NONINVASIVE METHODS IN CARDIOLOGY 2020

Edited by: **Cornélissen G., Siegelová J., Dobšák P.**

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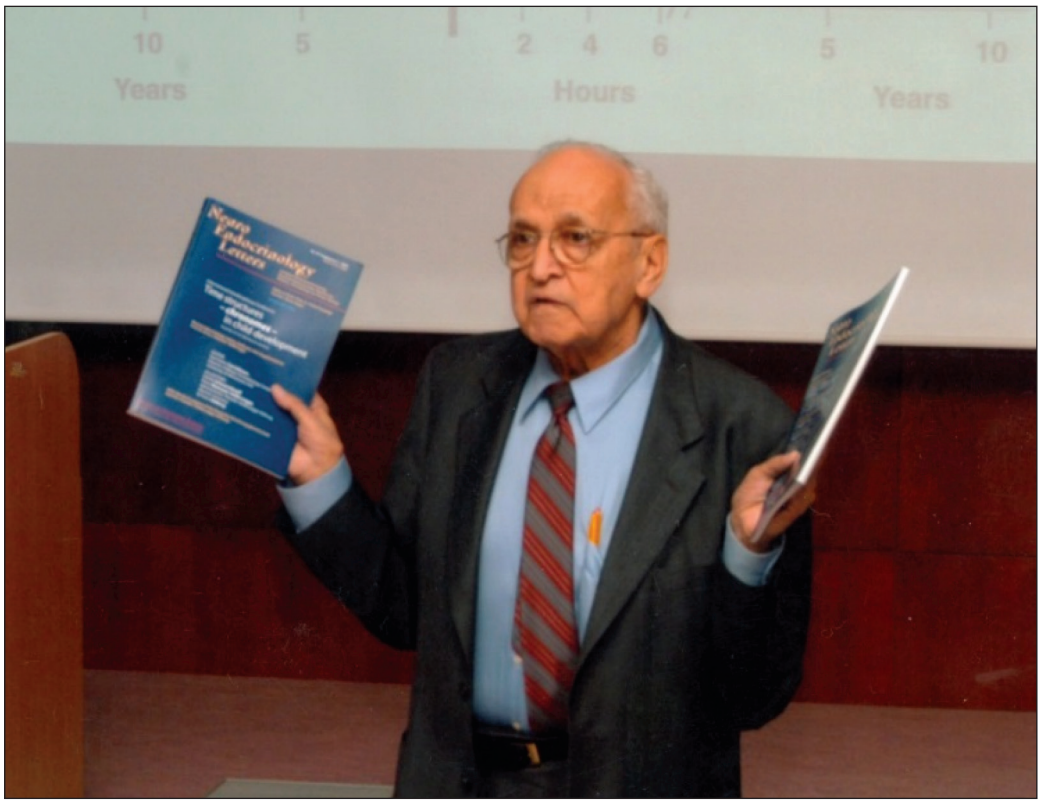
Scientific Project and International Cooperation between Masaryk University and University of Minnesota, University of Graz and University of Paris

Prof. MUDr. Jarmila Siegelova, DrSc.
Department of Physiotherapy, Faculty of Medicine Masaryk University

Scientific projects after Velvet Revolution in the Czech Republic are possible with the cooperation between Masaryk University and University of Minnesota, University of Graz and University of Paris.

Cooperation with University of Minnesota, USA

Cooperation with Professor Franz Halberg and with professor Germaine Cornélissen, Dr. Othild Schwartzkopff, Halberg Chronobiology Center of the University of Minnesota, USA and with Brno team including professor Bohumil Fiser, Jiri Dusek, M.D. and professor Jarmila Siegelova started in 1988. The common studies of circadian variability of cardiovascular variables and baroreflex sensitivity were published in many papers as the result of this common work and our Brno team participated in international projects Womb to Tomb, later BIOCOS, under the direction from Halberg Chronobiology Center from Minnesota.



Franz Halberg, M.D., Dr. h.c. (Montpellier), Dr. h.c. (Ferrara), Dr. h.c. (Tyumen), Dr. h.c. (Brno), Dr. h.c. (L'Aquila), Dr. h.c. (People's Friendship University of Russia, Moscow), Professor of Laboratory Medicine and Pathology, Physiology, Biology, Bioengineering and Oral medicine 5.6.1919 – 9.6.2013

In the years 1991 – 1995 we solved the project the Czech project from IGA belonging to Ministry of Health of the Czech Republic Pathogenesis and treatment of essential hypertension, chronobiology of blood pressure in health and disease (Patogeneze a léčba esenciální hypertenze, chronobiologie krevního tlaku ve zdraví a nemoci, IZ342). The results of this project were discussed repeatedly with Professor F. Halberg and Professor G. Cornélissen from University of Minnesota. The document of cooperation is shown in original.

Chronobiology Laboratories
University of Minnesota

Director: Prof. Franz Halberg

12/12/95

Prof. MUDr. Karel Horky, DrSc.
President, Society for Internal Medicine
Director, II Department of Medicine
Faculty of Medicine
Charles University
U nemocnice 2
110 00 Prague, CZECH REPUBLIC
FAX (42-2) 290609

Dear Prof. Horky:

Dr. Jarmila Siegelova has asked me to provide an opinion of her role in the international chronome endeavor of the International Society for Research on Civilization Diseases and the Environment, in which hers so far is the only Czech group in the project. This is my response to her request made with the hope that it will in no way be an imposition on you, or be at variance with her wishes. Hence, I also transmitted this message via her e-mail and am now following up on it by special mail directly to you.

In the USA and Western Europe in general, there is a very high opinion of the contributions by Dr. Siegelova and her group, notably Dr. Bohumil Fiser, Dr. Jiri Dusek and Dr. Mohamed Al-Kubati. I know only secondhand that Jarmila's cooperation with her colleagues in France is productive, as is that with the physiology group in Graz, Austria; but apart from these relations, in the U.S. Dr. Siegelova's contribution was picked as one of six (among, I presume, several hundred submittals), for a meeting in Florida in January 1995. Specifically, on the human newborn, she showed what was new to nearly everybody, that the newborn human babies' blood pressures undergo larger about-weekly swings than their about 24-hour periodicity. This is a basic finding at a time when there are trials to optimize the newborn nursery by instituting physical environmental cycles that optimize the babies' built-in rhythms; hence the Brnese group's findings have immediate practical implications and eventually applications in health care. Some of the ordeals and costs of the very

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premature baby's care may well be reduced if we figuratively ride the waves of the organism rather than trying to break them.

As in Florida in January 1995, in Milan, Italy, at an international conference this past spring, Dr. Siegelova was the star by dint of thorough data, documenting the chronome (or time structure) mapping, which in terms of immediate reward we feel is as important if not more important than the mapping of the genome.

The Fiser/Siegelova/Dusek/Al Kubati team was also invited to make a presentation at the University of Minnesota Supercomputer Institute. Thus, we learned from our colleagues who came from the city not only of Gregor Mendel and Kurt Goedel, but also of Jan Penaz, who in addition to having two of the above-named colleagues as his now-independent pupils, has introduced the noninvasive automatic monitoring of blood pressure into at least medical research, well before it became fashionable. Computer methods resolve endpoints such as the circadian blood pressure overswing that carries a 720% increase in the risk of ischemic stroke. It was my privilege to read a resolution amplified upon in Czech by Dr. Siegelova and her colleagues that may help reduce, in her homeland as well as in the U.S., the suffering and cost of stroke. In the U.S., this cost is $30 billion annually.

Dr. Siegelova and her team also deserve the merit (as a beginning, correlations notwithstanding), of testing drugs not only on a group basis but in N-of-1 studies. I have never seen a place where an instrument that presumably your support provided her was in use 364 days out of 365 (the missing day probably being Christmas).

I was hoping to meet you in person to interest you in chronobiology. This is perhaps the best time not only to wish you happy holidays but also to express the hope that on your next trip through the U.S. you will stop with me as an esteemed guest. I regret that I can offer no more than full hospitality from the time you arrive at the airport to the time you leave. You would follow in the

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footsteps of Jarmila, Bohumil and Jiri, who were most appreciated in our setting by dint of hard, productive work done competently. It would be everybody's gain if their support could continue.

Sincerely,

Franz Halberg
Professor of Laboratory Medicine and Pathology,
Physiology, Biology, Bioengineering and Oral Medicine
Director, Chronobiology Laboratories
University of Minnesota
U.S. Vice-President
International Society for Research on
Civilization Diseases and the Environment

P.S. Please see Figure 17, p. 39 of the enclosure.

12/12/95 9:16 PM

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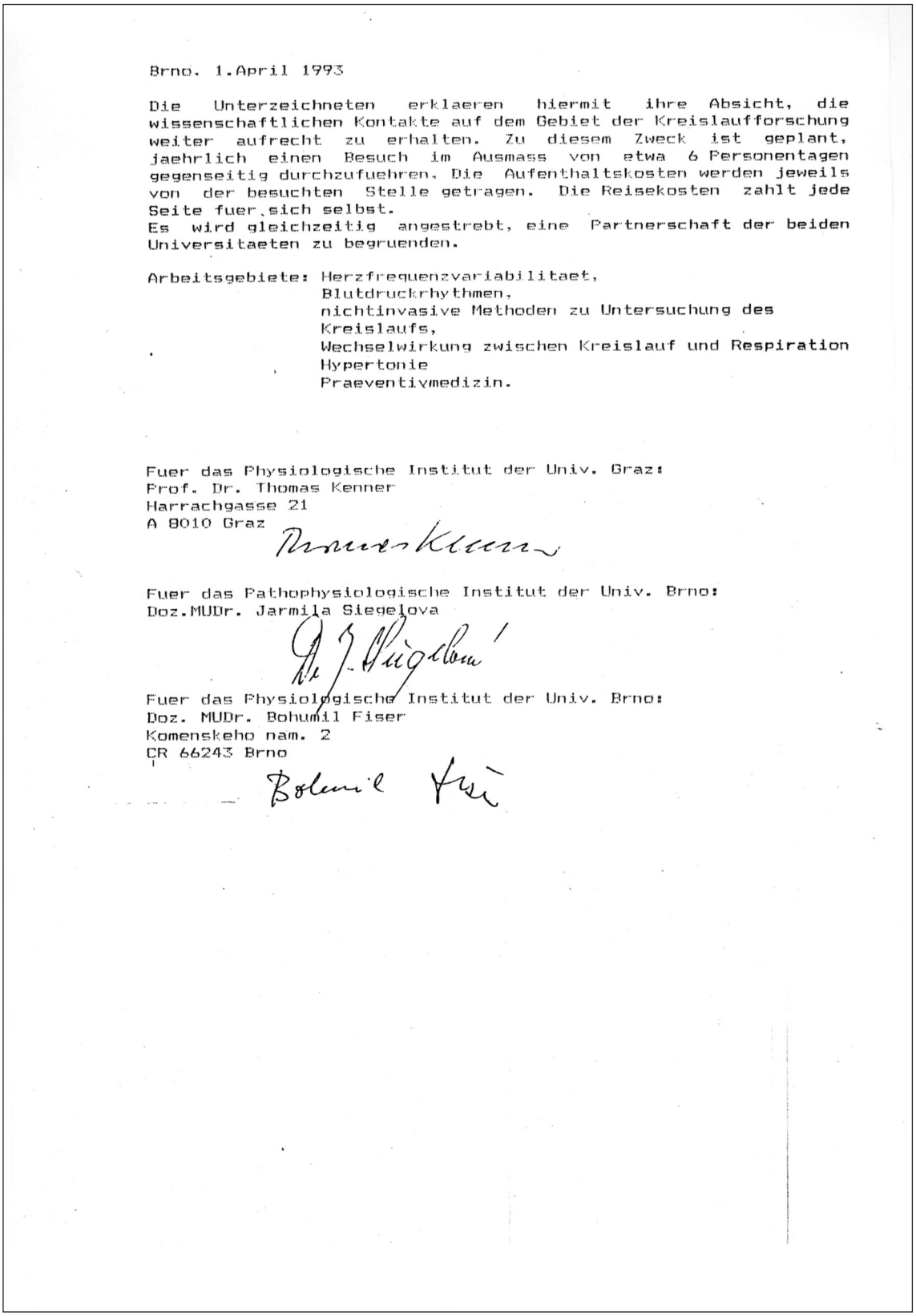
Cooperation with University Graz, Austria

The international cooperation started in 1990 with Professor Thomas Kenner from the Department of Physiology in University in Graz (Austria), where the original studies of heart rate variability, baroreflex sensitivity and chronobiology have been realized and included in the common international project of analysis of cardiovascular control in physiology and pathophysiology that was signed later in 1993, as it is shown in the document. From the year 1990 Prof. Kenner and Brigitte Kenner visited Masaryk University Brno three times a year and were active in all scientific activities organized by us in Masaryk University Brno.

**29.9.1932 - †22. 12.2018*
Prof. Dr. Thomas Kenner, M.D., Dr. h.c. mult.
Dr. h. c., Universität Jena, 1990
Dr. h. c., Semmelweis University Budapest, 1998
Dr. h. c., Masaryk University Brno, 2000
Rector (president) Karl-Frances-Universitat, Austria 1989-1991
Dean of Medical School, Karl-Fraces Universitat, Austria, 1991-1997



Brno, 1.April 1993

Die Unterzeichneten erklaeren hiermit ihre Absicht, die wissenschaftlichen Kontakte auf dem Gebiet der Kreislaufforschung weiter aufrecht zu erhalten. Zu diesem Zweck ist geplant, jaehrlich einen Besuch im Ausmass von etwa 6 Personentagen gegenseitig durchzufuehren. Die Aufenthaltskosten werden jeweils von der besuchten Stelle getragen. Die Reisekosten zahlt jede Seite fuer sich selbst.
Es wird gleichzeitig angestrebt, eine Partnerschaft der beiden Universitaeten zu begruenden.

Arbeitsgebiete: Herzfrequenzvariabilitaet,
Blutdruckrhythmen,
nichtinvasive Methoden zu Untersuchung des Kreislaufs,
Wechselwirkung zwischen Kreislauf und Respiration
Hypertonie
Praeventivmedizin.

Fuer das Physiologische Institut der Univ. Graz:
Prof. Dr. Thomas Kenner
Harrachgasse 21
A 8010 Graz

Fuer das Pathophysiologische Institut der Univ. Brno:
Doz.MUDr. Jarmila Siegelova

Fuer das Physiologische Institut der Univ. Brno:
Doz. MUDr. Bohumil Fiser
Komenskeho nam. 2
CR 66243 Brno

In the year 1997 – 1999 we solved the project the Czech project from IGA belonging to Ministry of Health of the Czech Republic Determination of baroreflex power in untreated hypertensive patients and after ACE therapy - inhibitors and Ca antagonists (Určení výkonnosti baroreflexu u neléčených

hypertoniků a po terapii ACE - inhibitory a Ca antagonisty, IZ 4313). The results of this project were discussed repeatedly with Professor F. Halberg and Professor G. Cornélissen from University of Minnesota, Professor T. Kenner, University Graz and Professor J.P. Martineaud, University Paris.

In the years 1995 – 1997 we solved the project also another Czech project from IGA belonging to Ministry of Health of the Czech Republic Sleep apnea and cardiovascular disease syndrome (Syndrom spánkové apnoe a kardiovaskulární choroby, IZ 1818-4).

The results of this project were discussed repeatedly with Professor F. Halberg and Professor G. Cornélissen from University of Minnesota, Professor T. Kenner, University Graz and Professor J.P. Martineaud, University Paris.

Cooperation with University of Paris, France

The international cooperation continued with Professor Jean-Paul Martineaud and Professor Dr. Etienne Savin, Medical Faculty, Lariboisiere Hospital, University of Paris (France) and was very intensively developed. There are common original studies of aortic compliance and blood flow regulation in cerebral arteries, baroreflex sensitivity in healthy subjects and patients with essential hypertension.

*Prof. Jean Paul Martineaud, M.D.R, *27.3.1931-†29.11.2010*
Professor of Physiology, University Paris VII-Denis Diderot, France (1968-1995)
Head, Service d´explorations fonctionnelles de l´hôpital Lariboisiere (1968-1995)

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Agreement.

Dept. Physiol.
Faculte de Medicine
Hopital Lariboisiere Paris
Service de Explorations Fonctionnelles
France

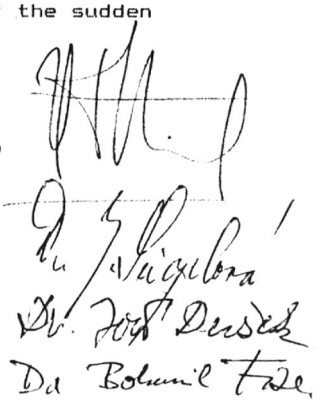
Dept Pathophysiol.
Medical Faculty
III. Dept. of Medicine Brno
CSFR

Dept. Physiol.
Medical Faculty Brno
CSFR

will participate in the development of non-invasive methods for cardiovascular diagnostis for essential hypertension.
Objectives of the proposed research are:
1.The development of non-invasive methods of measurement of peripheral resistence and variation of periperal resistence beat-to-beat and baroreflex sensitivity of periperal resistance.
2.The study of two groups of subjects, subjects normal and patients with essential hypertension and determination of the reference limits between healthy subjects and patients of following hemodynamics parameters:
a) total peripheral resistence
b) resistence in various parts of circulation.
c) peripheral resistance in different situations - 24-hours variability, exercise, postural changes.
d) baroreflex heart rate sensitivity and baroreflex peripheral resistence sensitivity in various situations.
the aim of the study will be The contribution to fundamental knowledges of essential hypertension. The improvement of understanding of baroreflex mechanisms in cardiac functions and vascular reactivity under different physiological and pathological conditions. The determination of normal range of peripheral resistence and vascular reactivity values. The development of diagnostic methods applicable for survey of hypertensive patients during therapy. The contribution to the estimation of the risk of atherosclerosis development and of the sudden cardiac death.

Sincerely prof. J.P.Martinaud, Paris

doc. MUDr. J. Siegelova, DrSc., Brno
doc. MUDr. B. Fiser, CSc.,
MUDr. J. Dusek, CSc.,



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Paris, le 05.04.1996

Madame le Docteur SIEGELOVA Jarmila
Faculté de Médecine et de Pharmacie
Chaire de Physio-pathologie
Komens keho nam. 2
66243 BRNO
(République Tchèque)

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49 92 81 02

With Professor Martineaud, Paris, we solved the project the project from Ministry of Education of France together with Professor Jean-Paul Martineaud, Professor Etienne Savin, Dr. Philipe Bonnin and from the Czech part Professor Jarmila Siegelova, Professor Bohumil Fiser and Jiri Dusek, M.D. in the years 1997 – 1998.

In the years 1999 – 2004 we solved the project from Ministry of Education of the Czech Republic Research Plan Early diagnosis of cardiovascular diseases (Výzkumný záměr **Časná** diagnostika kardiovaskulárních chorob, MSM141100004). The results of this project were discussed repeatedly with Professor F. Halberg and Professor G. Cornélissen from University of Minnesota, Professor T. Kenner, University Graz and Professor J.P. Martineaud, University Paris.

In the years 2005 – 2011 we solved the project from Ministry of Education of the Czech Republic Research Plan Early diagnosis and therapy of cardiovascular diseases (Výzkumný záměr **Časná** diagnostika a léčba kardiovaskulárních chorob, MSM0021622402). The results of this project were discussed repeatedly with Professor F. Halberg and Professor G. Cornélissen from University of Minnesota, Professor Kenner, University Graz and Professor J.P. Martineaud, University Paris.

In the years 1995 – 1997 we solved the Czech project from IGA belonging to Ministry of Health of the Czech Republic Sleep apnea and cardiovascular disease syndrome (Syndrom spánkové apnoe a kardiovaskulární choroby, IZ 1818-4). The results of this project were discussed repeatedly with Professor F. Halberg and Professor G. Cornélissen from University of Minnesota, Professor T. Kenner, University Graz and Professor J.P. Martineaud, University Paris.

In the years 2004 – 2006 we solved the Czech project from IGA belonging to Ministry of Health of the Czech Republic New methods in the rehabilitation of patients with compensated heart failure (Nové metody v rehabilitaci pacientů s kompenzovaným srdečním selháním, NR7983). The results of this project were discussed repeatedly with Professor F. Halberg and Professor G. Cornélissen from University of Minnesota, Professor Kenner, University Graz and Professor J.P. Martineaud, University Paris.

In the years 2009 - 2011 we solved the Czech project from IGA belonging to Ministry of Health of the Czech Republic "Increasing the effectiveness of rehabilitation due to combined aerobic training supplemented by electromyostimulation in patients with chronic heart failure" (Zvýšení **účinnosti** rehabilitace vlivem kombinovaného aerobního tréninku doplněného o elektromyostimulaci u nemocných s chronickým srdečním selháním, NS10096).

The results of this project were discussed repeatedly with Professor F. Halberg and Professor G. Cornélissen from University of Minnesota, Professor T. Kenner, University Graz and Professor J.P. Martineaud, University Paris.

In the years 2012 – 2014 we solved the project from Ministry of Education of the Czech Republic „Modification of the education system in the field of physiotherapy in order to increase competitiveness" (Modifikace systému vzdělávání v oblasti fyzioterapie za účelem zvýšení konkurenceschopnosti, OPVK CZ.1.07/2.2.00/280240). The results of this project were discussed repeatedly with Professor F. Halberg and Professor G. Cornélissen from University of Minnesota, Professor T. Kenner, University Graz.

In the years 2012 – 2014 we solved the project from Ministry of Education „OPTIMED - optimized teaching of general medicine, horizontal and vertical connections, innovation and efficiency for practice" (OPTIMED - optimalizovaná výuka všeobecného lékařství, horizontální a vertikální propojení, inovace a efektivita pro praxi, OPVK CZ.1.07/2.2.00/28.0042). The results of this project

were discussed repeatedly with Professor F. Halberg and Professor G. Cornélissen from University of Minnesota, Professor Kenner, University Graz.

In the years 2004 -2008 and 2008 until the present we solved the International project Rehabilitation in Internal Medicine, Tohoku University, Sendai, Japan, leader of the project Professor Masairo Kohzuki from Japan and Professor Petr Dobsak, Masaryk University. The results were presented partly in our Brno Noninvasive Methods of Cardiology.

Professor Masairo Kohzuki
Chairman, Department of Internal Medicine and Rehabilitation Science, Tohoku University Graduate School of Medicine, Sendai, Japan

From 80th of the last century, Prof. Franz Halberg and from 1994 Prof. Germaine Cornelissen became coordinators of international chronobiology project "Womb-to-Tomb Study", now BIOCOS (The BIOsphere and the COSmos). The chronobiological team of Masaryk University was part of both projects. On November 22, 1994 BIOCOS was described for the first time. The BIOsphere and the COSmos, BIOCOS, as the task of building a novel transdisciplinary spectrum was pursued, and further periods of decades, centuries, and thousands and millions of years were documented. Much of the evidence was provided very successfully by Germaine Cornelissen, PhD, Professor of Integrative Biology and Physiology at the University of Minnesota, so that the new periodicities were dubbed the Cornélissen-series at an international meeting in Ekaterinburg, Russia.

Professor Germaine Cornelissen, PhD,
director of Halberg Chronobiology Center
Professor of Integrative Biology and Physiology University of Minnesota, USA

In the thirty years of the duration of international cooperation and every year Congresses of Noninvasive methods in cardiology in Masaryk University, Brno, the number of members of the international project team increased in our Republic with Professor Petr Dobsak, who organized cooperation with Japan Universities, Assoc. Professor Michal Pohanka, Assoc. Professor Jiri Jancik, Dr. Jitka Svobodova, Dr. Hana Svacinova, Dr. Pavel Vank, Dr. Michaela Sosikova, Dr. Alena Havelkova, Mgr. Petra Palanova, Mgr. Veronika Mrkvicova, Mgr. Leona Dunklerova, Professor Marie Novakova, Mgr. Jana Svacinova. The congresses and symposia in Masaryk University were visited every time from abroad by famous scientific personalities - Prof. Franz Halberg and Prof. Germaine Cornelissen from University of Minnesota, USA, Prof. Thomas Kenner, Rector of University and Dean of Medical Faculty, University of Graz, Austria and Prof. Jean-Paul Martineaud, Medical Faculty, Hopital Lariboisiere, Paris, France, Prof. Dr. Etienne Savin, Hopital Lariboisiere, University Paris, France, Professeur Jean-Eric Wolf, C.H.U. du Bocage, Dr. Jean-Christophe Eicher, C.H.U. du Bocage, University Dijon, France, Professor Kou Imachi, M.D., Ph.D., T.U.B.E.R.O., Tohoku University, Sendai, Japan, Professor Masahiro Kohzuki, M.D. Ph.D., Tohoku University, Sendai, Japan, Professor Yambe Tomoyuki, M.D. Ph.D., Tohoku University, Sendai, Japan. In the last year there were in our meeting also new co-workers of Prof.T. Kenner, namely Prof. Dieter. Platzer, University Graz, Prof. Nandu Goswami, Prof. Maxmilian Moser, University Graz, Prof. Daniel Schneditz, University Graz, Mgr. Bianca Brix, University Graz.

Assoc. Prof. PD Dr. med. Nandu Goswami
Chairman of Dept. of Physiology
Medical University of Graz, Austria

All the scientists mentioned above in the last 30 years and the chronobiologic staff of Masaryk University presented and discussed scientific results in USA, France, Italy, Austria, Japan, Canada and other countries.

For the future, in the next years we plan further scientific work on the projects with University Minnesota, USA, under leading personality of Professor G. Cornélissen, for example the project BIOCOS, with Medical University Graz, Austria, under Assoc. Professor Goswami, with Tohoku University Sendai, Japan under Professor Kohzuki and with other personalities from abroad.

Chronobiologic Analyses of Weeklong around-the-Clock Records of Simultaneously Monitored Blood Pressure and Activity

Germaine Cornelissen[1], Zainab Farah[1], Denis Gubin[2], Lyazzat Gumarova[3], Linda Sackett-Lundeen[1], Thomas Kazlausky[4], Kuniaki Otsuka[5], Jarmila Siegelova[6], Larry A Beaty[1]

[1] Halberg Chronobiology Center, University of Minnesota, Minneapolis, MN, USA
[2]Department of Biology, Medical University, Tyumen, Russia
[3] Al-Farabi Kazakh National University, Almaty, Kazakhstan
[4] Ambulatory Monitoring, Inc., New York, USA
[5]Tokyo Women's Medical University, Daini Hospital, Tokyo, Japan
[6] Masaryk University, Brno, Czech Republic

Correspondence:

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Support:

Halberg Chronobiology Fund
University of Minnesota Supercomputing Institute
A&D (Tokyo, Japan)

Abstract

Among the many different factors that influence blood pressure, activity was once thought to be the major determinant of the circadian variation in blood pressure. Whereas the endogenous nature of the circadian rhythm in blood pressure is no longer disputed, there is great interest in monitoring activity concomitantly with blood pressure. Herein, we reanalyze a dataset on weeklong ABPM records obtained concomitantly with actigraphy from 20 clinically healthy young adults. The purpose of this investigation is to review different approaches available for the characterization of the circadian variation in physiological variables such as blood pressure, heart rate, and activity. Topics covered include rhythm detection, the estimation of rhythm parameters, and the visualization of their waveform. Methods to examine how circadian rhythms of different variables may relate to each other are also discussed.

Introduction

Most, if not all, physiological variables undergo predictable circadian variations [1]. Circadian rhythms are genetically anchored [2, 3], including that of blood pressure, which was long thought to be no more than a direct response to activity [4].

The endogenous nature of the circadian rhythm in blood pressure is apparent from its persistence during continued bedrest [5, 6], from its ability to free-run [7, 8], and more recently from the discovery of clock genes in the periphery as well as in the suprachiasmatic nuclei [4].

Many factors affect blood pressure [9]. Among them, activity plays an important role and can be easily monitored. Interest in measuring activity concomitantly with blood pressure stems in part from the merit of defining more precisely the active and resting spans, which may differ greatly among individuals.

Herein, we re-analyze a dataset of weeklong ABPM and actigraphy records from clinically healthy young adults [10], with the aim to illustrate different approaches to characterize the circadian variation in variables such as blood pressure, heart rate, and locomotor activity.

Subjects and Methods

Study participants were 20 clinically healthy volunteers (14 women and 6 men), 20 to 54 years of age (mean ± SD: 26.5 ± 9.2). They were students and researchers, with mostly a sedentary work schedule, following mostly similar regular diurnal sleep-wake schedules. Four were overweight and one was obese. On the average, body mass index (BMI) ranged from 18.2 to 36.4 (mean ± SD: 22.7 ± 4.6).

Each study participant provided concomitant weeklong records of blood pressure and activity. Blood pressure and heart rate were automatically measured around the clock at 30-min intervals by ambulatory blood pressure monitoring (ABPM), using the TM-2421 device from A&D (Tokyo, Japan). Wrist activity was recorded every minute using the MicroMotion Logger from AMI (Ardsley, NY). We use the zero-crossing mode (ZCM) to assess activity. ZCM measures movement frequency, which is represented by the number of times the voltage fluctuations of the analog signals exceed a predetermined threshold value. In addition to ZCM, the device also measures wrist temperature, light exposure, and sleep (0 or 1, representing awake or asleep, respectively). Of the 20 participants, 15 completed the 7-day/24-hour monitoring. Records from the other 5 were shorter, covering approximately 6 days.

Blood pressure and heart rate measurements were taken at the hour and half-hour. Occasional missing values were linearly interpolated. Records that were slightly shorter than 6 or 7 full days were extrapolated in order for the records to cover an integer number of days. When gaps exceeded 90 minutes, interpolation was done by averaging data obtained at the same clock hour on other days. Data from the MicroMotion Logger were averaged over consecutive 30-minute intervals, and assigned to the midpoint, which matched the times of blood pressure and heart rate measurements.

A template was prepared in Excel where the 30-min pre-processed data from both devices were entered in a specified cell range. In the same Excel sheet, formulae were entered to approximately compute the autocorrelation function of each variable, as well as the cross-correlation function of pairs of variables. Simple Pearson product moment correlation coefficients were computed instead of the exact autocorrelation and cross-correlation formulae. While not exact, they provide a good first

approximation of these functions. Plots of each autocorrelation and cross-correlation function were prepared in separate Excel charts. This template was saved, so that it could be copied onto another file and data from a different study participant entered in the specified cell range to replace those of the template file. This way, the autocorrelation and cross-correlation functions are automatically computed and all corresponding graphs are generated without effort.

The pre-processed data were analyzed by least squares spectra [11, 12], using a fundamental period of 7 days and a frequency range from one cycle in 7 days to one cycle in 1.1 hour. Another sheet in the template Excel file accommodates the results from the least squares spectra in specified cell ranges for each variable. Noise levels are estimated, and plots are prepared of each spectrum in separate Excel charts. Results from least squares spectra from study participants were entered into the designated cell ranges of copies of the template Excel file to automatically obtain all plots. While it would have been preferable to use a fundamental period of 6 days instead of 7 days for those records that only covered 6 days, results related to the circadian variation are not affected by the choice of a 7-day fundamental component for all 20 records.

Population-mean cosinor spectra were computed by averaging results from the individual least squares spectra. Since spectral analyses of all variables showed prominent about 24-hour and 12-hour components, 2-component models were used to reconstruct the circadian patterns of each variable.

Stability (IS) and fragmentation (IV) are two indices that have been proposed to characterize the circadian variation in activity [13, 14]. IS is a signal-to-noise measure, calculated as the ratio between the variance of the average 24-hour pattern around the mean and the overall variance. IV estimates the intra-daily variability and gives an indication of the fragmentation of the rhythm (i.e., the frequency of transitions between rest and activity) and is calculated as the ratio of the mean squares of the difference between consecutive hours (first derivative) and the mean squares around the grand mean (overall variance). IS and IV are calculated based on hourly averages. IS and IV were computed from all study participants.

The Student's t test was used to compare the MESOR and circadian amplitude of each variable between men and women. Linear regression assessed relationships of the circadian parameters as a function of age and BMI. A P-value below 0.05 was considered to indicate statistical significance.

Results

Figure 1 illustrates the autocorrelation (ACF) and cross-correlation (CCF) functions of systolic blood pressure (SBP), ZCM, and wrist temperature (Temp). The presence of a circadian rhythm in each variable can be clearly seen by the naked eye. It can also be seen from the cross-correlation functions that systolic blood pressure and ZCM are in phase, but that wrist temperature is out of phase with both systolic blood pressure and ZCM.

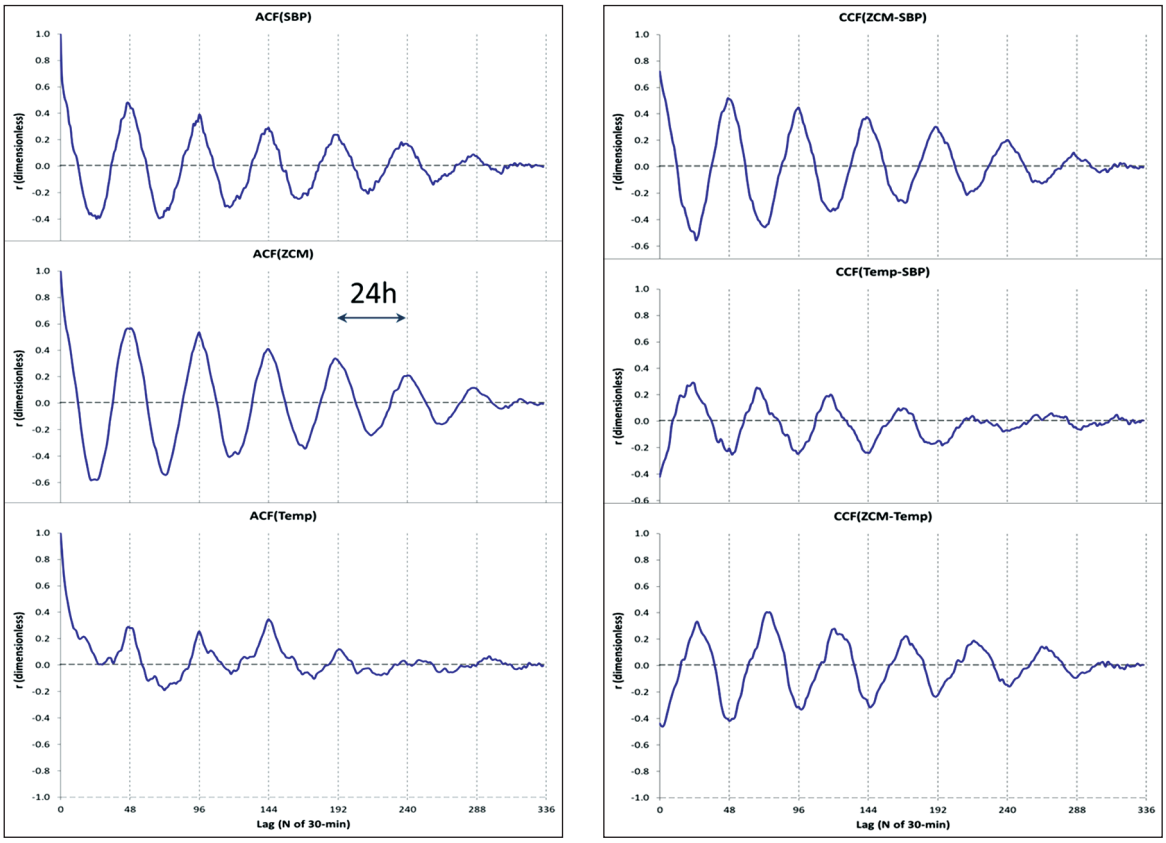

Figure 1. *Left: Autocorrelation functions of systolic blood pressure (top), activity (ZCM, middle), and wrist temperature (bottom) of one subject. Right: Cross-correlation functions of systolic blood pressure and ZCM (top), of systolic blood pressure and wrist temperature (middle), and of ZCM and wrist temperature (bottom). Note that the prominent circadian variation in these three variables is in phase between systolic blood pressure and ZCM, but that these variables are out of phase with respect to wrist temperature. © Halberg Chronobiology Center*

Figure 2 illustrates the least squares spectra of these three variables corresponding to the autocorrelation and cross-correlation functions shown in Figure 1. A large spectral peak at a frequency of one cycle per 24 hours emerges from the noise level in each case. Smaller peaks at harmonics of the circadian variation are also present. Population-mean cosinor spectra summarizing results from all 20 study participants clearly detect with statistical significance the presence of spectral components at frequencies of one and two cycles per 24 hours, Figure 3.

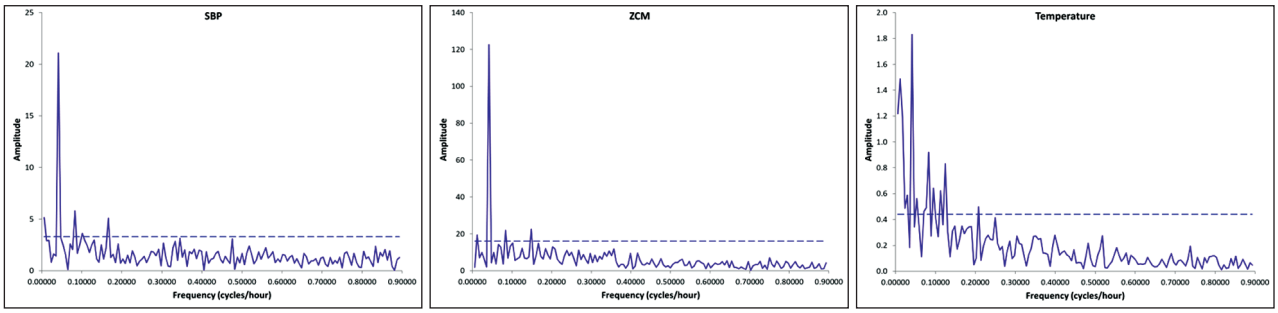

Figure 2. *Least squares spectra of systolic blood pressure (left), activity (ZCM, middle), and wrist temperature (right) of one study participant. The circadian variation is prominent, as seen by the large spectral peak at a frequency of 1 cycle per 24 hours. © Halberg Chronobiology Center*

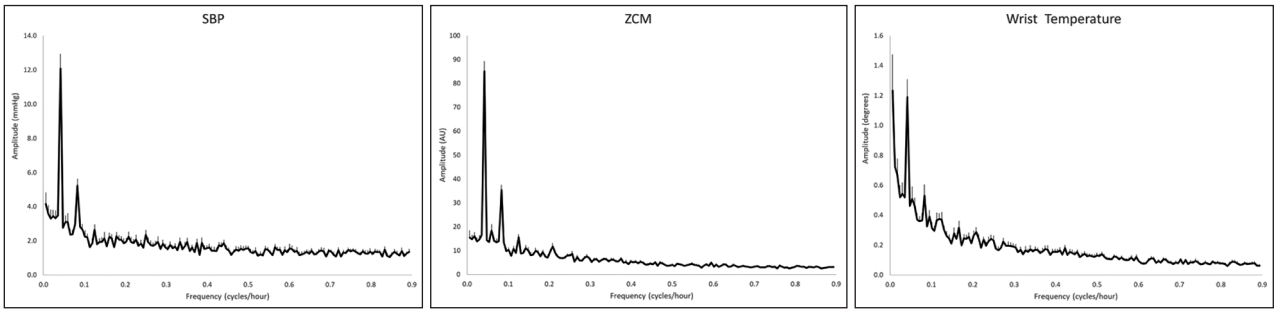

Figure 3. *Population-mean cosinor spectra of systolic blood pressure (left), activity (ZCM, middle), and wrist temperature (right), summarized across all 20 study participants. The 24-hour and 12-hour components are statistically significant. © Halberg Chronobiology Center*

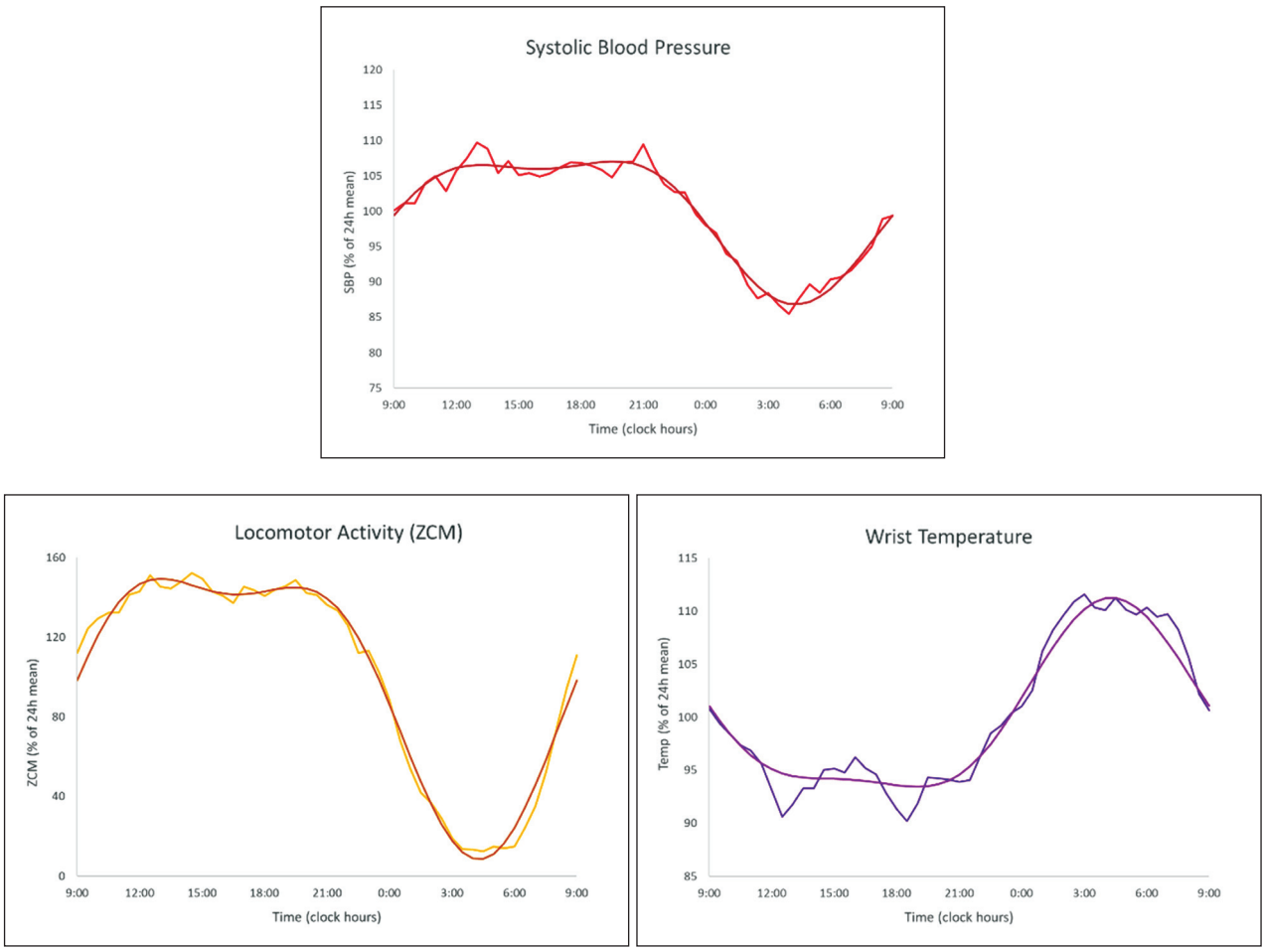

Figure 4. *Circadian waveform of systolic blood pressure (top), activity (ZCM, middle), and wrist temperature (bottom), reconstructed based on 2-component model, shown with the data expressed as a percentage of each record's arithmetic mean. © Halberg Chronobiology Center*

The circadian patterns of systolic blood pressure, activity, and wrist temperature are reconstructed in Figure 4 based on a 2-component model, consisting of cosine curves with periods of 24 and 12 hours, derived from results of the population-mean cosinor spectra.

Discussion

The stability and fragmentation indices averaged (± SD) 0.571 ± 0.152 and 0.475 ± 0.090, respectively, reflecting the relatively young population investigated herein. IS depends on the record length. It is higher in the 7-day (0.620) than in the 6-day (0.426) records ($t = 2.922$, $P=0.009$). It also correlates with activity (MESOR of ZCM) ($r=0.461$, $P=0.041$), and with the circadian amplitude of ZCM ($r=0.823$, $P<0.001$). It can be viewed as reflecting the percentage variance accounted for by the circadian variation in activity. Indeed, IS correlates strongly with the percentage rhythm of the circadian rhythm of ZCM, whether it is approximates by a single 24-hour component ($r=0.890$, $P<0.001$) or a 2-component model consisting of cosine curves with periods of 24 and 12 hours ($r=0.916$, $P<0.001$).

Anticipated gender differences are detected, despite the relative small sample size of this population. Women have a lower blood pressure than men (SBP: 112.8 vs. 129.4 mmHg, $t = 3.996$, $P<0.001$; DBP: 67.9 vs. 76.4 mmHg, $t = 3.533$, P-0.002). Women have also a smaller circadian amplitude of blood pressure as compared to men (SBP: 10.2 vs. 16.3 mmHg, $t = 4.760$, $P<0.001$; DBP: 7.9 vs. 11.3 mmHg, $t = 2.748$, $P=0.013$). Linear regression analyses as a function of age, BMI, and also accounting for gender find that the MESOR of heart rate is higher in women than in men ($t = 2.441$, $P=0.027$); that it decreases with advancing age ($t = 3.742$, $P=0.002$); and that it increases with BMI ($t = 2.559$, $P=0.021$). The model accounts for 57% of the total variance ($F = 7.076$, $P=0.003$). A similar model shows that the circadian amplitude of heart rate is larger in women than in men ($t = 2.654$, $P=0.017$) and that it decreases with advancing age ($t = 4.183$, $P<0.001$), accounting for 61% of the total variance ($F = 8.379$, $P=0.001$).

The acrophase of wrist temperature occurring during the night deserves some comment. Core temperature usually peaks in the afternoon, like activity, heart rate, and blood pressure. Differences in the circadian acrophase between distal skin temperature and body temperature are mainly related to counterbalanced physiologic processes of heat production and heat dissipation. Skin temperature measured on limbs corresponds mainly to distal vasodilation and heat transfer. Its circadian acrophase occurs approximately 90 to 120 minutes after the circadian acrophase of melatonin. Rectal, oral, and axillary temperatures are a closer approximation of core temperature and peak in the late afternoon or evening. They correspond to distal vasoconstriction and parallel heating of internal organs. For these reasons, the circadian acrophase is inverse to that of melatonin [13-15].

To summarize, the circadian rhythm of blood pressure, heart rate, activity and temperature accounts for a sizeable portion of the overall variance. These variables can easily be monitored around the clock. A number of different approaches are available to characterize the circadian variation in these variables and to explore how they are related to each other. Organizing the data in a systematic way in Excel facilitates the automatic analysis and graphic visualization of the results when a given procedure needs to be applied repeatedly to different sets of data that follow a specific protocol.

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Some Lessons Learned from a 43-year Record of Self-Measurements by a Physician-Scientist

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This article is dedicated to the memory of two outstanding pioneers and mentors of Chronobiology: Erhard Haus M.D., Ph.D. and Franz Halberg, M.D., Dr. multi

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Abstract

The study participant, a pathologist and scientist-chronobiologist self-measured systolic (S) and diastolic (D) blood pressure (BP), heart rate (HR) and oral temperature (Tb) for 43 years, spanning from 1965 to 2013 and from 38 to 86 years of age, with some times of no data collection, the longest between 1966 and 1971. The number of samples varied mostly between 4 and 12 samples per day. Mean arterial pressure (MAP), pulse pressure (PP), and pulse pressure product (PPP) were calculated from SBP, DBP, and HR. In the spring of 1973, he was diagnosed with Essential Hypertension (EH) and was started on anti-hypertensive medication(s). His intention for collecting these data was originally to look at changes during intercontinental flights and later became to monitor his treatment of EH. It was of interest to evaluate the circannual variation in these variables, to look for changes over time and changes in response to efficacy of the medications for the control of his EH.

Introduction

Chronobiology analysis is very important in the evaluation of blood pressure. Much work has been done on blood pressure rhythms from neonates (Halberg et al., 1986) to centenarians (Ikonomov et al.,

1991) and in many different frequencies from ultradians and circadians to infradians (circasemiseptan, circaseptan, monthly, circannual, transyears, and even solar activity cycles) (Cornelissen et al., 1994; Cornelissen et al., 1992; Nicolau et al., 1986). Blood pressure and oral temperature have been used to study jet lag (Halberg et al., 2007, Haus et al., 1981) and Shiftwork (Halberg J et al., 1989) for many years. This unusual long time series provides a unique opportunity to study multi-frequency rhythms, trends, efficacy of medications, and possible risks of adverse effects, among others. This kind of information cannot be obtained from 24-hour or 7-day/24-hour records from populations.

Subject and Methods

The study participant (EH) was a male pathologist and chronobiologist born September 8, 1926 in Austria. He first started self-measuring his SBP, DBP, HR, and temperature when he was a Pathology Instructor and Post Doctorate at the University of Minnesota. He was 38 years old when he began collecting these measurements on April 15, 1965, continuing until July 6, 1966. The majority of the 4 to 8 daily measurements where during the waking span, with very few during the sleeping time.

EH returned to performing self-measurements again on March 9, 1971 at 42 years of age, while he was the Medical Director in the Department of Anatomic and Clinical Pathology (1969-2003) at St. Paul Ramsey Hospital, St. Paul, Minnesota. During the years of measurements, he was also an Associate Professor (1961-1972) and Professor (1980-2013) in Laboratory Medicine and Pathology at the University of Minnesota, the Ramsey and Washington County Medical Examiner (1979-1985), and the Head of Pathology/Chronobiology Research at Regions Hospital (1971-2013). He continued to collect 4 to 12 measurements per day until the day of his death at 86 years of age on June 14, 2013 from a cardiac arrest at the same hospital (renamed Regions Hospital, St. Paul, Minnesota), where he was still working as a Staff Pathologist. As he aged, more samples were measured when he would wake up at night, therefore providing more measurements throughout the 24 hours. There were occasional times of interruption over the 43 years of measurements, from a few days at a time to weeks (i.e., from 3/6/79 to 3/21/79 while he had a total hip replacement; 4/19/85 - 5/7/85, and 7/19/85 - 8/6/85 during trips to help with research studies in Romania), to months at a time (i.e., from 9/3/85 to 12/9/85). Other factors that may have prevented sampling for short periods of time may include events like a broken blood pressure monitor or thermometer or being too busy. There were many trips over the 43 years of measurements, some domestic and many worldwide. These trips were not evaluated in the present analysis.

When measurements started, EH was using a sphygmomanometer with a blood pressure arm cuff for SBP and DBP, a mercury oral thermometer, and did a manual wrist HR reading. At some time during the end of the 1980s, he did switch from a mercury thermometer to a digital thermometer. On September 17, 1988, he switched to a finger blood pressure monitor and being the ultimate researcher, he did some comparison measurements between the finger monitor and the sphygmomanometer cuff method between then and the end of 1988. In 1991, he changed monitors again, doing some comparisons between the old and the new monitors. It was also important to him to do comparisons between holding the BP monitor at heart level vs. his arm on the table, which he did in 1992 with his old and new monitors, and again in 1993 when he switched from a finger monitor to an automatic cuff monitor. Starting April 4, 1971, EH self-rated his mood at the same times as the other measurements each day.

Diagnosis and Treatment: In the spring of 1973, EH was diagnosed with Essential Hypertension (based only on daytime values), starting Reserpine (0.1 mg mornings and nighttime) on May 15, 1973. Reserpine was replaced with Thiazide (50 mg x2) in mid-1977, followed by the addition of Propranolol

(Inderal 20 mg) on November 24, 1978 to be taken in the morning and at noon, with Thiazide (50 mg) continuing in the morning. This regimen continued when in March 1980, Propanolol (Inderal 20 mg) was taken 3x/day (morning, noon, and evening) and Thiazide (50 mg) 2x/day (morning and noon). This regimen continued with some changes in dosing and timing until February 24, 1987. Medications, dosing, and timing changed multiple times over the years. In 2012 and 2013, his regimen included the following medications (doses) and timing: in the morning: Furosemide (20 mg), Chlorthalidone (25 mg), and Metformin (1,000 mg), and in the evening: Nifedipine (90 mg), Ramipril (10 mg), Simvastatin (40 mg), Spironolactone (25 mg), Metformin (1,000 mg), and often at bedtime: Melatonin (5 mg).

In February 2002, EH was diagnosed with Non-Insulin Dependent (Type II) Diabetes Mellitus (NIDDM), starting Metformin (1,000 mg) on February 15, 2002, which continued until his death.

Analysis: The measured SBP, DBP and HR were used to calculate the Mean Arterial Pressure (MAP=((2xDBP)+SBP)/3), Pulse Pressure (PP=SBP-DBP), and Pulse Pressure Product (PPP=SBPxHR/100). Means, Standard Deviations (SDs), and Number of Data Points per month for SBP, DBP, HR, MAP, PP, PPP, Temperature, and Mood were calculated by a routine in R for each month of each year of the entire data span. Monthly means and SDs within each yearly span were then analyzed fitting a 1-year cosine curve to the data. The rhythmometric results at a trial period of 1 year (MESOR, Amplitude, and Acrophase), obtained each year for each variable were then analyzed by Population-Mean Cosinor. Analysis of Variance (ANOVA) was applied to visualize the yearly patterns for comparison with similar analyses performed on similar data by another chronobiologist (Sothern et al., 2004).

Results

Figures 1-4 show the long-term trends as chronograms in 7 of the 8 variables measured over the 43 years. There are very large long-term changes in most variables investigated. A circannual rhythm cannot be seen by the naked eye in these data. The analyses by population-mean cosinor detect a statistically significant circannual rhythm in heart rate and in the pulse-pressure product, but not in systolic or diastolic blood pressure (Figure 1).

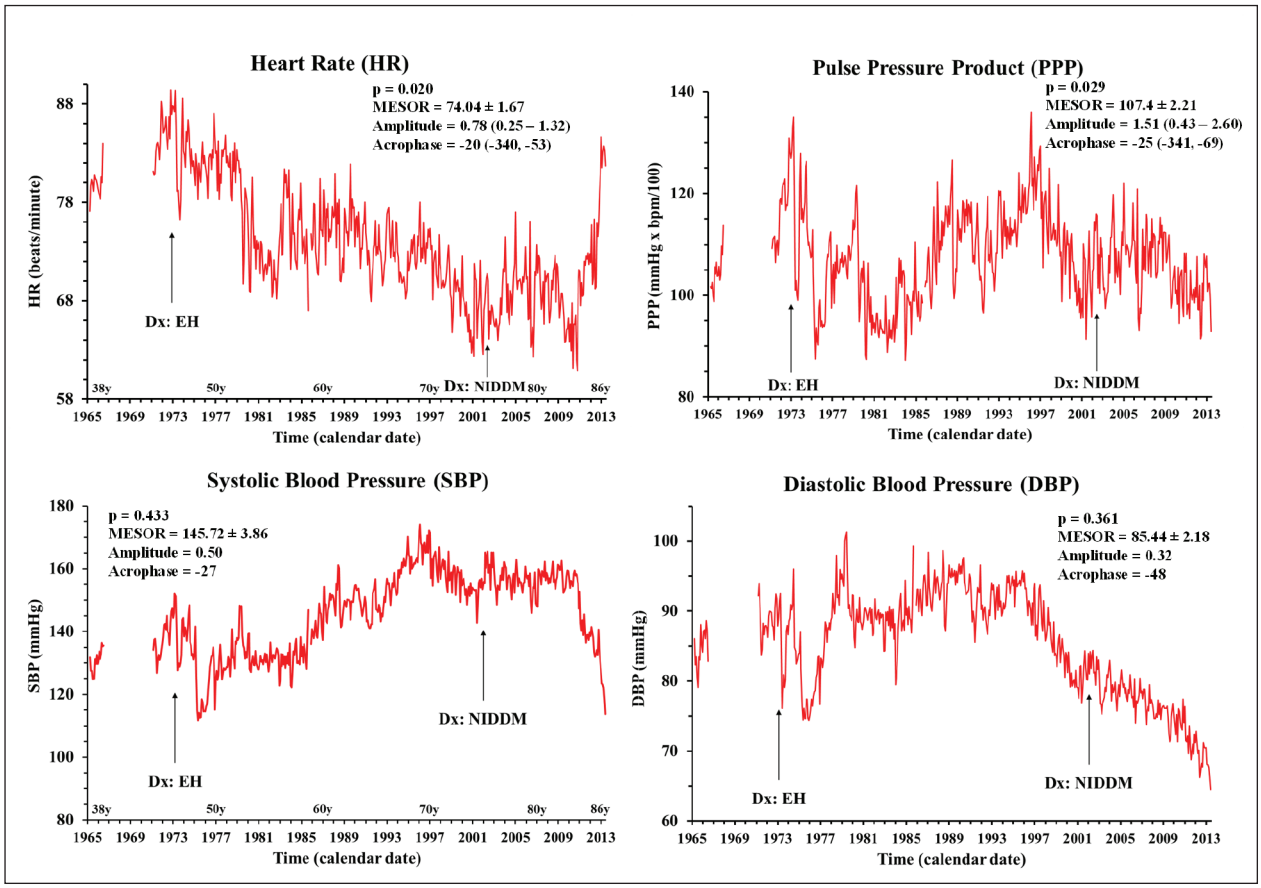

Figure 1: *Circannual variation is not discernable in chronograms due to huge trends in 43 years of self-measurements. A statistically significant circannual rhythm detected in heart rate (top left) and pulse-pressure product (top right), but not in systolic blood pressure (lower left) or diastolic blood pressure (lower right). Diagnosis of Essential Hypertension (EH) and Non-Insulin Dependent Diabetes Mellitus (NIDDM) denoted by arrows.*

There are also very large changes in the variability of all the variables self-measured over 43 years. Some of these changes may stem from many different factors (different schedules of taking the measurements, including the number of samples taken each day, changes in the devices used to take the measurements, change in medications (dosing and timing), work load, and intercontinental flights). Figure 2 shows the variability in HR, PPP, SBP, and DBP, as gauged by their monthly SDs.

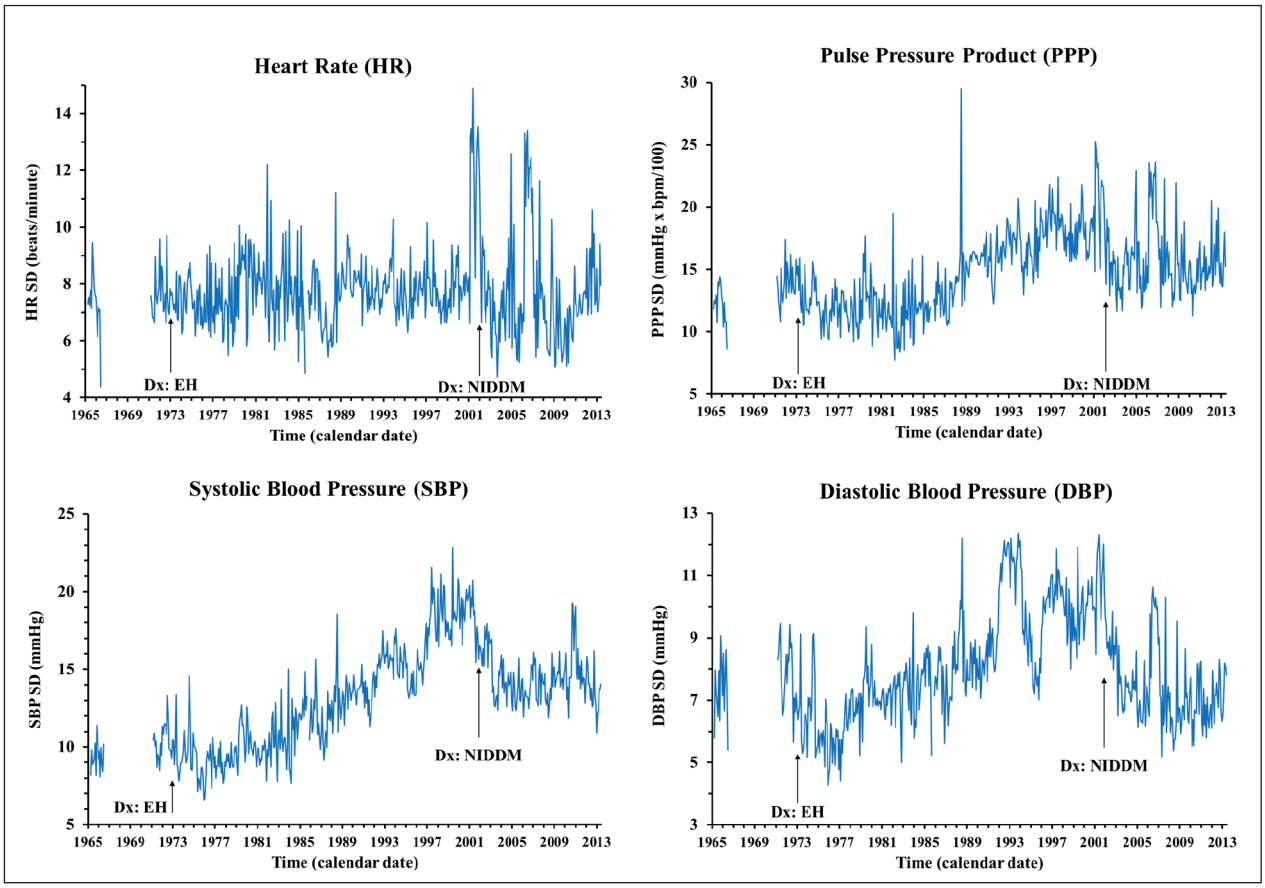

Figure 2: *Large variability in heart rate (top left), pulse-pressure product (top right), systolic blood pressure (lower left), and diastolic blood pressure (lower right) during 43 years of self-measurements. Diagnosis of Essential Hypertension (EH) and Non-Insulin Dependent Diabetes Mellitus (NIDDM) denoted by arrows.*

Despite the thorough monitoring of blood pressure two to twelve times per day, and despite the fact that this was a pathologist-scientist-chronobiologist knowledgeable in the treatment of high blood pressure who was on anti-hypertensive medication(s), one cannot say that his blood pressure was well controlled. Some trends in the monthly SDs do follow the changes in the monthly means; however, this is not consistently the case, as is shown toward the end of the record. This phenomenon is shown in both the MAP and PP in Figure 3.

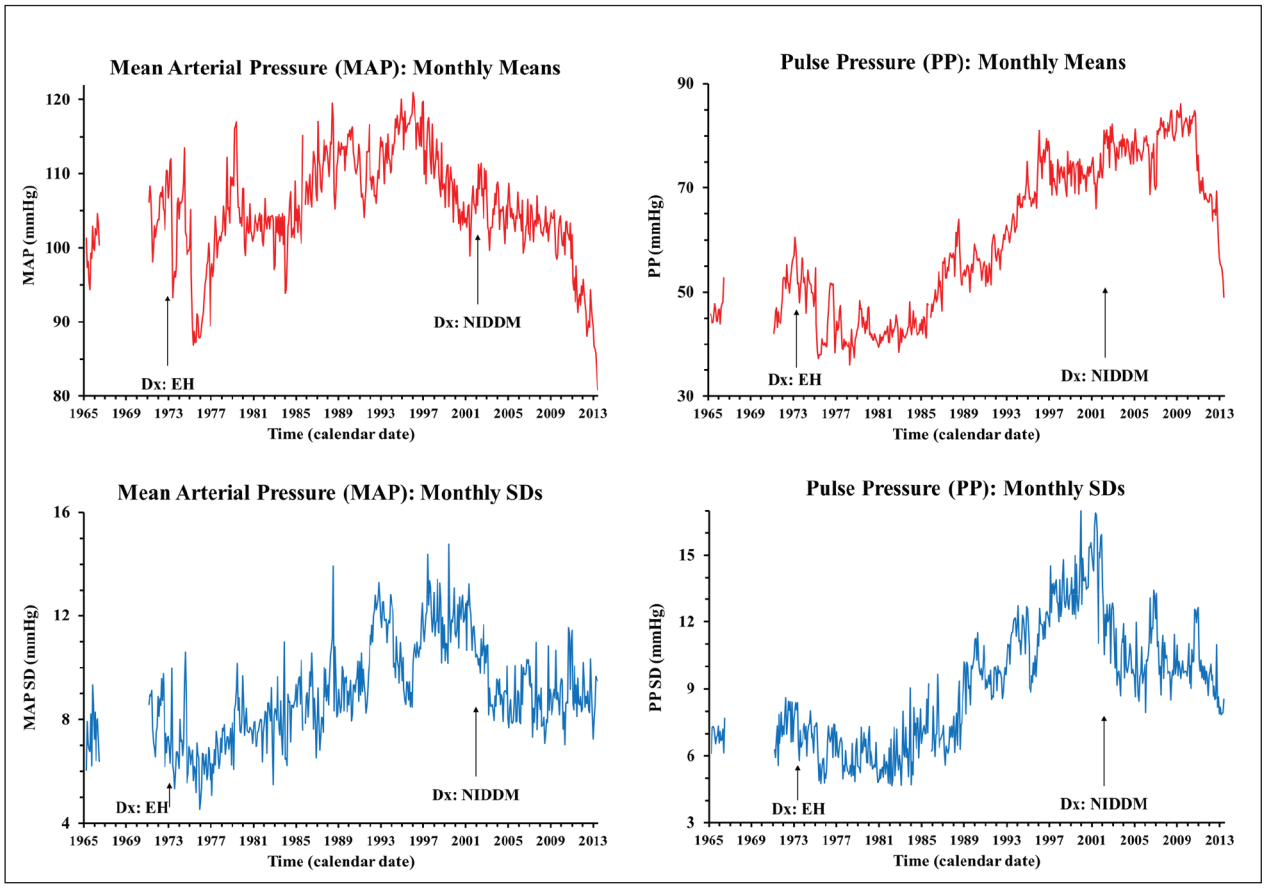

Figure 3: *Large increases in MAP and PP over 43 years of self-measurements despite the use of anti-hypertensive medications. Monthly means (top figures), monthly variation as demonstrated by the SDs (lower figures), MAP (left side), and PP (right side). Diagnosis of Essential Hypertension (EH) and Non-Insulin Dependent Diabetes Mellitus (NIDDM) denoted by arrows.*

Evaluating the oral temperature of EH is an excellent example of the fact that 98.6˚F is not necessarily everyone's "normal" temperature. The means of every month over the 43 years are almost all less than 98.6˚F, which includes those times when he had fever during illnesses. Most temperatures were missing from August 17, 1985 until the end of the year, and no temperatures were measured from January 1, 1986 through April 28, 1987. Oral temperature is an illustrative example of the merit of analyzing data one year at a time. The circannual variation is put to the fore by expressing each year's data as a percentage of that year's mean value, and then averaging the relative data across all years. Temperature is higher in the summer by only about 0.1˚F as compared to the winter, while the monthly SD is highest in December (Figure 4).

EH also registered a self-rated value for his mood at the time of most measurements as a number between 2 and 6, with 2 being okay and 6 being very excited or stressed, with most of his mood values being 5. The results of the population-mean cosinor for the monthly means and the monthly SDs for all variables are shown in Table 1.

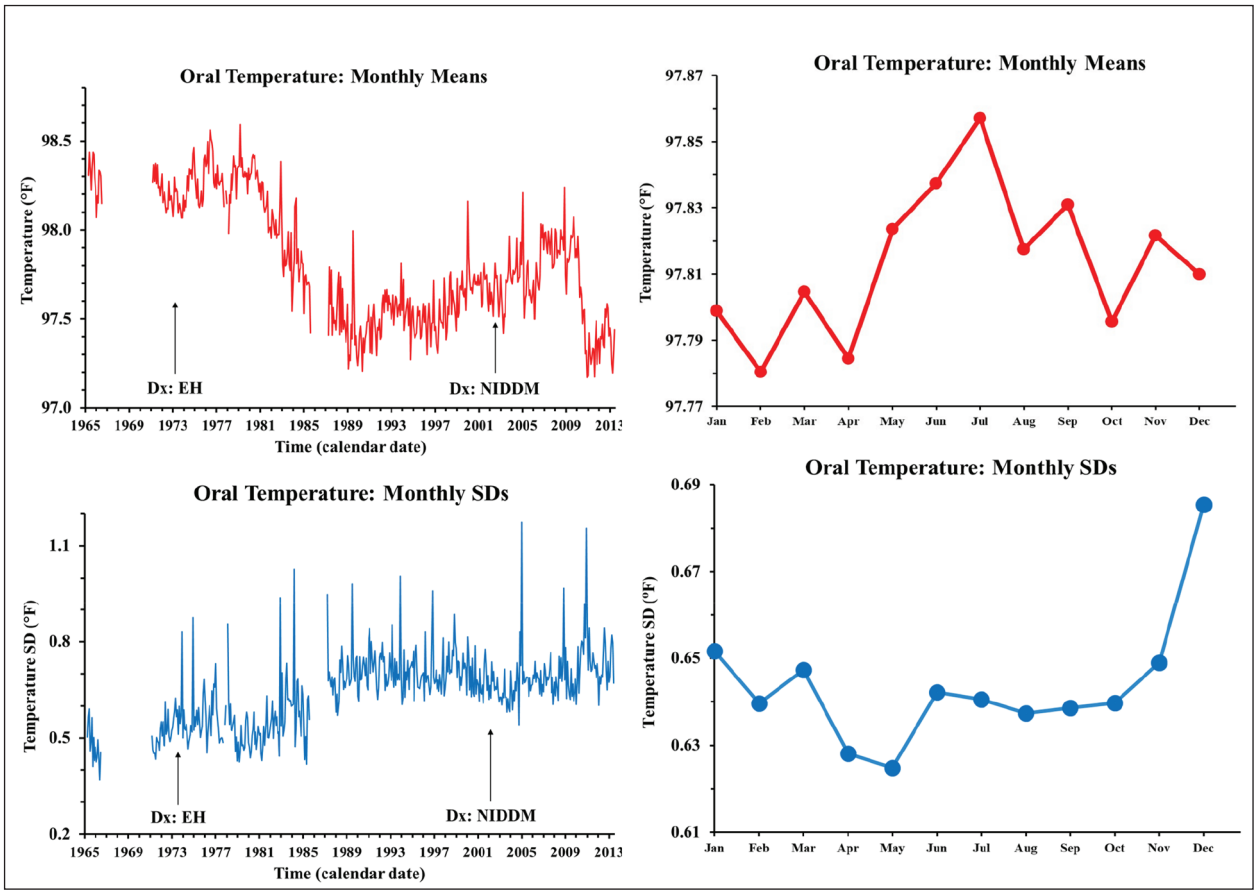

Figure 4: *Circannual changes in oral temperature shown during 43 years of self-measurements. Monthly means (top left), monthly variations as demonstrated by the SDs (lower left), expression of each year's data as a percentage of that year's mean value, and then averaging the relative data across all years for monthly means (top right), and SDs (lower right). Diagnosis of Essential Hypertension (EH) and Non-Insulin Dependent Diabetes Mellitus (NIDDM) denoted by arrows on left side of figure.*

Variable	No.	PR	p	MESOR		Ampltude			Acrophase			PR	p	MESOR		Ampltude			Acrophase		
				M	±CI	A	95% CI		Ø	95% CI				M	±CI	A	95% CI		Ø	95% CI	
Mean											SD										
SBP	43	32	0.433	145.717	3.864	0.503			-27			28	0.850	13.138	0.919	0.051			-277		
DBP	43	31	0.361	85.444	2.180	0.316			-48			27	0.485	7.988	0.470	0.087			-188		
HR	43	38	**0.020**	74.036	1.670	0.784	0.249	1.319	-20	-340	-53	19	0.141	7.758	0.320	0.159			-262		
MAP	43	31	0.340	105.536	1.938	0.372			-38			29	0.550	9.045	0.511	0.083			-194		
PP	43	36	0.720	60.275	4.443	0.242			-359			23	0.113	9.122	0.816	0.150			-336		
PPP	43	35	**0.029**	107.441	2.214	1.513	0.431	2.596	-25	-341	-69	26	0.166	14.799	0.819	0.274			-330		
Temp	42	33	0.074	97.810	0.102	0.021			-199			24	0.358	0.642	0.027	0.009			-339		
Mood	42	26	0.151	4.831	0.066	0.041			-347			22	0.133	0.704	0.048	0.020			-128		

Table 1: *Population-Mean Cosinor Results for 43 years of self-measurements.*

Even though there was not a statistically significant circannual rhythm by population-mean cosinor in all 43 years of self-measurements, each variable did show a statistically significant yearly variation in some, but not all years. In evaluating the percentage of occurrences when a circannual rhythm could be documented with statistical significance for each variable, it was surprising to see it was less than 50% (Figure 5).

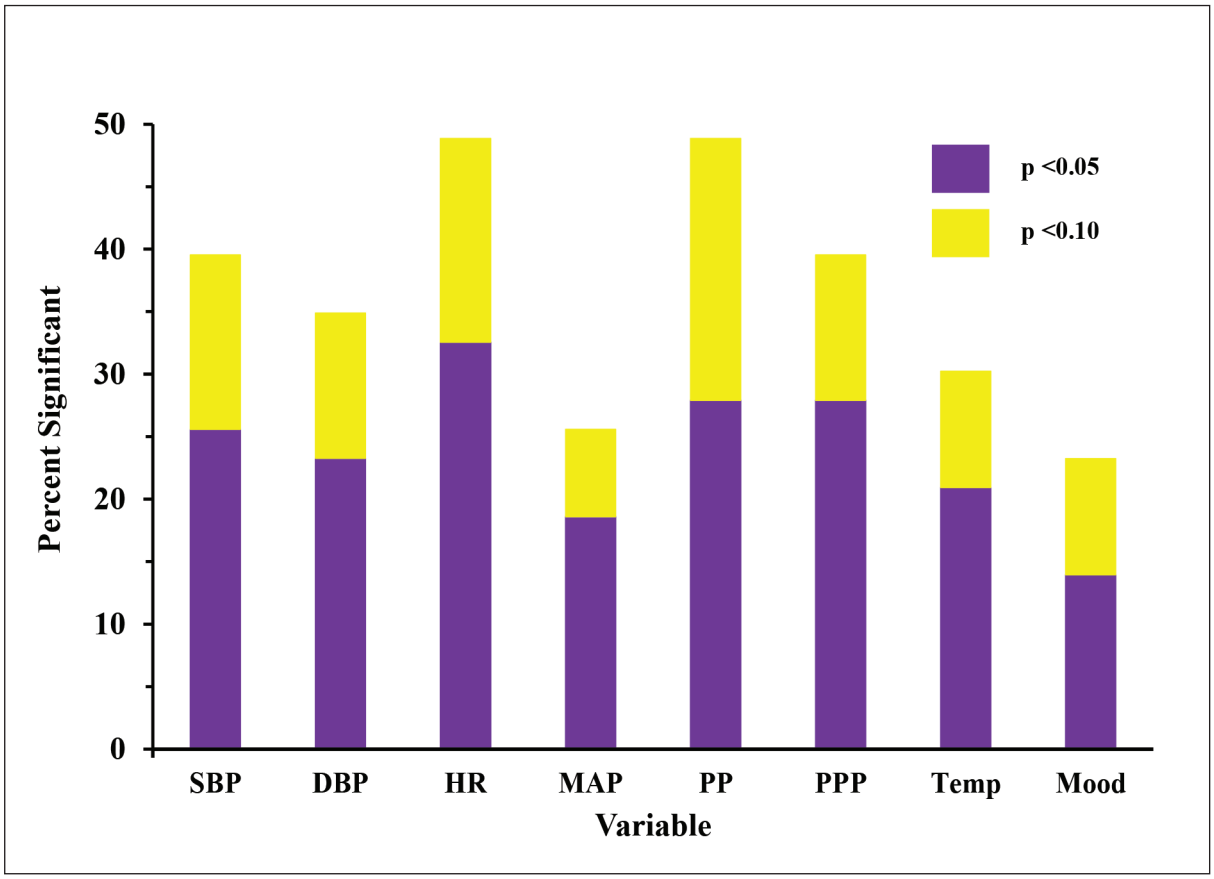

Figure 5: *A circannual rhythm is not invariably detected each year in 43 years of self-measurements.*

The wide distribution of acrophases over the 43 years of self-measurements for many of the variables evaluated supports the conclusion that a circannual variation is not discernable. Figure 6 shows that systolic blood pressure is not statistically significant as the 95% confidence ellipse overlaps the center and the amplitude is quite small. The acrophase estimate from the population-mean cosinor for SBP is -27° (January 28), however, by adding the acrophases for each individual year the wide distribution of acrophases supports the conclusion that a circannual variation is not discernable in systolic blood pressure. For systolic blood pressure, a yearly rhythm is documented ($P<0.05$) in 26% of the years, and reaches borderline significance ($0.05<P<0.10$) in 14% of the years; it is not detected in 60% of the years. Heart rate has a statistically significant circannual rhythm with an acrophase of -20° (-340°, -53°) [January 21 (December 11, February 23)]. Figure 7 shows an acrophase diagram with the overall statistically significant circannual acrophase with its 95% CI at the top of the figure and then the individual years below. This display, unlike that of Figure 6, also displays the acrophases by year. For heart rate, a yearly rhythm is documented ($P<0.05$) in 33% of the years and reaches borderline statistical significance ($0.05<P<0.10$) in 16% of the years; it is not detected in 51% of the years.

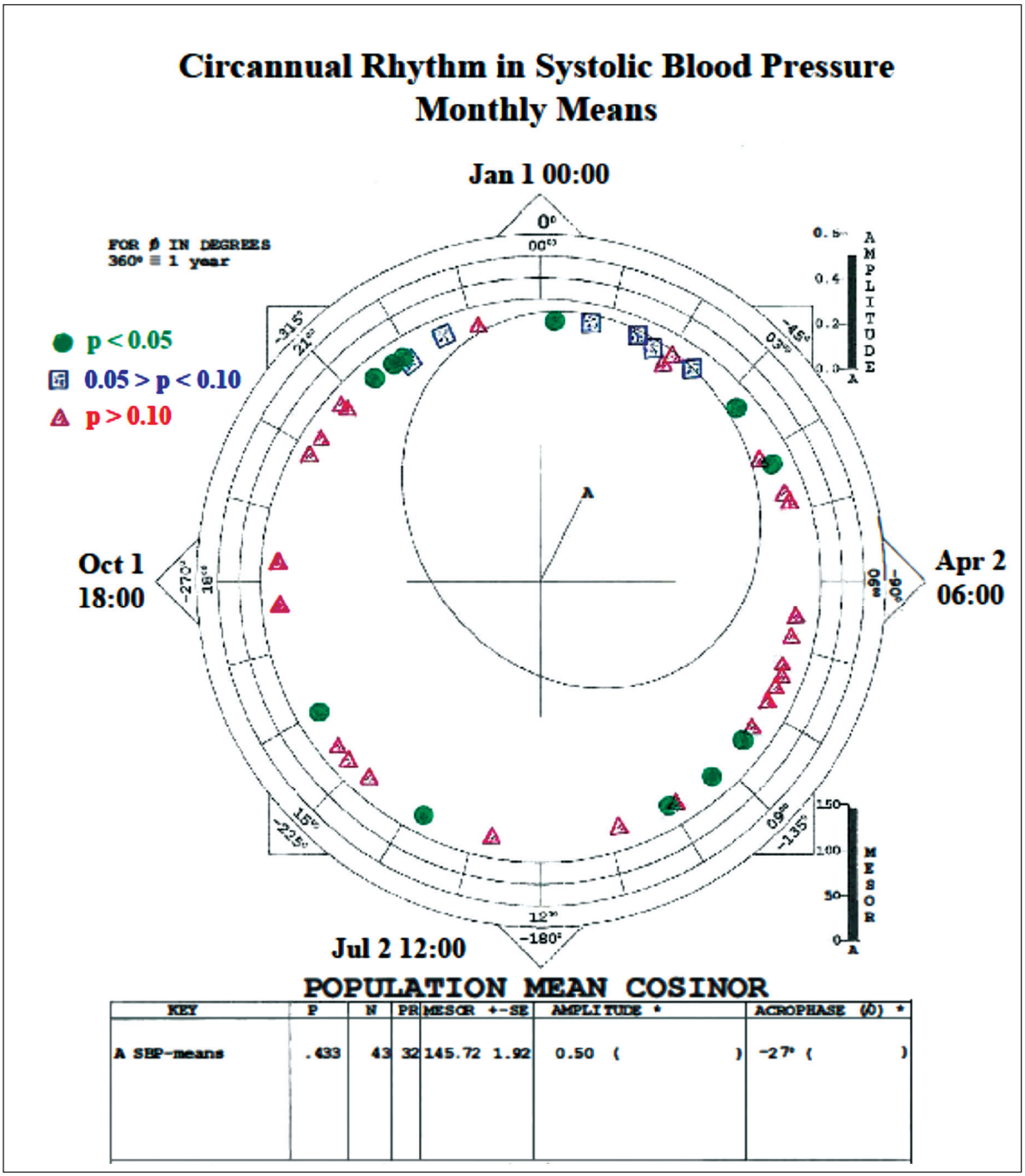

Figure 6: *Systolic blood pressure circannual acrophases are shown for each year, supporting that the wide distribution does not allow for a discernable SBP circannual rhythm. Colors are used to distinguish between years if the rhythm is statistically significant (P<0.05) (green), borderline significant (0.05<P<0.10) (blue), or not statistically significant (red).*

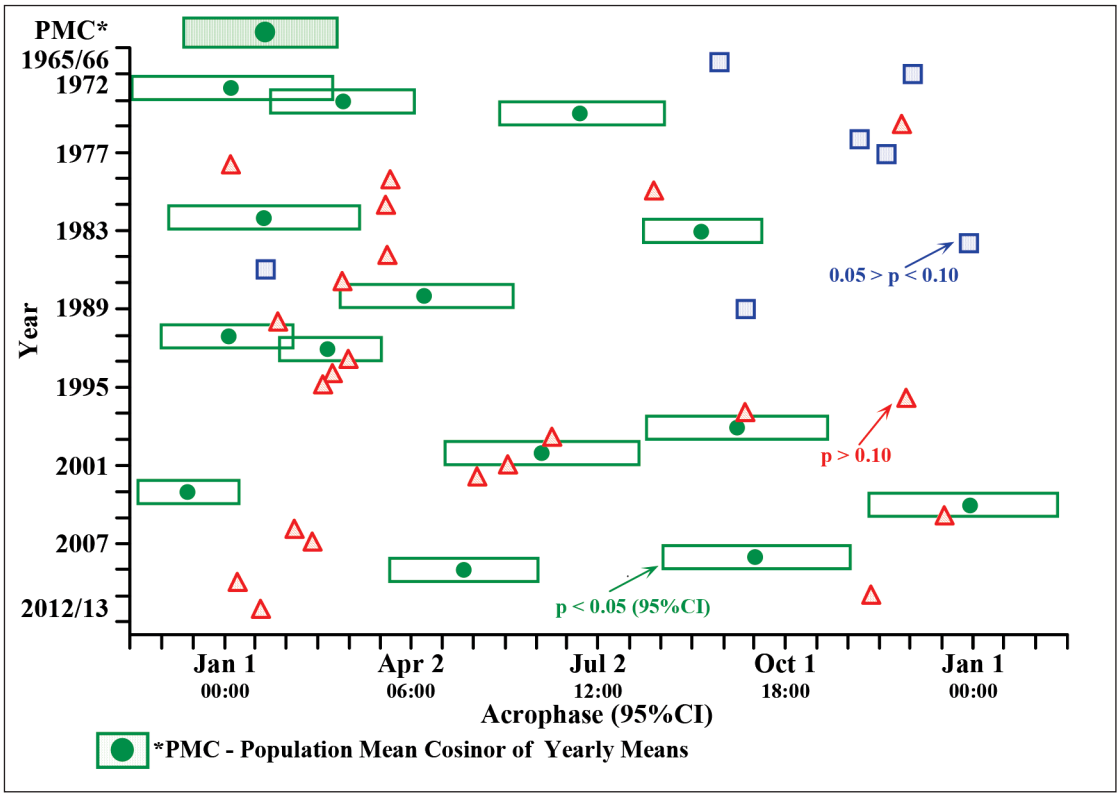

Figure 7: *The circannual acrophases of heart rate are shown for each year, with the overall rhythm also being statistically significant. There is still a large distribution of acrophases from one year to another and not all years reach statistical significance. Colors are used to distinguish between years if the rhythm is statistically significant at (P<0.05) (green), borderline significant (0.05<P<0.10) (blue), or not statistically significant (red).*

It is also interesting to note that there can be changing patterns of the circannual variation in different years in the same person. In the case of EH, the diastolic blood pressure is compared for 2-month intervals in different years in 3 different decades. Diastolic blood pressure is lower July-October in 1970-1975 but higher in 1982-1985. A circannual variation is statistically significant in 1970-1975; it only reaches borderline statistical significance in 1991-1995; and it is not statistically significant in 1982-1985 (Figure 8). The circannual patterns of diastolic blood pressure can also vary between individuals. When comparing yearly patterns of diastolic blood pressure of EH and those of another chronobiologist (RBS) during the same subspans of a few years (Halberg et al., 2004), they also differ from each other (Figure 9).

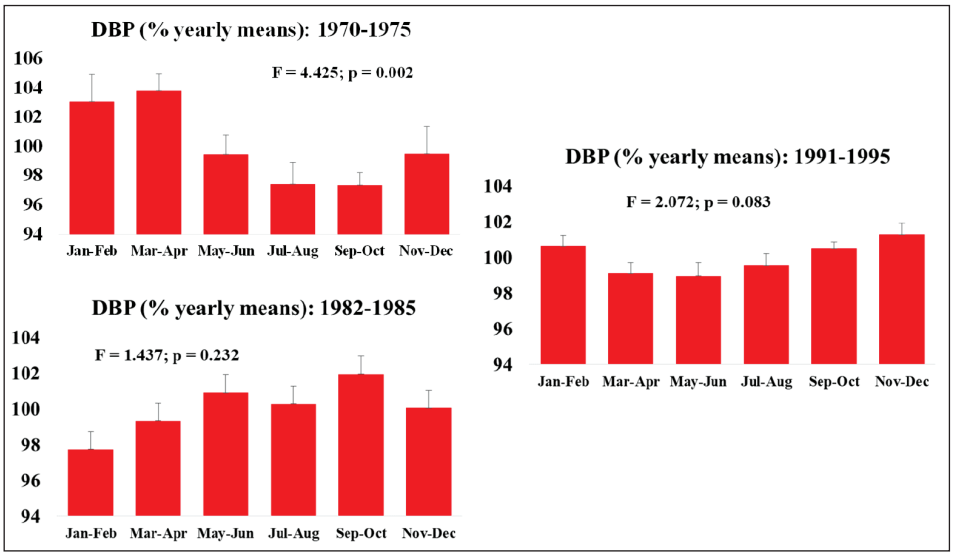

Figure 8: *Changing circannual variation of diastolic blood pressure in terms of shape and statistical significance. Two-monthly averages expressed as % of each given yearly mean.*

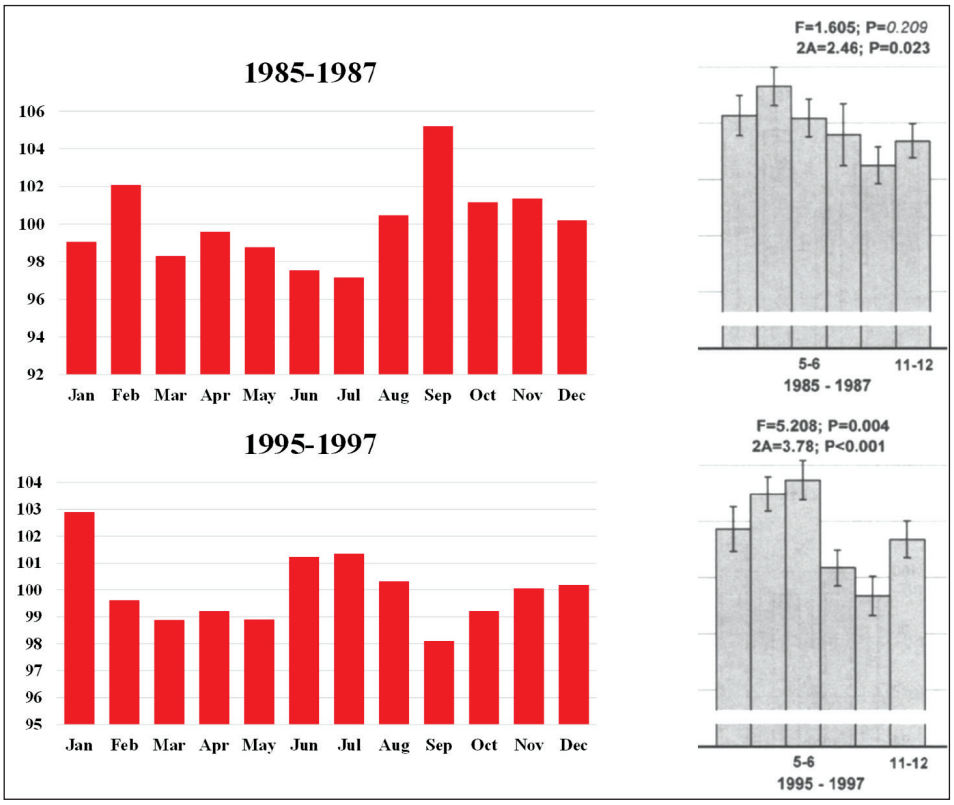

Figure 9: *Circannual patterns of DBP differ in different years and in different individuals during the same years. Monthly averages expressed as % of each given yearly means. The yearly patterns of DBP of the pathologist-scientist who self-measured for 43 years (left side) vs .those of another scientist (RBS) who self-measured several times a day for over 50 years (right side). DBP circannual patterns for 1985-1987 (top) and 1995-1997 (bottom).*

Another example of each person being different is apparent from Figure 10, which shows systolic blood pressure of the hypertensive pediatrician mother of the pathologist-scientist (Haus et al., 1993). She also self-measured herself 6 times per day, after 75 years of age. A free-running circannual variation was found in her data for the span from 1973-1978 (Figure 10). During this span, an about 61-week

component was detected with statistical significance. Further analyses are needed to determine whether this free-running circannual variation remains demonstrable in her remaining data and to analyze her son's data to look for the same frequencies.

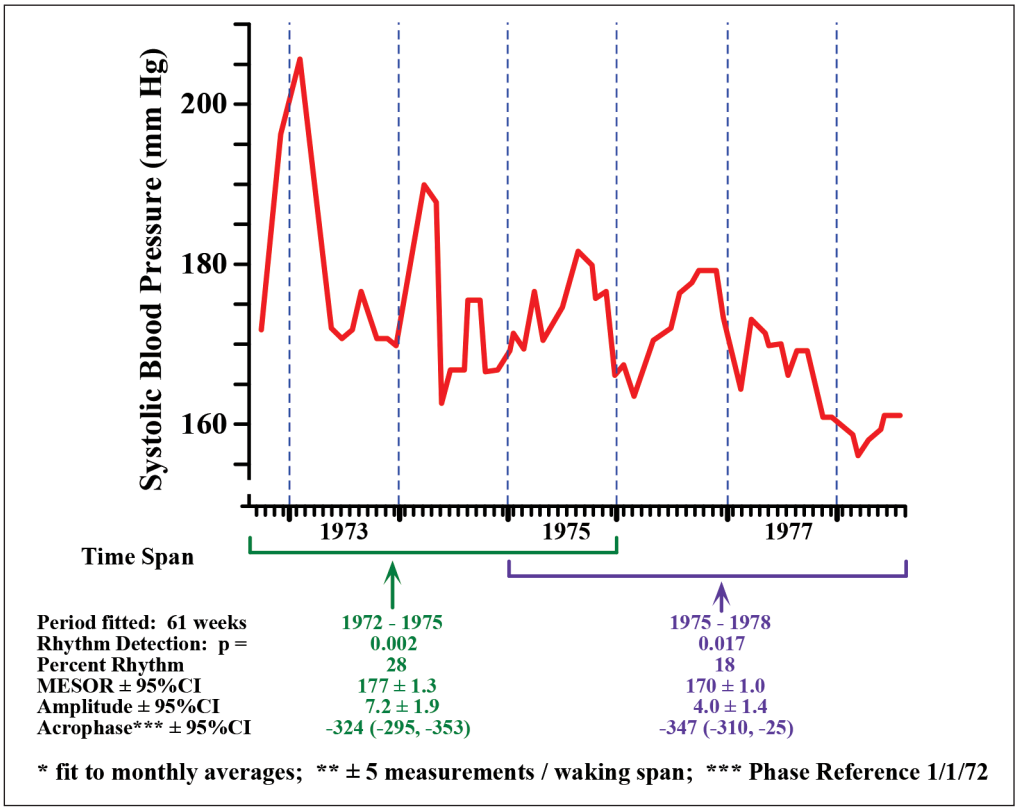

Figure 10: *Circannual rhythm of systolic blood pressure free-running from calendar year (61-week period) detected by Least Squares Spectrum in two consecutive overlapping 3-year spans in a female pediatrician doing self-measurements from 78 - 83 years of age.*

Discussion and Conclusion

Longitudinal records of blood pressure bring unique information regarding the extent of variability and how much is predictable. Self-measurements over long periods of time give much information, but they are not as consistent as monitoring by ABPM, as the person doing the self-measurements fits the measurements into their schedule or when it is easy and not at specific intervals. There are trends in the circannual variation of blood pressure over a lifetime of self-measurements. There are also many factors that affect blood pressure that may change over the collection span but need to be taken into account, such as sex, aging, stress, diagnoses, medications, activities or non-activity, number of samples taken per day, timing of samples. Contrary to ABPM, self-measurements include very few nighttime samples, and those included are likely taken while awake rather than while asleep. The lack of nighttime measurements greatly affects the estimation of the circadian rhythmicity.

Other investigators have reported a circannual variation in blood pressure, with higher values during the colder weather in the winter than during the warmer weather in the summer (Fares, 2013). These studies usually stem from population studies, each individual providing only one or a few measurements. Because self-measurements are taken at different times during the day, and because data were averaged over monthly spans, the large variability in the data may have hidden any circannual

variation in EH's blood pressure. The lack of nightly data may also have played a role. To reconcile these results, a long record obtained by ABPM (Watanabe et al., 2017) was examined.

There are even fewer longitudinal ABPM records spanning a decade or longer. In one such case, the analysis of the circadian rhythm on a daily basis showed large day-to-day variations in all circadian parameters. A plot of circadian amplitudes of systolic blood pressure as a function of time, after removing results obtained on days when data were insufficient, shows large swings undergoing an apparent yearly variation. A least squares analysis of the daily circadian amplitudes shows a large spectral peak at a frequency of one cycle per year (Figure 11). The higher values during the winter and lower values during the summer stem from a circannual modulation of the circadian amplitude of blood pressure, as also observed in another longitudinal ABPM record (Watanabe et al. 2003).

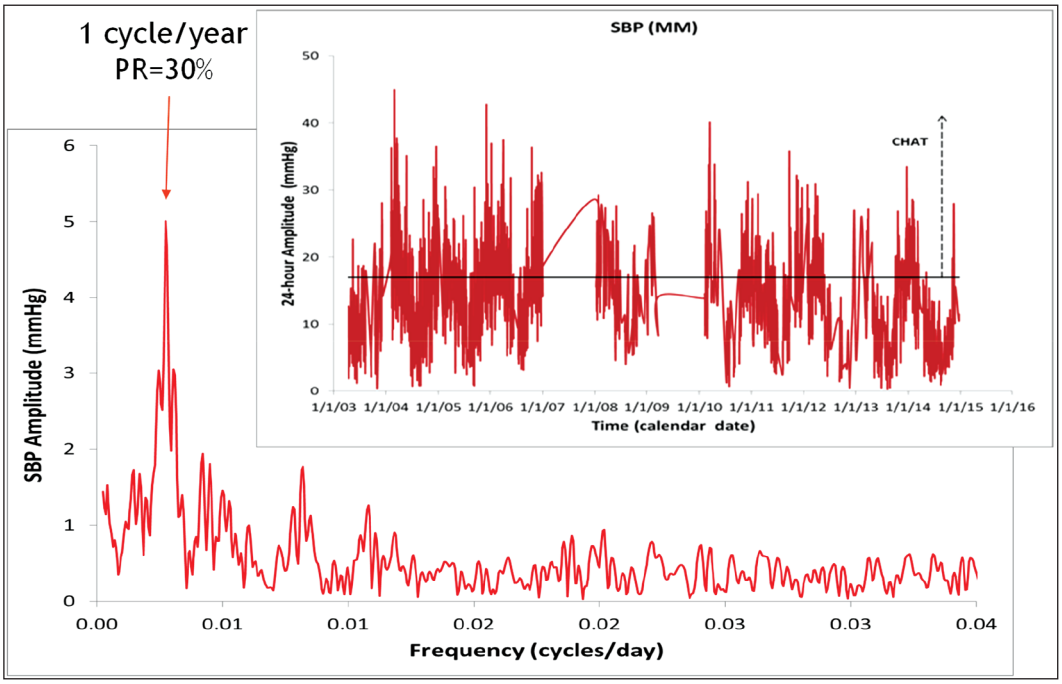

Figure 11: *Circannual modulation of the circadian amplitude of systolic blood pressure in a longitudinal ABPM record (Watanabe et al., 2017).*

Changes in circadian amplitudes over time may be useful in providing warning signs of increasing blood pressure, efficacy of anti-hypertensive treatment, and risk of adverse cardiovascular events. Lessons have been learned in the circannual analysis of EH's data, including the need for analysis as it is collected to help the individuals and their physician evaluate their medications and treatments. More will hopefully be learned from EH's data as we continue to analyze them chronobiologically for other periods, including circadian, circaseptan, monthly, and other cycles, including those reflecting solar signatures (Haus et al., 2012).

Acknowledgements

The authors acknowledge the valuable assistance of Carol Reilly and Doris Sackett, both from the Department of Pathology, Regions Hospital, St. Paul, Minnesota, who entered the 43 years of data into the computer.

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Tenth Anniversary of Departure for ever of Professor Dr. Jean-Paul Martineaud

Prof. MUDr. Jarmila Siegelová, DrSc.
Department of Physiotherapy, Faculty of Medicine Masaryk University

Professor Dr. Jean-Paul Martineaud
**27.3.1931-†29.11.2010*
Professor of Physiology, University Paris VII-Denis Diderot, France (1968-1995)
Head, Service d´explorations fonctionnelles de l´hôpital Lariboisiere (1968-1995)

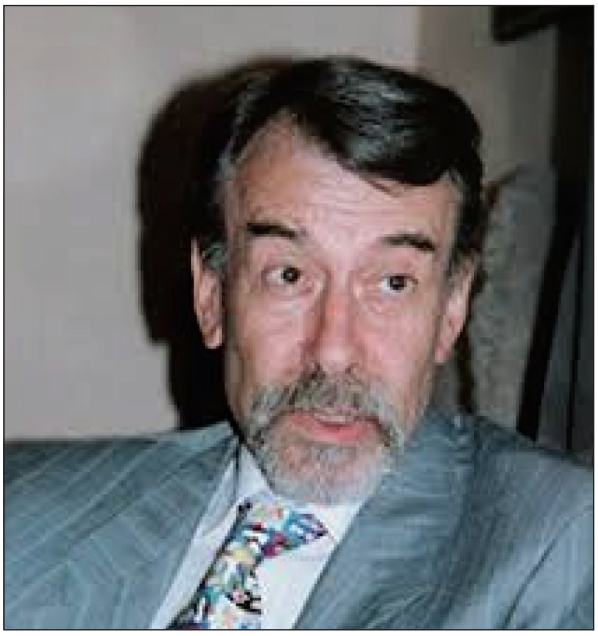
Prof. Dr. Jean-Paul Martineaud visited for the first time Dept. of Physiology, Faculty of Medicine, Masaryk University in 1976 and from this time he started with Prof. Jarmila Siegelova and Prof. Bohumil Fiser the common scientific interaction in the control of cardiovascular function in physiology and pathology. After the Velvet Revolution in Czech Republic in 1989 the common scientific cooperation between Dept. Physiology and Bioenergy, Medical Faculty, Paris University, Hopital Lariboisiere, St. Louis, France and Dept. of Physiology, Dept. of Pathophysiology, Dept. of Sports Medicine and Rehabilitation was made official from 1992. Common studies have been carried out in the field of clinical control of blood pressure in hypertension, in successful non-invasive techniques to measure blood flow in different parts of cardiovascular system, blood pressure and heart rare variability, baroreflex sensitivity. The experiments were repeatedly done in Paris, France and in Brno, Czech Republic.

The long lasting cooperation was partly limited in 2010, when after a short and serious disease prof. Jean Paul Martineaud died on November 29, 2010. In the Noninvasive Methods of Cardiology 2011 (https://www.med.muni.cz/noninvasive-methods-in-cardiology/cs) we published some results of our cooperation. In Noninvasive Methods of Cardiology 2020 we will publish the article from his pupil, Prof. B. Levy, head emeritus from his Dept. of Physiology in Paris, France.

We would like to thank prof. J.P. Martineaud for his excellent scientific work which he continued until his death, for his friendship and collaboration. We will remember him as an exceptional physiologist who had focused primarily on cardiovascular physiology and pathology.

In Memoriam Jean-Paul Martineaud

Professor Dr. Bernard Levy
INSERM Paris, France



Professor Dr. Jean-Paul Martineaud
**27.3.1931-†29.11.2010*
Professor of Physiology, University Paris VII-Denis Diderot, France (1968-1995)
Head, Service d´explorations fonctionnelles de l´hôpital Lariboisiere (1968-1995)

I met Jean Paul Martineaud in October 1968; I was a young medical student and was studying basic and human physiology at the same time. I had passed the competition to become an "Attaché-Assistant" (lecturer) I had to choose my "boss". Jean Paul had just been appointed professor, he was less than 40 years old, he was friendly, open-minded and only 15 years older than me. So, I chose to join him and we left for a long companionship. At that time, lecturers had to teach the whole human physiology: from the nervous system to the kidney, from the endocrine system to the bone physiology. We taught 3rd year medical students three afternoons a week from November to May. It was a real learning experience for our discipline and for pedagogy. Jean Paul brought us together for several hours each week to define with us the content of the teaching. This period lasted more than 10 years. In 1973, I had obtained a research post at Inserm but I continued to come and teach at rue des Saints Pères, 6 months a year. Jean Paul willingly entrusted me with the responsibility of training new assistants and we spent memorable moments together. During this period, when all Parisian physiology was housed in the New Faculty of Medicine, rue des Saints Pères, there was a rich and stimulating atmosphere on the fourth floor. The laboratories of Professors Bargeton, Durand, Florentin, Barres, Dejours, Delattre and several others were adjoining and we had frequent and rich exchanges. The French Society of Physiology brought us together twice a year and it was an opportunity to travel with Jean Paul, often in his car, to share our meals and our hotels and to spend long evenings during which he told us his "hunting stories". Especially his missions in Bolivia and Nepal among others. Jean Paul was an extraordinary storyteller and he demonstrated this much later in writing his books on the history of medicine.

As the years went by, it was no longer possible for me to continue teaching because of the increasingly heavy workload at Inserm, but Jean Paul had entrusted me with a medical session in his department where I measured the blood flow in haemodilalysis patients' arteriovenous fistulas. This period lasted until 2005; Jean Paul reached retirement age; the university then appointed me professor of physiology and the Assistance Publique-Hopitaux de Paris head of the department of non-invasive investigation of the Lariboisière hospital. Jean Paul stayed with us until the last day; he had his own office, continued to come to work every day (he wrote all his books on the history of medicine there). Often, even on Saturdays, he came to help with respiratory explorations where we had no doctor.

Jean Paul Martineaud was my friend, this friendship lasted almost 50 years.

Professor Dr. Bernard Lévy
Professor of Physiology, University Paris VII (1995-2013)
Head, Service d´explorations fonctionnelles de l´hôpital Lariboisiere (1995-2011)
INSERM (1991-2016)

Falls and Falls-Related Injuries: Do Circadian Rhythms and Melatonin Play Important Roles?

Nandu Goswami*[1], Carolina Abulafia[2], Daniel Eduardo Vigo[2], Maximilian Moser[1], Germaine Cornelissen[3], Daniel Cardinali[2]

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As humans age, the circadian amplitude of most physiological variables is reduced. The circadian phase becomes more labile and tends to occur earlier with advancing age. Indeed, falls and falls-related injuries in senior citizens follows a circadian variation. Thus, it is important in geriatric care to know the times of the day, days of the week, and times of the year when falls are more likely to occur at home or in the hospital. A better understanding of conditions in which falls occur, therefore, can lead to the implementation of countermeasures (such as adjusting the timing of anti-hypertensive medication if falls are related to undesirable circadian patterns of blood pressure and/or heart rate or adjusting the scheduling of hospital staff).

Another aspect that needs to be considered is the links between aging processes and factors associated with an increased risk of developing autonomic dysfunction. Circadian rhythms of autonomous nervous system (ANS) activity may play important role for maintenance of orthostatic tolerance (OT). For instance, a strong association between heart rate variability indexes and aging has been shown.

Finally, a prominent circadian rhythm characterizes melatonin, which peaks during the night. The circadian amplitude of melatonin decreases as a function of age, raising the questions whether such a decrease in the circadian amplitude of melatonin relates to a higher risk of falls and, if so, whether melatonin supplementation may be an effective countermeasure.

This talk concludes with the observation that whether one is concerned with disease prediction and prevention or maintenance of healthy aging, the study of circadian rhythms and the broader time structure underlying physiopathology is helpful in terms of screening, early diagnosis and prognosis, as well as the timely institution of prophylactic and/or palliative/curative treatment. Timing the administration of such treatment as a function of circadian (and other) rhythms also could lead to reduction of falls in older persons.

Keywords

Aging, falls orthostatic intolerance, autonomic, vagus nerve.

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Best Time of Exercise According to Circadian Rhythm

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Excellence Award

This award is conferred to

Prof. Jarmila Siegelova

for the excellent presentation titled

"Best time of exercise according to circadian rhythm"

in the event

"3rd SYMPOSIUM ON AYURVEDA, YOGA AND MEDITATION:
Integrative health prevention approaches"

organized by the Embassy of India, Vienna and the Medical University of Graz,
supported by Ministry of AYUSH, New Delhi

13. December 2019, Medical University of Graz, Austria

On the behalf of the organizing committee

Assoc. Prof. Nandu Goswami

Medical University of Graz

Division of Physiology

3rd SYMPOSIUM ON AYURVEDA, YOGA AND MEDITATION:

Integrative health prevention approaches

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Friday, 13th December 2019
10:00 am - 4:30 pm

Medical University of Graz, MEDCAMPUS
HÖRSAAL / Lecture Hall IV

Symposium Host:
Nandu Goswami

Medizinische Universität Graz, Auenbruggerplatz 2, 8036 Graz, www.medunigraz.at

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Introduction

Exercise is an easily accessible and inexpensive approach to improve cardiovascular health, control weight gain, and increase survival chances after a morbid event such as a myocardial infarction. It is, however, sometimes associated with untoward effects in vulnerable subjects. A contributory factor may be heart rate variability, which in the long term is increased in association with exercise, but may be decreased in the short term during exercise and the recovery span after exercise.

Brno Consensus under the leadership of Professor F. Halberg, G. Cornélissen, Professor T. Kenner, Professor B. Fiser, Dr. J. Dušek and me (Brno chronobiological team) described Vascular Variability Disorders (VVDs), associated with a statistically significant increase in cardiovascular disease risk, include in addition to a high blood pressure other alterations of the variability in blood pressure and/or heart rate.

Among others, an excessive circadian amplitude (CHAT) of BP was shown to dramatically increase cardiovascular disease risk.

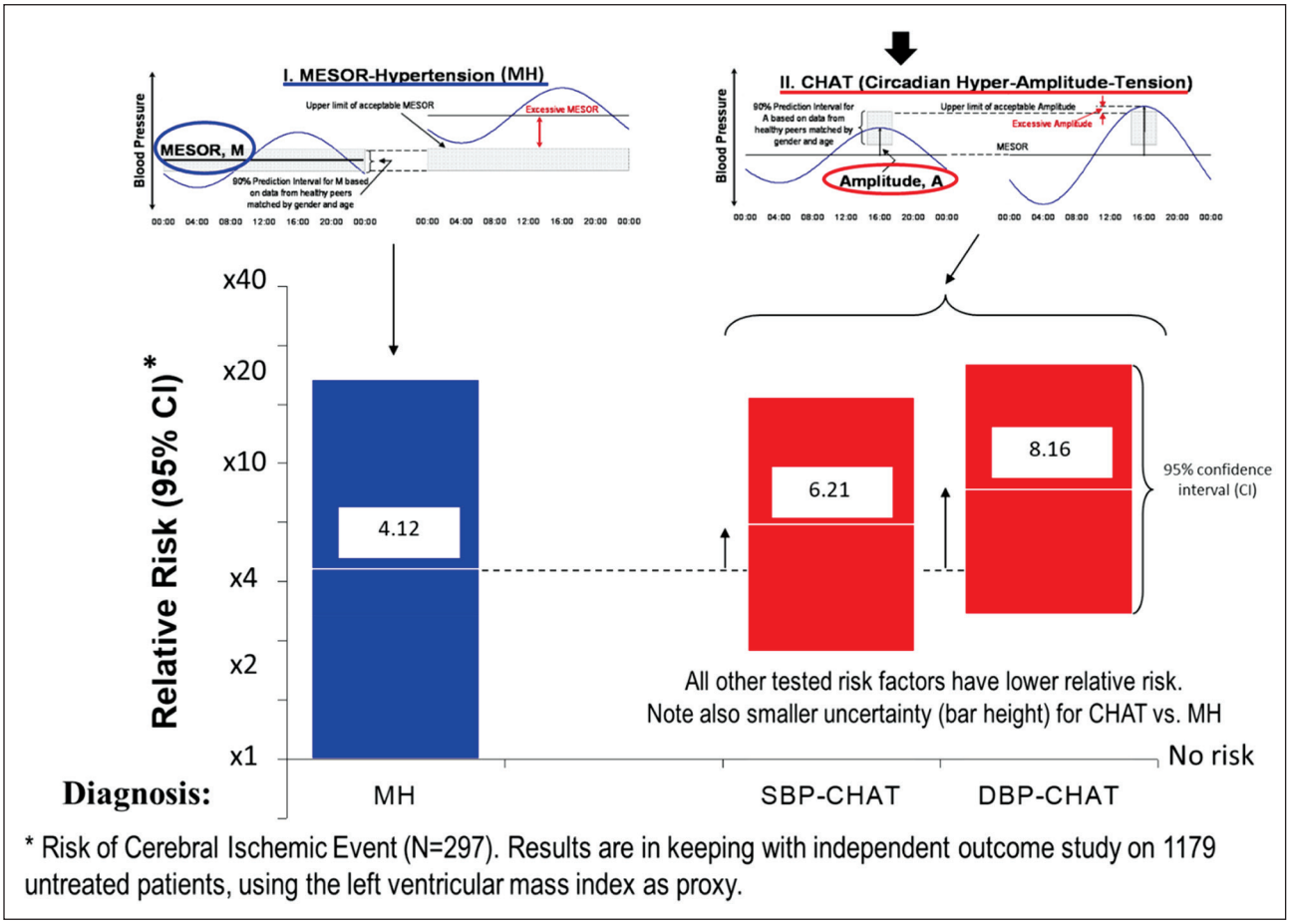

Figure 1: *Definition of some Vascular Variability Disorders from Brno Consensus 2008.*
MH- MESOR hypertension is an elevation of the blood pressure MESOR above the 95% prediction limit of clinically healthy peers matched by gender and age.
SBP CHAT and DBP CHAT- Circadian Hyperamplitude Tension is an elevation of the 24-h amplitude of blood pressure over the upper 95% prediction limit of clinically healthy peers matched by gender and age.

A: Exercises in different parts of the day

Aim

The purpose of the first part of the presentation is the seven day / 24h ambulatory blood pressure monitoring in one subject who exercises in the morning and in the evening hour.

Methods

Using 7-day/24-hour ambulatory blood pressure monitoring and timing of exercise was analyzed in 46 years old men.

Medical Instruments TM2431 (A and D, Japan) were used for ambulatory blood pressure monitoring (oscillation method). The regime of measurement of blood pressure was done for 7 days repeatedly every 30 minutes from 5 to 22 h during the day time and once in an hour from 22 to 5 h at night.

Results

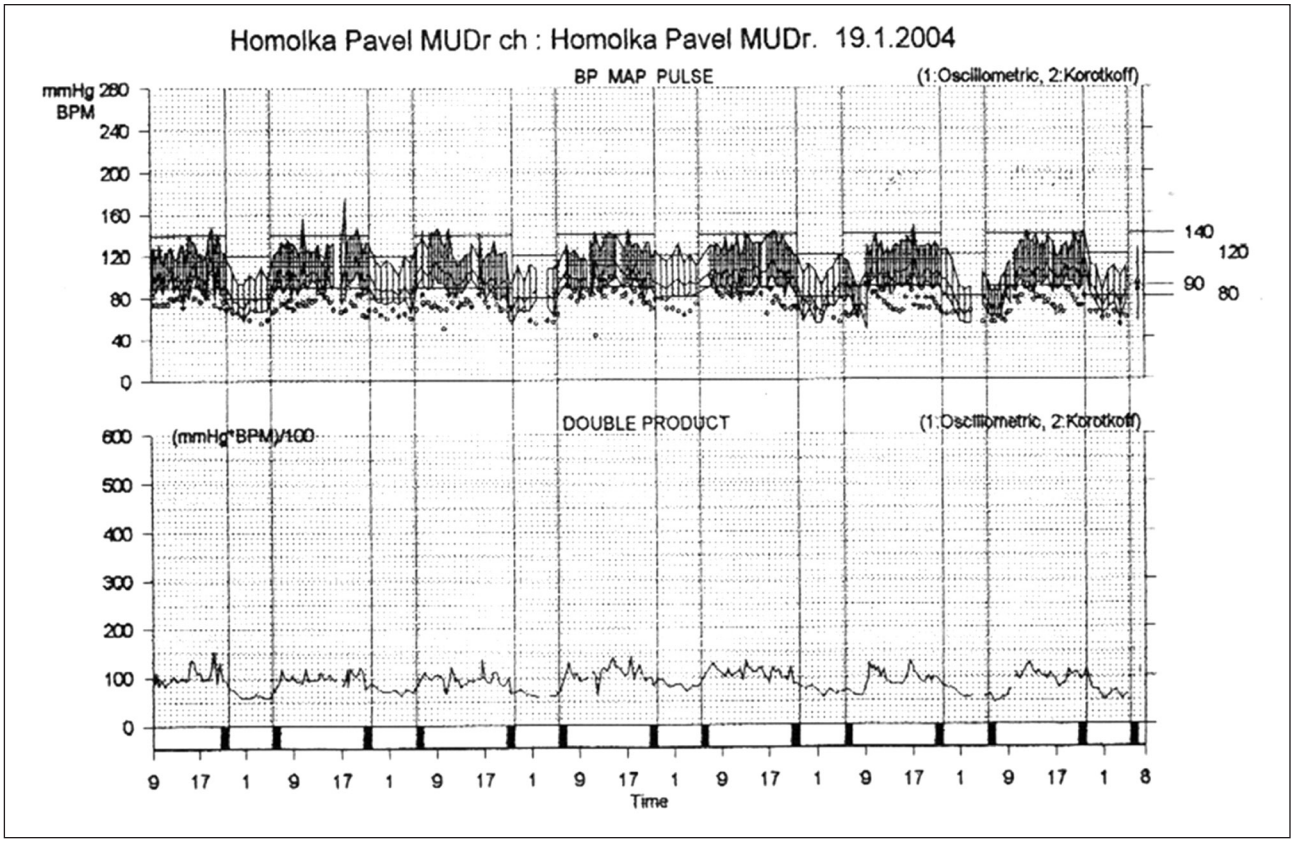

Figure 2: *The profile of 7-day / 24h systolic and diastolic blood pressure (ABPM) in one person at rest*

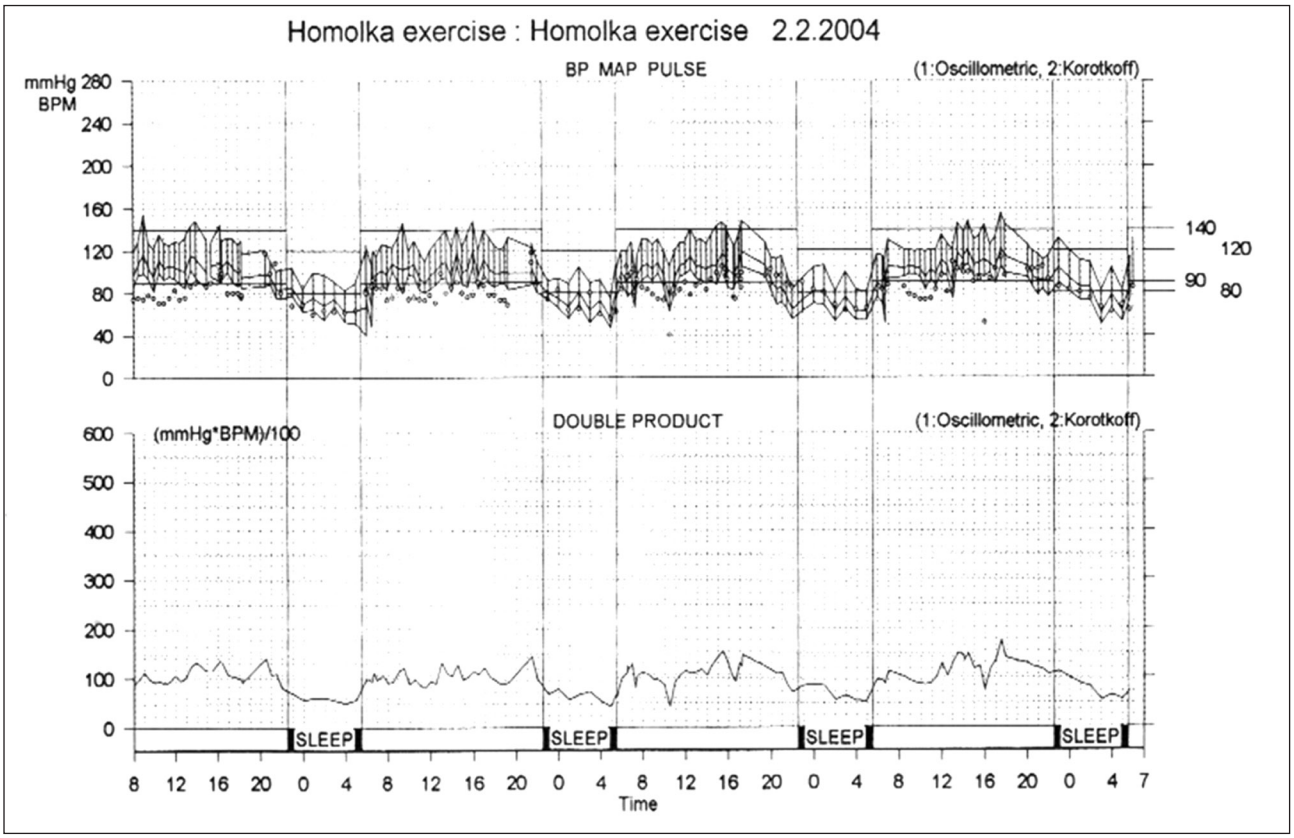

Figure 3: *The profile of ABPM in one person with exercise in the evening*

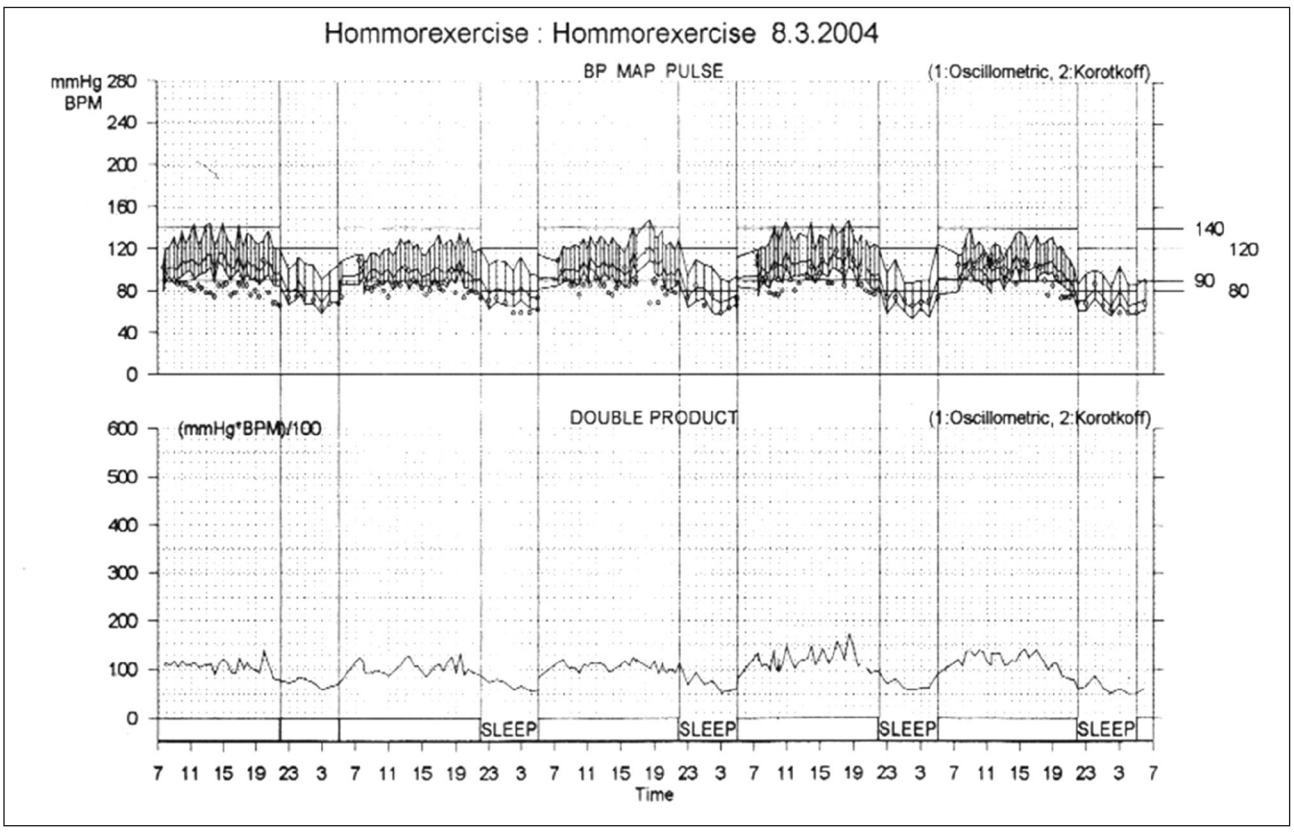

Figure 4: *The profile of ABPM in one person with exercise in the morning*

Longitudinally, the effect of exercising in the evening or in the morning was examined in one subject in Brno by around-the-clock monitoring of BP and HR for 4 to 7 days.

Part of the results was published by Halberg at al. in III[rd] International Conference, Civilization diseases in the spirit of V.I. Vernadsky, People's Friendship University of Russia, Moscow, Oct. 10-12, 2005, p. 419-421.

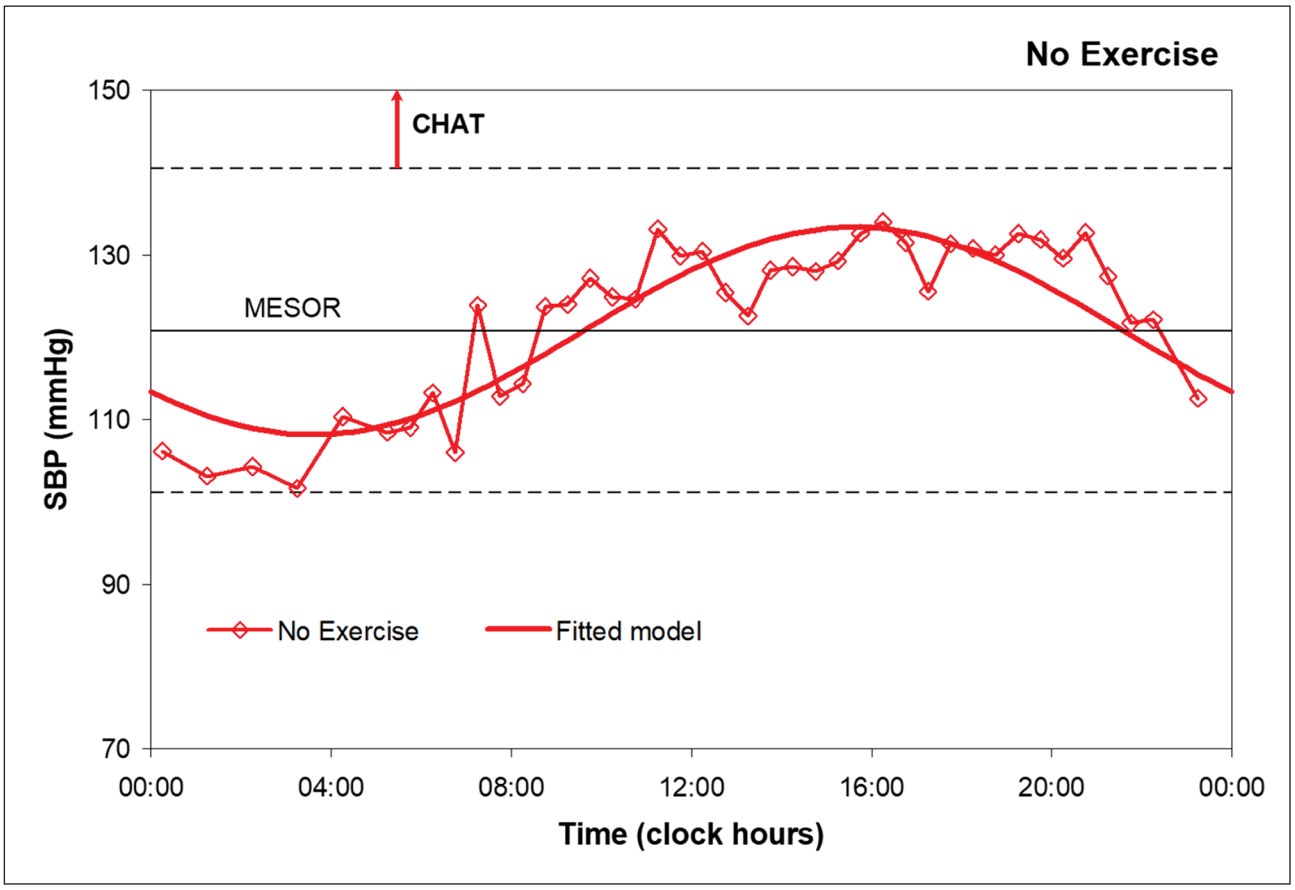

Figure 5: *Systolic blood pressure data of ABPM are shown with five component model fitted by the least squares to the data in one person at rest.*

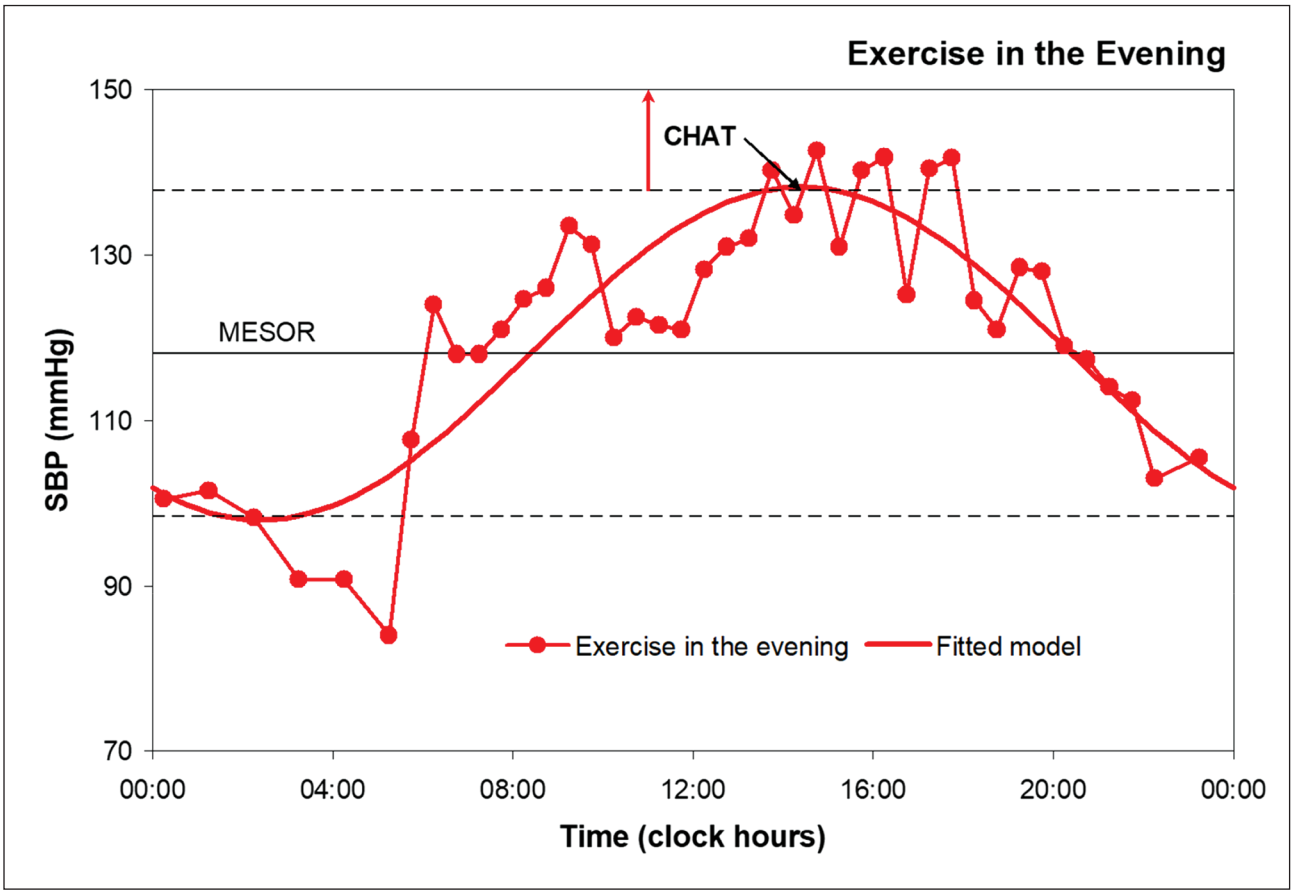

Figure 6: *Systolic blood pressure data of ABPM are shown with five component model fitted by the least squares to the data in one person with exercise in the evening.*

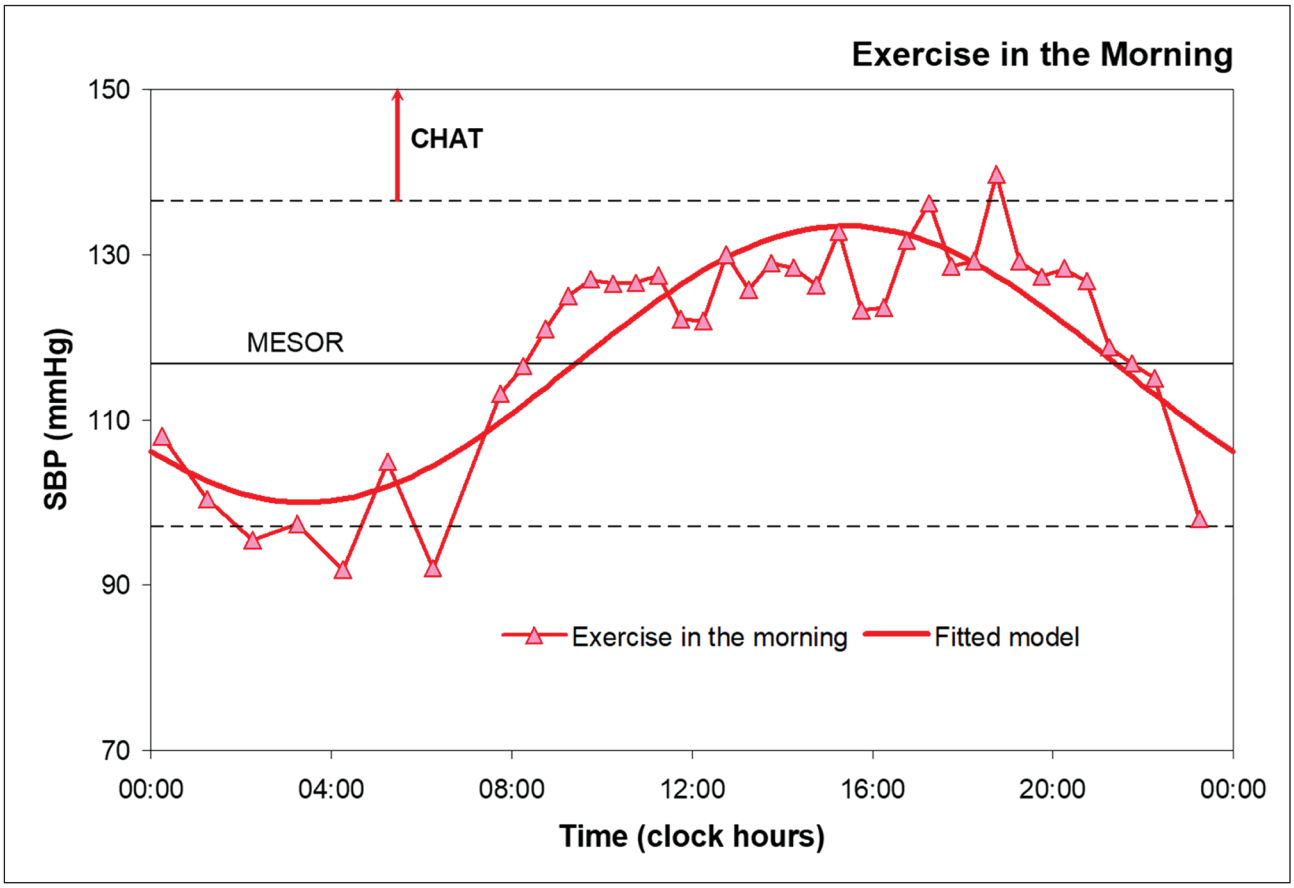

Figure 7: *Systolic blood pressure data of ABPM are shown with five component model fitted by the least squares to the data in one person with exercise in the morning*

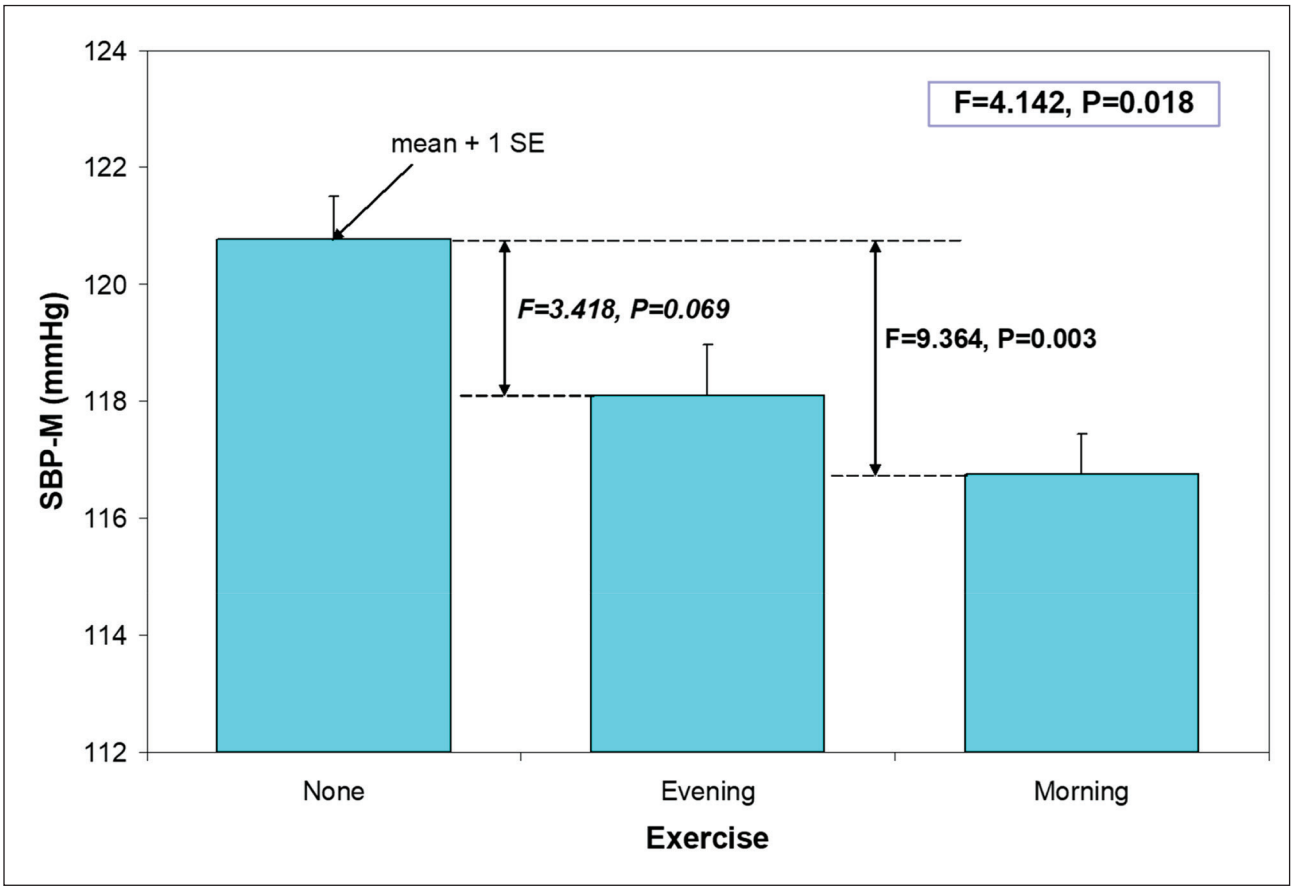

Figure 8: *MESOR of the circadian SBP of ABPM in one person at rest (None), with exercise in the evening, with exercise in the morning*

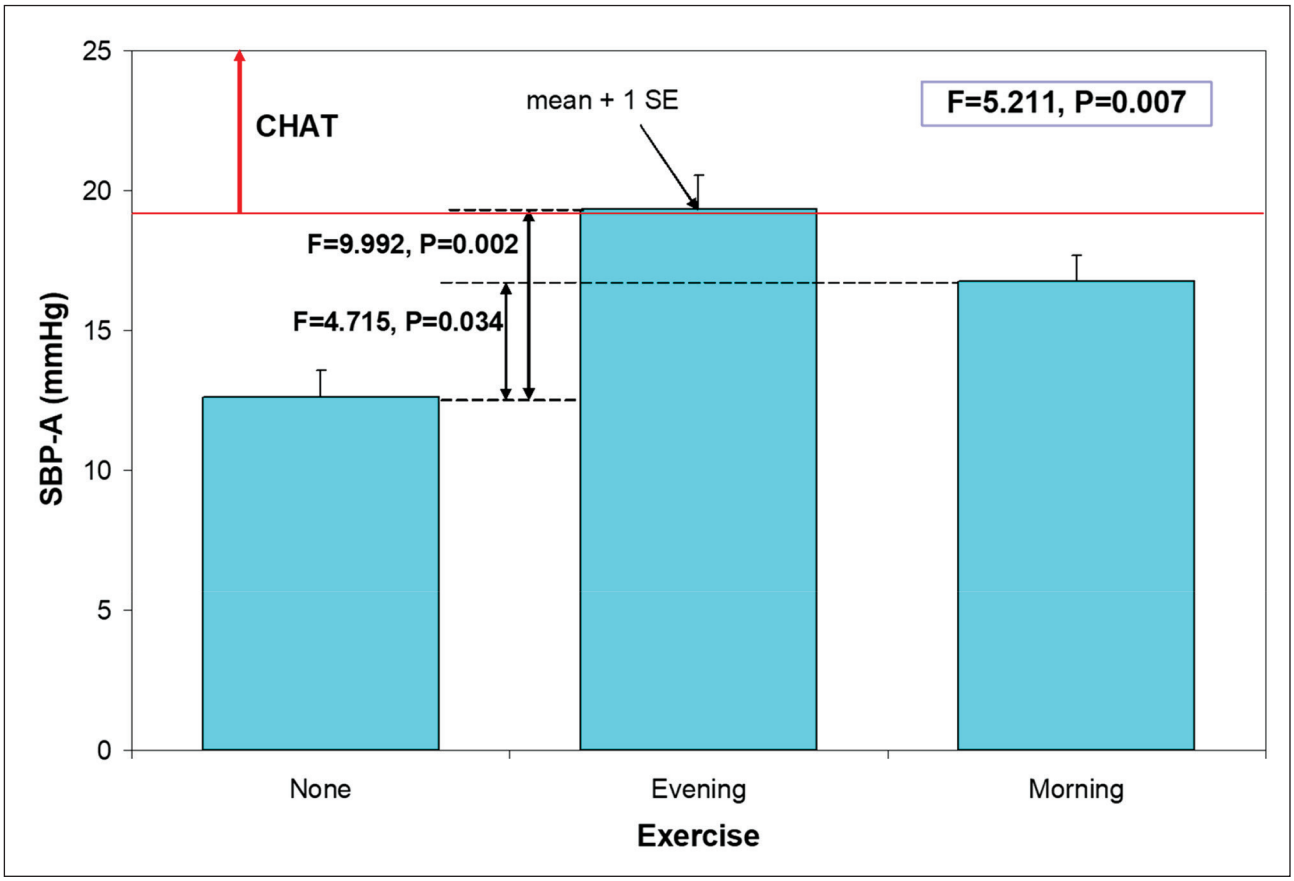

Figure 9: *Amplitude of the circadian SBP of ABPM in one person at rest (None), with exercise in the evening, with exercise in the morning*

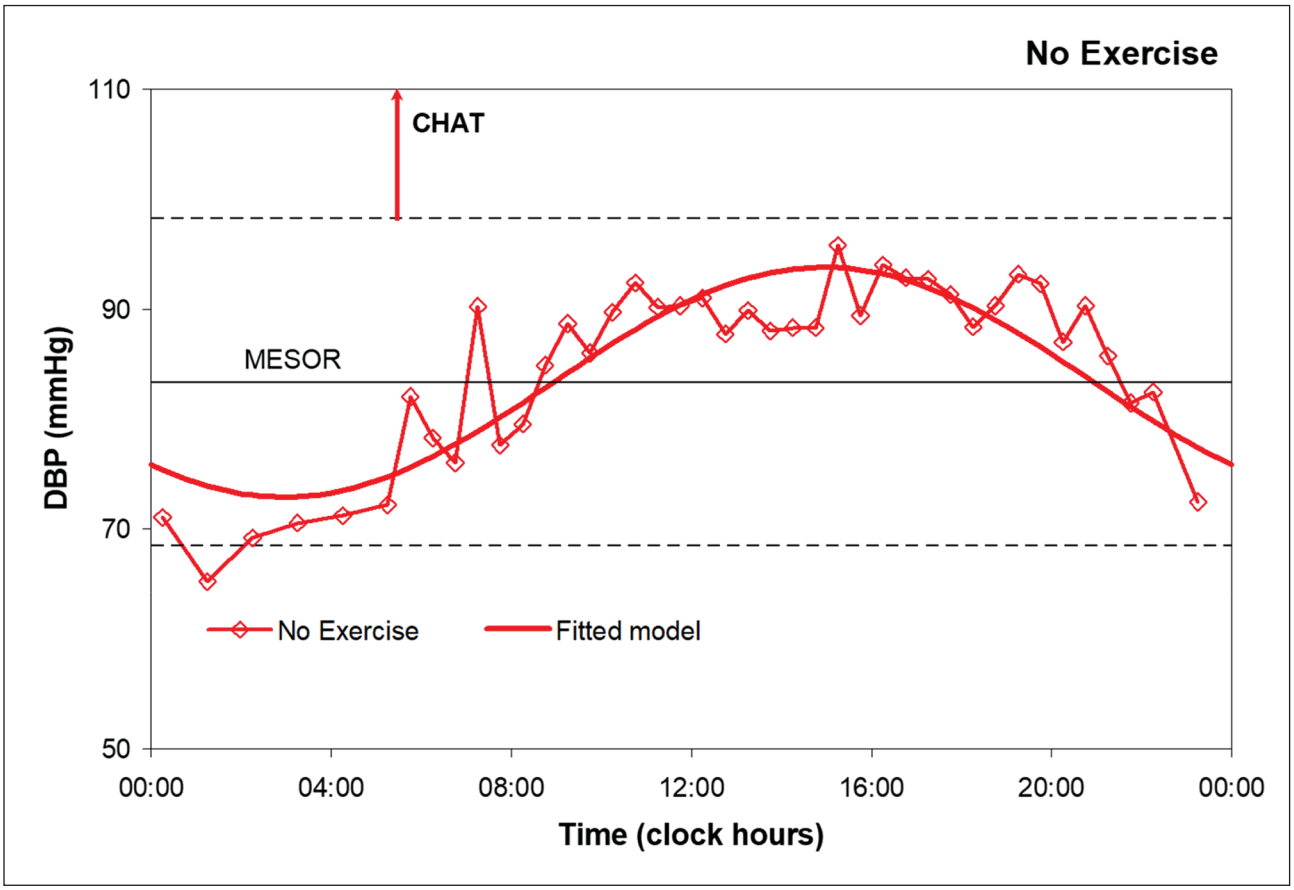

Figure 10: *Diastolic blood pressure data of ABPM are shown with five component model fitted by the least squares to the data in one person at rest.*

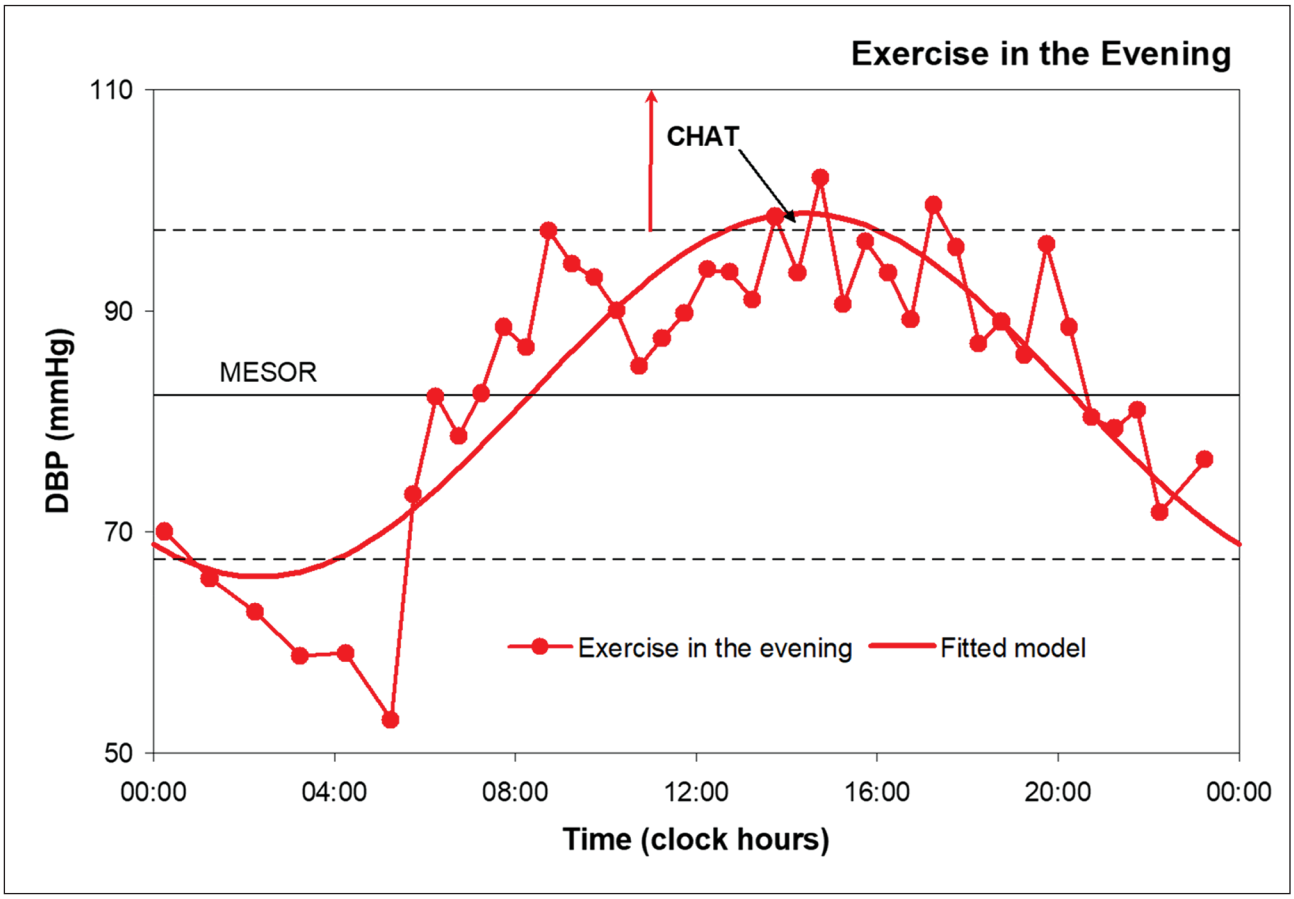

Figure 11: *Diastolic blood pressure data of ABPM are shown with five component model fitted by the least squares to the data in one person with exercise in the evening*

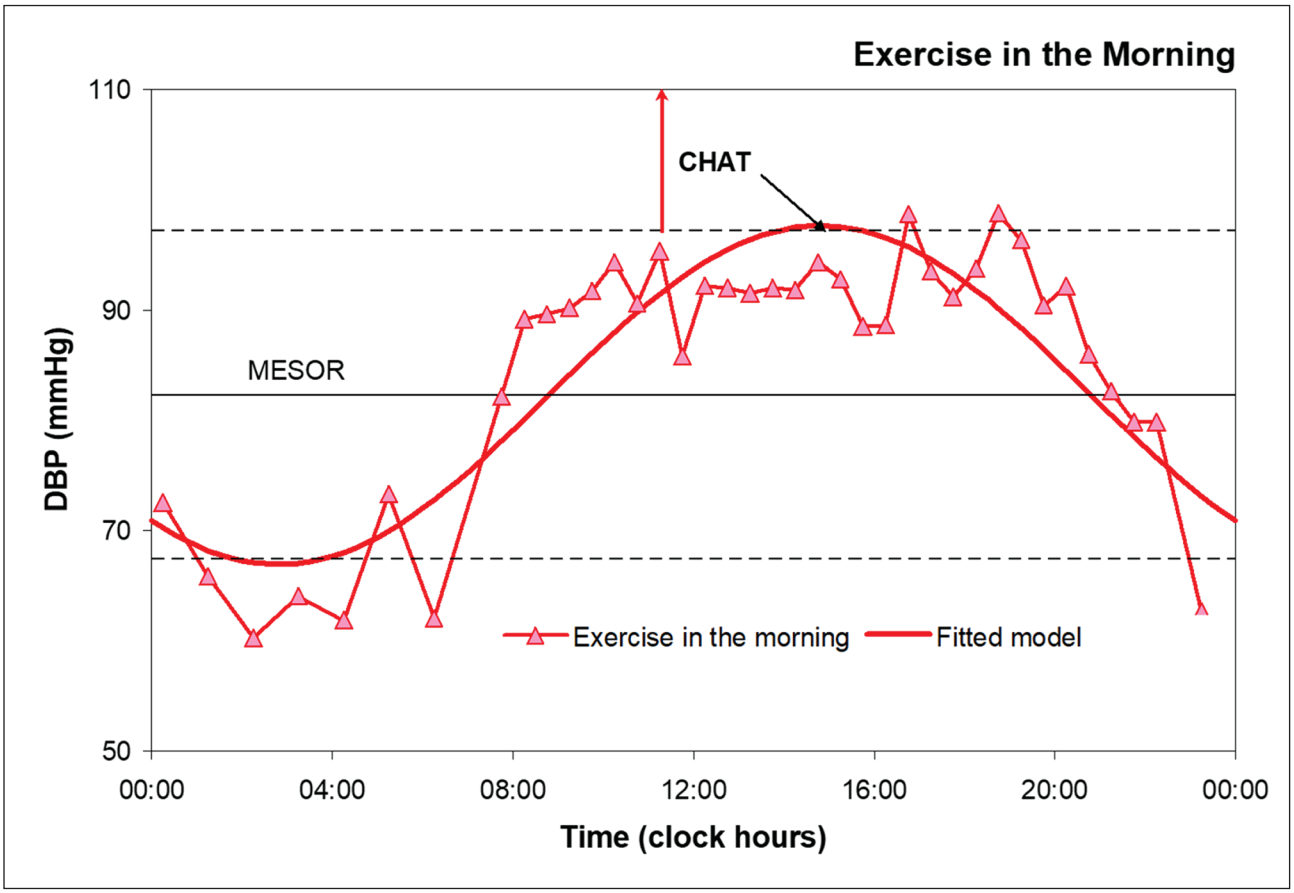

Figure 12: *Diastolic blood pressure data of ABPM are shown with five component model fitted by the least squares to the data in one person with exercise in the morning*

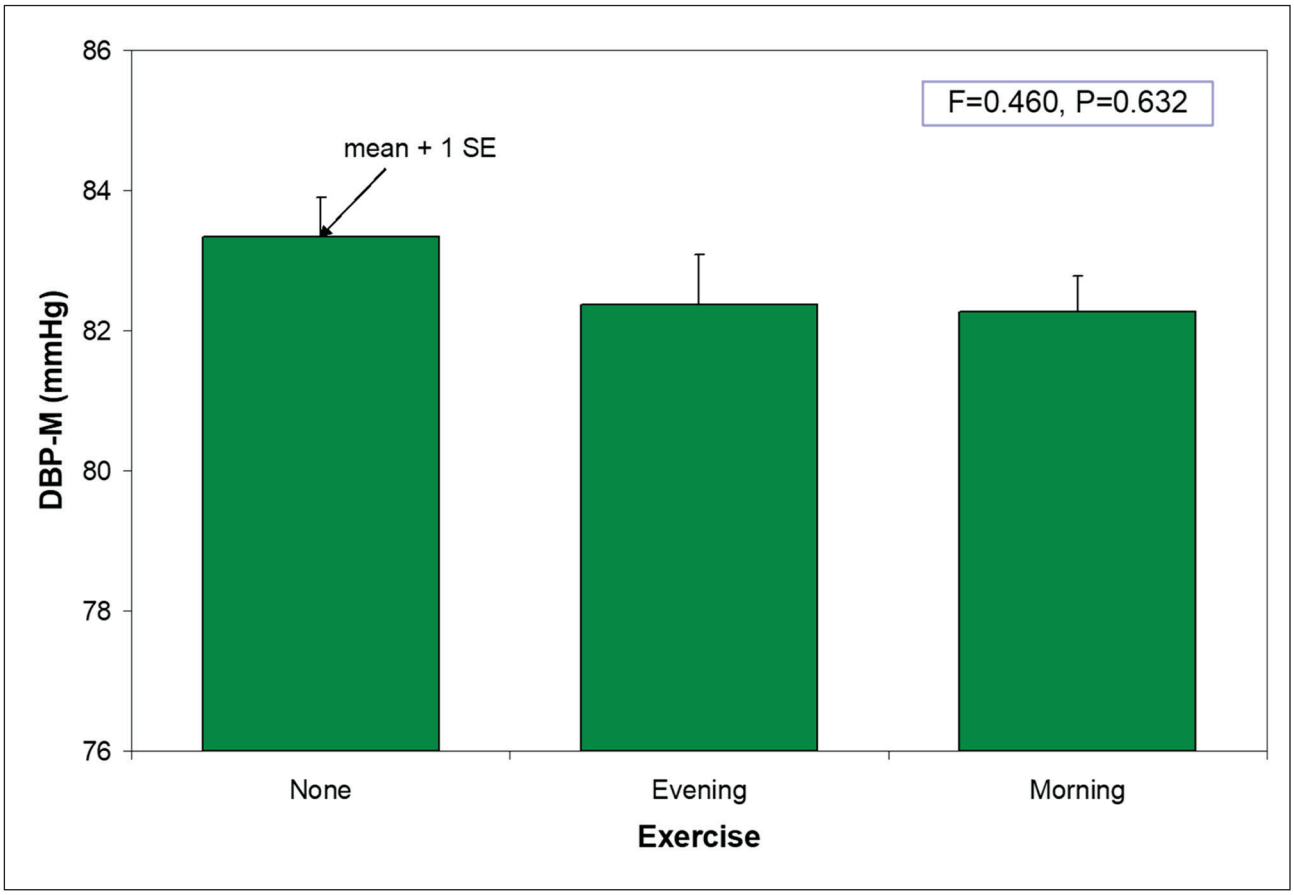

Figure 13: *MESOR of the circadian DBP of ABPM in one person at rest (None), with exercise in the evening, with exercise in the morning*

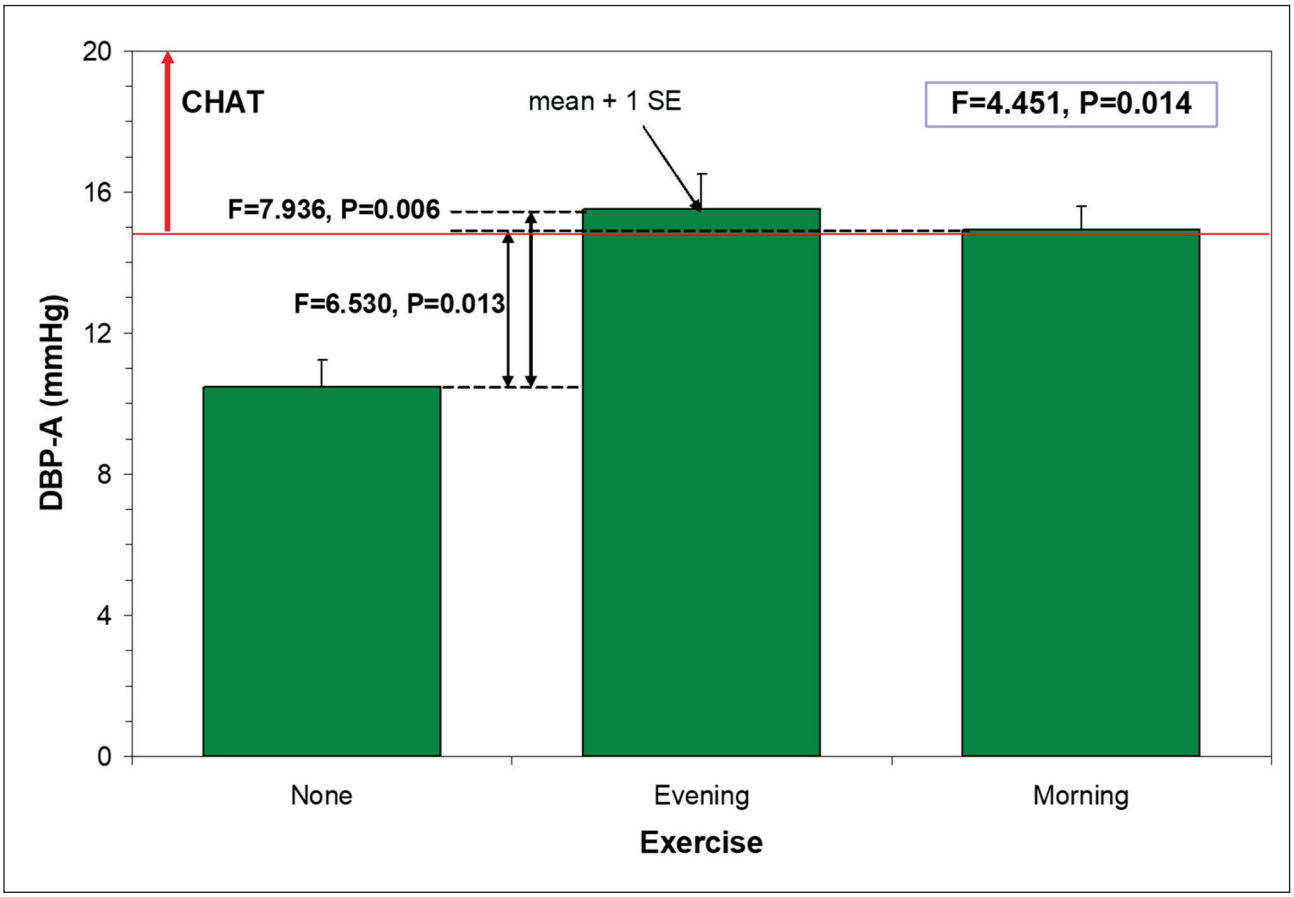

Figure 14: *Amplitude of the circadian DBP of ABPM in one person at rest (None), with exercise in the evening, with exercise in the morning*

Thus, in subjects who tend to have a large amplitude circadian rhythm in BP at the outset, exercising, notably in the evening, may bring the BP amplitude above the threshold beyond which cardiovascular disease risk is increased.

B
Blood pressure and different kind of exercise in healthy subject and in patients with ischemic hearT disease

The aim of the second part of the study is to evaluate seven day/24 -hour effect of different kind of exercise in the daily exercise activity, lasting one hour, on 24-hour blood pressure profile. We have compared the 24-hour blood pressure profile of 7-day ambulatory monitoring in days with exercise (0-24 h) and in days without exercise (25-48 h) in healthy subjects and outpatients. We used aerobic training in 41 healthy subjects, combined training in 20 healthy people, nordic walking in 19 subjects and combined training in 40 outpatients after myocardial infarction in cardiovascular rehabilitation. The set being monitored consisted of 40 patients with ischemic heart disease (IM) of the age 63 ± 6,3 years (age between 41 and 77 years) and ejection fraction (43 ± 12,3) %. The patients were subjected to phase II of cardiovascular rehabilitation (controlled ambulatory rehabilitation program) lasting two to three months with the frequency of three times a week at the Department of Functional Diagnostics and Rehabilitation of St. Anna Teaching Hospital. The duration of the training unit was 60 min and it consisted of warm-up phase (10 min), aerobic phase (25 min), toning phase (15 min) and relaxation phase (10 min). In the course of second phase rehabilitation the patients underwent 7-day ambulatory monitoring of blood pressure. During blood pressure recording they did not interrupt pharmacotherapy (ACE inhibitors, statins, betablockers, Ca antagonists).

Figure 15: *Aerobic training*

Figure 16: *Aerobic training*

Figure 18: *Resistant training*

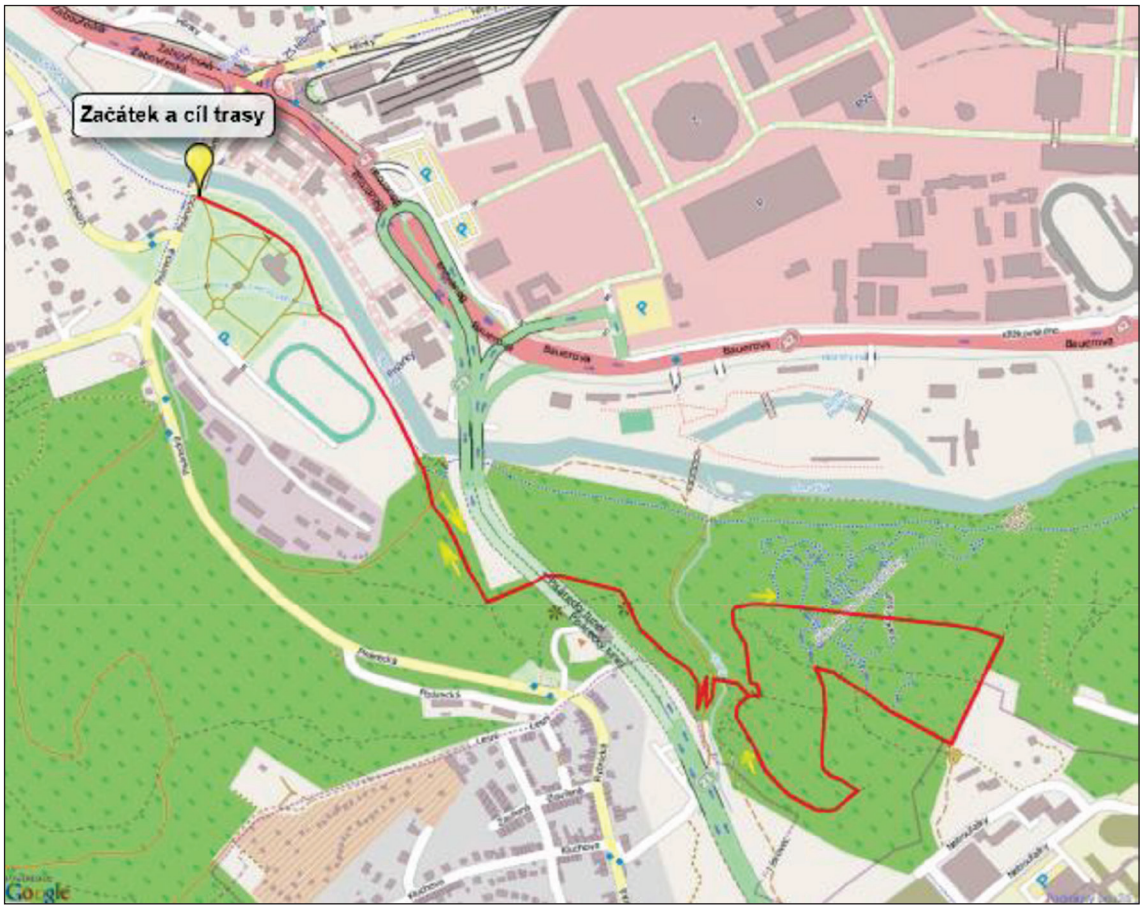

Figure 18: *Nordic walking*

Figure 19: *Aerobic training in patients with IM*

Figure 20: *Resistant training in patients with IM*

Methods and results

Blood pressure variability in the days with and without exercise

The healthy subjects (men) were classified as above mean 7-day SBP (subject No 1: 107 mmHg, subject No 21: 121 mmHg; median value: 121 mmHg). The variability of one-daytime SBP values during 7-day monitoring is seen in the following figures.

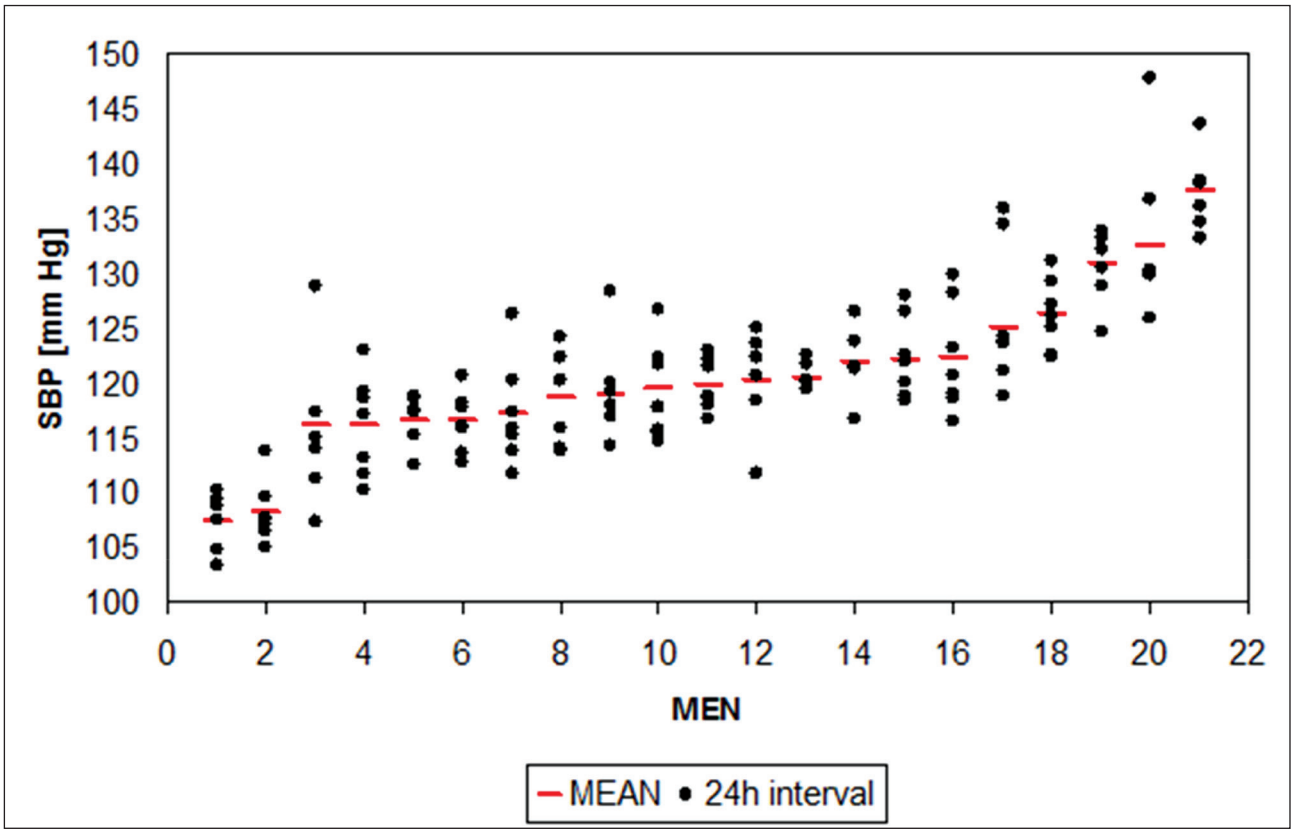

Figure 21: *The variability of 24-hour mean systolic blood pressure (black points) and 7-day mean systolic blood pressure (red line) at rest in 21 healthy subjects.*

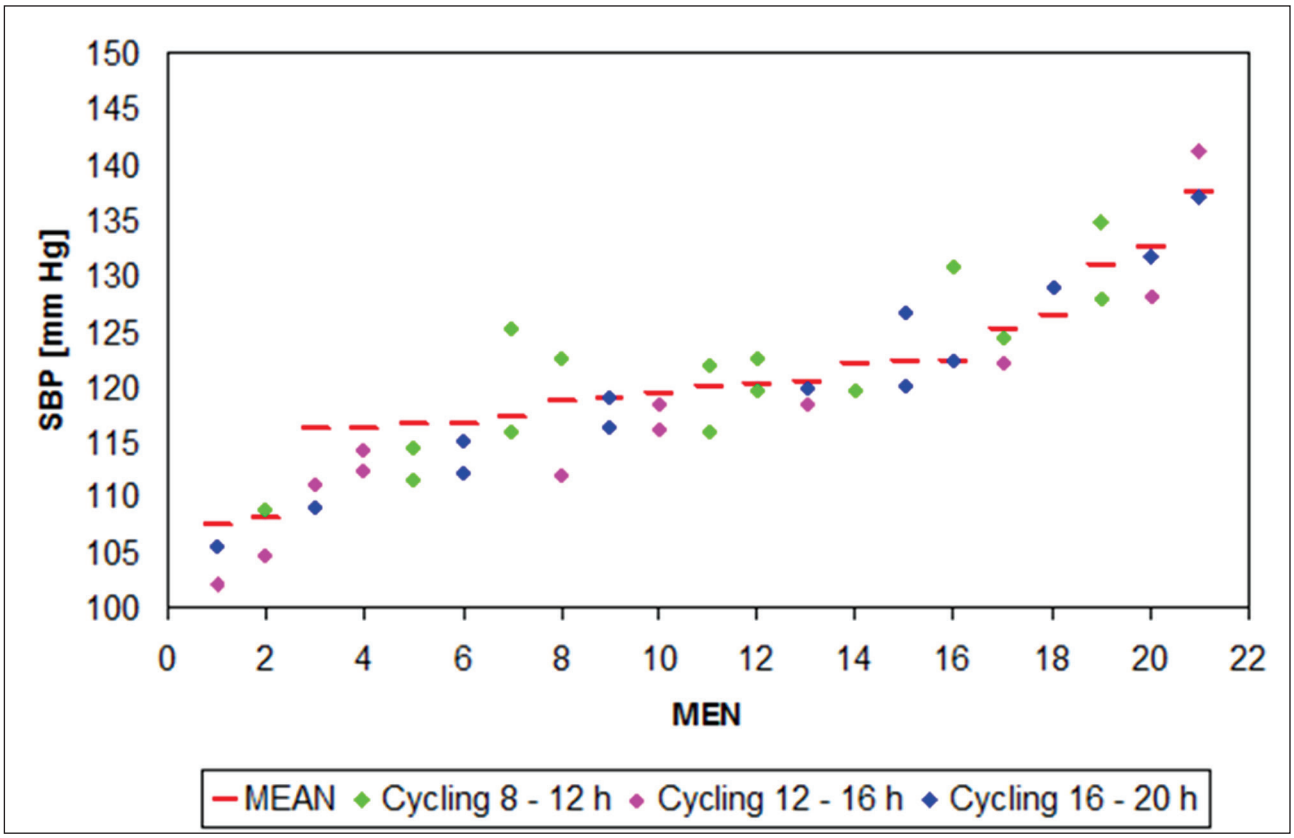

Figure 22: *The variability of 24-hour mean systolic blood pressure (points in color) and 7-day mean systolic blood pressure (red line) during aerobic exercise in 21 healthy subjects.*

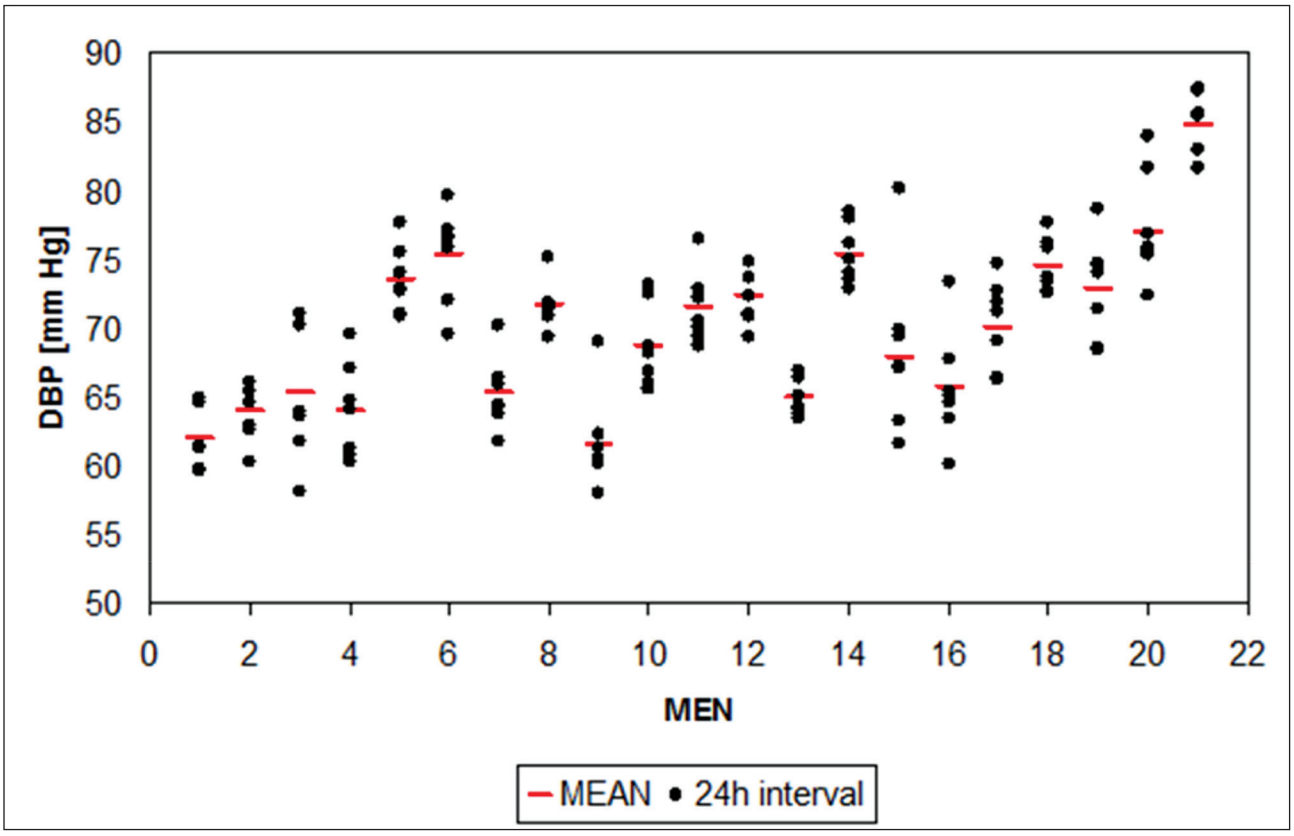

Figure 23: *The variability of 24-hour mean diastolic blood pressure (black points) and 7-day mean diastolic blood pressure (red line) at rest in 21 healthy subjects.*

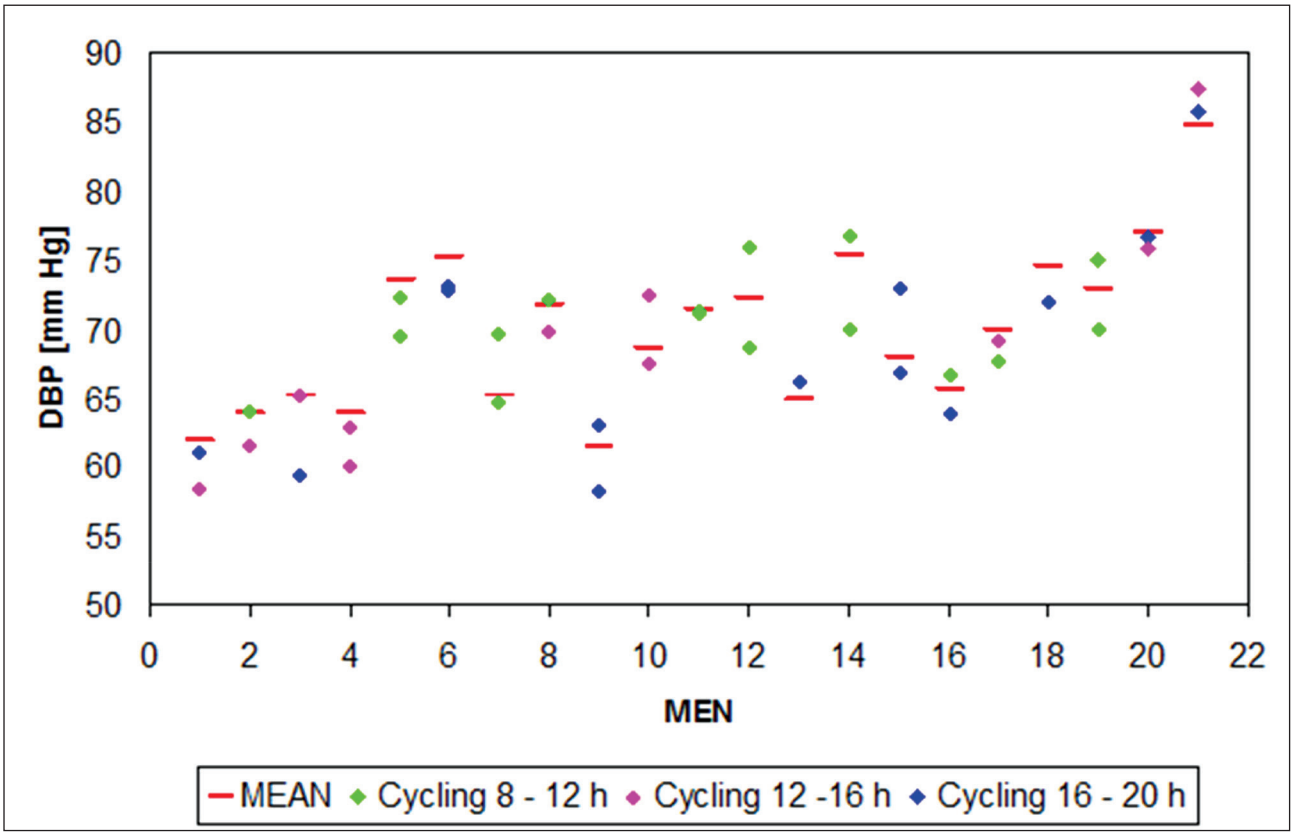

Figure 24: *The variability of 24-hour mean diastolic blood pressure (points in color) and 7-day mean diastolic blood pressure (red line) during combined exercise in 21 healthy subjects.*

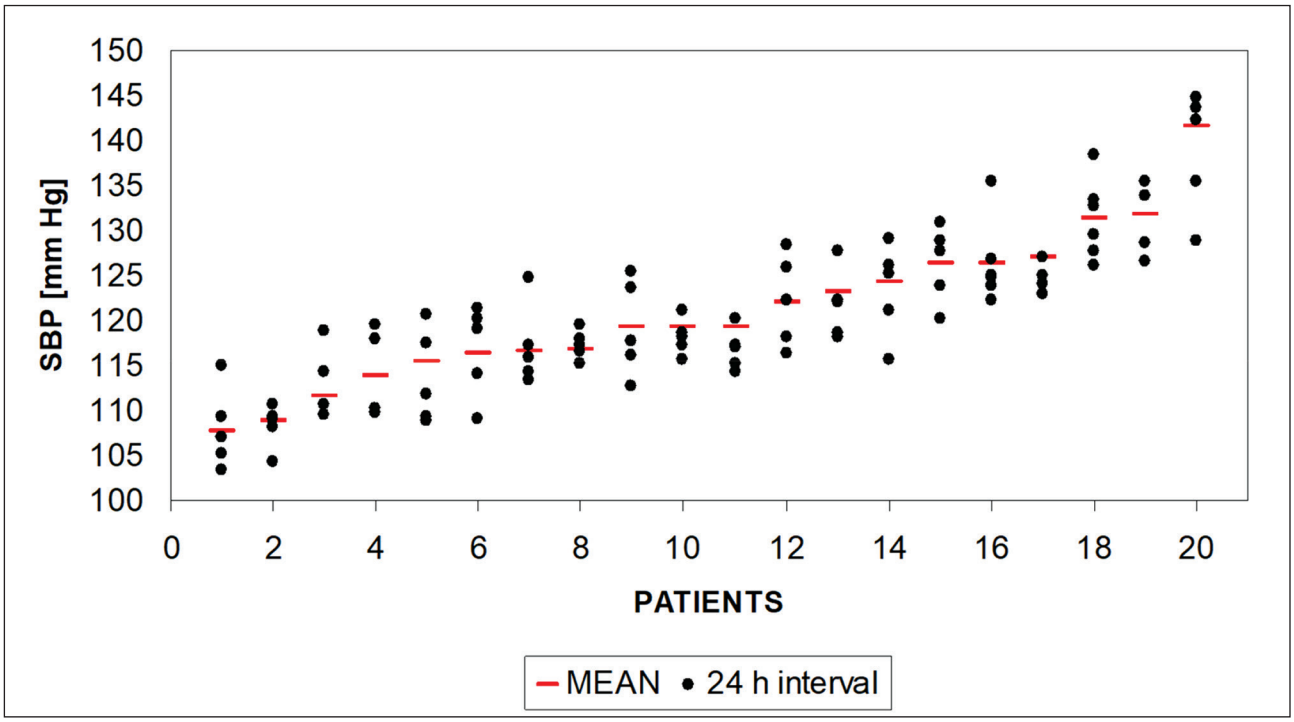

Figure 25: *The variability of 24-hour mean systolic blood pressure (black points), and 7-day mean systolic blood pressure (red line) at rest in 20 patients with coronary heart diseases*

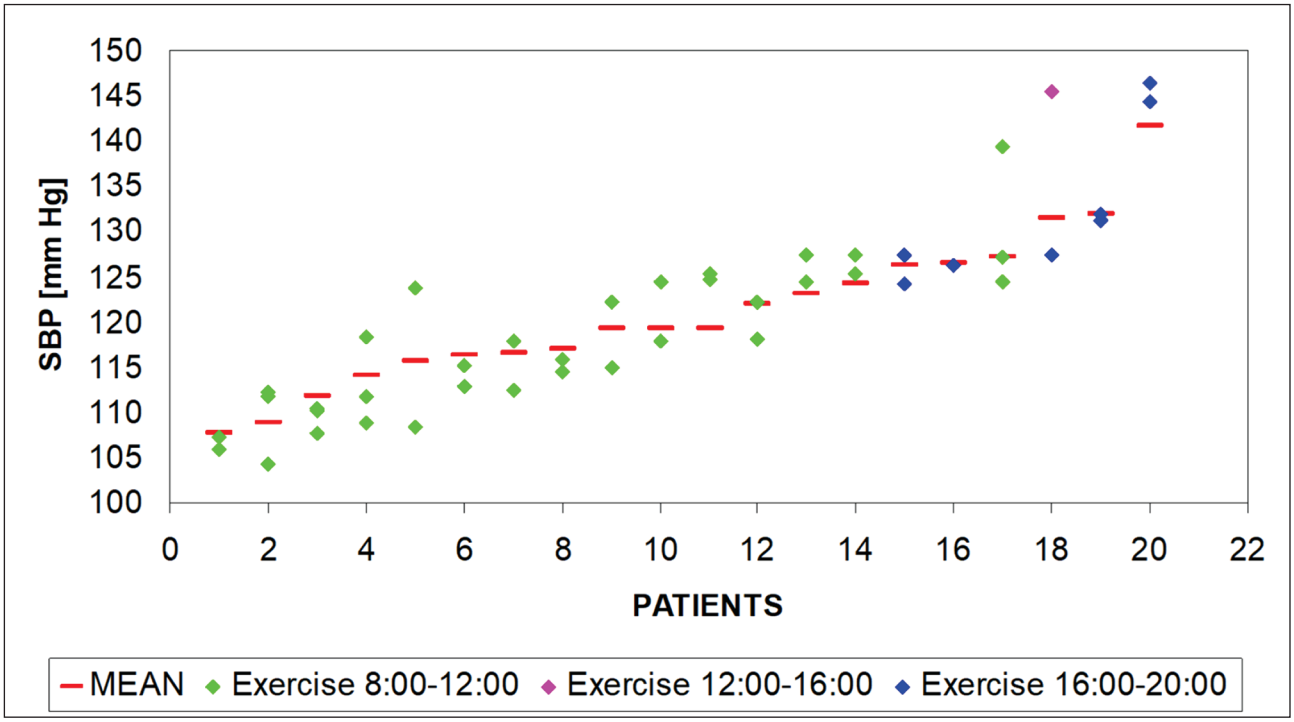

Figure 26: *The variability of 24-hour mean systolic blood pressure (points in color), and 7-day mean systolic blood pressure (red line) during combined exercise in 20 patients with coronary heart diseases.*

Conclusion

The first part of our studies showed that the exercise at 9 o´clock in the evening increases the Circadian Hyper-Amplitude Tension (CHAT). In the second study we also analyzed the timing of exercise in morning, noon and afternoon.

Our studies on healthy subjects and patients showed that the exercise in the daily time between 7:30 until 19:00 h does not evoke the Circadian Hyper-Amplitude Tension (CHAT) in healthy subjects and in patients.

From the results we can conclude that 24-hours blood pressure MESOR at rest and during exercise from day-to-day vary in healthy subjects as well as in patients with coronary heart disease IM were not different in the days with exercise and without exercise. The healthy subjects during different kinds of exercise activity get the similar results in 24 h blood pressure profiles in comparison with the days without exercise. On the basis of our results we recommend the 7-day blood pressure monitoring or home blood pressure monitoring. The education for long-lasting self-monitoring is the best approach for management of hypertension.

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Photo documentation of 3rd Symposium on Ayurveda, Yoga and Meditation: Integrative Health Prevention Approaches 2019, held in Medical University of Graz on 13.12.2019

Figure 27: *Assoz. Prof. Nandu Goswami, M.D., PD, MedUni Graz, Prof. Jarmila Siegelova, M.D., DrSc., Masaryk University, Brno*

Figure 28: *Prof. Jarmila Siegelova, M.D., DrSc., Masaryk University, Brno*

Figure 29: *Prof. Maxmilian Moser, M.D., PD, MedUni Graz, Brigitte Kenner, Graz, Prof. Jarmila Siegelova, M.D., DrSc., Masaryk University, Brno*

Efficacy and Safety of Intra-Dialytic Exercise Training in Hemodialysis Patients

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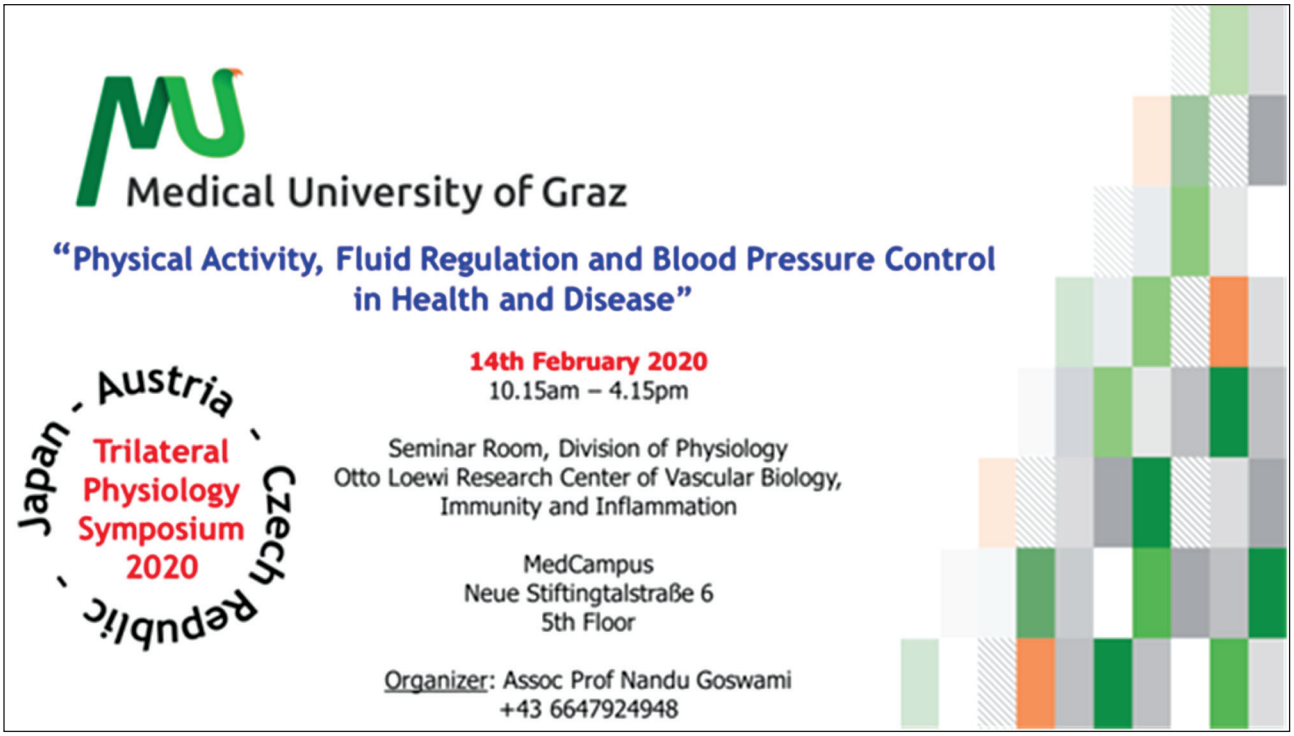

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Graz, 16.01.2020

Re: Official Invitation

This letter is to confirm that I, Assoc. Prof. Dr. Nandu Goswami, from the Otto Loewi Research Center, Division of Physiology, Medical University Graz, invite Prof. Petr Dobšák to Graz. He will visit our lab from 13. - 16.02.2020. The purpose of his visit is to give Prof. Dobšák an insight to our research methods and to discuss future cooperation possibilities.

Kind regards,

Assoz. Prof. PD Dr. med.
Nandu GOSWAMI
Lehrstuhl für Physiologie
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Assoc. Prof. Dr. Nandu Goswami

Introduction

End-stage Renal Disease (ESRD) affects 5%–10% of the world's population and with a ~6-7% growth continues to increase at a significantly higher rate (Fig. 1). Approximately 70-75% of patients with ESRD are undergoing dialysis treatment (hemodialysis or peritoneal dialysis) and around 25-30% lives with kidney transplants (1). Most dialysis patients can be allocated to three geographical regions: the United States, the EU and Japan, which together represent 40% of all dialysis patients (1). However, the dialysis patient population growth rate is much lower (1- 4%/year) in those countries than in other regions such as Asia, Latin America, the Middle East and Africa (8-9%/year). The prevalence of people treated for ESRD shows a high degree of variation across countries. In the EU, there is an average of 1.160 patients per million inhabitants (8.5% of the EU population suffers from diabetes and 90% of ESRD patients are over 65 years old). The countries with the highest prevalence are Portugal, Germany, Cyprus, Belgium and France. ESRD kills more people than breast od prostate cancer (1). Around 38.000.000 EU inhabitants have CKD stages 3 - 5, but most don´t know it because ESRD has no symptoms until the advanced stages. Regular ambulatory hemodialysis (HD) is the major treatment option for patients with end-stage renal disease (ESRD). Due to a high prevalence of chronic kidney disease, the numbers of HD patients are growing rapidly. Within the EU, last year 330.000 patients received a total of 50.000.000 dialysis treatments in 5.400 centers.

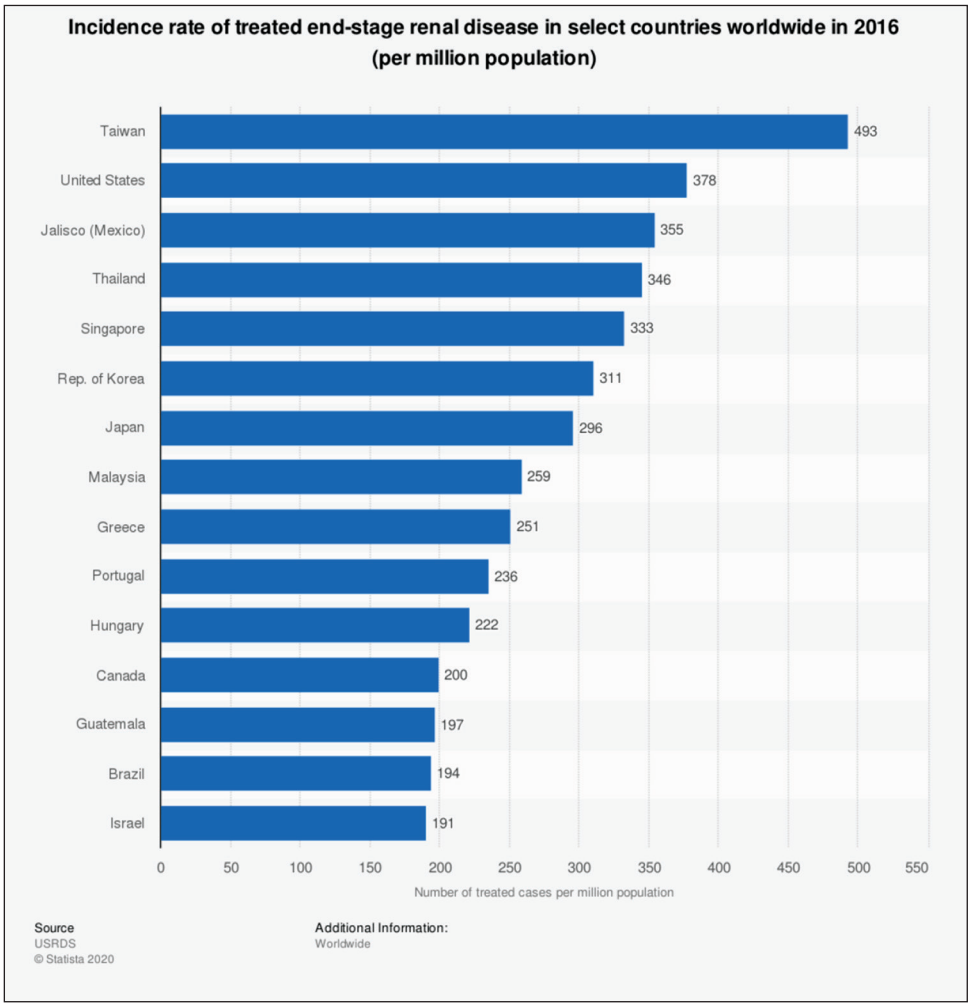

Figure 1: *Prevalence of treated ESRD in selected countries worldwide in 2016 per million population (1).*

In EU, out of 590.000 patients, 56% are on MD, 5% on peritoneal dialysis (PD) and 39% are living with kidney transplants. Transplantation is the most effective therapy; it is also the fastest growing of the three forms of treatment (+3% each year). Treatment of ESRD is quite expensive and costs tend to rise: dialysis alone costs 14.000.000 € per year to EU healthcare systems. Nowadays, the dialysis consumes 2% of healthcare budgets EU member-countries and the costs are expected to double in the next 5 years (1). The formidable development and investment in high-technology diagnostic and therapeutic procedures for patients with chronic kidney failure (CKD) in the past decades had increased the survival rate. Nevertheless, the overall mortality and quality of life of these patients is still not satisfactory enough. Dialysis patients are for long-term exposed to the negative impact of chronic disease that is systemic, progressive, incurable and further aggravated by sedentary lifestyle (2). The most typical pathologies in ESRD patients include low exercise endurance (VO_{2max}), poor physical condition, protein-energy malnutrition, inflammatory cachexia and uremic acidosis. Paradoxically, other side effects are related to the chronic treatment by hemodialysis 2-3 times weekly. During the HD procedure most of patients are in supine position for up to 4 hours, which brings further decondition. High level of fatigue and long-term tiredness are very frequent and unpleasant problems. Together, these factors result in a progressive downward spiral of deconditioning. In sum, the patients with ESRD are affected by renal failure itself, side effects of dialysis procedure and comorbidities worsening, which all contribute to very poor motivation to physical activity. Therefore, inactivity is right considered as the main cause of further progression of the disease, decreased aerometabolic capacity and skeletal muscle wasting. Thus, it is reasonable to encourage patients on HD or PD to increase their level of physical exercise. Intra-dialytic exercise is a common recommendation given to encourage patients to be physically active. The first studies about positive effects of exercise in patients with ESRD dates back to 70´s (3). Up to the present, exercise training has proven to be an immensely beneficial tool of improving health in patients with ESRD (Fig. 2), and dozens of published studies in the last two decades have clearly demonstrated the effectiveness of various forms of ID-RHB, especially in reducing fatigue, increasing physical fitness and overall quality of life (4, 5, 6, 7 and 8).

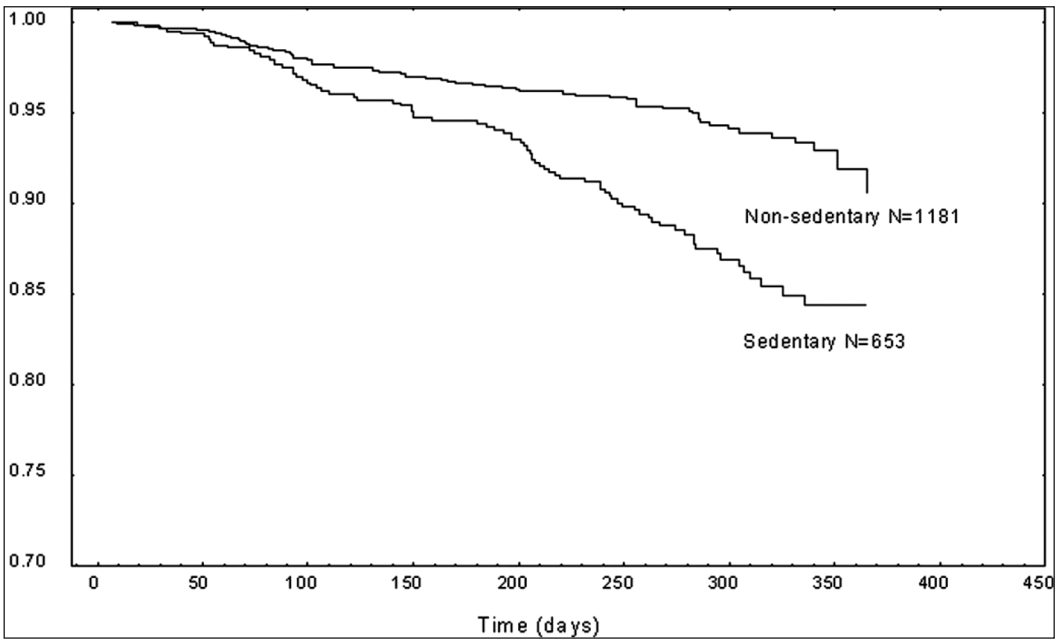

Figure 2: *Survival among sedentary and nonsedentary incident dialysis patients (Johansen KL, 2007).*

McAdams-Demarco et al. (2012) studied the survival in 143 maintenance HD patients stratified according to activity of daily living disability (Fig. 3). They demonstrated that ADL disability was independently associated with 3.37 times higher mortality (9).

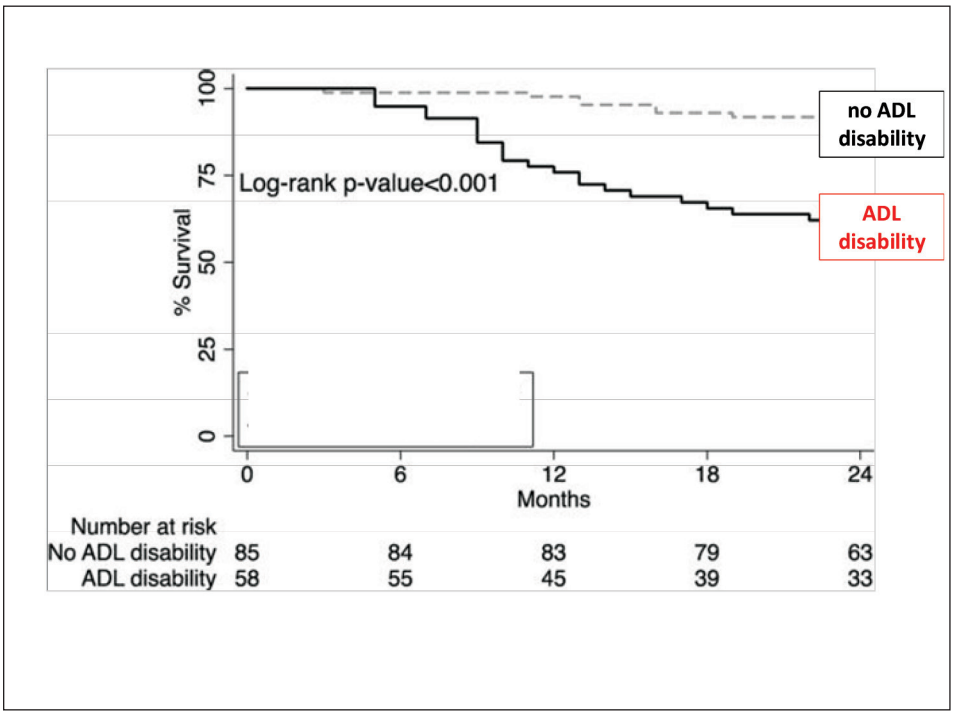

Figure 3: *ADL disability increases mortality in ESRD patients (9).*

Intra-dialytic (ID-RHB) program in St. Ann´s Faculty Hospital Brno

Since 2009 the Department of Sports Medicine and RHB in cooperation with 2nd Department of Internal Medicine (St. Ann´s Faculty Hospital in Brno) developed and started one of the first Czech projects of intra-dialytic rehabilitation (ID-RHB). Up to the present, there are no national (Czech) guidelines or recommendations concerning the design, prescription and realization of RHB programs for patients with ESRD (with or without dialysis). However, in the past 25 years, our team (physicians, physiotherapists, nurses) gained large experience with RHB programs for patients with cardiovascular diseases and the clinical application of new methods of exercise, such as neuro-muscular electrical stimulation (NMES) of large skeletal muscle groups in legs. Therefore, we applied our knowledge in this field to develop an intra-dialytic rehabilitation (ID-RHB) program. All the recruited patients participating in our project were on chronic HD or PD provided by the Dialysis Center, 2nd Department of Internal Medicine, St. Anne´s Faculty Hospital, Brno. All the studies realized were approved by local Ethics Committee and all included patients signed Informed Consent based on the "World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects" (updated in Fortaleza, Brazil 2013) and orders of GCP European community. Before inclusion in the ID-RHB program all the patients received an „Information Booklet". Basically, we used specific equipment that can be easily used in sitting or in supine position „bed-side ergometers" (MONARK® 881E Rehab Trainer; S). The selection of such devices was based on our firm conviction about the importance and effectiveness of endurance (aerobic) training in patients with chronic diseases, characterized by premature fatigue and large loss of the skeletal muscle mass (Fig.4).

Figure 4: *Training on bed-side ergometers*
(Dialysis Unit, II[nd] Department of Internal Medicine, St. Ann´s Faculty Hospital Brno).

Training on bed-side ergometers: training intensity was set at 60% of peak workload (W_{peak}) determined by bicycle ergometry. ID-RHB program lasted 20 weeks (time of active bicycling was 2 x 30 min). As a variant of ID-RHB training, the local neuro-muscular electrical stimulation (NMES), was also applied (Fig. 5). The NMES was done using dual-channel, battery powered (2 x 1.5V) stimulators REHAB X-2 (CEFAR®, S) or EPLHA 2000 (DANMETER® Co., DK) and self-adhesive electrodes PALS® Platinum 80 x 130 mm (Axelgaard, DK). The stimulated areas were the extensors of both legs and ID-RHB program with NMES lasted 20 weeks. Stimulation characteristics were set as follows: biphasic current, pulse width 400 μs, frequency modulation 40-60 Hz, working mode „on-off" (8s contraction - 12s relaxation) and maximal amplitude 60mA. Time-length of 1 NMES session was 60 min. Both methods (bicycling and NMES) were performed during HD procedure (usually between 2[nd] and 3[rd] hour of the HD procedure). Our study clearly showed that 20 weeks of given type of training results led to statistically significant improvement in physical performance, waste removal and quality of life (QoL). It was one of the first papers from Czech research team dealing with the ID-RHB exercise training (10).

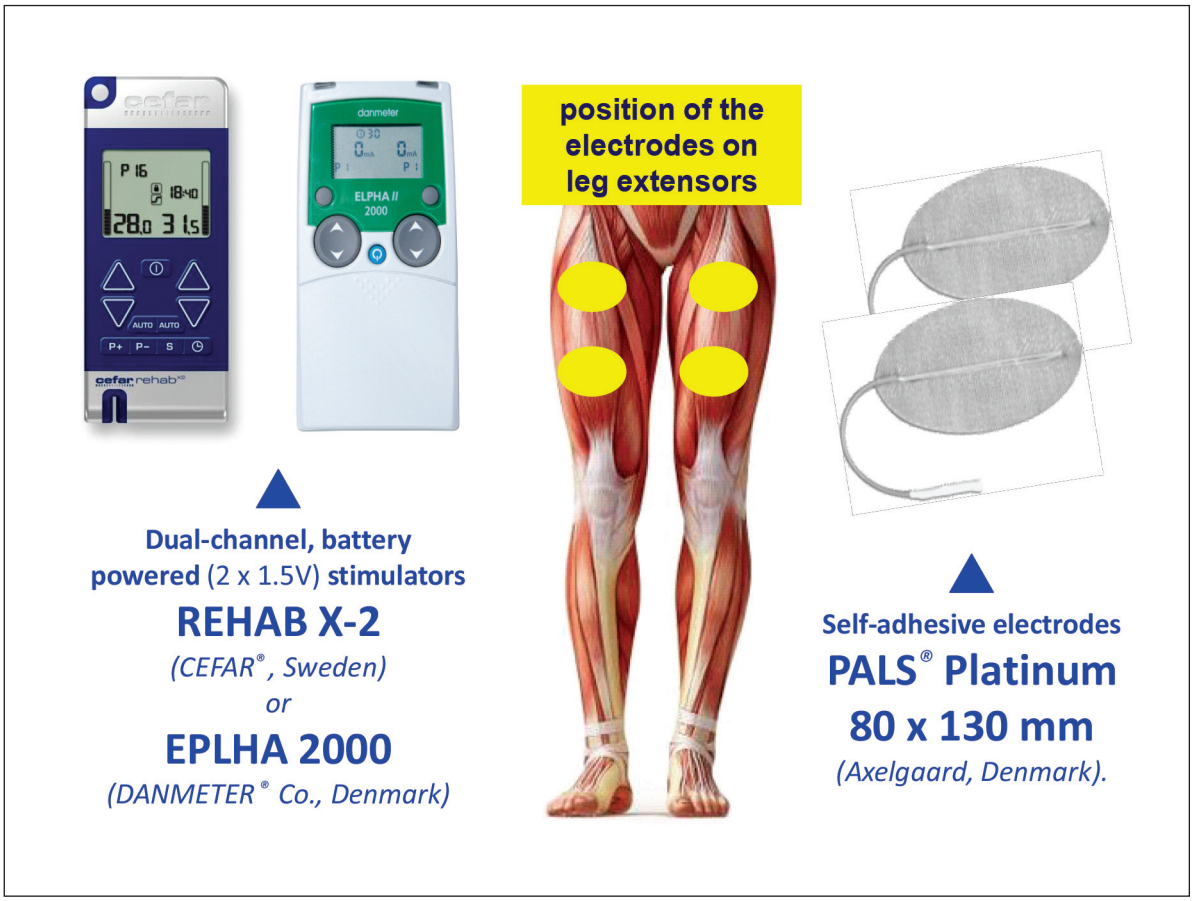

Figure 5: *Neuro-muscular electrical stimulation (NMES) as a variant of ID-RHB training*

In dialyzed patients, VO_{2peak} represents indisputable and exact indicator of health and also of RHB effectiveness (11 and 12). Low values of VO_{2peak} correlate strongly with increased mortality also in healthy population (13). Therefore, the next step in our ID-RHB program was the assessment of aerometabolic capacity (VO_{2peak}) in dialysis patients. In the past 6 years we conducted 3 separate clinical trials in HD and PD patients, using different types of exercise training. Special attention was paid to the assessment of aerometabolic capacity (also other parameters of functional performance and QoL). In the first study (2013-2014), a group of HD patients (n = 12; 5M, 7W; mean age 62.6 ± 13.1 yrs) performed NMES of leg extensors (60min), as a form of home-training (without participation in the ID-RHB ambulatory program). The NMES characteristics were set as follows: intermittent biphasic current, frequency modulation 40-60Hz, working mode "on-off,,, 2s ramp-up time, 8s period of contraction, 1s fall-down time, and 12s period of relaxation. After 20 weeks the mean value of VO_{2peak}/kg was increased, however without statistical significance (from 10.7 ± 2.9 to 12.9 ± 2.8 mlO_2/kg; NS). The second trial (2014-2015) involved 14 patients on PD (6M, 8W; mean age 61.9 ± 8.7 yrs). NMES of leg extensors was applied as home-based RHB training for 20 weeks. The NMES characteristics were the same as in the above mentioned trial. At the end of this home-based RHB program, the mean VO_{2peak}/kg was increased from 13.7 ± 3.0 to 15.9 ± 2.8 mlO_2/kg (Fig. 6), and this result was statistically significant (P = 0.003) (14).

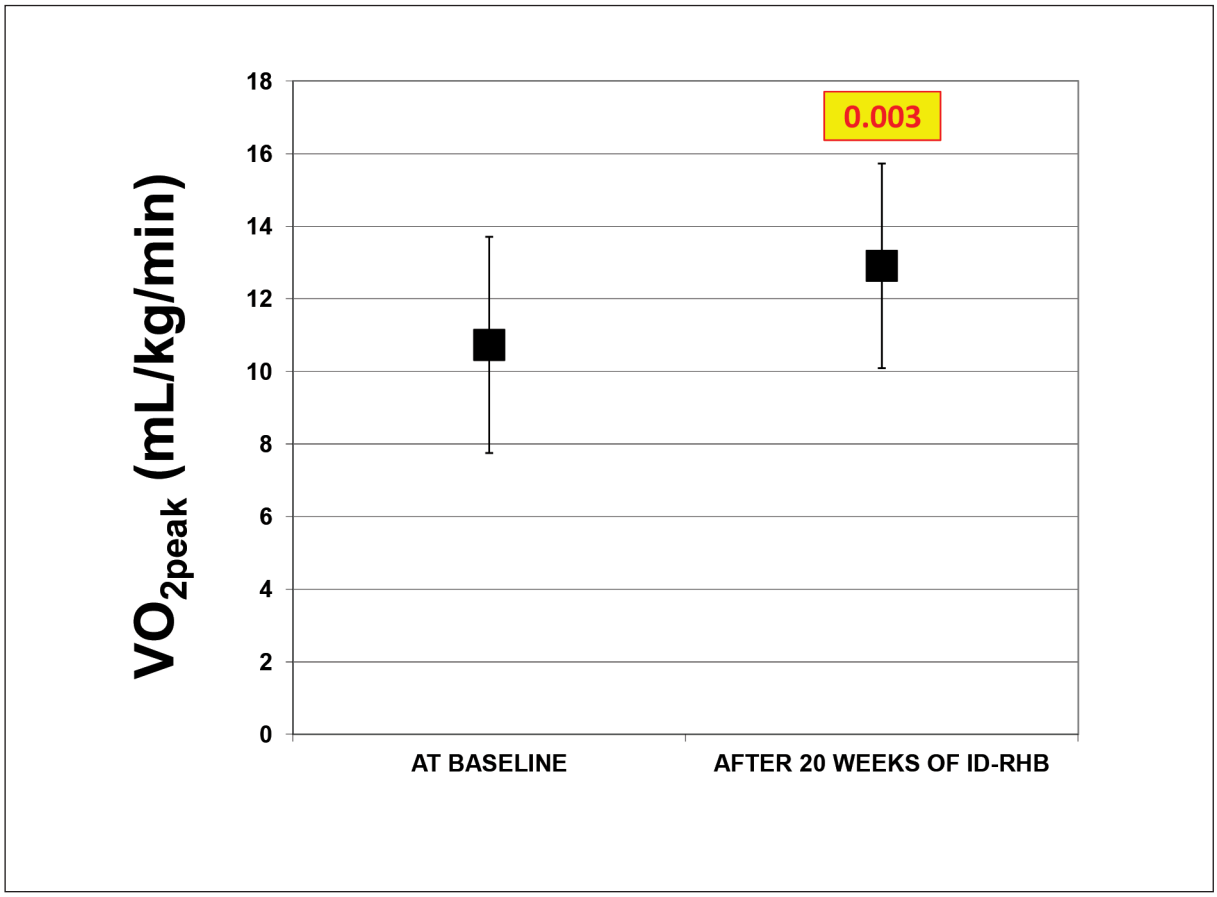

Figure 6: *At the end of ID-RHB program, the mean VO_{2peak}/kg was increased from 13.7 ± 3.0 to 15.9 ± 2.8 mlO_2/kg, and this result was statistically significant (P = 0.003)*.*

In the third study, we enrolled 22 HD patients (19M, 3W, mean age 50.2 ± 15.2 yrs) who participated in the ID-RHB program for 20 weeks using programmable bed-side bicycle ergometers letto2 (MOTOmed®, RECK Co., Germany). This device has easy setting, high safety standards and is equipped with special software enabling passive, assisted and active cycling. Time of 1 training unit was 54 min and consisted of: initial stretching of leg muscles before connecting to dialyzer (5 min), releasing exercise of leg muscles (5 min), passive cycling on ergometer (1 min forward + 1 min backward), active aerobic training on ergometer (30 min), passive cycling on ergometer (1 min forward + 1 min backward), releasing exercise of leg muscles (5 min) and terminal stretching of leg muscles after disconnection to dialyzer (5 min). After 20 weeks of ID-RHB program (Fig. 7), statistical analysis showed a significant improvement of VO_{2peak}/kg (from 17.2 ± 5.5 to 18.9 ± 4.7 mlO_2/kg; P = 0.002).

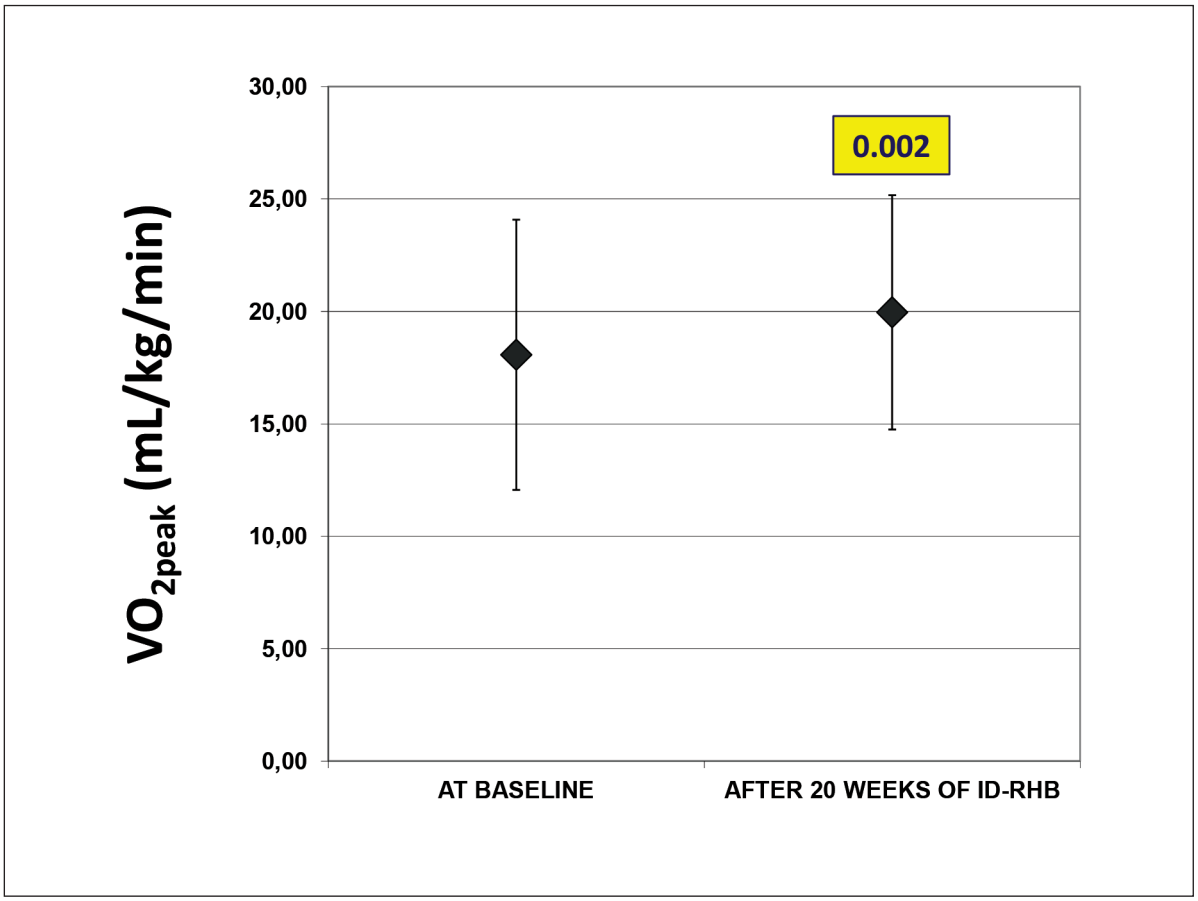

Figure 7: *After 20 weeks of ID-RHB program, statistical analysis showed a significant improvement of VO_{2peak}/kg (from 17.2 ± 5.5 to 18.9 ± 4.7 mlO_2/kg; P = 0.002).*

Discussion

Adequate dialysis is associated with reduced mortality. Because cardiovascular complications and fatigue are common in patients with ESRD, patients on HD usually have poor exercise capacity and are less physically active, which have been identified as independent risk factors of mortality (15). Indeed, better exercise capacity is related to lower risk of death (16 and 17). In other words - the longer the duration of exercise, the more prominent improvement is expected in VO_{2peak}. There are reports suggesting that for every one MET increase in VO_{2peak}, there will be 12% and 17% decrease in the mortality of male and female patients, respectively (18 and 19). Sietsema et al. (2004) studied the influence of the baseline value of VO_{2peak} on the survival in 175 ambulatory patients with ESRD. He showed that patients with peak VO_2 above the median value of 17.5 mL/min/kg had significantly better survival than those with lower values (20). A meta-analysis by Yang et al (2017) reported the effects of exercise on cardiopulmonary functions in ESRD patients; in total, five eligible studies were analyzed, involving 179 ESRD patients (21). The authors concluded that exercise plays an important role in improving the $VO_{2\ peak}$ values in these patients (21). Their conclusion is in full concordance with our 10-years experiences with ID exercise. At first, nor in a single case, the deterioration in the health status of ESRD patients was not a direct consequence of ID exercise. Second, from our point of view, the ID-RHB training is much safer for the patient than the actual hemodialysis process itself. Although ID-RHB has been reported to increase patient compliance some conflicting data have been

reported regarding the effects of ID exercise. However, it should be emphasized that patients with CKD represent a relatively high-risk population, endangered mainly by cardiovascular complications (arrhythmias, acute heart attacks, etc.). Thus, safety concerns may arise since unexpected injury may occur during exercise. A recent large meta-analysis by Pu et al. (2017) comprehensively evaluated the safety of ID exercise, as well as its effects and clinical outcomes by analyzing the existing literature (22). Their initial search yielded a total of 1389 records, among which, 27 studies only involving 1215 patients were relevant to the systematic review (22). Of these 27 studies, free were three-arm study with comparison of no exercise, resistance exercise and aerobic exercise. In total, the mentioned 27 trials collected and analyzed the results in 1215 subjects, among which, 723 were male and 492 were female. The average age was 53 yrs. There were 16 studies that focused on aerobic exercise, 4 on resistance exercise and 7 on a combination of aerobic and resistance exercises. The detailed exercise protocols varied among studies. The follow-up duration ranged from 8 to 48 weeks. Only two studies reported adverse events related to intra-dialytic exercise (23 and 24). Thirteen studies claimed that no adverse events were observed, while 12 did not mention adverse events. Two cases of hypotension (one in the intradialytic exercise group and the other in the control group) were reported in one study (22). Exercise-related limb pain and minor injury were found in four cases. Similar issues have been addressed by others before. Chung et al. (2017) conducted a meta-analysis containing 17 RCTs with 651 patients (25). They found that intra-dialytic exercise could ameliorate depression, and improve quality of life, hemoglobin (Hb) levels and peak VO_2 among these patients. Sheng et al. (2014) included 24 studies with 997 patients for meta-analysis and found that ID exercise could improve Kt/V, VO_{2peak}, quality of life and blood pressure; but the results of physical performance (6-minute corridor walk test) and Hb were contrary to Chung et al. (26). In sum, the large meta-analysis by Pu et al. (2017) concluded intra-dialytic exercise could improve Kt/V, exercise capacity, depression and quality of life as well as lower blood pressure among dialyzed patients (22). In other words - intra-dialytic exercise might not increase the incidence of adverse events.

Conclusion

In conclusion, all our clinical studies to date support the already published positive experiences on the benefits of ID-RHB training, which improves functional capacity and quality of life in hemodialyzed patients with CKD. These functional adaptations probably consist in multiple and not full elucidated adaptations of cardiovascular functions, skeletal muscles and central hemodynamic mechanisms. Thus, future studies should focus on clarifying all the mechanisms involved in functional adaptations to exercise (training), in order to determine the optimal intensity, type and volume of exercise in this highly vulnerable population.

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Acknowledgement

The foundation and development of our own ID-RHB program was substantially influenced by Professor Masahiro Kohzuki, M.D., Ph.D., and his research team from the Tohoku University Hospital in Sendai (Japan). *In 2012, Professor M. Kohzuki published a unique book („Renal Rehabilitation"; Ishiyaku Publishers, Inc., 2012), dedicated to the rehabilitation in patients with CKD (as first in Japan, and also as first in the World).*

Kohzuki M.: „Renal Rehabilitation“.

Ishiyaku Publishers, Inc., ***2012.***

First book in Japan, *and* ***first in the World*** ***!***

Night-to-Day Blood Pressure Ratio during Seven-Day Ambulatory Blood Pressure Monitoring

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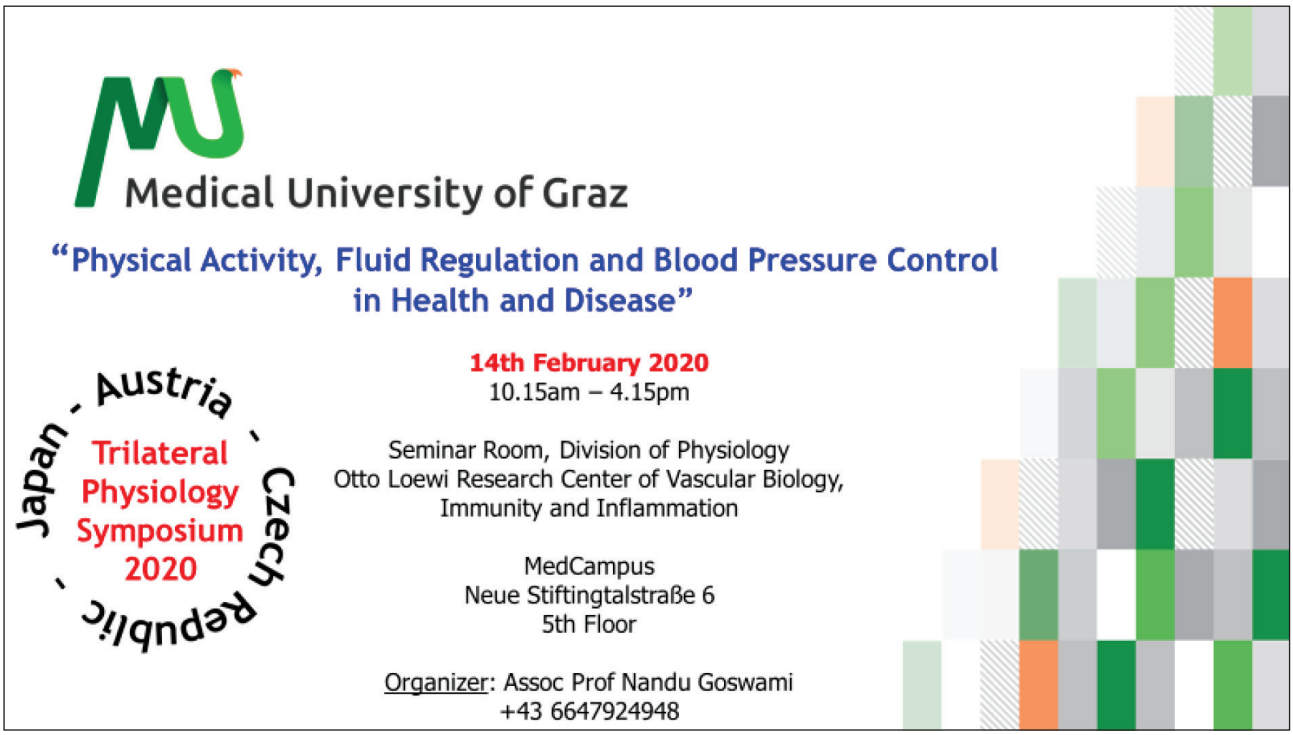

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Graz, 16.01.2020

Re: Official Invitation

This letter is to confirm that I, Assoc. Prof. Dr. Nandu Goswami, from the Otto Loewi Research Center, Division of Physiology, Medical University Graz, invite Prof. Jarmila Siegelová to Graz. She will visit our lab from 13. - 16.02.2020. The purpose of her visit is to give Prof. Siegelová an insight to our research methods and to discuss future cooperation possibilities.

Kind regards,

Assoz. Prof. PD Dr. med.
Nandu GOSWAMI
Lehrstuhl für Physiologie
Otto-Loewi-Forschungszentrum
Medizinische Universität Graz
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Assoc. Prof. Dr. Nandu Goswami

Introduction

Franz Halberg and Germaine Cornelissen, using ambulatory blood pressure monitoring showed the need to account day-to-day changes of blood pressure and heart rate and the necessity to circadian assessment of the hour-to-hour variability in cardiovascular parameters. The Chronobiology center of Minnesota started with the international project BIOCOS with seven day/24 hours blood pressure monitoring in Japan, Urausu, Hokkaido by Kuniaki Otsuka, In Department of functional diagnostics and rehabilitation (Dept. of Sports Medicine and Rehabilitation) St. Anna Teaching Hospital, Masaryk University, Brno, Czech Republic under the guidance of Jarmila Siegelova, in Moradabad, India, under the guidance of RB Sing, and others from Belgium, Italy, Mexico, Norway, Armenia, China as well as California and Minnesota, USA (1, 2).

Chronobiology, studied by Franz Halberg, started in 1947 in University of Minnesota, USA. Brno scientific meetings and congresses in Masaryk University, organized by us, included the studies in the period from 1990 and summarized all knowledge of chronobiology not only from the participants in Brno, but also other scientists all over the world with whom the main personalities Professor Halberg, Professor Cornelissen and Professor Kenner, published results. Brno Concensus in 2008 summarized chronobiologically interpreted blood pressure and heart rate monitoring under the leading personality of Prof. Franz Halberg which detects prehypertension, prediabetes and a premetabolic syndrome in vascular variability disorders, that interact with a reliably diagnosed as MESOR hypertension that can carry a risk greater than a high blood pressure alone and that can coexist to form vascular variability syndromes, unrecognized in a conventional health care, but some of them already treatable.

Figure 1: *Brno Consensus Proclamation 2008: Professor Bohumil Fiser, As. Professor Michal Pohanka, Professor Thomas Kenner, Brigitte Kenner, Dr. Othild Schwartzkopff, Professor Franz Halberg, Dr. Jiri Dusek, Professor Jarmila Siegelova, Brno Congress Noninvasive Methods in Cardiology 2008 (Brno Consensus)*

From 1988, when O`Brien and colleagues reported that an abnormal circadian blood pressure profile with a less marked decrease in night-time blood pressure led to an increased risk for stroke, the clinical significance of night-to-day blood pressure ratio is known (3). Subsequent studies confirmed the prognostic significance of night-to-day blood pressure ratio for the prediction of a higher rate of cardiovascular complications (4-10). One of large-scale studies based on International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes was published in 2007 (11). The investigators did 24-hour blood pressure monitoring in 7458 people (mean age 56.8 years) from Denmark, Belgium, Japan, Sweden, Uruguay and China. Median follow-up was 9.6 years. They found that night-to-day ratio of systolic and diastolic blood pressure adjusted for cohort, sex, age, body-mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, and antihypertensive drug treatment predicted total mortality, non-cardiovascular mortality and cardiovascular mortality. In fully adjusted models night-to-day ratio was additionally adjusted for 24-hour blood pressure. The results for fully adjusted night-to-day ratio were similar except systolic blood pressure and cardiovascular mortality where the hazard ratio 1.08 (0.99- 1.17) was not statistically significant. After the patients were, according the night-to-day ratio, divided in 4 categories with night-to-day ratio >1.0 (reverse dippers), 0.9-1.0 (non-dippers), 0.9-0.8 (dippers) and <0.8 (ultra-dippers), the total mortality was increased in non-dippers and reverse-dippers in comparison to dippers.

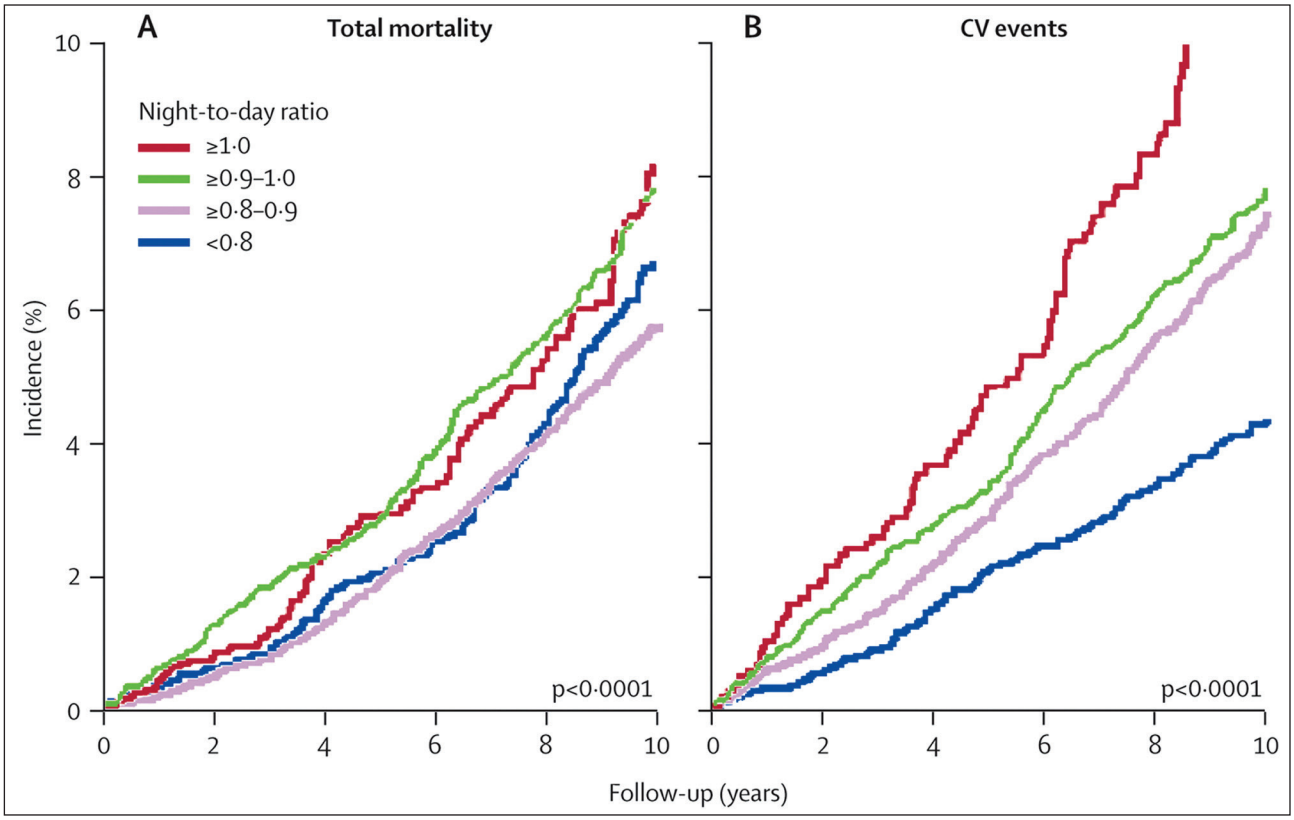

Figure 2: *IDACO 2007 (E O'Brien, J Sheridan and K O'Malley, Dippers and non-dippers, Lancet* **332** *(1988), p.397)*

Cardiovascular mortality was significantly increased in reverse dippers, as well as incidence of all cardiovascular events.

Although the prognostic significance of night-to-day blood pressure ratio was proved in a large group of patients, the clinical significance of this value depends on variation of repeated measurement in individual patients.

In the year 2010 we evaluated the night-to-day blood pressure variability during 7 days/ 24 hour of ambulatory blood pressure measurement in the healthy subjects and we found great variability in night-to -day ratio in systolic and diastolic blood pressure in the same person in repeated 24-hour blood pressure monitoring (12). The study was aimed to evaluating night to day blood pressure ratio in the days with exercise and compared it with the days without exercise during 7day/24hour ambulatory blood pressure monitoring in patients with ischemic heart disease.

Methods

Thirty healthy subjects (18 males, 12 females), 21 years to 73 years old, were recruited for seven-day blood pressure monitoring. TM 2421 A D Instruments (Japan) were used for ambulatory blood pressure monitoring (oscillation method, 30-minute interval between measurements). One-hour means of systolic and diastolic blood pressure were evaluated, when night-time was considered from midnight to 06:00 h and day time from 10:00 to 22:00 h, avoiding the transitional periods. Mean day-time and mean night-time systolic and diastolic pressures were evaluated every day.

Another group of thirty one patients with ischemic heart disease (all males), forty nine years to eighty four years old, were recruited for seven-day blood pressure monitoring. TM 2421 A D Instruments (Japan) were used for ambulatory blood pressure monitoring (oscillation method, 30minute interval between measurements) (13). The patients were monitored 7 days/ 24 h in the days with exercise and without exercise. One-hour means of systolic and diastolic blood pressure were evaluated, when night-time was considered from midnight to 06:00 h and day time from 10:00 to 22:00 h, avoiding the transitional periods. Mean day-time and mean night-time systolic and diastolic pressures were evaluated every day (14).

Dipper status was evaluated every day. Dippers were defined as those individuals with a 10-20 % fall in nocturnal blood pressure. Non-dipping was defined as a less than 10 % nocturnal fall, and those with no fall in blood pressure were defined as reverse-dippers (15).

The patients underwent phase II of cardiovascular rehabilitation in the Dept. of Sports Medicine and Rehabilitation two times a week, controlled ambulatory rehabilitation program, which was composed of aerobic and resistant training, three times a week, lasting three months.

Results

The subjects were classified as above mean 7-day SBP (subject No 1: 107 mmHg, subject No 30: 131 mmHg; median value: 123 mmHg).

Variability of night-to-day ratio during 7-day monitoring is seen in following slides.

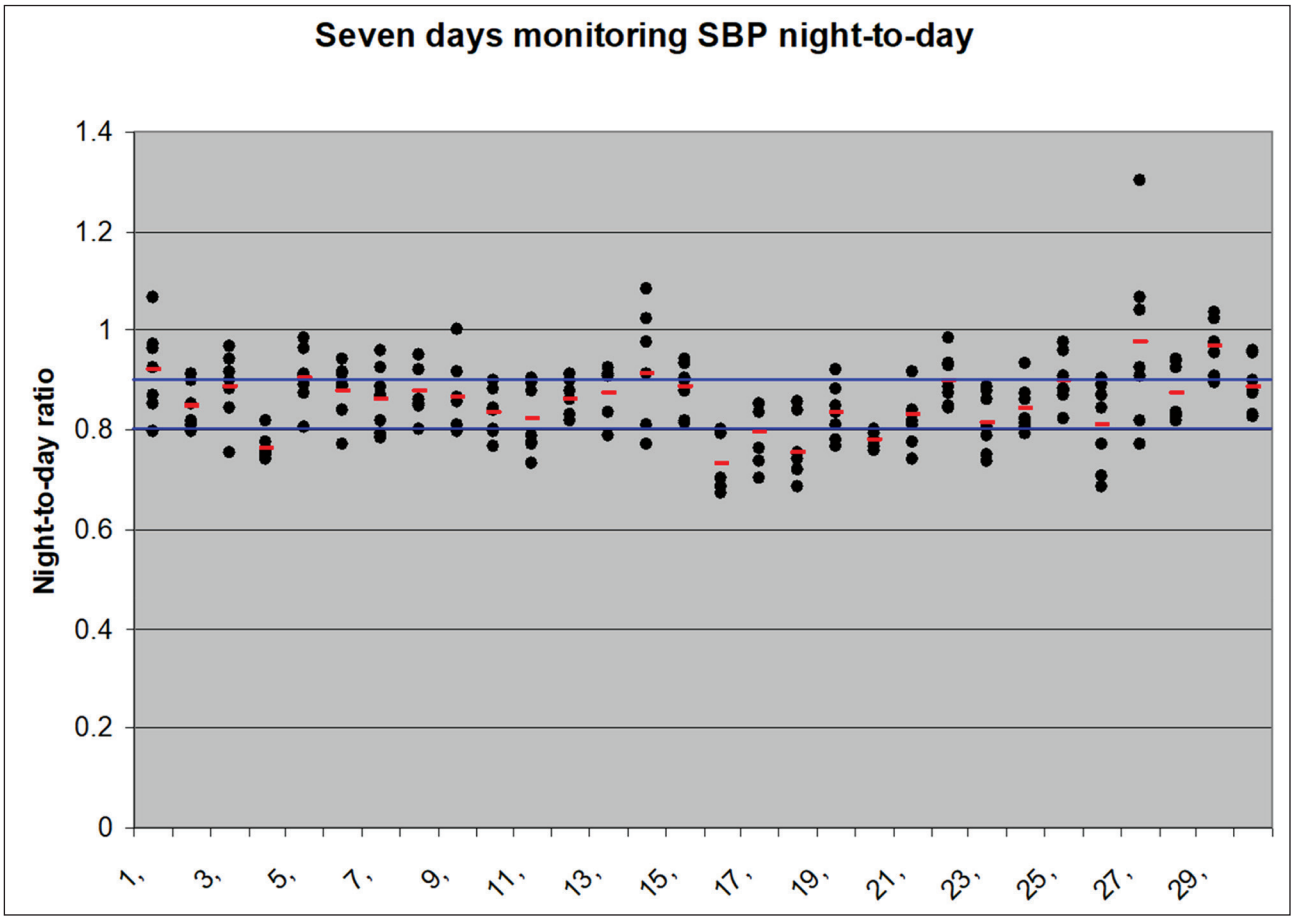

Figure 3: *Variability of night-to day ratio of systolic blood pressure evaluated from 7-day/24 h ambulatory blood pressure monitoring in healthy subjects at rest*

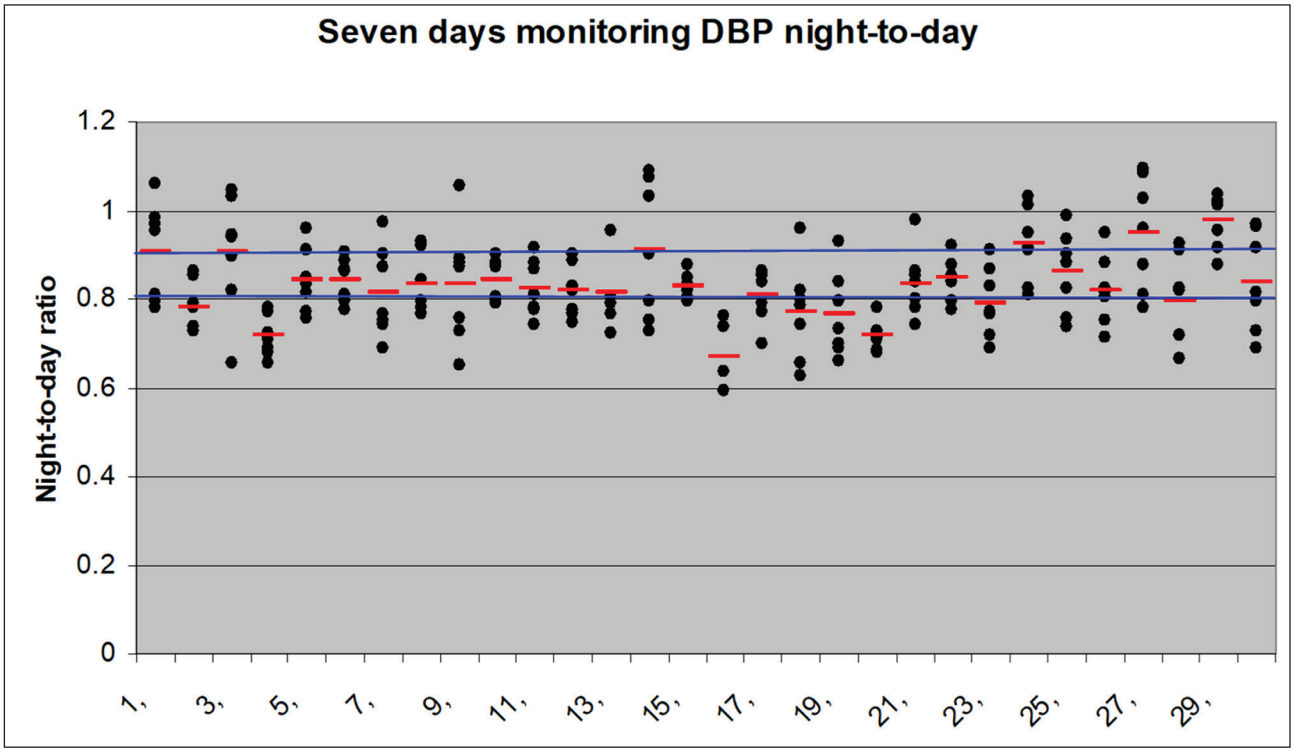

Figure 4: *Variability of night-to day ratio of diastolic blood pressure evaluated from 7day/24 h ambulatory blood pressure monitoring in healthy subjects at rest*

In the group of healthy subjects, only 4 subjects (13 %) were found which could be classified as SBP dippers or ultra-dippers every day. Most of the subjects were classified on various days differently, even 8 subjects (27 %) were one day classified as ultra-dippers and the other day as reverse-dippers.

No healthy subject classified as DBP dipper or ultra-dipper every day was found. Four subjects (13 %) were one day classified as ultra-dippers and the other day as reverse-dippers.

The day-to-day variability of night-to-day ratio is large in the group of healthy subjects. The dipping status classification in individual patient is not reliable.

Variability of night-to-day ratio during 7-day/24 h monitoring in 31 patients with ischemic heart disease in the days without exercise is seen in Fig. 5 for SBP and in the days with exercise in Fig .6 for SBP.

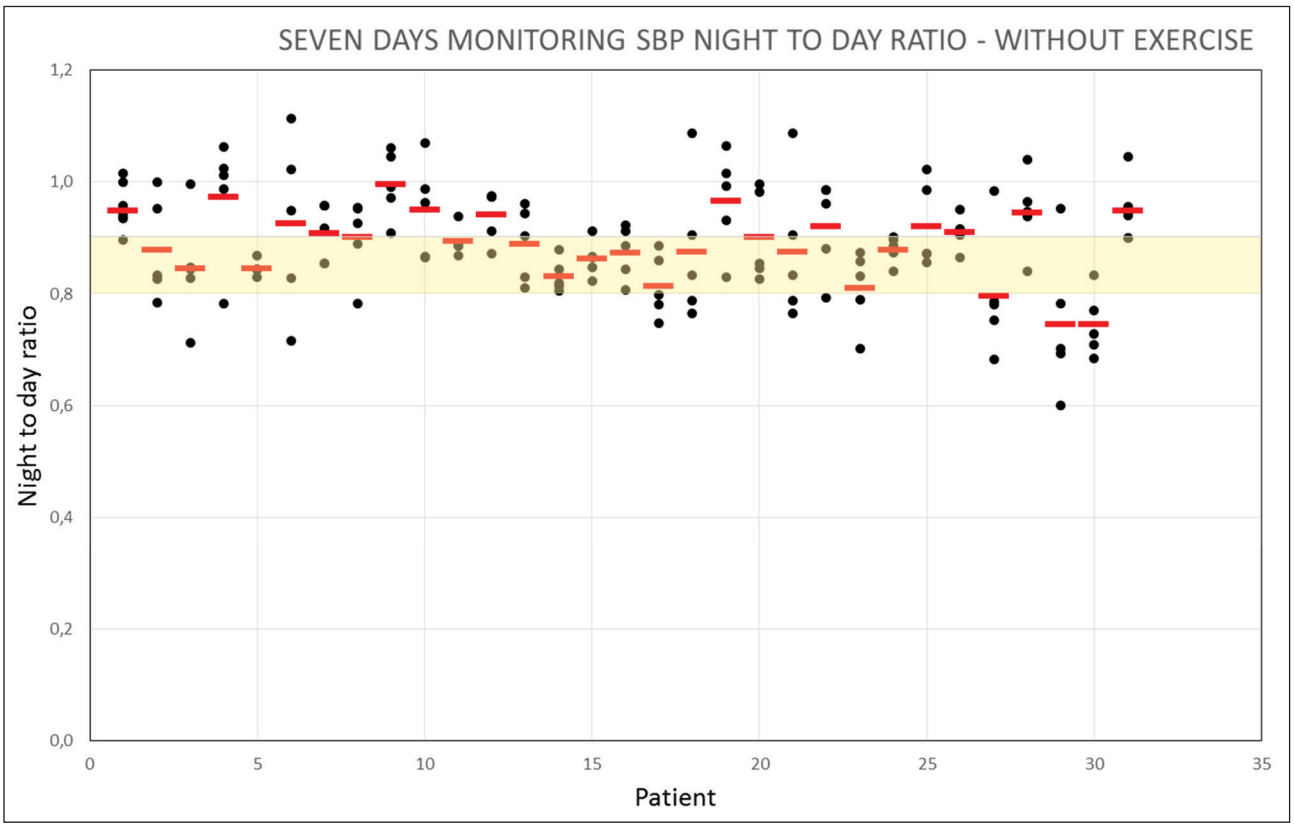

Figure 5: *Variability of night-to-day ratio of SBP evaluated from 7day/24 h ambulatory blood pressure monitoring in patients with ichemic heart disease in the days without exercise*

In the days without exercise, the dipping of night-to-day ratio of SBP was found only in 3 subjects (10 %), which could be classified as SBP dippers or ultra-dippers every day. Most of the subjects were classified on various days differently, even 3 subjects (10 %) were one day classified as ultra-dippers and the other day as reverse-dippers.

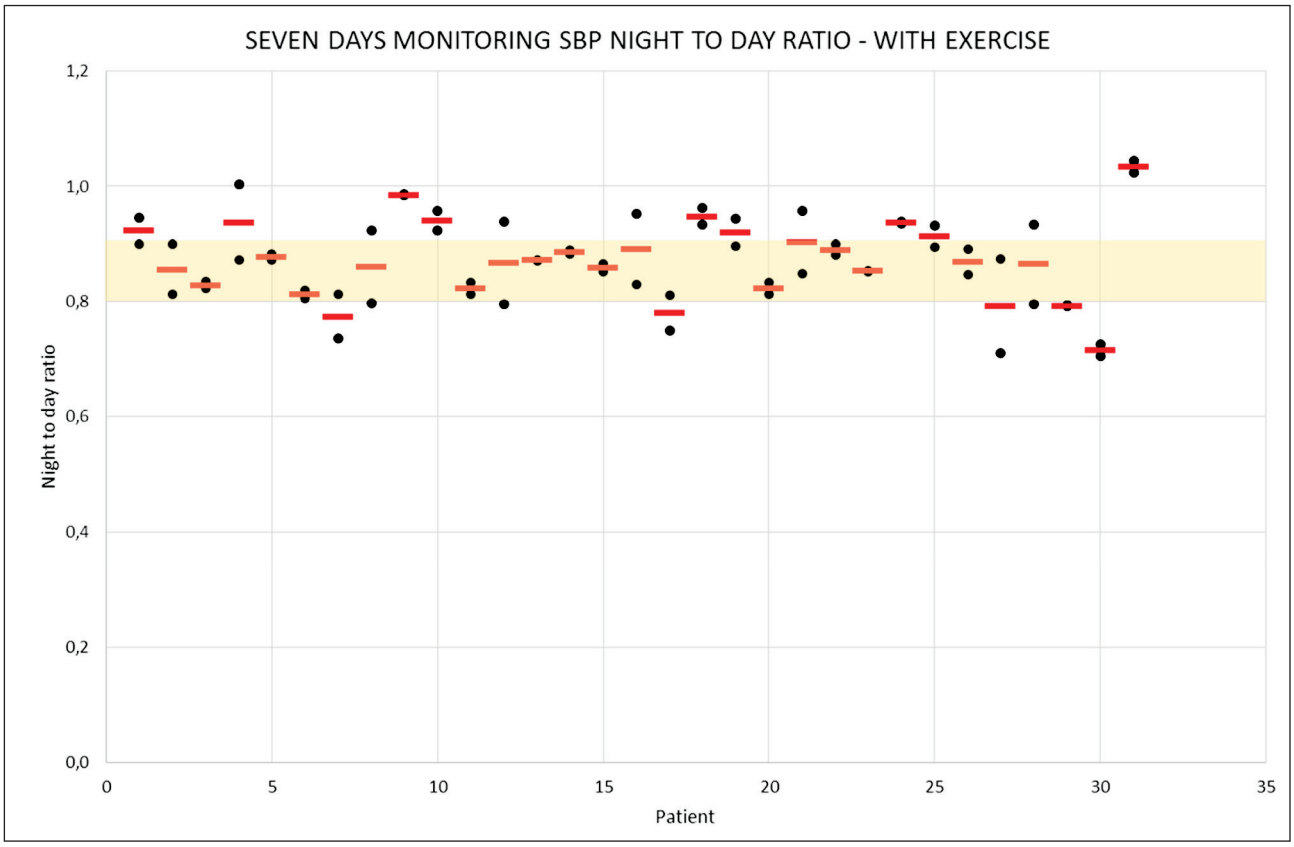

Figure 6: *Variability of night-to-day ratio evaluated from SBP from 7day /24 h ambulatory blood pressure monitoring in patients with ichemic heart disease in the days with exercise*

In the days with exercise in SBP only 4 subjects (13 %) were found which could be classified as SBP dippers or ultra-dippers every day. Most of the subjects were classified on various days differently, even 3 subjects (10 %) were one day classified as ultra-dippers and the other day as reverse-dippers.

Variability of night-to-day ratio during 7-day/24 h monitoring in 31 patients in cardiovascular rehabilitation in the days without exercise is seen in Fig.7 for DBP and in the days with exercise in Fig. 8 for DBP.

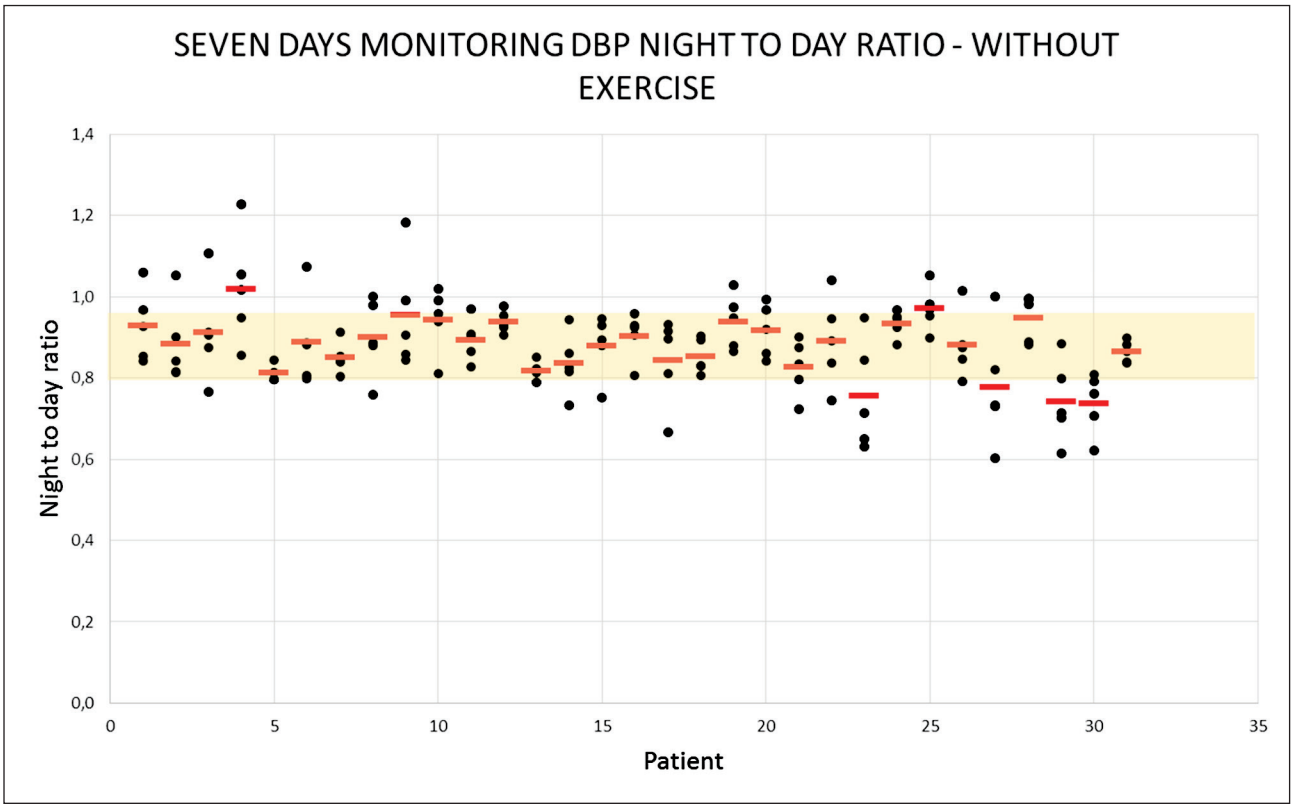

Figure 7: *Variability of night-to-day ratio evaluated from DBP from 7day /24 h ambulatory blood pressure monitoring in patients with ichemic heart disease in the days without exercise*

In the days without exercise (Fig.7) similarly no subjects were classified as DBP dipper or ultra-dipper every day. Two subjects (7 %) were classified as DBP dippers, others were classified one day as ultra-dippers and the other day as reverse-dippers.

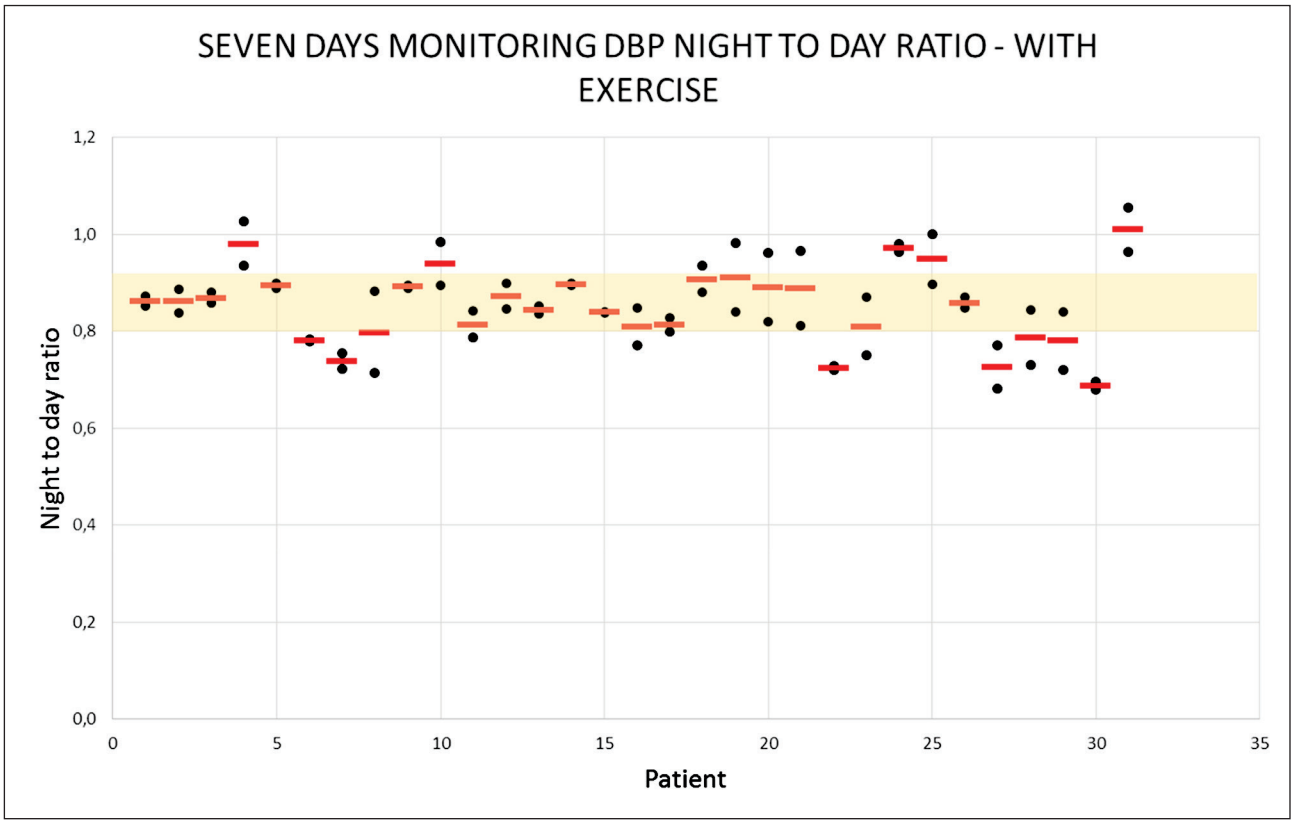

Figure 8: *Variability of night-to-day ratio evaluated from DBP from 7-day /24 h ambulatory blood pressure monitoring in patients with ichemic heart disease in the days with exercise*

In the days with exercise (Fig. 8), similarly no subject was classified as DBP dipper or ultra-dipper every day. Night subjects (27 %) were classified as DBP dippers, others were one day classified as ultra-dippers and the other day as reverse-dippers.

Our finding of large night-day ratio variability in individual subjects corresponds to the results of other studies. The night-to-day blood pressure ratio is subject to regression-to-the mean (16). In our studies with 7 day/24 h blood pressure monitoring in subjects with resting condition and the presented results in patients with ischemic heart disease in the days without exercise and in the days with exercise showed also large individual variability of night-to-day blood pressure ratio.

Dipping status has also a low reproducibility, with up to 40 % of individuals from Europe (17) and Asia (18) changing status between repeat recordings.

In our former study we demonstrated that the relation between night-to-day ratio and risk of cardiovascular events is not linear as it is in the case of mean 24-hour systolic and diastolic pressure (19). We observed at low circadian double amplitude which roughly corresponds to the difference between night and day blood pressure (5 mmHg of systolic and 4 mmHg of diastolic pressure) about 30 % higher incidence of cardiovascular events than at circadian double amplitude of 15 to 35 mmHg systolic and of 12 to 20 mmHg diastolic pressure but at double amplitude higher than 35 mmHg in systolic and 28 mmHg in diastolic pressure the incidence was double. This indicates the existence of overswinging or Circadian Hyper-Amplitude-Tension (CHAT) syndrome which is associated with a large increase in cardiovascular disease risk. The incidence of ultra-dipping is more frequent that the incidence of CHAT but existence of CHAT alone can lead to misdiagnosis of risk based on night-to-day blood pressure ratio (20 – 23).

In conclusion, despite the low night-to-day ratio of blood pressure predicted increased risk for cardiovascular events in large studies, the determination of this value is useless for management of arterial hypertension in individual patients.

Conclusion

Despite the low night-to-day ratio of blood pressure predicted increased risk for cardiovascular events in large studies, the determination during seven day/24 h ambulatory blood pressure monitoring showed large variability in healthy subjects and all patients in different consecutive days of monitoring.

The exercise program in cardiovascular rehabilitation does not influence variability of night-to-day ratio of blood pressure.

The day-to-day variability of night-to-day ratio is large. The dipping status classification in individual patients is not reliable.

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Figure 9: *Ao. Univ.-Prof.Mag. Dr. rer.nat. Andreass Rössler, Prof. Nandu Goswami, M.D., MedUni Graz, Prof. Masahiro Kohzuki, Tohoku University, Japan*

Figure 10: *Prof. Masahiro Kohzuki, M.D., Tohoku University, Japan, Prof. Dieter Platzer, PD and Prof. Daniel Schneditz, MedUni Graz, Prof. J. Siegelova, M.D., DrSc.*

Figure 11: *Assoc. Prof. Nandu Goswami, M.D., PD and Bianca Brix, MCS, MedUni Graz, Prof. Petr Dobsak, M.D., CSc., Masaryk University, Brno*

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Figure 13: *Prof. Dieter Platzer, PD and Prof. Daniel Schneditz, MedUni Graz, Prof. Jarmila Siegelova, M.D., DrSc. Masaryk University, Brno, Prof. Masahiro Kohzuki, M.D., Tohoku University, Japan*

Non-Invasive Methods in Experimental Cardiology – Benefits and Drawbacks

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Introduction

During the last 15 years, due to technological development and also due to an effort of researchers to refine animal experiments, many devices for non-invasive measurement of cardiovascular parameters were introduced to the market. This article is aimed to revise the most used techniques for blood pressure measurement, ECG recording and cardiac imaging in small animals (e.g. rodents) and to summarise their main benefits and limitations.

Non-invasive measurement of arterial blood pressure

In animals, the most commonly used non-invasive method for blood pressure monitoring is the cuff technique. The cuff is placed on a tail or limb of an animal and blood pressure is measured by determining the cuff pressure at which changes in blood flow occur during occlusion or release of the cuff. Several methods have been used for sensing the change in blood flow, such as: (a) photoelectric sensors, (b) oscillometric sensors, (c) Doppler sensors, (d) volume sensors, and (e) acoustic sensors.[1] Although some development in sensor technology has occurred, all of these methods share certain benefits and limitations – regardless of the type of sensor used.

The non-invasive methods of blood pressure measurement used in animal models and in clinical practice share the same benefits and limitations. Generally, non-invasive methods are considered to have four main benefits.[2] First, they are non-invasive and do not require surgery. Secondly, they can be used to obtain repeated measurements of blood pressure in conscious animals during studies of short or long duration. Thirdly, they usually require less expensive equipment than some direct methods (e.g. telemetry) and are also less expensive to operate. And last but not least, they can be used to screen for systolic hypertension or substantial differences in blood pressure among large numbers of animals. Thus, indirect methods should be considered when an investigator wishes to non-invasively detect substantial differences in blood pressure between groups, or substantial changes in blood pressure over a time, particularly when dealing with large numbers of animals. For example, tail-cuff methods can be useful and cost-effective for large-scale, high-throughput cardiovascular phenotyping.

However, non-invasive methods of blood pressure measurement have three main disadvantages that markedly limit their use in experimental studies. First, non-invasive methods only measure blood pressure in a very small sample of cardiac cycles. Because variability of blood pressure is generally quite large, the relatively small number of measurements typically obtained with a non-invasive method does not reflect an animal's exact average blood pressure. This problem significantly limits the value of non-invasive blood pressure methods, regardless of how accurate such methods are in measurement during an individual cardiac cycle.

Second, despite the non-invasive nature of the methods and well-intended efforts by researcher to train and acclimatize animals to undergo the procedures, tail-cuff methods in rodents impose substantial amounts of thermal and restraint stress that are known to affect blood pressure, heart rate and stress hormones.[3,4] Moreover, the assumption that all experimental groups within a given study would be expected to demonstrate similar quantitative responses to restraint stress may also not be valid.[1] Tail-cuff measurements are also commonly performed during the day, which disrupts rodent sleep cycles. Although it has been recommended to train animals for up to 14 days before tail-cuff measurements, positive effect of such training is disputable.[4]

Third, the accuracy of tail-cuff methods is disputable. Several studies have been published purporting to validate cuff methods based on correlations between indirect cuff measurements and direct measurements of blood pressure simultaneously or subsequently obtained with arterial catheters.[5-8] However, statistical analyses applied in the most of such studies are not sufficient for proving of large individual differences or even systematic differences between measurement methods.[9] Another major limitation of most tail-cuff methods is that they are not appropriate to measure diastolic blood pressure.[1,8] Finally, even if a non-invasive method can provide an accurate measurement of blood pressure at a particular moment, this does not validate the method for assessing an animal's exact average blood pressure or for detecting the course of the blood pressure during a day or a whole study. Therefore, these techniques are not recommended for studies focused on quantification of the relationship between blood pressure and other variables (e.g. effect of a drug, vascular damage, etc).[1]

Electrocardiography

In rodents, ECG is the most commonly recorded using mini-invasive technique. Needle ECG electrodes are placed under the skin of forelimbs, tail or chest.[10] Such procedure requires general anaesthesia of the animal. There are only a few fully non-invasive methods of ECG recording used in conscious animals. One of them is ecgTunnel® (emcaTechnologies, France). Mouse or rat is restrained in the plastic tunnel. ECG is recorded using four electrodes placed on the floor of the tunnel under the limbs of the animal. Such set-up allows to record 6 limb leads in the same connection as in standard human ECG.[11] Other method contains dressing rats in a cotton jacket with two electrodes attached on its inner surface.[12] Before the measurement, chest of the rat must be shaved. Measurement is performed in conscious rats placed in plastic restrainer. Several similar methods and their modifications were described.[13-15]

Same as in case of blood pressure measurement, all non-invasive methods of ECG recording in rodents share certain benefits and drawbacks. The major benefit is a possibility to record ECG in conscious animal without effect of anaesthesia. Abovementioned methods are also favoured due to lower cost as compared to invasive methods (e.g. telemetric monitoring). Therefore, non-invasive methods are effective in case of screening of ECG abnormalities in large number of animals (e.g. phenotyping, studies of general toxicity, etc.). Nevertheless, restraint-stress is significant limitation of the methods. Although, long-term recording of ECG using non-invasive methods is possible, level of the stress will affect heart action. Therefore, only short-term measurements are recommended. Also, placing the electrodes in the same position – especially in case of "jacket" method – is tricky and may affect the accuracy of evaluated parameters.[16]

Cardiac imaging techniques

Assessment of structure and function of the heart in rodents is possible with ultrasound, microcomputed tomography (microCT) and magnetic resonance (MR) imaging. Cardiac imaging in the rodent poses a challenge because of the small size of the animal and its rapid heart rate. Each aspect in the process of rodent cardiac imaging – animal preparation, choice of anaesthesia, selection of gating method, image acquisition, and image interpretation – requires careful consideration to optimize image quality and to ensure accurate and reproducible data collection.[17] In addition to anatomical views, each of the three modalities can assess function by measuring cardiac parameters, such as: fractional shortening, ejection fraction, stroke volume, cardiac output, and much more others.

Each modality has its advantages and disadvantages, which warrant careful consideration when planning an imaging study. Common advantage of all abovementioned methods is that they are non-invasive and therefore do not require surgery. However, in some studies, contrast substances are administered intravenously. The main limitation of all imaging techniques is their cost. They usually require very expensive equipment and are also expensive to operate.

From all abovementioned modalities, ultrasound imaging (echocardiography) is the most prevalent. Main advantage of ultrasound imaging is short imaging time (in comparison with other imaging techniques) and possibility to be performed in conscious animal. In such approach, animal has to be trained before the measurement. One of the limitations of ultrasound is that it requires the knowledge and expertise of a trained operator to position the transducer in order to obtain accurate, repeatable, high-quality images. Using a single operator to examine all animals in a given study minimizes this limitation.[18]

Conclusion

Animal models still play a crucial role in cardiovascular research. Although technological advances in invasive techniques, such as telemetry and heart catheterisation, are shifting attention away from non-invasive methods, these methods still provide a useful approach to the measurement of cardiovascular parameters in some experimental studies. However, proper validation of methods, standardisation of measuring procedures and specification of standard values of measured parameters is needed for obtaining reproducible data.

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