and informed consent to participate in this experimentation, which was approved by the appropriate institutional ethical boards. Their diet was mainly compound by rice and millet, fish and flesh and contained approximately 3 200 kcal /day; drinks were only water and fruit juices. (Table 1).

### Experimental protocol

The soldiers were divided in two groups of eleven subjects studied during a period of 24 hours, since 7.00 pm to 7.00 pm on the following day, with measurements every 3 hours. For each measurement, after maintaining subjects resting in supine position for thirty minutes, the ambient temperature (AT), rectal (RT) and skin (ST) temperatures, heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressure were determined. One group went first through a 24-h period with normal alimentation and very moderate activity, followed by a 24-h period of fasting but with free access to drinking water. While the other group had first the 24-h fasting period, a 24-h period of normal activity and alimentation without measurements, and then the 24-h period with normal alimentation and very moderate activity. All measurements were performed during the first and second or the first and third experimental periods respectively. All subjects were staying in the same room, which was well ventilated by opening doors and windows so that the room temperature was quite similar with ambient temperature.

To avoid order bias and influence of environmental temperature fluctuations, the individual results obtained for both groups during fasting or normal alimentation were joined and analyzed. Mean blood pressure (MBP) was expressed as: diastolic blood pressure + (difference systolic blood pressure - diastolic blood pressure)/3.

#### Precautions

Muscular exercises were forbidden during experimentation, subjects could only do their usual activities in the day time and were supervised in order to prevent accidental differences in activities. Fasting subjects stopped eating after the dinner but they had free access to drinking water which upper limits was restricted to 3 liters per day. During feeding period times for eating were 7.00 AM for breakfast, 11.30 AM for lunch, and 6.30 PM for dinner. All subjects were submitted to same sleep – awake periods: out of bed at 7.00 AM and bedtime 9.00 PM.

#### Data analysis

Data are presented as mean values ( $\pm$  standard deviation) for each group and were analyzed using the Halberg cosinor analysis (*Halberg, 1969*). Student's t-test for paired samples was used to assess effects of fasting between groups. Difference were considered significant if probability values were lower than 0.05.

## RESULTS

Since the data were collected at 3-hours intervals, only trial periods of 24, 12 and 8 hours could be examined. Each component (24h, 12h or 8 hours periods) for each variable (RT and ST, HR and MBP) were compared. Comparison of the two groups showed highly statistically significant differences ( $p < 0.001$ ) for the circadian and circasemidian components of rectal temperature and heart rate (except for 12-hours component of heart rate during the reference span). The 8-hours component is also statistically significant for rectal temperature ( $p < 0.001$ ) and is at least of borderline statistical significance for heart rate ( $p = 0.053$ ) during feeding but is present ( $p < 0.05$ ) during fasting.

It can be seen that the fasting was associated with:

1. For rectal temperature:

-a decrease in the MESOR (24-h mean value) by  $0.125 \pm 0.026^{\circ}\text{C}$  ( $p < 0.001$ ) and a decrease in the circadian temperature amplitude (double amplitude corresponds to the highest value at the daytime and the lowest value at night) by  $0.09 \pm 0.02^{\circ}\text{C}$  ( $p = 0.001$ ),

-a slight delay of the circadian acrophase: the delay in the circadian acrophase (the interval between midnight and the highest daytime values) was  $0.80 \pm 0.27\text{-h}$  ( $p < 0.005$ ),

-an increase in the amplitude of the circasemidian component of rectal temperature ( $p < 0.05$ ).

2. For skin thoracic temperature:



the values in fasting were generally lower than values in feeding but differences were not significant.

3. For heart rate:
  - a decrease in the MESOR by  $3.4 \pm 0.9$  bpm ( $p < 0.002$ ),
  - no change in the circadian amplitude:  $0.9 \pm 0.8$  bpm ( $p < 0.03$ ),
  - a delay in the circadian phase of heart rate:  $1.67 \pm 0.53$  h ( $p < 0.01$ ),
  - an increase in the amplitude of the circasemidian component ( $p < 0.05$ ).
4. For mean blood pressure:
  - values were between 100 and 92 mmHg, but there was no significant difference in the two situations.

Table 1. Daily diet in Senegalese Army

Meal	Food	Caloric value (kcal)	daily intake (%)	Water (l)
Breakfast 7.00 AM	bread, milk, coffee	580	18	
Lunch 11.30 AM	meat or fish and rice, vegetables and fruit	1 280	40	
Dinner 6.30 PM	meat or fish and rice or millet, fruit	1 340	42	
<b>Total</b>		<b>3 500</b>	<b>100</b>	<b>2.5-3.0</b>

## DISCUSSION

Core body temperature values measured in our study were a little higher than those usually observed in subjects who live permanently in moderate climates (*Eckburg et al., 1987, Halberg et al., 1967, Martineaud et al., 1977*). Diurnal variations of the core temperature observed in this study with usual feeding were comparable to those measured in hot climates (*Cissé et al., 1991*): lowest value  $36.2^{\circ}\text{C}$  at 4.00 AM, acrophase  $37.2^{\circ}\text{C}$  at 4.00 PM, MESOR  $36.8^{\circ}\text{C}$  and amplitude  $1.1^{\circ}\text{C}$ . Because in this study subjects were maintained at bed rest for thirty minutes before any measurement, then in common life with physical activities diurnal rectal temperature will be lightly higher. Indeed it was established that in hot climate core body temperature largely exceeds value of  $37^{\circ}\text{C}$  during the hottest hours of the day (*Halberg et al., 1967, Martineaud et al., 1977*).

But circadian rhythm of thermoregulatory mechanisms seems to be coordinated for maintaining a strict control of core body temperature during the night,

because the same values of approximately 36°C are observed in all subjects in any climatic conditions (*Cissé et al., 1991*). Nevertheless diurnal values are partially depending on ambient temperatures: indeed rectal temperature can physiologically increase to 37.7°C. In other words, it appears that as an adaptive phenomenon, human beings are better able to adjust core temperatures to high ambient temperatures during the daytime than during the night time (*Cissé et al., 1991*).

In this study performed during a warm season, we found a substantial increase in body temperatures during afternoon with normal feeding; after lunch rectal temperature was higher by 0.2°C than during fast. Therefore it is the thermogenesis induced by nutriment which explains this difference in body temperatures. Indeed it has been shown in previous studies that the post-prandial thermogenesis due to the specific dynamic action of proteins is obvious when ambient temperature is high (*Krauchi et al., 1994*).

Then ordinary diet induces thermogenesis which reaches at least 10% of energy intake (*Monk et al., 1996*) and can last several hours after food intake. When ambient temperature is higher than temperature of thermic comfort, heat produced by nutriment can not be used for thermoregulation and has to be eliminated partly immediately and partly with some delay, i.e during the night when environmental conditions are more auspicious (*Cissé et al., 1991*) and this process explains some increase in day time core temperature. But during the night thermoregulatory mechanisms are quite efficient and the period of minimal temperature is the same with a normal diet as in the fasting. Then in our experiment, the circadian rhythms of central temperature persisted during fasting period without change in acrophase but with decreases in the MESOR of rectal temperature and circadian amplitude; this feature was associated with an increase in amplitude of the circasemidian rhythm of rectal temperature, i.e the about half-day component. These changes are clearly induced by the food ingestion and intestinal absorption increasing the post-prandial metabolism. Then decreases in MESOR and diurnal amplitude are an adaptation to the fast (*Cissé 1986, Cissé et al., 1991*), corresponding to stimulation of neoglycogenesis and some other metabolic processes (*Schonbaum et al., 1990*). But the basic circadian rhythm is unchanged as shown by the persistence of the same acrophase.

Determination of a cutaneous temperature confirmed a well know notion : skin temperature mainly depends on the ambient temperature varying in the same way, minimal at night-time, maximal in daytime but the amplitude of the variation was only 1°C. At the highest environmental temperatures, in the afternoon, corresponded maximal cutaneous temperature almost similar in fasting and in feeding situation. Nevertheless in this case elimination of heat produced by post-prandial thermogenesis induced an increase in skin blood flow (*Martineaud et al., 1997*) but it was not sufficient for a significant increase in superficial temperature.

As expected (*Krauchi et al., 1994*), this study found a circadian variation of blood pressure and heart rate: mean values in these young subjects were lower than in normal Senegalese population, certainly because soldiers were well trained and developed a reinforced vagal tonus due to training. In feeding as well in fasting subjects the circadian profile of heart rate was significantly correlated with the circadian profile of central temperature, representative itself of heat production. Then in fasting subjects, MESOR of heart rate decreased but acrophase was not significantly modified and amplitude of the circasemidian component increased. Consequently these changes are representative of metabolic and hormonal adaptations to the fast (*Reinberg, 1975*). Last there was no clear relation between blood pressure and feeding.

In this study we found that, in hot climate, the circadian rhythm of central temperature was present in two different nutritional situations but that core body temperature during the day was increased significantly in feeding compared to fasting without significant alteration of cutaneous temperature implying induction of diet thermogenesis. This increase could diminish performance of workers and sportsmen, and explain differences in seasonal performances. Furthermore there is a known relationship between vigilance performance and body temperature during the circadian and it is likely that diurnal temperature can be a reliable marker of human circadian functioning (*Reinaud et al., 1977*). Our findings suggest that in hot climates, the population particularly workers and sportsmen, should favor a poor proteic diet to the advantage of carbohydrates because these induce a low thermogenesis and a lesser increase in core temperature.

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## BIOLOGICAL CLOCK AS CALENDAR

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The mammalian biological clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus controls the circadian time-keeping system and drives many overt rhythms, among them the rhythm in the pineal melatonin production. Duration of the nocturnal melatonin signal conveys the information on day length, i.e., on the photoperiod into organisms. In all mammals so far studied including the man, the melatonin signal is shorter in the long summer days than in shorter winter days. A question remains whether the seasonally modulated rhythmic melatonin production reflects a seasonally modulated state of the circadian clock, i.e., whether the SCN clock is itself photoperiod dependent.

To solve this question, intrinsic SCN rhythmicity was studied in rats maintained under artificial long summer days, with a 16-h photoperiod and in those maintained under short winter days, with an 8-h photoperiod. Two SCN rhythms were followed, namely the rhythm in the light-induced c-fos gene expression which is exhibited mainly in the ventrolateral (VL) SCN, and the rhythm in the spontaneous c-fos gene expression elevation, which is expressed mostly in the dorsomedial (DM) SCN. Both these SCN intrinsic rhythms were photoperiod dependent. Moreover, memory on the photoperiod was stored in the SCN intrinsic rhythmicity: when rats maintained in long days were transferred to short ones, profiles of the VL-SCN as well as the DM-SCN rhythms adjusted just gradually, i.e., in more cycles, to the change of the photoperiod. Effect of the photoperiod on the SCN was not mediated by the melatonin signal: the SCN rhythmicity in long days differed from that in short days even in pinealectomized rats.

In conclusion, the circadian SCN pacemaking system is photoperiod dependent. Therefore, the SCN does not program and communicate just time of the day information but also season of the year information.

## **NON-INVASIVE MEASUREMENTS IN MAN**

# **PRENATAL AND PERINATAL PSYCHOLOGY AND MEDICINE: NEW INTERDISCIPLINARY SCIENCE IN THE CHANGING WORLD**

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## **INTRODUCTION**

The encounter with the unborn is the beginning of the continuum of human life towards self-realization. We need to extend the standard definition of life's continuum to include the prenatal experience, which is a part of life's continuum, helping to shape us and determining who we are and what we will become. For the unborn it is primarily through the imprinting process that this experience is initiated and realized. For the mother, pregnancy this encounter with the unborn is a chance for self-realization. For a rest of us this encounter with the unborn is the chance to extend and deepen our own understanding of this life continuum wherein there can be found no possible separation between the physical and psychological dimensions of our existence.

## **PRENATAL AND PERINATAL PSYCHOLOGY AND MEDICINE**

Prenatal and perinatal psychology and medicine is a relatively new interdisciplinary scientific field within medical and psychological research and practice which attempts to integrate different disciplines dealing with the basic questions of life and its disturbances.

Emphasis is placed on the interdisciplinary character, which enables different scientific specialties such as medicine, psychology, psychoanalysis, anthropology, human ethology, sociology, philosophy and others to meet, find a common language and go through the process of mutually creative influence, or, as it were a "cross fertilization".

Prenatal and perinatal psychology and medicine can also serve as a "psychosomatic" model stressing the indivisibility of "psychological" and "physical" processes in the continuum of human life from its very beginning and also the indivisible development of all functions of the central nervous system and the immunological and neuroendocrinological processes.

One of the important intentions of this new scientific field is the publication of different methodologies, both from experimentally oriented methods and studies and also from more introspective methods with an effort to look for and find a common language in order to diminish semantic misunderstandings as well as to define a scientific theory applicable to this new interdisciplinary and integrative approach. Integration linguistically means, among other things, assimilation, fusion, incorporation, combination, unification and harmony. The latter, harmony, should be stressed in particular - harmony and cooperation between

different integrated approaches and views, methods and methodologies, theories, ideologies and practices, rather than confrontation and disagreement.

Society at large must encourage a sense of responsibility in parents-to-be and counsel couples long before conception about their commitment toward the new life; it is essential that this new life be highly respected from the very beginning and considered to be an equal partner in the dialogue. This dialogue begins at conception and continues through the prenatal, perinatal and postnatal stages of life. It influences the outcome of the birth and the way the individual during his childhood, adolescence and adult life will treat other people and his ability to love and respect others and make commitments.

## PRENATAL STAGE

The prenatal stage of life represents a unique opportunity for the primary prevention of psychological, emotional and physical disorders in later life (*Fedor-Freybergh et al., 1988, 1952*). At this stage we also can develop preventive procedures to decrease premature birth and perinatal morbidity and mortality. In order to understand the enormous potential power of the prenatal processes and their impact on the individual's prenatal and postnatal health, we have to ask ourselves what does the prenatal stage of life imply.

Pregnancy can be conceived as an active dialogue between mother and child (*Fedor-Freybergh, 1983*). This dialogue is not limited but is enlarged via the dialogue between the mother and the father and the mother's psychosocial environment. This discourse is a part of a very active and mutually interdependent process taking place on several levels. As a minimum, these include the psychological, emotional, biochemical and psycho-neuroendocrinological levels.

I have never heard a mother refer to the child in her womb as "my embryo", or "my foetus". The mother says "my baby" or even calls the child by a personal name. Generally, pregnant mothers show a high degree of sensitivity and sensibility towards their unborn child which, by contrast, many professionals lack. The child is a very active partner in the pregnancy, an "active passenger in utero" (*Chamberlain, 1988*). The mother-child interaction, consequently, has not only a biological but also a psychological and social character.

This mother-child dialogue begins on an unconscious level - probably from the very beginning of the unborn child's development. From the mother's side, the dialogue will become a reality when she, consciously or unconsciously, makes the move to experience the unborn "it" as the unborn "you". This event initiates her into the beginning of a conscious encounter with her child. The transition from "it" to "you" is just one consequence of the sensitivity and sensibility of the unborn and the enormous creative potential in the psyche of the mother. The dialogical experience is independent of the degree of morphological development of the child (*Fedor-Freybergh, 1983, Fedor-Freybergh et al., 1988*).



There is a strong impact of hormonal, psychological and immunological influences already on the whole embryonal and fetal development.

## BIRTH

Birth is a part of a comprehensive human development. The circumstances around the birth, the birth itself and the consequences for the child, the mother and the father in the postnatal period will essentially depend on the prenatal stage of life and its bonding impact on the child, the mother and the father. It is wise not to separate the role of the father from the role of the mother and child and also not to separate the labour from the continuum of the prenatal experience.

The father should be involved and incorporated into the entire prenatal care from the very beginning and treated as an equal partner in the process. The father's experience will vitally influence his activity during labour and very much his bonding abilities with the child during birth, the prenatal and postnatal periods.

Pregnancy can be considered as the first ecological position of the human being, the womb as the first ecological environment (*Fedor-Freybergh, 1983, Fedor-Freybergh et al., 1988*). It is surprising to see how few professionals, even psychologists, realize this basic fact, and that there is still a large number of obstetricians, gynecologists and other professionals who merely consider the womb as a "baby-carrying" anatomical organ and are still unaware of the "toxic pollution" of potential psychological and social threat to the unborn child.

The dialogue between the unborn child, mother and father creates a "primary togetherness" (*Fedor-Freybergh et al., 1988*), which in turn helps to foster strongly compelling psycho-physical predispositions. Potentially, any such inborn predilection has the ability to orient and shape forthcoming emotional and social responses, especially in regard to interpersonal relationships. The consequences of these experiences of primary togetherness run along a wide range, including love and ethical behavior.

The human life has to be considered as an indivisible continuum where each of the developmental stages is equally important, all stages interdependent and not separable from the whole individual's life continuum. In this continuum, the individual represents an indivisible entity of all functions on both physiological or physical, psychological and social levels. The physical, biochemical, endocrinological, immunological and psychological processes represent a whole, which cannot be divided (*Fedor-Freybergh et al., 1988*).

In order to understand the process during the prenatal stages of life, a new language is required and a new scientific theory is needed. Such a language must assist us in getting beyond the semantic problems and confusion existing in so much medical and psychological vernacular (*Fedor-Freybergh, 1990*).

It is not possible to separate any stage of human development from the rest of an individual's life continuum. The life continuum is one of the basic needs in human life in order to maintain homeostasis and equilibrium. The disturbance of

the individual's life continuum on a momentous scale would lead to illness or in extreme cases, where homeostasis cannot be regained, results in death.

Any discontinuity from outside or from inside the individual organism will violate these basic biological and psychological needs, both in prenatal and postnatal life. Discontinuity is increasingly becoming a more serious problem today causing the spread of ecological, social and political disturbances throughout the world. No group of people or any nation is wholly immune from the upheaval of disorienting developments on ecological and social levels (*Fedor-Freybergh et al., 1988*). Many in the scientific community are very much aware of the effects of such events, and see how the discontinuity and disequilibrium beget many of today's mental and social diseases (*Tyano, 1987*). In the field of prenatal and perinatal psychology and medicine, we are very much aware of the dangers discontinuity can generate in the unborn and in the newborn.

## PSYCHONEUROENDOCRINOLOGY

The latest development of two relatively new and innovative lines of medical and psychological research, namely psychoneuroendocrinology and psychoneuroimmunology are very promising. Research in these two areas is particularly important in serving as the scientific basis for the philosophy behind prenatal and perinatal psychology and medicine.

Various highly specific biochemical functions (hormones, neurotransmitters and other polypeptide structures) are needed in direct connection with input phenomena for the transformation and storage of both sensorial and mental types of information. Crucial to the formation of the primary central nervous system on the hypothalamic-pituitary-ad renal level, some of these functions are already detectable in the very beginning of the development of the human being. Thus the embryo successively develops a high sensibility and competency for the potential ability of perception and learning (*Fedor-Freybergh, 1985*).

The intrauterine experience is also a learning process for the child (*Fedor-Freybergh, 1990*). This learning is a vital prerequisite for survival since it makes it possible for the organism to adapt itself to new circumstances. Without adaptation there would be no survival and one cannot adapt one self without making and having had experiences upon which to base the adaptation. Such a process requires memory, whether consciously retained or subconsciously imprinted. The information processing which reaches the child from the very beginning of its development will be received via different biochemical pathways and then transformed and stored as memory traces (this could eventually be useful to a theoretical understanding of certain psychotherapeutical procedures, such as hypnosis, dream analysis, prenatal memories etc.). At this stage the embryo already shows evidence of responding to and retaining the impact or imprint of sensory experiences in a biochemical language, which remain as a potential learning source. These prebirth memory

imprints may in turn be revoked as informational sources (whether negative, positive or ambivalent in character) during later life.

The implications of these preliminary findings are far reaching. It will require nothing less than radical rethinking the standard human-embryo development paradigm wherein structure is presumed to precede function. To the contrary, as we have indicated earlier, there is a strong evidence (*Fedor-Freybergh, 1983*) in support of the primacy of function over structure, the morphological organ. It is the morphological structure which develops as a result of the inborn primal functional urge. An organ would not develop if there was no functional urge compelling it to do so. In the same way, the mental capacity of the human being is not posterior to the completed morphological structure of the brain, nor to its subsequent introduction into and experiencing of a particular sociocultural environment after birth. The unborn already has its psychological processes functioning long before birth; no child is tabula rasa.

We must reaffirm that the mother is not just a "receptacle" for the child's growth, but an active initiator and participator. Today it is imperative to reestablish the woman as the primary choice maker in this powerfully creative process. Indeed, she is involved in a procreative process with great creative powers of her own. The future mother needs to be aware of these powers and how to be in touch with them in order to be better equipped to guide and augment this creative undertaking. Pregnancy can also enable the mother to withdraw into a kind of "creative regression" in order to enter into an intimate dialogue with her unborn child.

In order to make an informed and stress-free choice, family planning education must begin well before conception. Responsible parenting is not necessarily an automatically bestowed gift from "Nature" or even an easily acquired talent, but very often needs to be taught. That requires research concerning appropriate socio-pedagogical implementation within the family and in our educational system. It is vital that an integration of prenatal and perinatal studies into medical and psychological curricula at the universities is provided.

## PRENATAL CARE

We need to establish a new educational system which would prepare people for conscious parenthood. There is a need for a radical change of prenatal care, where not only medical but also very much psychological and social life circumstances of both parents would be taken into serious consideration. The prenatal care should consider the child as an active partner in a psycho-social dialogue with his parents who are given the opportunity to have their encounter with their unborn child in a free and non-violent society.

The ideal child should already be loved prenatally. There should not be unwanted children. Unwanted children are morally threatened and a moral threat to society. Unless we can achieve these mental and social conditions concerning the prenatal stage of life, all positive changes in the world would be superficial and there would also be the danger of a threat to basic human needs and rights,

to cultural and traditional values, and to civilization and freedom itself (*Fedor-Freybergh, 1992, David et al., 1988, Matějček et al., 1987, 1994*).

Pregnancy can sometimes be experienced by both the mother and the father as a life crisis, which does not necessarily imply a negatively charged situation. Any crisis may be envisioned as a challenge, which can bring about creative and positive solutions or alternatives. We can quite often see that during pregnancy, old, latent and unsolved conflicts become manifest. Frequently these can be worked through during the course of the pregnancy in a very constructive way. Indeed, it should be pointed out that many of the conflicts and problems that a pregnant woman may experience are not the direct result of her pregnancy or her baby. Unresolved issues may re- evoke psychological conflicts within her own personal psyche. In this way the pregnancy often gives the mother and father a unique opportunity to further their own inner psychological development, sometimes within psychotherapeutical settings (*Fedor-Freybergh et al., 1988*).

## PSYCHOTHERAPEUTIC RESEARCH

Psychotherapeutic research and practice has again shown how decisive negative emotional influences and disturbances in the prenatal dialogue are for mental conditions and diseases in later life. Dr. Janus has observed that psychological traumas and prenatal and perinatal problems have largely been shown in about two thirds of psychotherapeutic adult patients. It becomes exceedingly evident how important the emotional maturity, mental health and social awareness of the parents of the unborn child are. The need for psychotherapeutic intervention on both the pregnant mother and father-to-be is becoming more relevant.

No guilt or inferiority feelings should be imposed upon the pregnant parents nor any moral judgement placed upon them. We need to be aware that not all pregnant women have the opportunity or possibility to provide their unborn child with optimal nurturing conditions either economically or emotionally or within their social structures. Pregnancy is always a dynamic process of constantly fluctuating emotions, attitudes and even intellectual discourse. The mother-child dialogue is almost always characterized by a mixture of positive, negative and ambivalent emotions. The society has a responsibility to ensure that the mother-father-child unit can not only survive but develop and grow in the best possible circumstances.

Moreover, it must be added that a living organism has a strong propensity to adapt and even to repair damage, or to compensate for some failure from a previous developmental stage of the life continuum. What is unfulfilled in one stage of experience can be applied to the next and, eventually, worked out to the inner satisfaction of the human being.

## RISK PREGNANCY

The term "risk pregnancy" is still used almost exclusively in its biological sense. This means it is reserved for somatic disturbances, physical diseases or handicaps experienced by the mother during pregnancy, which could have a bearing on the biological health of the baby. Here we can see again how firmly institutionalized medicine and medical philosophy, with its static terminology and categorizations, results in the body-mind division and in continued promulgation of psychophysical parallelism. In a holistic and comprehensive view of human life we cannot make divisions between so-called "somatic" and "psychological" phenomena. Psychologically, medically and anthropologically considered, all life events are experienced as indivisible phenomenological situations wherein body and mind (soma and psyche) represent an entity of mutual influence and interdependence within a particular socio-cultural environment. In this way, all events of either a so-called "somatic" or "psychological" character, which could adversely affect the well-being and health of the mother or her unborn child, are seen as potential or real risks. It is therefore necessary to create a new kind of prenatal care whereby all risks can be screened in good time, and where parents would be given the opportunity for comprehensive care, including access to psychotherapeutic counseling (*Fedor-Freybergh, 1983, Fedor-Freybergh et al., 1988*).

Pregnancy and delivery are not diseases per se, only very exceptionally, but they sometimes can become a disease due to a doctor's intervention. We have to give credit to the inner wisdom of the pregnant woman and help her with our knowledge, our empathy and the scientific information to cope with her problems and with the potential or real risks if and when they occur.

This brings us to the topic of health. What was said before about the holistic and comprehensive view of all human functions will be true also in considering the issues of health and disease. The last definition of health by the World Health Organization is "a state of complete physical and mental well-being which results when disease-free people live in harmony with their environment and with one another" (*WHO, 1986*). As Zikmund (*1993*) points out, this definition, though including all three dimensions of life manifestations of man - biological, psychological and social, has several shortcomings. In his analysis of the dimensions of health and disease he accentuates the functional aspect of health and disease and defines health as functional optimum of all of life processes, biological, psychological and social.

The psycho-physical organism tries constantly to maintain its health. It strives toward recovery, away from destruction; it strives toward homeostasis, away from disorganization and chaos. Health has clearly a very strong dynamic and creative dimension and in 1976 (*Fedor-Freybergh*) I described health as "the dynamic movement along the creative path towards self-realization". Self-realization has to be understood as containing biological, psychological and social dimensions. Self-realization with regard to (a) the constructive integration of the dialectically changing, individually depending conditions with a simultaneous maintenance of the homeostasis of the "milieu intérieur", and (b)

the balance in the striving for satisfaction of the individual during the continuous confrontation and adaptation of the psychoendocrine system with and to the "milieu extérieur" of ordinary day-to-day life situations. By adaptation is meant not just the adaptation of the individual to the environment, but also the possibility to transform the environment to suit oneself.

We must abandon the restrictive, positivistic objective approach to the individual and to the society. These approaches ignore the subjective specificities of each individual and each society with their own soul and spirituality, their own needs, feelings and thoughts. We have to strive after the renaissance of individual human uniqueness in a world where the individual and his environment should represent a spiritual unity in ecological and ethnic peace. That is even more true for such a subtle situation as the prenatal stage of human development. But is it not so that, from a subtle and delicate process, large and important movements in philosophy, practice and global change can result? According to the "butterfly effect", events are interdependent to that degree that the very subtle and seemingly insignificant movements of a butterfly's wing are able to set off, somewhere far away, a large typhoon. This butterfly effect can be likened to the prenatal stage of human development. With this in mind, therein lies the unique opportunity to prevent the world from evil.

## THE NEEDS OF HUMAN BEING

The next topic I wish to stress are the basic needs of the human being. Invariably these needs are described as eating, sleeping and sex. But I feel that there is one more, very basic need which has never been addressed and that is the need for taking care of someone and the need of being taken care of. The being for whom we care becomes the most important being in our life and has also become a part of our lives. It is irrelevant whether the one we care for is an adult, a child, a prenatal child, a dog, a cat or a small bird - in other words all living things.

This being cared for and being taken care of is one of the prerequisites of our survival and provides the homeostasis and equilibrium between us and our environment. When we are being taken care of we can be healed and cured and when taking care for someone we can heal and cure as well.

Another wonderful way to express this is with the words of Antoine de Saint-Exupéry (1946): "On ne connaît que les choses que l'on apprivoise", . ."Tu deviens responsable pour toujours de ce que tu as apprivoisé."

In this way the bonding process is created and feelings of reassurance and well-being are established.

In order to predict how successful the bonding process between mother, father and child will be, we need to have a good knowledge of the personalities of the father and mother, their past, their expectations and visions, their fears and ambivalences. The importance of individual family history is becoming increasingly more apparent. The individual's life starts at the latest in the house of its grandparents, who do or do not pass on to their children (the present

parents-to-be), the basic values of morality, ethics and respect for life, who then will or will not pass on these values to their unborn child.

An interdisciplinary approach invites interdisciplinary discussions where the same topic can be viewed from different aspects. It should serve as a unique opportunity for the cross-fertilization between the different sciences and practices, rather than the more traditional multidisciplinary approach. It was expressed in the leading article of *Lancet* (1985) "Psychiatrists and immunologists do not meet much, and when they do they tend to speak in different tongues". (*Leading article, Lancet, 1985*)

An interdisciplinary dialogue is not only possible but even extremely creative and vitally necessary, and the possibility of common understanding and thought within the language of different disciplines, primarily between the "humanistic" and "natural" sciences, is reachable. In this journal there has been an interdisciplinary (not to be confused with multidisciplinary) dialogue from the very beginning, which has contributed to tearing down many established barriers.

In an issue of the *Universitas* (*Robert Schurz: "Ist Interdisziplinarität möglich?" Universitas 11, 1995, 1070-1089*), a distinguished German journal for interdisciplinary sciences, a paper was published questioning whether interdisciplinary communication is possible at all. It was a paper with a very careful methodology which concluded that interdisciplinary communication is a difficult task, probably not attainable but certainly worth aiming for.

## PRENATAL SCIENCE

I believe that we have succeeded so far because of the use of "prenatal science" as a model for the indivisibility of the "psychological" and "somatic" processes in the continuum of human life, and that the phenomena and processes of the central nervous system and the immuno- and neuroendocrine processes are inseparable has also been put into the praxis. In our journal, the *International Journal of Prenatal and Perinatal Psychology and Medicine*, psychoanalysis, endocrinology, immunology, developmental psychology, obstetrics and midwifery, just to mention a few, have crossed each other's paths and today we are able to talk together at our congresses and read each others thoughts in the journal without interpreters.

In order to undertake such a challenge, a common language is required, a language that would be understood across disciplines and also would be able to assist in getting beyond semantic problems. One of those confusions is due to the reductionism still so very much inherent in the medical and psychological vernacular and represents one of the major epistemological problems in the science of prenatal and perinatal life.

There is a contradiction in the major tendencies in society at large as well as in the family and in individuals. On one hand there are increasing tendencies towards integrative processes within politics, economics, etc. on a world scale

while, on the other hand, there is a disintegration of the family and of microsocial structures with the consequent alienation of the individual.

There is enormous progress being made in information processing and communication with internet, e-mail and with cellular telephones in everyone's possession while, at the same time, there is a decrease in and deterioration of communication from person to person. Fairy tales are out, CD-ROMs are in.

I certainly do not advocate nostalgia for "the good old days". When the worst atrocities of World Wars I and II took place, internet did not exist. But there were fairy tales and the most degenerate war criminals loved children and dogs. That is, however, another issue. What I want to talk about here is the clandestine decline and disappearance of tradition and cultural values, of good education and of good manners, of sensitivity and common sense, and the ever-increasing alienation of the individuals from the very beginning of their life.

The prenatal child has become an object of research and observation, he or she is born as an object in alienated surroundings, brought up as an object and lives as an object patronized by authorities. Basic values such as closeness, love, solidarity, intimacy, intuition and natural instincts are suppressed by technocratic and bureaucratic manners. In this world of uncertainty and alienation, the individual is threatened by the deprivation of his or her basic rights.

In the *International Journal of Prenatal and Perinatal Psychology and Medicine* we have been very conscious of the dimensions of health and disease, both in children and in families, and have stressed the importance of primary health and primary prevention as early as in the prenatal stage of life (*Int. J. of Prenatal and Perinatal Psychology and Medicine, Vol. 5, No. 3*).

We strongly believe that the health of the individual is determined very early in prenatal life and that we should put emphasis on our possibilities to optimize prenatal care for mother and child worldwide. It could be worth a thought to propose that the United Nations devote one year to "The Year of the Unborn Child".

As we have said elsewhere (*Int. J. Prenatal and Perinatal Studies, Vol. 4, No. 3/4, pp. 155-160*), if we want to create a healthy, non-violent, creative human being, society or economic system, we have to return to the primary urges and functions of that human being, that society or that system. We have to guarantee the most optimal conditions possible at the very primary stages of development, whether in a human being or in a society. Only then can we achieve a true primary prevention of illness, mental and physical disturbance, hate, intolerance, violence and war, in the individual, in the family and in society.

Looking back to the UN "Year of the Family" and reviewing the atrocities around the world done to families, children and to entire societies and ethnic groups, we cannot but with deep sadness acknowledge that merely to make declarations is not enough. The world can be changed only if we achieve a change in the basic understanding of respect for life from the very beginning. It starts with a deep respect for the unborn child in its first ecological position in



the womb, respect for the mother, respect for the child at birth, and welcoming it with great dignity as an equal partner in society.

Respect for human life from the beginning will also bring about new ways of treating prematurely born children with dignity (*Marina Marcovich, Otwin Linderkamp, Ernest W. Freud*).

This also has to do with learning empathy for other human beings. We have said that the life of the individual begins, at the latest, in the home of its grandparents. There the parents of this individual receive all basic norms and values of ethics, morality, empathy, respect for life and others, which they will then transmit to their own children even before they are conceived. Thus, we need to review the restrictive, positivistic, objective approach to the individual and to society - an approach which ignores the subjective specificities of each individual and of each society with their own soul and spirituality, their own needs, feelings and thoughts.

We have to strive for the renaissance of individual human uniqueness - that the individual and his environment should represent a spiritual unity in ecological peace.

The great humanist, writer and philosopher, Václav Havel (*1994*), President of the Czech Republic, stressed in his speech in Philadelphia, USA, on July 4, 1994, the uniqueness of the individuals, their rights, individual knowledge and the ability to transcend, the individual's respect toward the miracle of being, wonder of the cosmos, of nature and of their own existence. He said "The only reliable way towards coexistence and togetherness in peace and creative co-operation in the multi-cultural world of today must be anchored in human hearts and minds much deeper than any political opinions, antipathies or sympathies, namely, in the human ability to transcend - transcendence as an understanding hand offered to someone close as well as to a stranger, to the human community, to all living beings, to nature, to the cosmos; transcendence as the deep and joyfully experienced need for harmony with that which is not us, with that which we do not understand, which seems to be distant in time and space, but with which we are secretly in contact because this, together with us, builds one, unique world. Transcendence as the only real alternative to non-existence." (Translation from Czech by the Author)

In the last few decades or, even more so, in the last few years, we have witnessed rapid changes in the world, where at great speed most positive tendencies towards liberalization and democratization of societies have taken place. At the same time new dangers and fears from different movements towards new totalitarianism and fundamentalism in philosophy and practice are growing. It is therefore of extreme importance in this time of philosophical, political and social transitions to stress the awareness of the optimization of human life conditions from the beginning. We are convinced that only a change of attitude, basic philosophy and practice concerning the prenatal conditions of human life would lead to a humanization of those societies toward non-violence

and common respect for life and tolerance for individual freedom and self-realization.

Unless we can achieve those mental and social approaches concerning the prenatal stage of life, all positive changes in the world would stay on the surface and there would always be a danger of threat against basic human needs and rights, against cultural and traditional values, against civilization and freedom.

The vision is of a society with high respect for life expressed by every individual and hence of achieving a socially healthy, non-violent world.

The title of the 11th ISPPM Congress in Heidelberg, 1995, „a time to be born“, proposed by the past president of the ISPPM, Rudi Klimek, stressed: not only the individual freedom of mother and child to decide the term of labour as the result of the creative dialogue they have had during the pregnancy, but also that it is time for the birth of a new awareness by society that the prenatal and perinatal stages are the most crucial and decisive in human life.

Awareness that the unborn child is already a personality, a psychological and social partner to its parents, and, through them, to society as a whole must be brought to the fore.

Indeed, the history of humanity is also the history of children and this history begins at the very start of life, at the very latest at conception. Studies of Psychohistory (*Lloyd DeMause, Robert MacFarland, Alenka Puhar, et al.*), studies in Epidemiology (*Matějček et al., 1987*) and studies in Psychotherapy (*Janus, Hau, Caruso, Benedetti, et al.*) have clearly shown the impact of being loved, wanted and respected on the individual and their ability to cope with their own problems and with the problems in society.

## CONCLUSION

There is a change in the consciousness of society concerning the vital importance of the events from the prenatal and perinatal period for the physical, mental and social health of human individuals. There is an increasing awareness, interest and even involvement in both professional and political environments for the importance of and the need to improve prenatal life and the circumstances surrounding birth.

If we can ensure that every child is loved and wanted from the very beginning, that it will be given respect and that respect for life is placed highest on the scale of human values, and if we can optimize the prenatal and perinatal stages of life without frustration of basic needs, without aggression and psychotoxic influence, the result could be a non-violent society.

The way you treat your child is the way the child will treat the world. This includes the unborn child, and this is also the whole truth about primary prevention.

The prenatal stage of life represents a unique opportunity for the primary prevention of psychological, emotional and physical disorders in later life. At this stage we can also develop preventive procedures to decrease premature birth and perinatal morbidity and mortality. In order to understand the enormous

potential power of the prenatal processes and their impact on the individual's prenatal and postnatal health, we have to ask ourselves what the prenatal stage of life implies.

In closing I indeed agree with what André Gide said, "Everything has been said already, but as no one listens, we must begin again."

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# SPECTRAL ANALYSIS OF BLOOD PRESSURE AND CARDIAC INTERVAL FLUCTUATIONS IN HYPERTENSIVES AND NORMOTENSIVES

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## INTRODUCTION

The assessment of cardiac autonomic status is very important in clinical medicine and is based on investigations of heart rate variability, blood pressure variability and baroreflex sensitivity. Spectral analysis of blood pressure and cardiac intervals is used in determination of heart rate variability, blood pressure variability and enables us to determine baroreflex sensitivity. The baroreflex heart rate sensitivity (ms/mmHg, BRS) is low in patients with essential hypertension. This fact was demonstrated by classical phenylephrine method (*Gribbin et al., 1971*) and by spectral method (*Siegelová et al. 1994, 1995*). The mean value of the group of hypertensives is of about one half of the mean value of the group of normotensive subjects. Because of a large scatter of individual values in both groups there are many normotensives with a lower BRS than the mean value of the hypertensive subjects and vice versa. On the other hand the gain of the blood pressure component of baroreflex is normal in essential hypertension (*Grassi et al., 1998*). This is a different finding than in patients with heart failure where both the heart rate component and the blood pressure component are decreased (*Grassi et al., 1995*). The aim of the present study was to compare BRS in patients with essential hypertension and in healthy young subjects with low BRS. It is an important question whether young normotensives with low BRS can be at risk for development of hypertension later and such a study can contribute to the solution of the problem. The estimation of the blood pressure component of baroreflex in the present study is based on the evaluation of the short-time blood pressure variability. It was demonstrated that this variability is decreased in subjects with high BRS (*Mancia et al., 1986*) because of homeostatic function of baroreflex in damping the blood pressure oscillations.

## METHODS

The blood pressure was non-invasively continuously recorded in finger arteries by Peñáz volume-clamp method (*Peñáz, 1973*) for 5 minutes (Finapres, Ohmeda) during the metronome-controlled breathing (0.33 Hz) in a group of

non-treated subjects with essential hypertension (EH, n=10, mean±SD: age 49±11 years, systolic/diastolic blood pressure - 155±23/99±12 mmHg). The diagnosis of essential hypertension (EH) was established by detecting elevated blood pressure (more than 140/90mmHg) on the basis of sphygmomanometer measurements on three different occasions within one month. The possibility that patients had secondary causes of hypertension was excluded by clinical examination. The other control groups consisted of subjects selected from large group of controls. BRS (ms/mmHg) was determined by spectral analysis of spontaneous fluctuation of systolic blood pressure and cardiac interval. The results were compared with a group of 10 healthy young subjects with low BRS (<6ms/mmHg, LBRS) and with a group of subjects with high BRS (>25 ms/mmHg, HBRS). Both control groups were selected from the population of 100 healthy young adults (age 20-22 years) as subjects with the lowest, respectively the highest baroreflex sensitivity. The method of BRS determination is described elsewhere (*Al-Kubati et al., 1997*). At least 30 min before the test the subjects were resting and adjusting to the environment (room temperature 20 degrees centigrade). Meanwhile, a plethysmographic transducer, Finapres Ohmeda was affixed. If the skin of the hands was cool, the subject was asked to put the hands into warm water for several minutes. The blood pressure was monitored for 10 min at rest. Three minutes' recording was taken at the end of the resting period for further analysis. Then the subject was instructed to breathe in synchronism with a metronome at 0.33 Hz for 5 min. The last 3 minutes were recorded and analyzed. The two recordings, one made during spontaneous breathing and the second during metronome-controlled breathing were evaluated by means of power spectral analysis. From the non-invasive continuous blood pressure recording, beat-to-beat values of systolic and diastolic blood pressure and pulse intervals were derived and analyzed. The values of all three circulatory variables were linearly interpolated at 2 Hz to ensure equidistant sampling in each time series. The baseline linear trend was removed from all signals. The power spectral densities and cross-spectral densities were calculated from the auto- and cross-correlation functions using Hanning's spectral window. The value of cross-spectral power density of pulse intervals and systolic blood pressure fluctuation [ $\text{ms} \cdot \text{mmHg}$ ] was divided by the value of power spectral density of systolic blood pressure fluctuation [ $\text{mmHg} \cdot \text{mmHg}$ ] at 0.1 Hz. The obtained value, modulus, was considered to be the measure of BRS [ $\text{ms}/\text{mmHg}$ ]. The coherence at 0.1 Hz, i. e. the degree of linear coupling between systolic pressure and pulse intervals fluctuation was calculated from both recordings, for spontaneous and metronome-controlled breathing, respectively. The study was approved by the ethics committee of the Masaryk University in Brno and all subjects gave their written informed consent.

## RESULTS

The variation of systolic blood pressure at 0.05 Hz (mean±SD) was  $44.1\pm 35.3$  mmHg<sup>2</sup>/Hz in HBRS and  $194.1\pm 141.2$  mmHg<sup>2</sup>/Hz in LBRS. The results confirmed the former finding that the blood pressure variability is lower in subjects with high BRS and vice versa. On the other hand in hypertensive subjects the blood pressure variability was low despite both low heart rate variability and low BRS. Variation of systolic blood pressure at 0.05 Hz was  $61.8\pm 26.5$  mmHg<sup>2</sup>/Hz (EH versus LBRS:  $p<0.05$ , Wilcoxon). At 0.1 Hz the variation of systolic blood pressure was higher in EH than in LBRS and HBRS (EH:  $52.9\pm 26.5$  mmHg<sup>2</sup>/Hz, HBRS:  $17.6\pm 15.9$  mmHg<sup>2</sup>/Hz, LBRS:  $35.3\pm 13.2$  mmHg<sup>2</sup>/Hz; EH versus HBRS  $p<0.05$ ).

It is concluded that the low variation of blood pressure at 0.05 Hz corresponds to the normal blood pressure component of baroreflex in patients with essential hypertension. The increased blood pressure variation at 0.1 Hz in this group of patients reflects the impaired heart rate component of baroreflex.

## DISCUSSION

The analysis of spontaneous beat-to-beat fluctuations of arterial pressure and interbeat interval has several advantages, mainly the comfort during the measurement. Two basic approaches have been proposed and validated, based on time-domain and frequency-domain measurements. With time-domain approach, the sequence of three or more consecutive heart beats identified, characterized by progressive increase in systolic blood pressure and progressive lengthening of pulse interval, are characterized by a progressive reduction in systolic blood pressure and progressive shortening of pulse interval. The difference in spectra of normotensive subjects and patients with essential hypertension indicates that the low BRS in both groups is caused by different mechanisms. The low BRS in healthy subjects can be caused by low baroreceptor sensitivity because both components of baroreflex - the blood pressure component and the heart rate pressure component - are attenuated. This resembles the situation in heart failure patients, where low baroreceptor sensitivity was proved in animal experiments. The high level of aldosterone stimulating Na/K-ATPase decreases the sensitivity of baroreceptors. This state can be reversed by digoxin, the potent Na/K-ATPase inhibitor (*Wang et al., 1992*). In humans, the low baroreflex sensitivity for both heart rate and blood pressure components (*Semrád et al., 1997*) studied by various methods (*Al-Kubati, 1996*) supports this hypothesis. In patients with essential hypertension the situation is different. In mild and moderate hypertension the resetting of baroreceptors is responsible for the shift of the set-point to a higher level of blood pressure, but the slope of blood pressure-cardiac interval curve which correspond to BRS and the slope of blood pressure-muscle sympathetic activity curve remain unchanged (*Grassi, 1987*). In severe hypertension the set-point further moves to higher values of blood pressure but the decrease in slope takes

place (*Korner et al., 1974*). This was not the case of our hypertensive subjects. Most probably the high sympathetic activity observed in essential hypertension accompanied with low parasympathetic activity is responsible for the decrease in BRS at intact baroreceptor sensitivity (*Mancia, 1997*). It is necessary to notice that the magnitude of fluctuation of blood pressure can be different in hypertensives and this fact can weaken our statement about normal baroreceptor sensitivity in essential hypertension. On the other hand the results of experiments with vasoactive drugs support this hypothesis (*Grassi, 1987*). The problem whether the low BRS contributes to the development of hypertensive disease and in which extent remains unsettled. Only a prospective study on a large number of subjects can answer this question. The spectral method for BRS determination is non-invasive and in our modification with controlled rate of respiration would be suitable for such testing.

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## BLOOD PRESSURE COMPONENT OF BAROREFLEX IN PATIENTS WITH ESSENTIAL HYPERTENSION

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### INTRODUCTION

The treatment of essential hypertension with ACE-inhibitor enalapril significantly decreased blood pressure. Baroreflex sensitivity studied by spectral method (*Robbe et al., 1987*) expressed in ms/mmHg (BRS) was increased significantly in comparison with placebo therapy, but remained low in comparison to normotensive subjects (*Siegelová et al., 1995*). Similarly the treatment with verapamil (240 mg per day in slow-releasing formulation) in monotherapy resulted in small significant increase in BRS in group of hypertensives with very low BRS, but BRS normalization was not achieved (*Siegelová et al., 1994*).

The aim of the present study was the measurements of blood pressure component in hypertensives treated with ACE-inhibitor trandolapril together with slow-releasing verapamil in combination. The blood pressure component of baroreflex was evaluated by means of a technique developed in our laboratory.

### METHODS AND SUBJECTS

We examined 18 patients with mild essential hypertension (men, aged  $48 \pm 5$  years, body weight  $88 \pm 9$  kg) after 3 months of the combined therapy with trandolapril (2 mg, in one morning dose) and diltiazem (retard, 90 mg, twice a day, EH TD) with mean BRS ( $\pm$ S.D.)  $8.2 \pm 3.4$  ms/mmHg. The diagnosis of essential hypertension was proved by WHO criteria and the secondary hypertension was disclosed. The patients with EH treated in combination with trandolapril and diltiazem were compared with 10 normotensives with high BRS  $> 10$  ms/mmHg (C-HBRS) and with 10 normotensives with low BRS  $< 5$  ms/mmHg (C-LBRS). Both normotensive control groups were selected from the population of 100 healthy adults. Another group of 10 non-treated patients with essential hypertension (EH) with BRS  $4.7 \pm 1.8$  ms/mmHg was examined and compared, too.

The blood pressure component of baroreflex was examined by the following procedure. The subjects were studied supine. Two inflatable cuffs (width 20 cm) were placed over the thighs of the subjects. The thigh cuffs were abruptly inflated to 180 mmHg (or over 20 mmHg above the patient's systolic pressure)



after the subject had been recumbent for at least 20 min. 5 min later a rapid decrease in cuff pressure to 60 mmHg elicited a decrease in systolic and diastolic blood pressure. The pressure of 60 mmHg in the occluding cuffs was chosen in order to prevent an increased venous return from legs and stimulation of low pressure receptors. Blood pressure in digital arteries was recorded continuously by Peňáz non-invasive technique (*Peňáz, 1973*) with Finapres BP Monitor 2300 (Ohmeda, Engelwood, USA). After a decrease in blood pressure of approximately 10-20 mmHg the blood pressure returned back to the original level (*Savin et al., 1997*). The curve of systolic and diastolic blood pressure return is S-shaped with a linear central part. The slope of the systolic blood pressure return (SLOPE-SBP) and the slope of the diastolic blood pressure return (SLOPE-DBP) were calculated by means of linear regression and expressed in mmHg/s. The magnitude of SLOPE-SBP and SLOPE-DBP corresponded to the gain of the blood pressure component of baroreflex. The Ethics Committee of the Masaryk University Teaching Hospital approved the study.

#### Statistics

The results are summarized as means  $\pm$  SD. The statistical significance of differences between EH and EH TD was determined by Wilcoxon test for paired data, that between EH and C by Wilcoxon unpaired test. Further analysis was then performed by analysis of variance.

## RESULTS

The combined therapy with trandolapril and diltiazem for 3 months significantly decreased systolic and diastolic blood pressure and significantly increased BRS in comparison with placebo therapy (ANOVA,  $p < 0.05$ ). The results of the analysis of the blood pressure component of baroreflex revealed that the gain of the whole baroreflex in EH TD and in EH (mean SBP  $166 \pm 12$  mmHg, DPB  $102 \pm 8$  mmHg) corresponded to healthy subjects with high BRS.

The following values of SLOPE-SBP and SLOPE-DBP respectively (mean  $\pm$  S.D.) were found: EH TD -  $0.93 \pm 1.33$  and  $0.55 \pm 0.65$ ; C-LBRS -  $0.48 \pm 0.18$  and  $0.30 \pm 0.14$ ; C-HBRS -  $1.29 \pm 0.62$  and  $1.18 \pm 0.58$ ; EH -  $1.04 \pm 0.64$  and  $0.92 \pm 0.68$ .

The values of SLOPE-SBP and SLOPE-DBP in C-LBRS were significantly different from the other groups (ANOVA,  $p < 0.05$ ).

## DISCUSSION

The mechanism which corresponds to the normalization of BRS after therapy with ACE-inhibitor trandolapril and slow-releasing verapamil in combination is unknown. Nevertheless, some results of other laboratories together with the results of the present study can contribute to the elucidation of problems

related to two questions: Why BRS is low in essential hypertension and which changes of baroreflex are responsible for the treatment-induced BRS increase? The gain of baroreflex is the product of three parts of baroreflex, baroreceptor sensitivity, the amplification of neuronal net and the effectivity of the effector branches of the reflex modulating cardiac output and peripheral resistance. A low baroreflex gain was found in patients with heart failure, where reduced muscle sympathetic nerve activity (MSNA) modulation by baroreflex was found (*Grassi et al., 1995*). This finding can be explained by a low sensitivity of baroreceptors. Aldosterone, the concentration of which is increased in heart failure, stimulates Na/K-ATPase of receptors. This results in hyperpolarization of receptor cells and decreased frequency of efferent train of spikes (*Wang, 1992*). A low baroreceptor sensitivity is probably responsible for a decrease in BRS in normotensives with low BRS. The correlation of low BRS with low slope supports this hypothesis. On the other hand deactivation of baroreceptors and stimulation by vasoactive drug-induced changes in blood pressure can influence MSNA, so that it remains unchanged in essential hypertension compared to normotension, at variance from the reduction in the heart rate alteration (*Mancia, 1997, Grassi et al., 1998*).

An attractive hypothesis that a low baroreceptor sensitivity is compensated by the increased responsiveness of smooth muscle of hypertrophic arterial wall (*Folkow, 1978*) is not supported by the available evidence. A long-lasting therapy with ACE-inhibitor enalapril decreased blood pressure and normalized forearm blood flow after 5 min of ischaemia, which indicated regression of hypertrophy of the resistance vessels. BRS, however, remained low in patients treated with enalapril, reaching approximately one half of age-matched normotensive controls (*Siegelová et al., 1995*).

It seems that sympathetic overactivity documented by increased MSNA in subjects with essential hypertension (*Mancia, 1997*) inhibited the baroreflex-mediated vagal response. Angiotensin II activates the sympathetic nervous system both centrally and peripherally (*Zimmerman, 1981*). The reverse of this influence was not achieved by enalapril in one morning dose, probably because of insufficient trough-to-peak ratio. The trough-to-peak ratio of trandolapril is higher. Verapamil increased the threshold in sinoatrial pacemaker cells. The increased variation of interbeat intervals at constant variation of the slope of diastolic prepotential is the consequence of it. The normalization of BRS in hypertensives after combined trandolapril-verapamil treatment can be the result of synergistic influence of both drugs. If this explanation is correct then the increase in BRS reflects the suppression of sympathetic activity which can be very important for prevention of sudden cardiac death and other cardiac and vascular alterations that lead to hypertension-related morbidity and mortality.

It is concluded that the gain of the whole baroreflex in patients with essential hypertension with combined therapy with trandolapril and diltiazem for 3 months (EH TD) corresponds to healthy subjects with high BRS.

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# **EFFECTS OF REHABILITATION IN MODERATE CONGESTIVE HEART FAILURE USING LOW-FREQUENCY ELECTRICAL STIMULATION OF INFERIOR LIMB MUSCLES**

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## **INTRODUCTION**

Exercise intolerance is the most frequent complaint of patients with congestive heart failure (CHF). An increase in pulmonary venous pressure may lead to dyspnoea during exercise and muscle fatigue is the primary determinant of exercise capacity. A skeletal muscle metabolic dysfunction, characterized by depressed oxidative capacities, contributes to this fatigue. Low-frequency electrical stimulation (LFMES) has been shown to induce an increase in the muscular oxidative capacities and could represent a new form of mild physical training. The aim of this study was to evaluate the effects of LFMES on maximal and submaximal exercise capacity, skeletal muscle metabolism, vasomotor response to exercise and autonomic tone in patients with CHF.

## **PATIENTS AND METHODS**

26 patients (23 M and 3 F, aged  $56,41 \pm 8,5$ ) with idiopathic dilated cardiomyopathy (n=12) or ischemic heart disease (n=14), in NYHA class II-III and in stable condition were subjected to low-frequency (10 Hz) electrical stimulation bilaterally applied to quadriceps and gastrocnemius muscle at a rate of 1 hour/day, 5 days/week during 5 weeks, using 2 portative dual-channel stimulators ELPHA 2000 (DANMETER, Odense, NV, Denmark). Initial and final assessment included 6-minute walk test, maximal bicycle exercise testing with  $VO_2$  measurement, 24-hour Holter ECG monitoring with spectral and non spectral analysis of heart rate variability (HRV), plasma norepinephrine (PNE) levels, Doppler evaluation of common femoral artery blood flow at rest and after the exercise.

Statistical analysis was performed using the McNemar test of symmetry, the Wilcoxon paired, the  $\chi^2$  and the Friedman tests. Statistical significance was defined as a p value  $< 0.05$ .

## RESULTS

	initial	final	p
distance in 6min (m)	415.1±10.5	472±11	< 0.05
peak VO <sub>2</sub> (ml/kg/min)	16.80±4.5	18,9±6	< 0.05
VO <sub>2</sub> AT (ml/kg/min)	11.50±2.8	14,2±3,6	< 0.05
MVFA (cm/s) rest	13.9±9.4	12.4±5.2	NS
post exercise	29.1±18.3	37.9±21.7	< 0.05

(VO<sub>2</sub> : oxygen consumption, AT : anaerobic treshold, MVFA : mean blood velocity in common femoral artery)

Maximal and submaximal exercise capacity and exercise-induced vasodilatation were increased by LFMES, whereas no significant effect on HRV, PNE levels or nuclear magnetic resonance (NMR) parameters could be demonstrated.

## DISCUSSION

Many studies have been conducted on the effects of LFMES on skeletal muscles, but the number of results in humans is limited (*Maillefert, 1998*). Patients with CHF frequently have moderately reduced skeletal muscle volume, which possibly contributes to exercise intolerance. In our study we showed that LFMES did not induce variations in heart rate, arterial blood pressure, cardiac output and rhythm. Chronic LFMES leads to early changes in the activity of enzymes involved in the energy metabolism, with an increased activity of oxidative enzymes and a decreased activity of glycolytic enzymes (*Brownson, 1988*). Structural changes include an increase in the capillary density (*Brown, 1976*) and in the volume density of mitochondria and in the volume of sarcoplasmic reticulum (*Heilmann, 1981*). Consequently, the contractile properties are modified. The time-to-peak values of isometric twitch contractions, half-relaxation time and resistance to fatigue are increased (*Hudlická, 1982*). A classical training usually uses systemic exercises, which require an increase in cardiac output and it has not been shown that such exercises can be tolerated by all patients with severe heart failure or arrhythmias. The results of our study suggest that LFMES is safe, well tolerated and induces an increase in exercise capacity in patients with CHF. This seems to be mainly mediated by an improvement of vasodilatation without effect on autonomic tone.

## CONCLUSION

LFMES of inferior limbs muscles induces an improvement of exercise capacity in patients with chronic CHF. LFMES could represent an alternative to classical training in these patients, which could be conducted easily at home without any cardiac risk.

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## **EXPERIMENTAL STUDIES**

# THE SIMPLE LINEAR MODEL OF THE CARDIOVASCULAR SYSTEM AND ITS APPLICATION

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## INTRODUCTION

The fundamental features of the circulation depend on the fact that the cardiovascular system is a closed loop - as described by William Harvey in 1628. Since the first physical model of this system was designed by Ernst Heinrich Weber in 1850, many more or less complex physical or mathematical models have been described. Especially, it is necessary here to mention the model by Guyton (*as summarized in his textbook 1991*). A very simple linear model was used to calculate the expected pressure drop after experimental occlusion of the portal vein (*Kenner, 1959*). In the time of the availability of computer power, it is the question if there is any demand for a simple and linear model. - The idea to revive the simple model (*Kenner 1959*) came up for three reasons.

- 1) For the first rough interpretation of recorded biologic reactions a simple model appears to be more effective than a very complex and sophisticated model.
- 2) We have made some preliminary measurements in the dialysis unit of the Department of Medicine of the University Hospital in Graz. In this case the interpretation of blood pressure changes after the occlusion of the AV-shunt of dialysis patients was of interest. An example will be discussed below.
- 3) A simple model is easy to understand and, therefore, of didactic value.

## METHODS

The model

The model consists of one pump with the property  $H$  (dimension: inverse resistance),

an arterial compartment (index  $a$ ), a peripheral resistance  $R$  and a venous compartment (index  $v$ ).

The following symbols are used:

$Q$  cardiac output

$p$  pressure

$VB$  blood volume

The very simple linear model is described by three equations:



- (1)  $VB = pa.Ca + pv.Cv$  (blood volume)  
 (2)  $pa - pv = R.Q$  (peripheral resistance)  
 (3)  $Q = pv.H$  (Frank-Starling mechanism)

From these equations it is easily possible to plot Q versus pv, to demonstrate the effect of a variation of the blood volume, a variation of the compliances and a variation of the peripheral resistance. Furthermore, it turns out that in all essential equations the nondimensional product or quotient

(4)  $H.R = pa/pv$   
 acts as one main parameter. It may be reminded that H includes contractility and heart rate. In order to summarize the results in compact form, two abbreviations are introduced:

(5)  $VB/(Ca + Cv) = MCFP$   
 (mean circulatory filling pressure according to Guyton 1991)

(6)  $Ca/(Ca + Cv) = k$   
 (ratio of arterial and total compliance)

For our special problem the most interesting result is the effect of an increase of the resistance on the arterial pressure. We find:

(7)  $pa = MCFP (1 + H.R)/(1 + k.H.R)$

## PARAMETERS AND EXAMPLE

The product H.R, under normal conditions, has a value of about 20. The value of k is about 1/20. Therefore, if the experimentally induced increase of the total peripheral resistance can be estimated, then the expected increase of the arterial pressure (*ceteris paribus*) can be calculated from equation (7).

Patient G., male, 72 years. The measurements were made in the hemodialysis unit after informed consent of the patient.

Cardiac output (indicator dilution): 6.1 l/min. The flow through the arterio-venous access shunt was measured with ultrasound: 1.9 l/min. The blood pressure was measured with the cuff technique and, continuously, with the Penaz-technique. The control value was about 150/85 mmHg. Using the data mentioned above, the increase of the total peripheral resistance due to complete occlusion of the shunt was calculated to be 45%. From equation (7) an expected increase of the mean blood pressure (*ceteris paribus*) of 19% was estimated. During a 15 sec occlusion the mean blood pressure rose to a plateau, which was only 10% above the control value before and after the occlusion. The difference is primarily due to a reduction of H. However vascular reactions influencing the actual value of R cannot be excluded.

The reduction of H consists of inotropic and chronotropic components and is in part due to the myocardial sensitivity to the increased afterload and in part due to the effect of baroreceptor control.

The baroreceptor sensitivity (BRS) was measured and was found to be about 2.5 ms/mmHg, a rather low value. This index characterizes primarily the chronotropic mechanism. In other preliminary observations in dialysis patients the BRS may even be zero.

## CONCLUSION

A very simple linear model of the circulation can be used to interpret some basic interrelations between fundamental parameters and variables of the system. As an example the reaction of the system to a sudden increase of the peripheral resistance is demonstrated.

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## **EXPRESSION OF CELL-DEATH GENES DURING THE DEVELOPMENT OF RIGHT VENTRICULAR HYPERTROPHY IN MONOCROTALINE-TREATED RATS**

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### **INTRODUCTION**

The tumor suppressor gene P53 has come to be known as a master guardian of the genome and a member of the DNA damage-response pathway. P53 can lead to either growth arrest or apoptosis in DNA damage cells. The growth-suppressive role of P53 occurs by activating the expression of the P21Waf1/Cip1 gene, which is a potent cyclin dependent kinase inhibitor. Induction of P21 by P53 results in cell cycle arrest in G1 or G2 to allow DNA to take place. If repair is not successful, P53 may promote cell death by apoptosis via the inhibition of BCL-2 and the activation of BAX. BCL-2 and BAX genes are key regulators of apoptosis: BCL-2 is a potential antiapoptotic factor whereas BAX is a death-promoting factor (*Hirsch, 1998, Ko, 1996*). Both genes encode protein subunits of a mitochondrial megachannel called permeability transition pore. If the mitochondria undergoes these transition of permeability, factors such as Apoptosis Inducer Factor (AIF) and cytochrome c were released, which induce apoptosis (*Saini, 1998*).

The purpose of this study was to investigate the expression of P53, P21, BCL-2 and BAX mRNA during the development of pressure overload right ventricular hypertrophy induced in rats by a single injection of monocrotaline.

### **METHODS**

Male Wistar rats received (i.p.) a single injection of 60mg/kg monocrotaline (MCT rats) or saline (control rats) and were killed after 14, 21 or 31 days. The hearts were removed and were dissected in right ventricle (RV), left ventricle (LV) and septum (S). Total RNA were extracted and retrotranscript in cDNA. Changes in P53, P21, BCL-2 and BAX transcript levels in the hypertrophied ventricle and the unaltered left one were quantified by RT-PCR. Apoptosis associated chromatin-cleavage was assessed in situ by the TUNEL assay on embedded paraffin section of the hearts.

## RESULTS

MCT caused a progressive increase in the ratio of RV to LV+S weights from days 21 to 31 that was significantly greater than the control values (140% and 227,5% , respectively), indicating the development of RV hypertrophy in the MCT rats. The results of RT-PCR showed that P53 was up-regulated at 21 days in the MCT rats compared to the control rats (76%) and p21 was significantly increased at 31 days (27%). The ratio of BCL-2 to BAX, which gives evidence of the balance between death-repressor and death-activator proteins, decreased significantly at day 21 and 31 in the MCT rats by -40% and -70% , respectively, indicating that cells underwent apoptosis.

## DISCUSSION

A cardiac hypoxia and a pressure overload on the right ventricle could produce an oxidative stress and therefore, an overexpression of P53 (*Wilson, 1992*). Up-regulation of P53 can lead in one hand to cell growth arrest via P21 and in the other hand to cell death of hypertrophied cardiomyocytes via BCL-2 and BAX.

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## AMINO Guanidine AND ALLOXAN-INDUCED DIABETES

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### INTRODUCTION

Diabetic patients have a significantly greater incidence and severity of angina, acute myocardial infarctions, congestive heart failure and other manifestations of atherosclerosis than the non-diabetic population. It has been reported even in the absence of ischemic heart disease, impairment of ventricular performance can occur. Firstly we decided to investigate cardiac performance in the model of alloxan-induced diabetes in rats using isolated working heart technique.

### METHODS

Diabetes was induced by an intravenous injection of alloxan (60mg/kg) dissolved in 0.1 M citrate buffer (pH 4,5). Control rats were injected with citrate buffer alone. Both control and diabetic rats were used 48 hours after vehicle or alloxan injection. Animals in the diabetic groups were excluded if blood glucose was less than 3g/l. In addition a separate group of alloxan-injected and control rats received orally and daily a dose of 250 mg/kg of aminoguanidine during 2 days before the evaluation of cardiac performance. Cardiac performance was assayed by the isolated perfused heart working technique. After 30 min of perfusion, the main coronary artery was ligatured and the ligature was maintained for 10 min. It was then cut and reperfusion continued for 10 min. Aortic flow rate and heart beat were decreased in the diabetic group whereas diabetic rats showed to be more resistant to ischemia compared to control group. After aminoguanidine pretreatment aortic flow rate recovered initial value in diabetic group although no change in glucose blood level was observed. It has been demonstrated that advanced glycosylation products inactivate nitric oxide and involve an impairment in endothelium-dependent relaxation. It has also found that aminoguanidine is an inhibitor of semicarbazine-sensitive amine oxidase and detoxify toxic aldehydes. Aminoguanidine selectively inhibits the cytokine-inducible isoform of NO synthase which appears to be responsible for the excess production of NO linked to diabetes mellitus. In a second part we decided to evaluate the antioxidant properties of aminoguanidine. Indeed hyperglycemia is increasingly regarded as the cause of diabetic

complications especially via its ability of reducing sugars to glycate proteins and produce reactive oxygen species. So we investigated the protection provided by aminoguanidine by two approaches: 1) Electron Paramagnetic Resonance (EPR) spectroscopy using spin trapping techniques to assess the superoxide and hydroxyl radical scavenging effects of aminoguanidine and 2) spectrofluometric methods to investigate the protection provided by aminoguanidine against the oxidation of allophycocyanin (a fluorescent protein) induced by a peroxy radical generator.

## RESULTS

Our results demonstrated that aminoguanidine was able to scavenge hydroxyl and peroxy radicals. So these radical scavenging properties of aminoguanidine may help to explain the prevention of diabetic complications as vascular dysfunction by this compound. In addition TUNEL techniques made on diabetic rat hearts showed apoptotic cells surrounding the vessels. In the separate diabetic group which had received aminoguanidine treatment no apoptotic cells were present close to the vessels. Using immunohistochemistry techniques we noted that apoptotic cells were not cardiomyocytes.

## DISCUSSION

Although in vivo studies investigating the effects of diabetes on severe ischemia are controversial. Paradoxically, in vitro studies are more consistent in demonstrating that heart are less susceptible to injury following a severe episode of ischemia (*Norton, 1996, Yildiz, 1998*). In the other hand, aminoguanidine has been shown to be capable of blocking the formation of advanced glycation end products (AGEs). There is accumulating evidence that the formation of AGEs increases with aging and is implicated in the pathogenesis of diabetic atherosclerosis. Further experiments are needed to discover the type of cells involved in apoptotic process in alloxan-induced diabetes (*Saini, 1998*). However apoptotic process in this model of diabetic rat could explain the impairment of cardiac performance.

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# NEW PERSPECTIVES IN CARDIOPROTECTION: IN VITRO ANTIISCHEMIC EFFECT OF CAPSAICIN AND CALCITONIN GENE-RELATED PEPTIDE

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## INTRODUCTION

Single or multiple brief periods of regional or global ischemia and reperfusion prior to a prolonged ischemic insult showed cardioprotective effects. The mechanism underlying this phenomenon, called „ischemic preconditioning“, remains unclear. There is now an increasing amount of evidence which suggests the involvement of endogenous myocardial protective substances such as calcitonine gene-related peptide (CGRP) in ischemic preconditioning. It has been also shown that capsaicin evokes CGRP release from sensory nerves. The present study was designed to further explore the possible cardioprotective effect of CGRP and capsaicin in the rat model of isolated and perfused working heart.

## MATERIAL AND METHODS

Male Wistar rats (b.w. = 290-320 g) were anesthetized by pentobarbital sodium. The hearts were rapidly excised, mounted on a Langendorff apparatus and perfused by Krebs-Henseleit buffer (KHB) at a constant temperature 37° C. The experiment was divided in 3 groups: 1. CGRP  $5 \times 10^{-8}$ M group (n=5), 2. capsaicin 30  $\mu$ mol group (n=5) and 3. control group (n=6). Study protocol: a) preischemic period (10min in Langendorff mode and 15min in working heart mode), b) period of global ischemia (30min at 37° C) and c) reperfusion period (15min in Langendorff mode and 20min in working heart mode). CGRP and capsaicin were added to the perfusate medium in the 5th minute of the working heart mode (for 5min in preischemic period). Coronary, aortic and cardiac output and the heart rate were measured. All data were analyzed using a one-way ANOVA test and all values expressed as means  $\pm$  S.E.M. Significance level is chosen as  $p < 0,05$ .

Capsaicin and CGRP were obtained from Sigma Chemical Company (St.Louis, MO, USA).

## RESULTS

In the preischemic period the analysis of hemodynamic parameters showed no significant difference in all groups. During the reperfusion period we noticed a statistically significant increase of the values of coronary, aortic and cardiac output in the group treated with capsaicin 30  $\mu\text{mol}$  compared to the group with CGRP  $5 \times 10^{-8} \text{M}$  ( $p < 0.01$ ). All hearts in the control group developed ventricular arrhythmia, both fatal ventricular fibrillation and ventricular tachycardia. Pretreatment with capsaicin 30  $\mu\text{mol}$  caused a significant improvement of cardiac functions and a reduction in the incidence of ventricular arrhythmia. There was an overall decrease in heart rate ( $p < 0.05$ ) in the groups with capsaicin and CGRP during the reperfusion period compared to the initial values in preischemic period.

## DISCUSSION

Calcitonin gene-related peptide, a principal transmitter in capsaicin-sensitive sensory nerves, is present in the hearts of animals and humans and has numerous physiological properties, several of which are thought to be beneficial to the ischemic myocardium (*Li, 1996, Källner, 1998*). Capsaicin is the active ingredient causing the pungent effects of red hot peppers. Although capsaicin has been extensively studied in the nervous system, few studies with capsaicin have been performed in the myocardium. In the myocardium, capsaicin has been shown to cause release of CGRP from terminal nerve endings and protects against myocardial injury induced by ischemia-reperfusion in the isolated perfused rat heart (*D'Alonzo, 1996*). There is now an increasing amount of evidence to suggest that the ischemic preconditioning stimulates the release of endogenous myocardial protective substances, such as CGRP. An exogenous administration of them could mimic a classic ischemic preconditioning. In this study the cardioprotective effect was observed only in the group treated by capsaicin 30  $\mu\text{mol}$ , suggesting the possible involvement in preconditioning-like cardioprotection. In contrast, no significant cardioprotective effect of CGRP  $5 \times 10^{-8} \text{M}$  was found on the cardiac recovery in this experimental model. The mechanisms responsible for the beneficial effects of capsaicin (and CGRP) on the ischemic myocardium remain unclear. Both - capsaicin and CGRP- are involved in the  $\text{Ca}^{++}$  handling in myocytes and nerves and the intracellular  $\text{Ca}^{++}$  regulation needs to be explored with regard to the antiischemic properties (*Poyner, 1992*).

The results presented in this study suggest that pretreatment with capsaicin 30  $\mu\text{mol}$  (but not CGRP  $5 \times 10^{-8} \text{M}$ ) induced a preconditioning-like cardioprotection, further supporting the conclusion that capsaicin may play an important role in the mediation of ischemic preconditioning.



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Biological rhythms in medicine, their importance in diagnostics, therapy and preventions  
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Chronomedicine. The current disease-cure-oriented health care system does too little too late, at too great an expense for those few who can afford it. For instance, a beat-to-beat electrocardiogram is already available, from an individual monitored for a year in apparent health. Blood pressure has been recorded mostly at 15-min intervals for over a decade. We can then summarize variability along the frequency of the cardiac and then of the respiratory cycle and can use cardiac and then respiratory rhythm characteristics as compacted endpoints for summaries via further repeated passes for the analysis of longer and longer data sections to assess rhythms with lower and lower frequencies. These broader and broader spectral windows on more and more data, with more and more compacting, can fit into an affordable memory for storage, so that the analyses can continue as a feature of recycling. Circadian hyperamplitude-tension, briefly CHAT, as noted carries the greatest risk of stroke. It is to be avoided as best one can, not only during space travel, but for all the many persons at risk on earth. This task is as important for vascular disease prevention, and is as much in the public domain, as are vaccinations for infections. The reference values collected in this practical endeavor of physiological monitoring may also serve a basic and applied chronoastro-biology in the context of cross-spectral analyses with the incoming stream of information gained from space-borne vehicles. We may learn where we come from, to better attempt to choose among the directions into which we can evolve.

1.

Otsuka K., Cornélissen G., Halberg F.: Age, g6. OD ČASOVÉ NESPECIFICKÝCH MĚŘENÍ K CHRONOBIOLOGICKÝM PŘÍSTUPŮM JAKO „CHRONOMEDICINA A CHRONOASTROBIOLOGIE“: VÝZVA VÝROBCŮM FROM TIME-UNSPECIFIED MEASUREMENTS TO CHRONOBIOLOGICAL SPECIALTIES SUCH AS CHRONOMEDICINE AND CHRONOASTROBIOLOGY: CHALLENGES FOR MANUFACTURING  
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At any science fair in Brno, the home city of J. G. Mendel, best known as the founder of genetics, biotechnology should be in the foreground. Chronobiologic data revealing that the same dose of the same hormone can stimulate or inhibit DNA synthesis, in a rhythmically changing sequence, suggest that chronobio-technology is more than a play on words. It is not generally known that in fact Mendel published more on meteorology than on plant hybridization. By providing a living example for monitoring the environment, the time structures of which are now coded in our genes, Mendel laid the groundwork for chronoastrobiology. Brno was also the home of K. Gödel, the mathematician who provided notes of healthy caution, e.g., for those who work on software to analyze the results of the automatic monitoring of blood pressure, started in Brno by J. Penaz and brought to the clinic by the team of J. Siegelová, B. Fišer, J. Dušek and B. Semrád. These investigators pioneered blood pressure chronotherapy guided by a longitudinal analysis with an individualized control chart, with drugs by the local pharmaceutical manufacturer Lachema.  
Chronomedicine. The current disease-cure-oriented health care system does too little too late, at too great an expense for those few who can afford it. Engineering for concomitantly resolving the external conditions and the internal schedules (chronoengineering in the broad sense, in the service of a project on the BIOSphere and the COSmos (BIOCOS)) could change this status quo.

Chronobioastrology informs us about what happens after the fait accompli of a crash, as did the autopsy in classical pathology. We can use the currently available software for repeated passes over a