

Masaryk University · Faculty of Medicine · Brno · Czech Republic

NONINVASIVE METHODS IN CARDIOLOGY **2013**

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



Brno 2013

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Under the auspices of

Ing. Miloš Zeman, CSc., President of the Czech Republic

Ing. Zdeněk Škromach, Vice-President of the Senate of the Czech Republic

doc. PhDr. Mikuláš Bek, Ph.D., Rector of Masaryk University Brno

prof. MUDr. Jiří Mayer, CSc., Dean of Faculty of Medicine, Masaryk University Brno

Reviewed by: prof. MUDr. Zdeněk Placheta, DrSc.

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CONGRESSES ON NONINVASIVE METHODS IN CARDIOLOGY

After the Velvet revolution in 1989 we started international cooperation among University of Minnesota, USA, Prof. Franz Halberg, Prof. Germaine Cornélissen, University of Graz, Austria, Prof. Thomas Kenner, University of Paris, France, Prof. J.P. Martineaud and Masaryk University of Brno, Prof. Bohumil Fišer, Dr. Jiří Dušek, Prof. Jarmila Siegelová. The cooperation was realized also by the meetings held two times per year in Brno; the results from the common studies were published in the books *Noninvasive Methods in Cardiology* 1994, 1996, 1999, 2002, 2003, 2004, 2007, 2008, 2009, 2010, 2011, 2012. The editors of these books were Prof. Franz Halberg, Prof. Thomas Kenner, Prof. Bohumil Fišer, Prof. Jarmila Siegelová. At the occasion of *Noninvasive Methods in Cardiology 2013* we want to remember the people who are no more with us.

Professor F. Halberg was presented by video transmission in Brno Workshop in May 3 to 4, 2013, and presented for the last time his scientific work; he died on June 9, 2013.

Professor Bohumil Fišer died on March 21, 2011. That is why this book *Noninvasive Methods in Cardiology 2013* is devoted to what would have been the 70th birthday of Professor Bohumil Fišer.

prof. MUDr. Jarmila Siegelová, DrSc.
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PROF. MUDR. B. FIŠER, CSC., MINISTER OF HEALTH OF THE CZECH REPUBLIC 2000–2002

MICHAL POHANKA

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I am very pleased to remember Professor Bohumil Fišer, Minister of Health of the Czech Republic, under whom I worked in the function of Deputy Minister.

Professor Bohumil Fišer performed this function very responsibly, with the strength of his whole personality. After 11 years, Professor Fišer as Minister of Health is still highly valued and honored, as it is proved by the following documents.



Fig. 1 Ing. Miloš Zeman, CSc., President of the Czech Republic

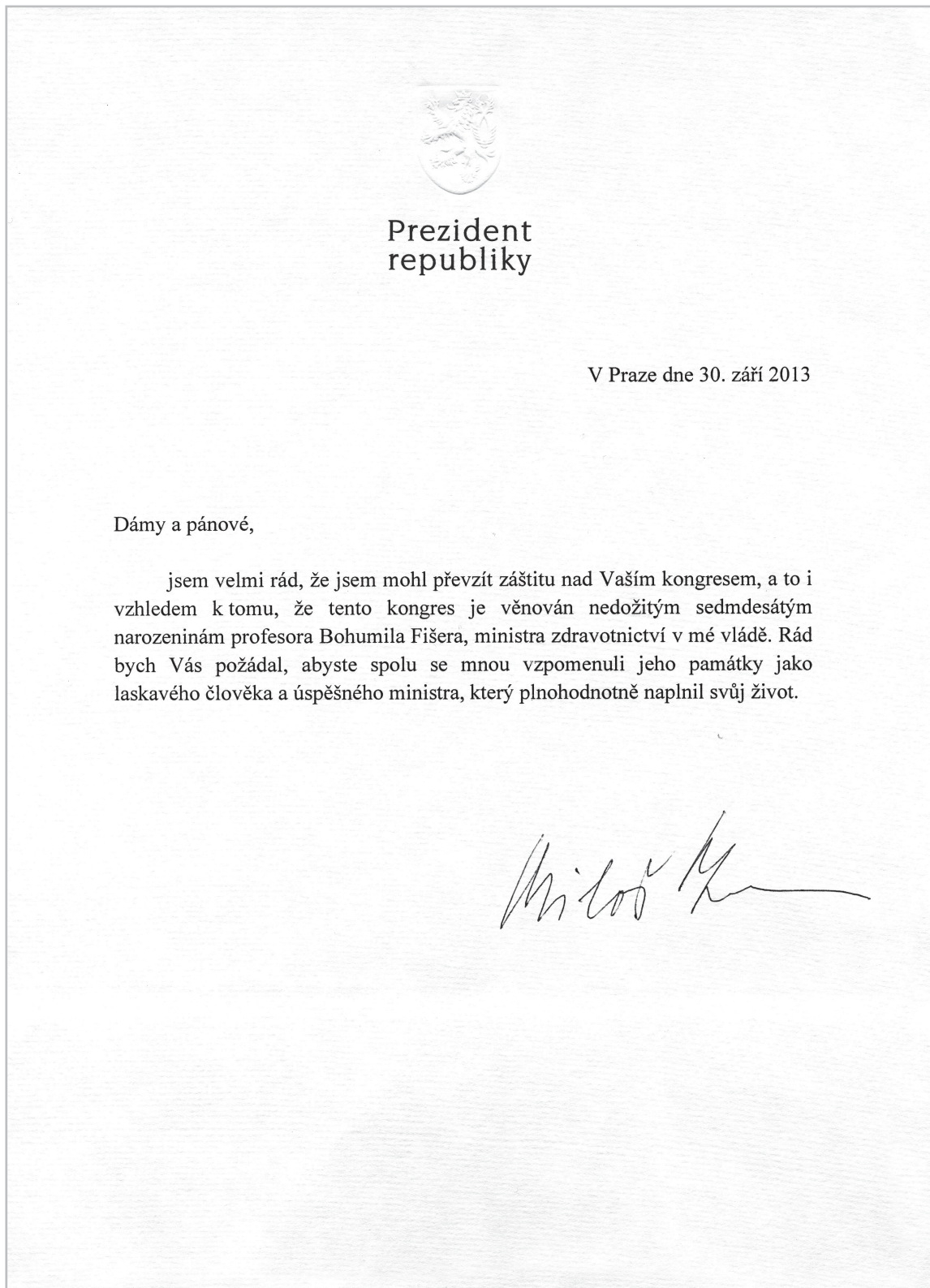


Fig. 2 The letter of Ing. Miloš Zeman, CSc., President of the Czech Republic

Ladies and gentlemen,

I am very glad that I can take patronage of the congress “Noninvasive Methods in Cardiology 2013”. This is also due to the fact that this congress is devoted to what would have been the 70th birthday of Professor Bohumil Fišer, Minister of Health in my government. I want to ask you to remember with me a kind man and a successful minister who successfully fulfilled his life.



Fig. 3 Ing. Zdeněk Škromach, Vice-President of the Senate of the Czech Republic



Fig. 4 Professor Bohumil Fišer, Minister of Health of the Czech Republic in 2000

REMEMBERING PROFESSOR BOHUMIL FIŠER (22 OCTOBER 1943 – 21 MARCH 2011)

ZDENĚK KOUDELKA

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I have a great respect for the memory of Bohumil Fišer. He was a person who reached a top as a scientist and as a teacher. He was a very successful professor and the Head of the Department of Physiology in the Medical faculty of the Masaryk University. He was a dedicated scientist, but he was also very interested in politics. He was very probably influenced by his father – veterinarian in Brno, who was also very active in the municipal council of the city of Brno in the Czechoslovak Republic. He had to leave his post just during the German occupation of the Czech Republic, when he was replaced by a Nazi representative.

Professor Fišer became very active in the socialist party and was eventually chosen by then prime minister Milos Zeman to become minister of Health in his Government (9 February 2000 – 12 July 2002). To this day he is considered as the one of the most successful Health ministers. It is also proved by the fact, that he stayed in this post for more than 2 years, which was a record at that time, broken just by Leoš Heger.

Bohumil Fišer was my political colleague and he was for me and many others a great political authority. He was for me an example of an ideal politician and a public personality. To this day I admire his ability to understand and exactly explain the merits of complicated political events.

According to my opinion it was very appropriate, that the first book of Jost Academy, *Úvahy o politice* (1) (Essays about Politics), included a paper by B. Fišer: “*Politics from the view of a Scientist*”. His text shows his non traditional opinions on the political events from his position as a doctor of medicine and a scientist. In his text he has shown a deep knowledge of the social sciences and his text is very readable as he shows very interesting and new views on the historical political events. He has also successfully shown the correlations between historical and present politics. He was not afraid to leave a path of political correctness and has openly published his opinions on how to solve some very sensitive issues. One example is his suggestion as how to solve the problems with the Roma minority. His vision was to do it through an education of the Roma children in boarding schools of British type, which would also provide a material support. He was also a big critic of corruption, but his opinions were realistic and he did not join the kind of extreme criticism. This became some kind of mantra for some journalists resembling the communistic mantra about the fight between the social classes. His text is available on the pages of the Repository of Masaryk University (2).

He always viewed politics from the left side of the political spectrum, but he was never a populist. His vision was to secure the well being by introducing the European standards on important issues for all citizens. It is logical, that the most important issues were medical care and education.

When he died, the main speaker on his funeral was the current president of the Czech Republic Mr. Miloš Zeman. He described professor Fišer very nicely and accurately and he also mentioned his nickname “Bohoušek” (diminutive of Bohumil), which was used by his friends and supporters. This nickname shows the love of the people who worked with him and who were his friends. It shows a good heart and a friendly personality of the man who was always ready to help to the others in need.

I am missing the company of Bohoušek, who was a great companion and lover of Moravian wine. My memories of him will always be very nice.

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SOME CONSIDERATIONS ABOUT THE TITLE “EVERY-DAY-PHYSIOLOGIST” WHICH WAS INVENTED BY FRANZ HALBERG DURING A STAY IN BRNO

THOMAS KENNER

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In connection with discussions about medical education and medical and physiological activities, Franz Halberg coined the title “Every-day-physiologist” for the three of us: Prof. Bohumil Fiser, he himself and me. The title includes a special consideration of the relation between physicians and patients.

I interpret the meaning of this friendly title that it describes our common attempt to use our research and our activities and also our planning especially for the improvement of practical medicine. To treat a patient, means to lead her or him from symptoms of disease and weakness to restoration of health and strength. There are always scientific components: the diagnostic process and the therapy. The therapeutic procedures and the training for the rehabilitation follow experience from research. And there are equally important components of humanity.

On the way from Graz to Brno, we made a stop in Vienna and – among other ways – we visited an exhibition, where I found a text which seems to me worthwhile to be presented here:

*“What I feel is **an art of balance of gravity and serenity**, devoid of troubling and disturbing subject matter, an art that could have soothing, calming influence on the mind, something like a good arm chair that provides revelation from physical fatigue.”*

This text was written in the year 1908 by the famous French painter HENRI MATISSE – and was presented in the Viennese House “ALBERTINA” in an Exhibition, where pictures of Matisse and his friends and followers were presented.

I had the impression, that this description of positive influencing and positive thinking is not only applicable in connection with pictures and arts, but also describes vividly, how in a hospital a physician should speak, act and behave in order to be perceived by a patient as somebody who is able to generate and distribute balance, gravity and serenity. It is clearly necessary that the activity of a physician should be felt and accepted as something positive and “as soothing, calming influence on the mind.”

Another text comes in my mind, a text, which is much older than Matisse’s text and life time, and in addition has some relation to what we could even imagine to be activities in a modern hospital. It was written by the monk St. Benedict around the year AD 400 as part Nr. 36 of his rules for the behavior of persons in a monastery. This short text Nr. 36 describes the care for sick persons. It starts with the sentence: “*The care for the sick is more important than any other obligation... The sick have to accept the help gratefully... However it is important to tolerate even overdoing patients.*” In addition there are descriptions about necessary activities like bathing, eating and drinking. The text ends with the remarkable sentence: “*The Abbot (the chairman) is responsible for any mistake, which the young make*”.

We had often discussed with Prof. Bohumil Fiser current problems of medical schools. He was involved in problems of organization and reform as physiology teacher, and also as minister of health. Of course he was also informed about reform activities in Austria. An when I told him about major changes in Austria – like the separation of former Medical Faculties in our Universities in order to become new Medical Universities – it was relaxing to know that he listened and understood the problems.

ATTINGER'S MODEL

Ernst O. Attinger was chairman of the Division of Biomedical Engineering of the University of Virginia, where I worked several years – he introduced a simple model of human systems, in order to describe different possible strategies to react to problems. Despite the fact that goals of societies or groups are often but vaguely defined, the difference between desire and actual achievements can be used as an indicator of the state of health of the system. For this lack between the desired goal and the actual achievement he used the name “goal-gap ratio”. This ratio is defined as the quotient of goal or desire and actual achievement. Attinger (1) argues that a high goal-gap ratio – the achievement is markedly lower than the goal – may lead to frustration. If this occurs, three alternative reactions are possible.

Attinger's model is a feedback system, which is able to recognize the actual achievement and to compare this achievement with the desired goal. As an index of missing quality the value of the so-called goal-gap ratio indicates the necessity of reactions or at least modifications to actual loads. Considering the estimated value of the goal-gap ratio, a decision about the further strategy of correction has to be found. As mentioned above, three possible strategies can be chosen.

1. The first one leads through exhaustion to extinction.
2. The second passes through negative aggressive behavior and social unrest to socioeconomic and political instability. A positive feedback raises the instability, and leads to a further increase of goal-gap ratio and unrest.
3. The third choice is characterized by positive aggressive behavior that results in designing constructive solutions of problems in order to decrease in the goal-gap ratio through negative feedback.

One problem, which Attinger did not mention is the additional source of problems: in case of marked increase of bureaucracy any improvement is markedly inhibited.

THE NEW AUSTRIAN LAW “UOG 2002”

As former rector of the Karl-Franzens-University in Graz it seems to me interesting to present here some related problems, which several years ago had discussed with the – at that time MINISTER OF HEALTH Bohumil Fiser.

Before the new law with the title “UOG 2002” (UOG stands for “Universitäts Organisations-Gesetz”) was introduced in Austria, the rector of a University was the chairman of the senate, and there was no additional board.

The actual modification in Austrian Universities according to the new law “UOG 2002” modifies these Universities into a business. The highest leadership is now manifold: 1. the rector, 2. the senate, 3. the chairman of the senate, 4. the university-board of external board-members, 5. the chairman of the university-board.

Of course, a generation of quarrel between senate and university-board has high probability. Example: in the University of Arts and Music in Graz, a quarrel blocked the election of a rector for more than one year.

An additional change of matters by the new law was the separation of the former Medical Faculties and the formation of Medical Universities.

In my opinion this separation is an amputation and I shortly report about **The reaction to the amputation.**

In an interview in June 2006 the Rector of the new Medical University in Graz gave the following answer to the question about the future of the Austrian Universities (2): “With the new University-law (UOG 2002) the Universities received a far reaching autonomy which is now increasingly used. In industry such a phase of reconstruction takes seven to eight years. We are now since two years in this phase and perform today things the very first time...” Furthermore, he expressed his hope that within the next five

years a stability will be reached so that an evaluation of the change will be possible. My comment to these open words about the current troubles is as follows: It seems to me irresponsible to make a new law, which creates serious problems for estimated eight years in an institution of health care, education and research, where students are supposed to learn for 6 years.

In any case the “goal gap ration” was markedly increased. A tremendous growth of bureaucracy blocks the “goal gap ration” at a high level.

THE NEW DIFFICULTIES

Through the UOG 2002 Austrian Universities received the right to act like industrial units. This is in agreement with modern trend of neoliberalism. The rector received a marked increase of power and competence. He is no more elected out of the professors or academic personnel of the University, but his position is advertised officially and who ever thinks to be able to fulfill the demands can apply. The appointment of the rector depends on the senate and the so called university board.

In addition, at the same time came the most painful addition to UG 2002: A reform of the employment law regulating all matters concerning employment, position, duration of position, income, rights, retirement, etc. This addition apparently, leads now to the most dangerous uncertainties for young scientists and young professors.

Last but not least the law UG 2002 orders that the three “classical Universities” which so far contained Medical Faculties (Vienna, Innsbruck and Graz) had to split off these Medical Faculties in order to generate three new Medical Universities. This “amputation” took place on January 1 st 2004.

As mentioned above, with respect to the medical education each of the three Medical Universities in Austria started to develop a specific new curriculum – different from the curriculum of the two other Medical Universities. This led in all locations to massive changes.

In Graz the classical curriculum, which until recently was similar in all former countries of the Austrian Monarchy was replaced by a so called module-system. This system is based on so called problem based learning (PBL). Difficulties were arising for several reasons. The new system demands cooperation of different specialities within each module. E.g., the anatomist, the physiologist, the chemist and the cardiologist would talk about hypertension. This may sound interesting, however, the organization of the increased number of lectures and lecturers became increasingly difficult. Since PBL has to be taught in small groups the teaching load for professors and assistants from non-clinical and clinical specialities, increased tremendously. For the students the loss of systematic teaching appears to be a major problem. Besides all that, the wide application of so called “virtual teaching” through internet and consequently the application of written multiple-choice examinations – in my opinion – are extremely problematic. Furthermore, the Medical Universities had to introduce entrance examinations as a reaction to a decision of the EU-high court in 2005. Until then all Austrians who had passed the so called Matura (final examination after 8 years Gymnasium) had free access to study medicine. The new situation permitted all persons from EU-countries, especially many students from Germany, to study medicine – and also other specialities – in Austria under the same conditions as Austrians.

SUMMARY

As retired Professor and former rector of the still complete Karl-Franzens-University in Graz, it was always valuable to discuss such recent difficult problems with the physiologist, the “every day physiologist” and Minister Bohumil Fiser. At this point I just can express my thankfulness to my good friend.

It is most difficult to understand or even to explain the motivation of the new laws. So far, the negative effects are in the foreground, in particular due to the marked increase of bureaucracy.

The University of Graz was founded in 1585. The Medical Faculty was introduced in 1863. In a book which was published 1913 on the occasion of the celebration of the 50th anniversary of the new Medical

Faculty, the following sentences can be found: “In these days the University of Graz celebrates together with the Medical Faculty an important anniversary, because only after the introduction of the Medical Faculty the University has gained completeness and from this completeness the rank of a fully important UNIVERSITAS LITERARUM. Until 1863 the University was only patchwork! In 1863 she became a completeness.” 141 years later this completeness was lost again. We are back to be patchwork.



Fig. 1 Professor B. Fišer and Professor T. Kenner in Masaryk University Brno in 2009

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IN HONOR OF BOHUMIL FISER: EDUCATOR, PHYSIOLOGIST, CHRONOBIOLOGIST, ADMINISTRATOR, CZECH MINISTER OF HEALTH, AND EXECUTIVE BOARD MEMBER OF THE WORLD HEALTH ORGANIZATION

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Figure 1 Bohumil Fiser

Two and a half years have passed since Professor Bohumil Fiser's untimely death. Yet, his achievements are still fresh in our memory and continue to inspire all who were fortunate to know him. His extensive bibliography illustrates the active scientific career of Bohumil (Figure 1). The innovations he brought to the field led him to head the department of physiology at what used to be Purkinje - now Masaryk - University. The Czech Republic could not have chosen a better person to serve as Minister of Health. The responsibilities Bohumil shouldered expanded even further when he served on the executive board of the World Health Organization.

Bohumil was also a gentleman, a kind man everyone would wish to have as a friend. And a friend he was to us and to chronobiology. The Minnesota connection with Brno started in April 1990 when Franz Halberg and I were invited by Professor Pavel Prikryl and Professor Jarmila Siegelova to participate at an International Symposium on Hypertension they organized in Brno (1). This was the start of a long and rewarding ongoing cooperation.

Vividly I remember my first encounter with Bohumil Fiser. On January 13, 1995, he, Jarmila Siegelova and Jiri Dusek arrived in Minnesota. Franz Halberg was at the airport to greet them. They all came immediately to my home where I had readied the new ambulatory blood pressure monitors from the A&D Company (TM-2421) we had just received. These devices needed to be compared with those from the Colin Medical Company (ABPM-630) we had previously used to be sure the data could be pooled and analyzed as

longitudinal records. We all placed cuffs from each monitor on each arm and started a week-long session of around-the-clock measurements (2).

Blood pressure monitoring had been one of Bohumil's specialities already. He was there in Brno with Jan Penaz as a young scientist-subject when the first continuous beat-to-beat blood pressure recorder on the finger for automatic use was developed (3). To the study of short-term variations made possible by this device (4, 5), Bohumil recognized the merit of monitoring blood pressure over much longer spans to obtain a more accurate diagnosis of "hypertension". He supported around-the-clock blood pressure monitoring for 7 days at the outset in a consensus document he guided with Professor Thomas Kenner (6), in order to account for the often encountered large day-to-day variability in circadian characteristics. The fact that weeklong records allow a glimpse at the circaseptan variation (7) is a dividend that led to interesting new results in relation to depression (8), as documented in our international project on the BIOSphere and the COSmos (BIOCOS).

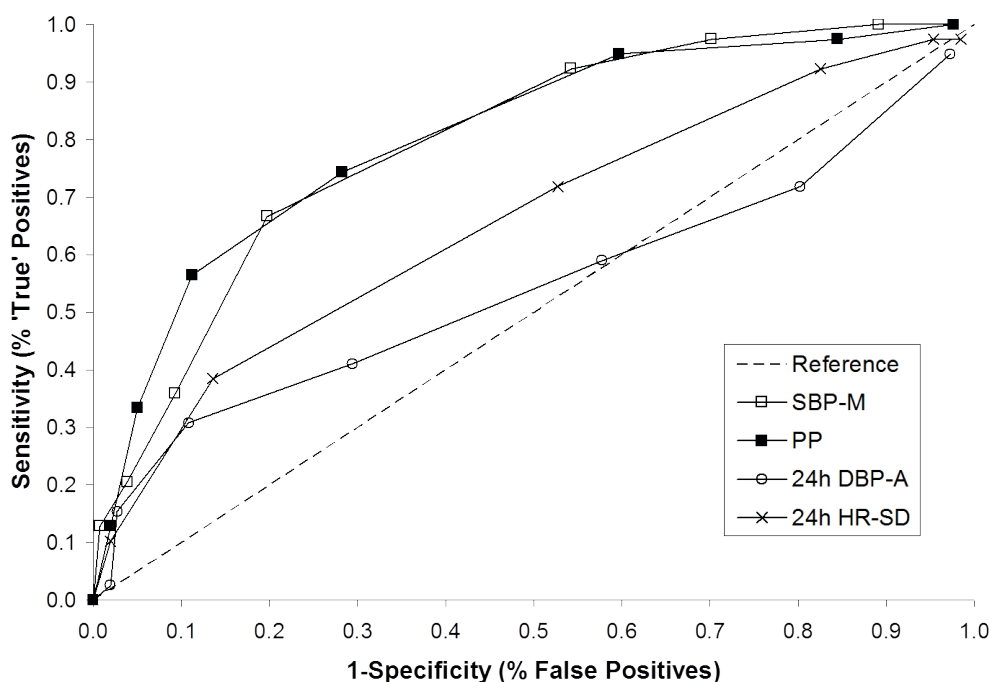


Figure 2 ROC curves of some VVDs. The percentage of morbid outcomes (such as a stroke) among subjects testing positive (e.g., for CHAT or for MESOR-hypertension) is known as the sensitivity of the test (e.g., circadian amplitude or MESOR of blood pressure). CHAT has a sensitivity of 28.2%, as compared to 92.3% for the case of MESOR-hypertension. The specificity of a given test is the percentage of subjects with no adverse outcome among those testing negative. CHAT has a specificity of 94.6%, as compared to 45.7% for the case of MESOR-hypertension. SBP & DBP: Systolic & Diastolic Blood Pressure; PP: Pulse Pressure; HR-SD: Standard Deviation of Heart Rate; -M: MESOR; -A: Amplitude.

Bohumil was an advocate of the chronobiologic approach to blood pressure monitoring, recognizing that in addition to an elevated blood pressure (MESOR-Hypertension; where MESOR stands for the Midline Estimating Statistic Of Rhythm, or rhythm-adjusted mean value), alterations in the variability of blood pressure and heart rate constitute Vascular Variability Disorders (VVDs) associated with an increased cardiovascular disease risk in their own right (6). VVDs include an excessive circadian amplitude of blood pressure (CHAT, brief for Circadian Hyper-Amplitude-Tension), an odd phase of the circadian blood pressure rhythm but not that of heart rate (ecphasia), a circadian period deviating with statistical significance from 24 hours (ecfrequentia), an excessive pulse pressure, a deficient heart rate variability, and an excessive pulse-pressure product. Acceptable limits for the MESOR and for the circadian amplitude and acrophase are specified by gender and age.

With calculations prompted and guided by Bohumil, the sensitivity and specificity of some of the VVDs are illustrated in Figure 2. Corresponding efficiency coefficients are provided in Table 1. The efficiency coefficient is the percentage of correct diagnoses in the light of outcomes. For CHAT it is 85.9%, as compared to 51.9% for MESOR-hypertension. These values strongly suggest the merit of assessing the blood pressure variability, notably the circadian amplitude of blood pressure, since the diagnosis of CHAT is not meant to be used as a substitute, but rather as a complement to the diagnosis of MESOR-hypertension. Similar results are obtained for a deficient heart rate variability, Table 1.

Table 1 ROC results of some VVDs

	Sensitivity (%)	Specificity (%)	Positive PV	Negative PV	Efficiency Coefficient
SBP-M	92.3	45.7	20.5	97.5	51.9
PP	56.4	88.8	43.1	93.1	84.5
DBP-2A	28.2	94.6	44.0	89.7	85.9
HR-SD	25.6	95.7	47.6	89.5	86.5
.....					
Non-dipping					
SBP	43.6	62.0	14.8	87.9	59.6
DBP	35.9	72.1	16.3	88.2	67.3

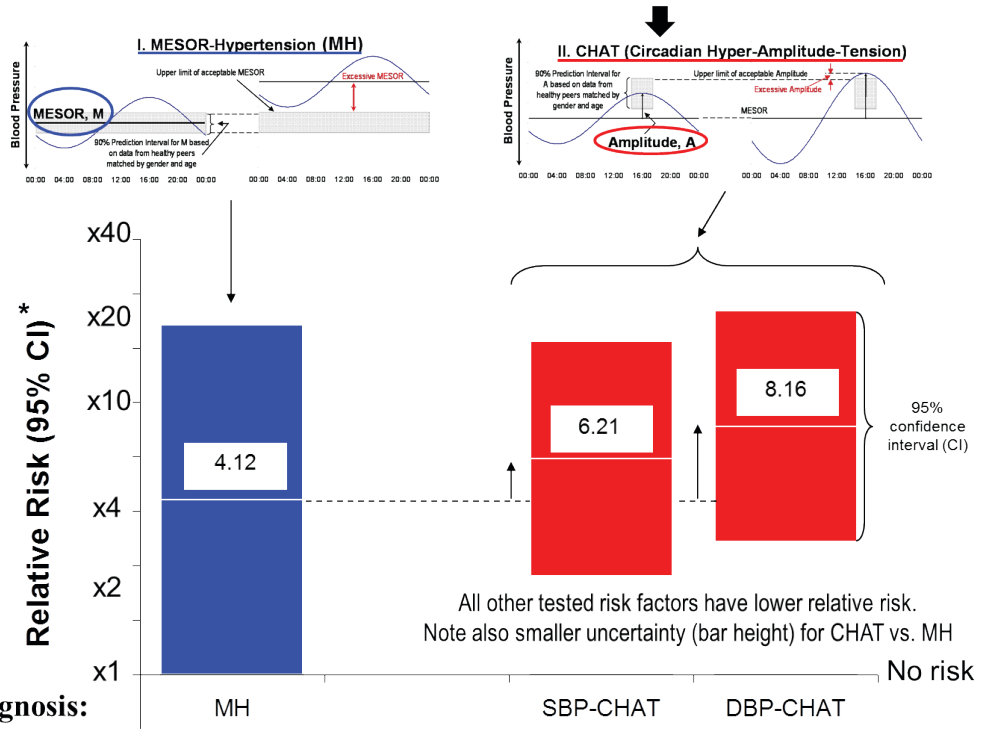
PV: Predicted Value.

That CHAT is a more specific marker of risk than MESOR-Hypertension is also apparent from Figure 3. The relative risk of having a cerebral ischemic event within 6 years from the monitoring among patients with no target organ damage at the outset is 4.12 for MESOR-hypertensive patients as compared to MESOR-normotensive subjects. In other words, MESOR-hypertensive patients have a 312% increased risk of having an adverse cerebral event within 6 years by comparison to MESOR-normotensive subjects. The 95% confidence interval of the relative risk, represented by the height of the bar is barely above the horizontal line at X1 corresponding to equal risk. By contrast, systolic and diastolic CHAT have a relative risk of 6.21 and 8.16, respectively, that is a risk numerically larger than the risk associated with a high blood pressure. Moreover, their 95% confidence intervals are narrower and well above the equal risk line, in keeping with the higher specificity of CHAT as compared to MESOR-Hypertension (Table 1 and Figure 2).

From Table 1, it can also be seen that VVDs have a higher efficiency coefficient than the day-night ratio of systolic and diastolic blood pressure used for a classification in terms of “dipping”. This result is in keeping with results from another outcome study using the left ventricular mass index (LVMI) as a proxy outcome measure (9; cf. 10, 11). On data he collected in Brno with Jarmila Siegelova and Jiri Dusek, Bohumil documented the problem of exclusive reliance upon a classification by dipping when a chronobiologic approach to blood pressure was available, pointing to the merits of the latter and the shortcomings of the former (12, 13).

As minister of health and executive board member of WHO, Bohumil Fiser provided data for the documentation of an about-50-year cycle in stroke incidence (14), Figure 4. An about 50-year cycle also characterized the incidence of stroke deaths in Minnesota for the span from 1950 to 1998 (15). Nonlinearly, the period was estimated as 51.1 years with a 95% confidence interval spanning from 49.0 to 53.1 years. An upward trend in the incidence of stroke deaths after 2000 was also observed in Slovakia (16), in Lund, Sweden (17), and in Arkansas, USA (18). About 50-year cycles have also been detected in other variables, such as anthropometric measurements at birth in Russia, natality and homicides in the USA, an index of international wars, as well as the incidence of large earthquakes and tsunamis (19). Known to economists as the Kondratiev cycle, this component deserves further scrutiny of the role of space weather and/or geomagnetism in physiology (20).

In 2011, Franz wrote about Bohumil’s untimely death (2): “BIOCOS has lost a friend. It will be hard to find a better one. But Bohumil will live on in the unified science that he helped create, transcending disciplinary barriers.” As apparent at this meeting on Noninvasive Cardiology, very much indeed, Bohumil’s legacy lives on.



* Risk of Cerebral Ischemic Event (N=297). Results are in keeping with independent outcome study on 1179 untreated patients, using the left ventricular mass index as proxy.

Figure 3 Higher specificity of CHAT as compared to MESOR-Hypertension as markers of cardiovascular disease risk

Stroke Incidence in Czech Republic

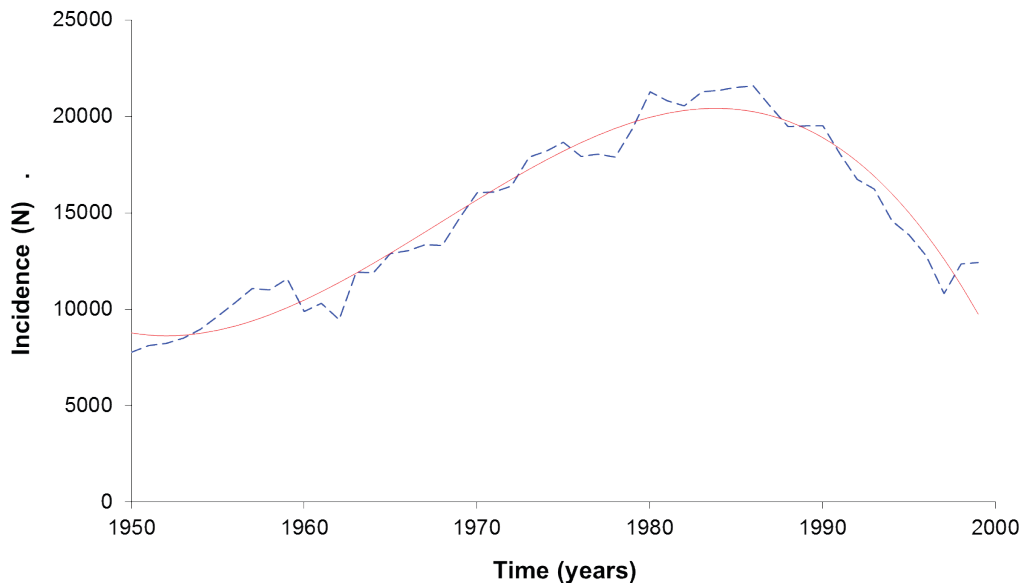


Figure 4 Increase in stroke deaths after 1997 in the Czech Republic: part of an about 50-year cycle?

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**PROFESSOR BOHUMIL FIŠER,
A SCIENTIST AND A TEACHER
AT THE DEPARTMENT OF PHYSIOLOGY,
FACULTY OF MEDICINE,
MASARYK UNIVERSITY, BRNO**

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Professor MUDr. Bohumil Fišer, CSc., a respected physiologist at Faculty of Medicine of Masaryk University, died on March 21, 2011, at the age of 68 years.

Professor Fišer was born on October 22, 1943, in Brno. In 1966, he graduated from Faculty of Medicine, J. E. Purkyně University in Brno. He had already some research experience by that time – he had worked at Medical Physics Department and Physiology Department during his studies. He chose the Department of Physiology of J. E. Purkyně University (later renamed Masaryk University) for his professional career and devoted all his life to physiology. Despite insidious disease he worked at the department till his last days.

He devoted his life to physiology because he felt a possibility of joining his knowledge of mathematics and his talent for an exact approach to the elucidation of physiological problems. He directed his colleagues and students with his exact thinking and the ability to spread a joy at physiological investigation. As a scientist, he was a very active one. Due to a broad spectrum of problems which Prof. Fišer studied, it is not easy to make a brief summary of all research areas in which he worked; therefore, we would like to present a survey of his publications which are documented at our department. He published 41 original articles in journals with an impact factor, 273 original articles in other journals and books from symposia and 395 abstracts from congresses and conferences. Citations listed in Web of Science exceed 530. A list of papers in journals with impact factor can be found in Appendix.

Out of this remarkable number of publications we would like to mention the most important results of our collaboration at Department of Physiology. Namely, it is a paper from 1973 focused on cardiac function in patients with atrial fibrillation, which was done in co-operation with prof. MUDr. Bořivoj Semrád, CSc. Modelling of two hypotheses of the conduction of electrical activity in His bundle was used – a model of a concealed conduction and a model of summation of atrial action potentials. The modelling clearly showed a priority of a hypothesis of summation of action potentials. It is necessary to emphasize that at that time modelling was rarely used in physiology.

In the seventies of the last century we applied, under the leadership of our common teacher Prof. Peňáz, spectral analysis to the variability of a non-invasively continuously recorded blood pressure by an original Peňáz's device. Blood pressure variability was evaluated together with variations in blood flow, heart rate, and respiration. This study involved analysis of interrelationship between variations in different circulatory and respiratory parameters, and the individual characteristics and repeatability of the spectra. This was the first spectral analysis of non-invasively recorded blood-pressure variations worldwide, and we would like to mention that this pioneer study was performed at a time when there were no computers available at the Faculty.

Our next key study on baroreflex sensitivity determination by the spectral method was done as early as in 1992. BRS was analysed at different rates of respiration in the respiratory and 0.1 Hz ranges and, based on these results, we decided to use a 0.1 Hz frequency range and a controlled breathing at a frequency of 0.33 Hz in further BRS studies.

Since then we have performed dozens of studies in this field. Out of those we would like to mention our studies on risk stratification of patients after myocardial infarction, because they showed the importance of non-invasively determined baroreflex sensitivity together with other risk factors known at that time.

The results of these studies were quickly accepted and included in an American study on the decision to implant a cardioverter defibrillator after myocardial infarction (BAILEY JJ, HODGES M, CHURCH TR: *Decision to implant a cardioverter defibrillator after myocardial infarction: the role of ejection fraction v. other risk factor markers. Med Decis Making* 27: 151-160, 2007).

One of the important characteristics of Bohumil Fišer was his extraordinary ability to establish contacts with experts from other institutions not only in Brno, but at international level. There is no space for listing all studies done with various departments and thus only some of them will be mentioned.

Since ninetieths, Prof. Fišer collaborated on numerous projects. In collaborations with Prof. Jarmila Siegelová and American department headed by Prof. F. Halberg and later by Prof. G. Cornelissen, he studied for almost two decades circadian blood pressure variation. Together with Prof. Savin from France he focused his attention on autoregulation of cerebral circulation studied by non-invasive methods.

In numerous animal experiments in the 70th and 80th of last century, mainly on isolated heart perfused according to Langendorff and on isolated multicellular heart preparations, Professor Fišer studied cardiac contractility. Many of these studies were done in collaboration with Department of Physiology in Halle.

Formal professional life of Bohumil Fišer was affected by political circumstances. Although he defended his theses already in 1977 and he was indisputably a research talent, his possibilities to collaborate with departments abroad were restricted in 70th and 80th. He was awarded a degree of Associate Professor of Normal Physiology only after political changes at the end of 20th century (1989). He became a Professor in 1995, after democratic changes in our country. V 1995, he took over Department of Physiology LF MU. He headed it next 13 years.

Prof. Fišer loved to teach and the students perceived it. He belonged to those teachers who managed to fill up any lecture hall. He knew how to comment with humour on every sort of information and relate it to his life experience. The students knew that they would be instructed and entertained at the same time. And this is the very component of his pedagogical success: information based on a story is scarcely forgotten. Surely there are hundreds of doctors who feel to be his disciples.

Prof. Fišer was not a scientist closed in his laboratory. He actively participated in reconstruction of academic community of Masaryk University as a member of Academic senate in the 90th. He was an active organizer of Czech Physiological Society ČLS JEP, mainly between 1993 and 1998, when he was elected into executive board of this society.

Bohumil Fišer's personality was characterized with deep social feeling and need of affecting public changes in hectic era at the end of 90th, when our society was transforming to democratic system. This fact brought him to his membership in Labour Party and to the position of Minister of Health. Due to his work in WHO (member of executive board in 2003-2006) he became internationally recognized personality.

Prof. Bohumil Fišer was an exceptionally humble person, with enormous ability to solve problems, tolerant, with sense of humour. And due to these features he became a popular person worldwide.

Faculty of Medicine, Masaryk University in Brno lost in Professor MUDr. Bohumil Fišer, CSc., eminent scientist, great teacher and a personality which markedly influenced the development of the faculty during the last two decades.

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full papers in journals with impact factor:

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Prof. Bohumil Fišer was Head of the Department of Physiology, Faculty of Medicine, Masaryk University, Brno 1995–2008, Minister of Health in the Czech Republic in 2000–2002, member of executive committee of WHO 2003–2008. He was a highly respected scientist of worldwide renown in the field of normal and pathological physiology and a successful organizer in health service.

During his studies at the Faculty of Medicine of Masaryk University (1960–1966) he had been working in the Institute of Medical Physics until 1964. In 1964 he started to work, together with me, in the Department of Physiology. The Department of Physiology in University of J. E. Purkyně (Masaryk University) was very well known all over the world. The head of the department was prof. MUDr. Vladislav Kruta, DrSc., who cooperated with the physiologists from England, France, Netherlands, Switzerland and others. Some of younger coworkers in his team became professors in the future.

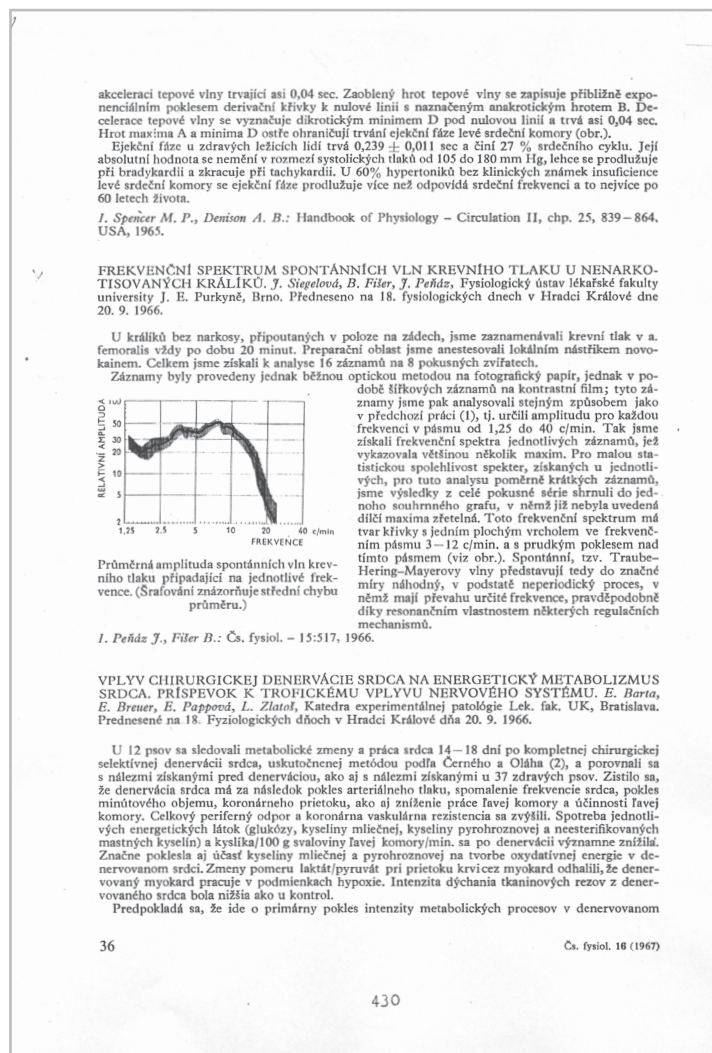
Professor Kruta was sending his coworkers in the Dept. of Physiology abroad and saw in the international cooperation the best means for international scientific work. Prof. MUDr. Jan Peňáz, CSc., was in the Netherlands, prof. MUDr. Pavel Bravený, CSc., was in the USA, prof. MUDr. Miloš Kukleta, CSc., was in France, prof. MUDr. Bořivoj Semrád, CSc., was in Germany, prof. MUDr. Bohumil Fišer, CSc., was in the Netherlands, prof. MUDr. Jarmila Siegelová, DrSc., was in Germany, doc. MUDr. Josef Šumbera, CSc., was in Switzerland, assistant professor MUDr. Zdeněk Franz, CSc., was in France. The young colleagues assistant professor MUDr. Pavel Buriánek, CSc., and assistant professor MUDr. Jaroslava Hlávková started their work in Brno.

The important scientific events in 1969 were International Symposium of J. E. Purkyně in Prague and in 1970 Congress “Association des Physiologistes” in Brno, both organized by Professor Kruta and his colleagues from the Dept. of Physiology. This fruitful period influenced Professor Fišer in his own scientific work, not only in publishing, but also in meeting experts and scientists and in discussions and dealing with scientific questions.

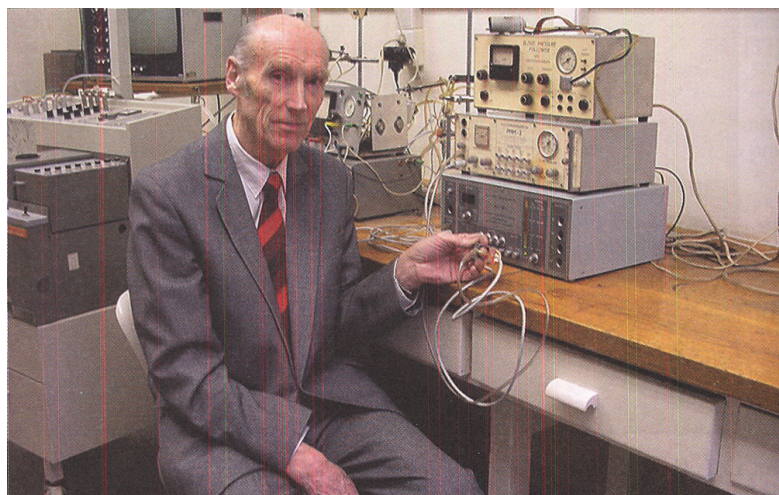


Prof. MUDr. Vladislav Kruta, DrSc., 1908–1979, Head, Dept. of Physiology, 1953–1970

The first scientific and publication activities of Professor Fišer started in 1966 in cooperation with Professor Jan Peňáz and were concentrated on frequency analysis of blood pressure oscillations in rabbits.



At that time Professor Peňáz developed noninvasive volume-clamp method of blood pressure measurement on finger. The figure shows the first prototype of Peňáz equipment in 1966.



Professor MUDr. Jan Peňáz, CSc.

To compare the noninvasive measurement of blood pressure with the invasive measurement of blood pressure in arteria brachialis, it was important to measure blood pressure continuously invasively and noninvasively by beat by beat measurement simultaneously; the experiment is shown on the next figure. The experiment was done by Prof. Semrád and Prof. Peňáz on the person of Professor Fišer.

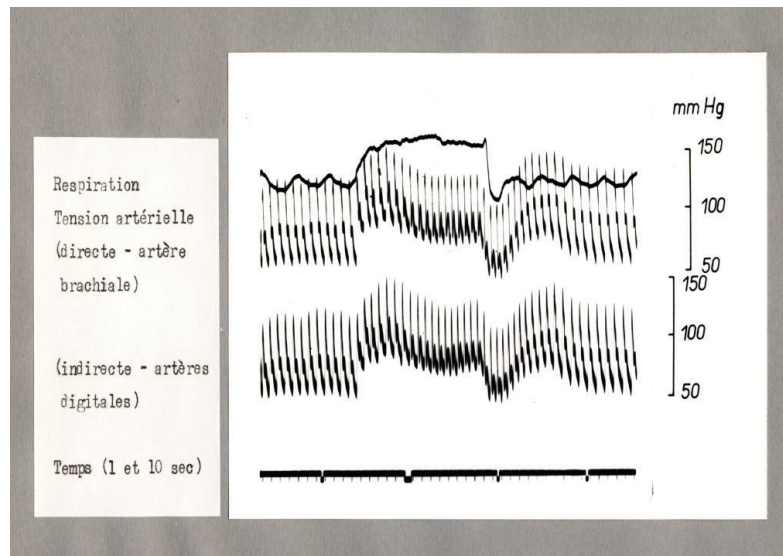


Figure 1 Invasive and noninvasive measurement of blood pressure on the person of Professor Fišer

Professor Fišer and Professor Semrád performed the analysis of pulse pressure and pulse interval in patients with atrial fibrillation, using various mathematical methods and method of Monte Carlo including the heart rate rhythm regulation of heart contractility in man. The study of heart contractility in man confirmed the findings of contractility regulation in isolated heart experiments discovered by Professor Vladislav Kruta, Professor Pavel Bravený and others co-authors from the same physiological department. His scientific work from the studies mentioned above was finished by CSc. thesis in 1978.



Figure 2 Professor Fišer, Professor Peňáz and Professor Siegelová in Brno, 2008, at the occasion of 100th anniversary of the birthday of Professor Kruta

He also contributed to the first clinical measurement of cardiac output and first electrophysiological examination of the human heart in St. Anna Teaching Hospital together with Professor Bořivoj Semrád, Professor Karel Zeman and senior lecturer Josef Šumbera.

Professor Fišer presented the results of his scientific experiments concerning the interrelationships between heart rate fluctuations and blood pressure fluctuations using autocorrelation functions and power spectral densities on the XXVI. INTERNATIONAL CONGRESS OF PHYSIOLOGICAL SCIENCES in New Delhi, India in 1974 and XXVIII. INTERNATIONAL CONGRESS OF PHYSIOLOGICAL SCIENCES in Budapest, Hungary in 1980.

He had a possibility to meet the experts on cardiovascular physiology all over the world. He was able to speak English, German and French and also to publish in all three languages.

International cooperation of Professor B. Fišer in science and research could be fully extended only after the Velvet Revolution in 1989.



Figure 3 Czech-English Congress of Physiological Society in Prague



Figure 4 Discussion with Professor J. Widdicomb, M.D. (London) in Charles University, Prague

COOPERATION PARIS, FRANCE AND BRNO, MASARYK UNIVERSITY

The cooperation with Professor Jean-Paul Martineaud (27 March 1931 – 29 November 2010), Medical Faculty, Lariboisière Hospital, University de Paris (France) was very intensively developed and common hemodynamic studies were provided as a non-invasive measurement of aortic compliance and blood flow regulation in cerebral arteries, both in healthy subjects and patients, and published in international journals.



Figure 5 Prof. Fišer, Prof. Siegelová and Prof. Jean Paul Martineaud, M.D., Paris, France (cooperation from 1976 to 2010) in Dept. of Physiology Brno



Figure 6 Experiments were done in Paris, Hopital Lariboisiere, Professor J.P. Martineaud, his team and Brno team (Professor Fišer, Professor Siegelová)

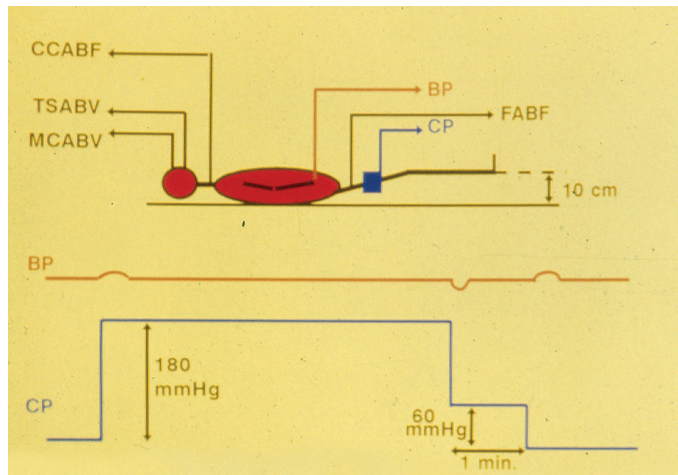


Figure 7 Scheme of experiment

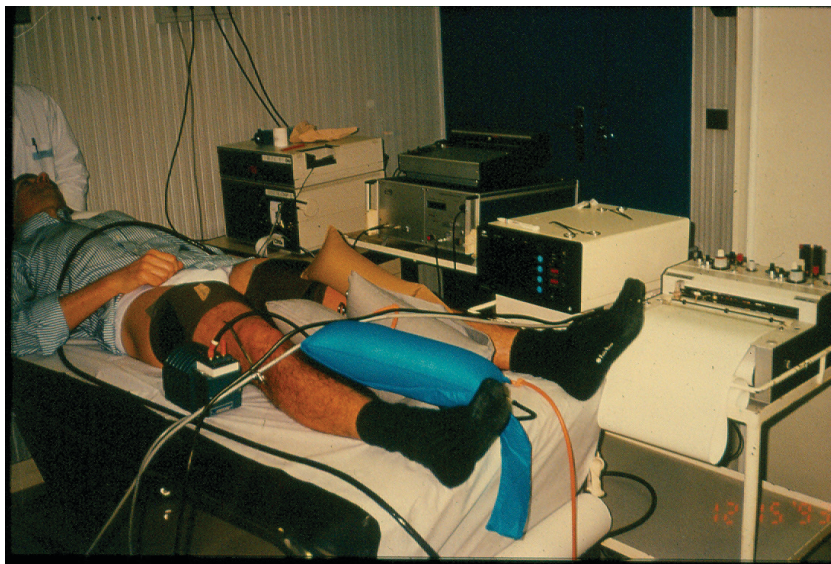


Figure 8 Measurement of middle cerebral artery (DOPLER) and blood pressure (FINAPRES OHMEDA)

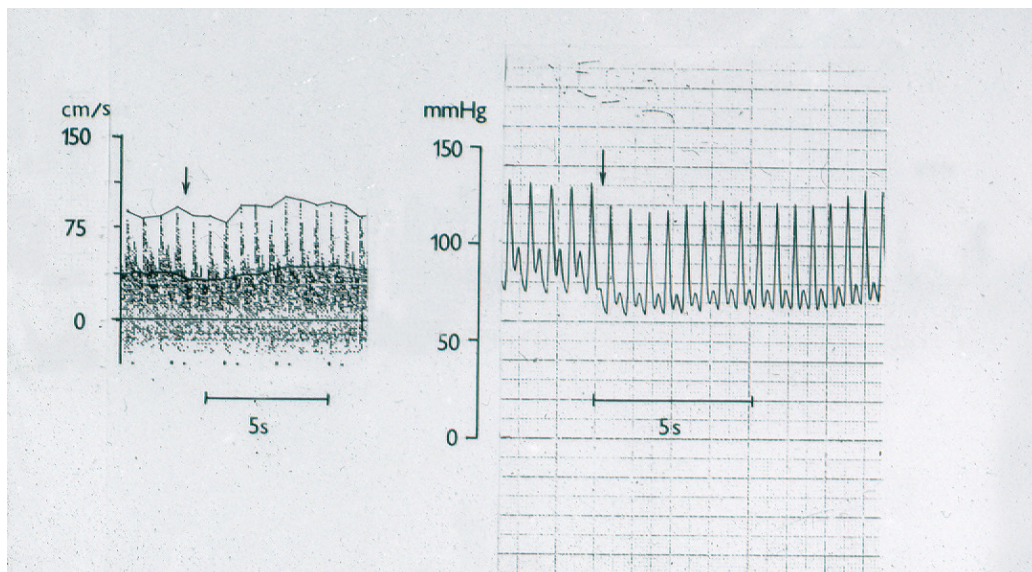


Figure 9 Middle cerebral artery (MCA), and blood pressure (mmHg) during occlusion and after cuff release (5 s and 5 s) for 1 subject

The study Blood Flow Control of extra and intracranial arterial vessels during moderate hypotension was carried out in ten healthy subjects to precise characteristics of autoregulation in the cephalic circulation. It consisted of measurements of blood velocities in middle cerebral artery (MCA), intracranial branch of internal carotid artery, and in temporal superficial artery (TSA), extracranial branch of external carotid, during a sudden and moderate fall (-9%) in arterial systemic pressure. In this situation, flow velocities in MCA and TSA decreased abruptly, -16% and -30% respectively, during the first cardiac cycle. The recovery was different in the branches of the common carotid artery: it was fast in MCA, beginning with the second cardiac cycle and completed in five seconds; while it was longer in TSA, remaining low till approximately the thirtieth second. It is suggested that myogenic autoregulation can be present in extracranial as well as in intracranial arterial vessels and would be efficient in one minute roughly. In cerebral arteries, however, other mechanisms developed and a faster recovery is probably explained by intervention of the autonomic nervous system, perhaps via the baroreflex. Then autoregulation protects effectively the cerebral blood flow in the case of a sudden hypotension.

Tab. 1 Middle cerebral artery (MCA), superficial artery (TSA) velocities ($\text{cm}\cdot\text{s}^{-1}$) and common carotid artery blood flow (CCA) $\text{ml}\cdot\text{min}^{-1}$ and blood pressure (mmHg) at rest, during occlusion and after cuff release (1,5 and 10 s) for 10 subjects (values are means \pm SD, * = $p < 0.05$; comparison with rest value)

	Rest	Occluding	Cuff release		
			1s	5s	10s
MCA $\text{cm}\cdot\text{s}^{-1}$	50.3 ± 11.6	50.1 ± 10.2	41.8 ± 11.6 *	49.3 ± 10.9 *	51.6 ± 10.5 *
TSA $\text{cm}\cdot\text{s}^{-1}$	10.9 ± 2.5 *	10.6 ± 2.6	7.4 ± 2.5	8.2 ± 2.2	8.2 ± 2.4
CCA $\text{ml}\cdot\text{min}^{-1}$	305.1 ± 23.4	299.1 ± 23.7	232.7 ± 33.2 *	281.5 ± 43.3 *	292.5 ± 29.6 *
Blood pressure mm.Hg	101.4 ± 23.4	299.1 ± 9.9	89.8 ± 10.3	86.4 ± 10.0 *	90.5 ± 10.0
Heart rate $\text{beats}\cdot\text{min}^{-1}$	87.0 ± 17.0	82.0 ± 14.0	88.0 ± 14.0	92.0 ± 12.0	86.0 ± 15.0



Figure 10 Prof. Fišer, Prof. Siegelová and Prof. Jean Paul Martineaud, M.D., in Prague



Figure 11 Prof. Siegelová, A. Siegelová, Prof. Fišer, and Prof. Jean Paul Martineaud, M.D., in Brno

SCIENTIFIC COOPERATION UNIVERSITY GRAZ - UNIVERSITY BRNO

The international cooperation continued 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 were realized and included in the common international project of analysis of cardiovascular control in physiology and pathophysiology.

Prof. Dr. Thomas Kenner, M.D., Dr. h.c. multi, was honored by Dr. h. c. Universität Jena, 1990, by Dr. h. c. in Germany, Semmelweis University Budapest, 1998, by Dr. h. c. in Hungary, Masaryk University Brno in the Czech Republic, 2000, by Doctor Honoris Causa Masaryk University, 2000.

The book E. Wetterer, Th. Kenner: Grundlagen der Dynamik des Arterienpulses Springer-Verlag, Berlin, Heidelberg, New York 1968, is the fundamental scientific work which gave rise to Professor Fišer studies about cardio-ankle vascular index, aortic compliance and pressure wave velocity as measures of arterial stiffness.

Stiffness of large arteries has been related to cardiovascular mortality. It can be expressed by pressure wave velocity (PWV), aortic compliance (C) and by the cardio-ankle vascular index (CAVI). C was measured noninvasively in normotensive and hypertensive human subjects and in human cadavers' aortas, PWV and CAVI were calculated. Despite completely different experimental situation the results of both analyses were similar. Also regression coefficients between C and blood pressure were similar in both experimental conditions.

The mathematical approach consisted in calculating PWV and CAVI in a group of normotensive and hypertensive subjects where the aortic compliance was non-invasively measured and comparing the results with published data obtained from isolated aortas of human cadavers.

The stiffness parameter beta is reported to be independent of blood pressure and is calculated as

$$\text{BETA} = \ln(P_s / P_d) \times D / dD$$

where P_s and P_d are respectively the systolic and diastolic blood pressure in mmHg. D is the diameter of the blood vessel and dD is the change of D . D/dD can be replaced by $2 \times V / dV$ where V is the volume of the tube, the volume of aorta in our case.

$$\text{BETA} = \ln(P_s / P_d) \times 2 \times V / dV$$

The relationship between volume elastic modulus $V \times dP / dV$ (index of the stiffness) and PWV is expressed by the formula

$$\text{PWV}^2 = (V \times dP / dV) / \rho$$

where ρ is blood density. Aortic compliance is dV / dP . Thus

$$V / dV = \rho \times \text{PWV}^2 / dP$$

If we substitute equation (4) for equation (2) we obtain the stiffness parameter

$$\text{BETA} = \text{CAVI} = \ln(P_s / P_d) \times 2 \times (\rho / dP) \times \text{PWV}^2$$

and volume measurement by ultrasound is superfluous. The last equation expresses the relationship between CAVI and PWV. On the other hand, direct comparison of these parameters with compliance (dV / dP) is not possible because the value V (aortic volume) is missing. We used in our comparison the estimates of V from cadaver studies.

The cadaver study includes 27 aortas from the subjects 20 to 83 years old. The results are published in Kenner Wetterer monograph.



Figure 12 Professor Fišer

The compliance data were obtained by noninvasive measurement from 8 healthy men 27 ± 9 years old (from 21 to 49 years) with 24-hour blood pressure $121 \pm 10 / 75 \pm 8$ mmHg, from 10 not-treated hypertensive men 48 ± 8 years old (from 38 to 58 years) with 24-hour blood pressure values $147 \pm 12 / 88 \pm 9$ mmHg and from 6 hypertensive patients treated with verapamil (slow release formula) 240 mg/24 h for 3 months. The mean age was 43 ± 9 years (from 32 to 53). Twenty four-hour blood pressure values were $143 \pm 7 / 88 \pm 4$ mmHg before the treatment and $131 \pm 4 / 80 \pm 4$ mmHg at the time of compliance investigation. The method and the results of compliance measurement are described elsewhere.

The results of the cadaver study are seen in Fig. 13. From the Figure it is clear that the slopes of the curves (which correspond to the compliance dV / dP) are pressure-dependent. The parameters of the best fitted polynomial curves are seen in the table. Together with compliance values at 80 mmHg (value of diastolic pressure), the parameters of linear relationship between compliance and pressure and calculated PWV at 90 mmHg (value of mean arterial pressure) and CAVI (which is not pressure-dependent). PWV was calculated according to the equation. Because PWV is aortic pulse wave velocity which is different from cardio-ankle pulse wave velocity, we calculated at first aortic beta according to the equation and then we calculated CAVI using the regression equation $CAVI = 7.5 + 0.15 \times \text{aortic BETA}$. For CAVI we assume $P_s / d = 120 / 80$ mmHg.

Aorta, pressure-volume diagram

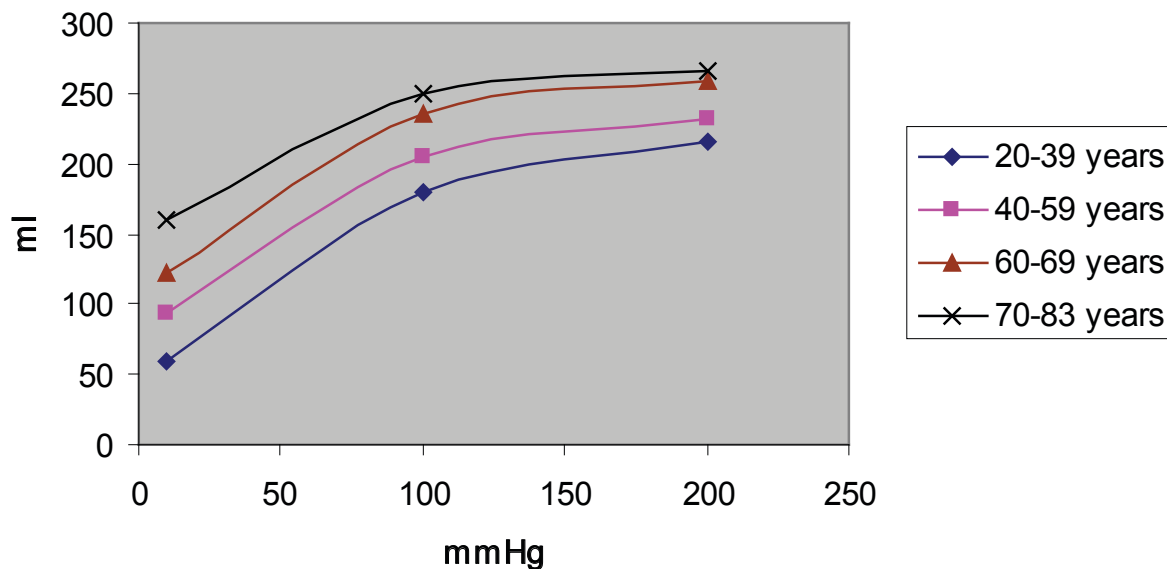


Figure 13 Pressure-volume diagram of cadavers' aortas

The results of the analysis of our compliance data are seen in the next table. The compliance values were non-invasively measured as well as coefficients A and B, which we used for calculation of compliance at 80 mmHg. The volume V was not measured in our study and thus we used the values of V from cadavers' aortas studies for the calculation of PWV estimate again for mean pressure of 90 mmHg. Calculation of CAVI we performed identically as in cadavers' aortas analysis.

Tab. 2 Cadavers' aortas study

Ages (n) years	a	b	c	A	B	dV/dp (80mmHg) ml/mmHg	PWV m/s	BETA aortic	CAVI
20-39 (8)	40.54	1.897	-0.0051	1.897	-0.0102	1.081	11.71	21.08	10.66
40-59 (9)	76.77	1.778	-0.0050	1.778	-0.0100	0.978	13.20	26.78	11.51
60-69 (5)	105.10	1.849	-0.0054	1.849	-0.0108	0.985	14.20	31.00	12.15
70-83 (6)	144.40	1.510	-0.0045	1.510	-0.0090	0.790	15.95	39.11	13.36

Legend: parameters a, b, c correspond to equation; volume = a + b* pressure + c* pressure²; parameters A, B: compliance = A + B* pressure; dV/dP (80mmHg): compliance at pressure 80 mmHg; PWV: pulse wave velocity; BETA: aortic stiffness; CAVI cardio-ankle vascular index.

Tab. 3 Human noninvasive study

Group (n)	dV/dp ml/mmHg	A	B	dV/dp (80mmHg) ml/mmHg	PWV m/s	BETA aortic	CAVI
Normotensives (6)	1.18 ±0.25	2.328	0.0154	0.969	11.77	21.29	10.69
Hypertensives (10)	0.96 ±0.21	2.219	0.0144	0.923	13.37	27.48	11.62
Treated hypertensives (6)	0.90 ±0.11	1.843	0.0122	0.745	13.86	29.50	11.92

Legend: dV/dp (±SD): measured compliance. Other parameters as in Table 1.

Despite a completely different experimental situation the results of both analyses are similar. The most interesting finding is similar regression coefficient B despite the fact that the smooth muscle cells in cadavers' aortas are dead.

Stiffness of large arteries has been related to cardiovascular mortality. It can be expressed by pressure wave velocity (PWV), aortic compliance (C) and by the cardio-ankle vascular index (CAVI). C was measured noninvasively in normotensive and hypertensive human subjects and in human cadavers' aortas, PWV and CAVI were calculated. Despite a completely different experimental situation the results of both analyses were similar. Also regression coefficients between C and blood pressure were similar in both experimental conditions.

**Figure 14** Professor Fišer



Figure 15 Professor Siegelová, B. Kenner, Professor Fišer in University Graz in the scientific meeting

COOPERATION WITH UNIVERSITY OF MINNESOTA

The personality of chronobiologist Professor Franz Halberg, (5 July 1919 – 9 June 2013): 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, Director, Halberg Chronobiology Center, University of Minnesota.

Cooperation with Professor Fišer from University Brno and Brno team (Professor Siegelová, Dr. Dušek) took place from 1988 to 2011. The common cooperation led to the nomination of Professor Franz Halberg as Doctor Honoris Causa Masaryk University in 2000. He was a founder of chronobiology, proposed 24-hours blood pressure measurement in 1948. Later he and his team from Halberg Chronobiology Center proposed 7-day blood pressure measurement in 1990.



Figure 16 Prof. Franz Halberg, M.D., Dr. h. c. multi, and prof. MUDr. Bohumil Fišer, CSc., in Brno during symposium Noninvasive methods in cardiology 2003



Figure 17 Professor Halberg, Dr. Souček, Professor Siegelová, B. Kenner, Professor Kenner, Professor Fišer in Brno congress



Figure 18 Professor Fišer, Professor Halberg, Professor Honzíková and Professor Bravený in Brno 1996, Symposium Cardiovascular Coordination in Health and Blood Pressure Disorders, dedicated to 70th Anniversary of Professor Peňáz



Figure 19 Professor Halberg, Professor Bravený, B. Kenner, Professor Kenner, Professor Siegelová, Professor Peňáz and Professor Fišer in Brno 1996, Symposium Cardiovascular Coordination in Health and Blood Pressure Disorders, dedicated to 70th Anniversary of Professor Peňáz

Cooperation with Professor Franz Halberg and with Professor Germaine Cornélissen, Halberg Chronobiology Center of the University of Minnesota, USA started in 1988. The studies of circadian variability of cardiovascular variables and baroreflex sensitivity were published in many papers as the result of this common work.

In 1995 Professor Bohumil Fišer was invited as a distinguished scientist for a lecture to the Supercomputer Institute of University of Minnesota (USA) and presented there the paper about the use of supercomputers in prevention of stroke and cardiac death.

Brno congresses were organized as MEFA Congresses 1990–2006 every year and Noninvasive Methods in Cardiology Eds. Halberg F., Kenner T., Fišer B., Siegelová J. in the years 1994, 1996, 1999, 2002, 2003, 2004, 2007, 2008, 2009, 2010, 2011.

Blood pressure control in man was the main task of the common chronobiological studies. The common work showed that blood pressure measurement in doctor's office is not reliable and sufficient for the diagnosis of hypertension. The measurement of blood pressure using measurement of blood pressure beat-to-beat was described in further studies about baroreflex sensitivity, heart rate variability, blood pressure variability. BIOCOS project showed that we need measurement of blood pressure for longer period of time, not only 24 hours, but seven day ambulatory blood pressure monitoring.



Figure 20 Congress Noninvasive Methods in Cardiology 1999, Brno, St. Anna Hospital

The BIOCOS project in 2006 in Brno discussed the circadian blood pressure variability, MESOR hypertension, Circadian Hyperamplitude Tension, heart rate variability and the risk of further cardiovascular diseases connected with circadian blood pressure changes and the discussion finally was integrated in Consensus on means and need to detect vascular variability disorders and vascular variability syndrome. The vascular variability disorders were also published in the paper devoted to Professor Fišer and his work in the following figures.

Prof. Fišer untimely death notwithstanding, he will be with us in spirit in our efforts to change a medicine based on a number of diagnoses to an objective assessment of many novel rhythms and other variability alterations in cardiovascular parameters. Thereby, health care can change from one based on sheer intuition and hard-to-define experience listing a number of diagnoses to an objective assessment of many novel biological rhythms.

Prof. Bohumil Fišer was a physiologist, scientist and teacher par excellence. He was an extremely busy and productive scientist and excellent organizer of physiological department.

We should never forget that the historical progress in science and medicine was achieved also due to the work of Professor Bohumil Fišer.

**Bohumil FISER (*22.10.1943-†21.03.2011):
Chronobiologist, Emeritus Head of the Physiology
Department at Masaryk University (Brno, Czech Republic),
Czech Minister of Health, and Executive Board Member
of the World Health Organization: His Legacies
for Public and Personalized Health Care**

**Franz Halberg¹, Germaine Cornélissen¹,
Thomas Kenner², Jiri Dusek³,
Brigitte Kenner², Othild Schwartzkopff¹,
and Jarmila Siegelova⁴**

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Republic

In 2003, one of us (JS) dedicated a special volume of papers dealing with non-invasive cardiology [1] to Bohumil Fiser, MD, our dear friend, Figure 1, and, his relatively young age notwithstanding, our mentor and supporter. In that volume, GC and JS laid the basis for a chrononeonatology. Another of us (OS) emphasized the need for long-term, preferably lifetime monitoring of blood pressure and heart rate as a concern for everybody and hence for government and ethics committees.



Figure 1. Bohumil Fiser (1943-2011).

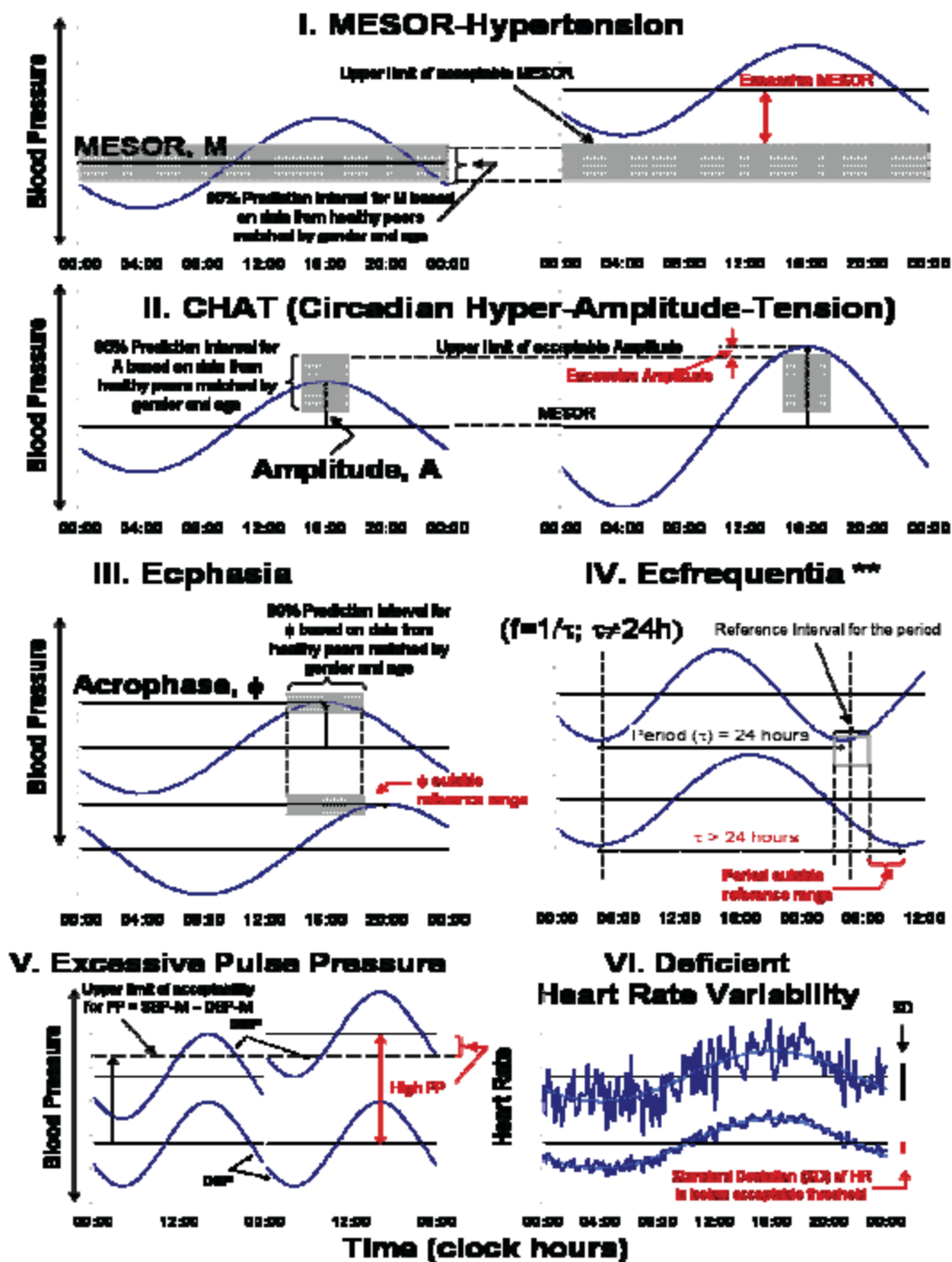


Figure 4. Vascular Variability Anomalies (VVAs) picked up by chronobiologically interpreted 7-day around-the-clock records of blood pressure and heart rate monitoring become Vascular Variability Disorders (VVDs) when they are replicated in successive 24-hour/7-day records. If several VVDs coexist, the risk of an ischemic stroke within 6 years increases from about 5% to near 100%. To the five VVDs in the consensus, we can add a sixth, a circadian desynchronization of the endocrines and the circulation more recently documented as ecfrquentia in association with adynamia and depression recurring mostly twice-yearly in an extensively studied 62-year-old woman [10]. © Halberg.

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PROF. FRANZ HALBERG, M.D., PH.D., DR. H. C. MULTI, 5 JULY 1919 – 9 JUNE 9 2013

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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,
Director, Halberg Chronobiology Center, University of Minnesota, USA

Brno Chronobiology team that cooperated with Halberg Chronobiology Center under the guidance of Professor Franz Halberg from 1988 was deeply sad that Professor Franz Halberg, the great scientific personality, exceptional man, passed away on Sunday, June 9, 2013. Franz Halberg was 94 years and was active until the last days of his life; he cooperated with Masaryk University of Brno and with us. We lost a good friend and a great scientist.

Franz Halberg is a founder of modern chronobiology. Unlike other famous scientists devoting their activities mostly to presentation of honorary lectures at international scientific conferences, Prof. Halberg pursued his scientific work. This fact is demonstrated by the list of his scientific 34000 papers, on WEB of Science which contains 1149 scientific papers, Science Citation Report of Franz Halberg contains 12670 citations, and his H-index is 51. Prof. Halberg has dedicated almost 60 years of his life to chronobiological research.

Chronobiology, the study of mechanisms underlying diversity in time, and chronomics, the mapping of chronomes – time structures, could complement genetics. It is the study of mechanisms underlying diversity in space and also genomics, the mapping of the genomes. Halberg focused on the chronobiologic-chronomic assessment of blood pressure and heart rate variability as the alternative to the spotcheck of blood pressure advocated by official current guidelines. Chronobiology allows us to approach risks, diagnosis and treatment dependent on time, especially of the dynamics of time, gender, age, ethnicity and geographical location.

His chronobiological studies represent a new original Minnesotan branch of science based upon resolving the chronome and its mapping from womb to tomb. Womb-to-tomb chronome initiative consists

in extension of a unique existing data archive and reference standard bank on variables of biomedical interests: heart rate, blood pressure, body temperature, a lot of chemical determinations on blood, saliva and urine.

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

Needless to say, not only those researchers who are deeply interested in this field, but also others who are less interested, have all been strongly impressed by such incomparable records of work achieved by Prof. Halberg. In recent years he has been strenuously promoting chronobiological research further in the field of clinical medicine on the worldwide scale.

In the year 2000, Prof. Franz Halberg from University of Minnesota, USA, received the degree of honorary doctor of Masaryk University and thus has the honor to be a member of Masaryk University Brno. In the last 15 years, the cooperation between Masaryk University and University of Minnesota was intensive and was enlarged also to the international project BIOCOS.

The international project on The Biosphere and the Cosmos originated on June 30, 1997, when the Russian Academy of Medical Sciences convened a special session at its headquarters in Moscow to discuss and, at the end of this meeting, to unanimously endorse a project on "The BIOSphere and the COSmos" (BIOCOS).



Figure 1 Professor Franz Halberg during Symposium in Masaryk University Brno in 2003

The role of chronomics within the context of Non-communicable Diseases and Mental Health is mostly studied in cardiovascular variables but is not limited only to the cardiovascular system. The same methodology remains applicable to a wide range of problems. Cancer prevention and optimization by the scheduling of treatment administration is another important problem. But the main focus of BIOCOS in health promotion upon the circulation by "prehabilitation", to reduce the cost of rehabilitation by education of use of chronobiology.

Chronobiology, studied by Franz Halberg, showed broad spectrum of rhythms in us and around us; they are being marched up by the dozens but have not yet been recognized in terms of their pertinence to everyday life. It should be taught that circadians, now a fashion in molecular biology, tip the scale between life and death, as do extra-circadians, the many different, more or less periodic changes evolved and built into human physiology under the influence of cosmos. Infradians are apparent in military-political affairs, including aggression, notably crime, international battles and terrorism; in economics, in opinion polls, in education and, most important, in health care. Chronobiologically interpreted blood pressure and heart rate monitoring detects prehypertension, prediabetes and a premetabolic syndrome in vascular variability disorders, that interact with a reliably diagnosed MESOR hypertension that can carry a risk greater than a high blood pressure and that can coexist to form vascular variability syndromes, unrecognized in a conventional health care, but some of them already treatable. It is not yet generally known that in the human newborn, variables such as heart rate or blood pressure have an about-weekly component which is more prominent than the 24-hour change and awaits testing as a gauge of risk, or that in the incidence spectrum of sudden cardiac death (ICD10, code I46.1) an about 5-month and an about 17-month (transyear) component, cyclic signatures of space weather, replace Minnesota's midcontinental winters and summers. Dependent on geography, a host of congruent spectral components is found in both spectra of the solar wind and other aspects of space weather on the one hand and in the human circulation, in electrical accidents of the heart and in the extreme depression resulting in suicide on the other hand. When cardiovascular health and its relation to cosmos is viewed in 40 years of around-the-clock measurements, there is selective congruence between about 5-month components in solar flares and in the heart rate of a clinically healthy man. These are the latest discoveries of Prof. Franz Halberg.

Professor Halberg was quite unhappy that his ideas are ahead of the development of science for tens of years. He suggested the ambulatory 24-hour blood monitoring in 1948. The first scientific study using this method in the Czech Republic was published in 1994. Also the treatment of oncological diseases on the chronobiological basis started many years after Halberg suggested it. The last Halberg proposal for diagnosis of vascular variability disorders on the basis of ambulatory blood pressure and heart rate monitoring or self-monitoring lasting several days is nowadays not broadly accepted, even if it enables the risk stratification of hypertensive patients. The risk-stratification guided treatment is more effective than the treatment based on the diagnosis only.

Franz Halberg was a founder of modern chronobiology. Unlike other famous scientists devoted their activities mostly to presentation of honorary lectures at international scientific conferences, hold every year in Brno. Prof Halberg was unhappy that his ideas are ahead of the development of science for tens of years. He suggested the ambulatory 24 hours blood monitoring in 1948. In 1990 started the cooperation between Masaryk University Professor Jarmila Siegelová, Professor Bohumil Fiser and University of Minnesota, Halberg Chronobiology Center, namely Professor Franz Halberg and Professor Germaine Cornélissen. The first scientific study using this method in the Czech Republic was published in 1994 by us.

In 1990 Prof. Franz Halberg and Prof. Germaine Cornélissen visited for the first time Masaryk University in Brno and presented chronobiological results in cardiovascular parameters in man on the Brno Symposium. Immediately, an intensive cooperation started between Brno team, consisting of Prof. Bohumil Fiser, emeritus head of the Physiology Department, Czech ministry of health, Executive board member of WHO, Dr. Jiri Dusek, me and Prof. Franz Halberg and Prof. Germaine Cornélissen from University of Minnesota.

In Brno we carried out at that time the beat-by-beat noninvasive measurement of blood pressure, developed by Prof. Jan Penaz and young scientist Prof. Fiser, measurement of baroreflex sensitivity and heart rate variability and we had the equipment for ambulatory 24-h blood pressure monitoring for adults. University of Minnesota lent us equipment for oscilometric measurement of blood pressure in new born children. At the beginning we started with common scientific work and our data were measured in the Czech population, at first faxed, later on line via e-mail sent to Chronobiological laboratories in Minnesota, Halberg Chronobiology Center and analyzed in the University of Minnesota, USA. Then for 22 years until

now the chronobiological data from Brno were immediately analyzed by Prof. Germaine Cornélissen and the results of these analyses served not only for scientific work, but also for therapy of the Czech population. Between the years 2000 and 2008 the Brno team consisting of Prof. Fiser, Dr. Dusek and me collected 73 888 sets of blood pressure and heart rate measurements and all data were analyzed the following day by Prof. G. Cornélissen. The daily data exchange and analysis continues until now. Very important chronobiological data are found in new born children blood pressure, in blood pressure changes after administration of low dose aspirin, in baroreflex sensitivity, in groups of normotensive subjects and hypertensive patients with antihypertensive therapy and without therapy. The cooperation resulted in a lot of common publications.

From 1990 every year, sometimes two times per year, common meetings were organized in Brno, such as MEFA Congress or chronobiological congress presenting a lot of latest findings and scientific lectures, with the participation of Prof. Cornélissen, Prof. Halberg from Minnesota, Prof. Thomas Kenner, former president of University of Graz, Austria and Prof. J.P. Martineaud, Hopital Lariboisiere, Medical Faculty Paris, France. Prof. Germaine Cornélissen prepared a lot of publications for congresses and symposia in Brno.

The last symposium hold in Brno in May 3 and 4, 2013 was by videoconference taken together with Brno and Minnesota scientist Professor Franz Halberg and Professor Germaine Cornélissen as can be seen in the figure. We believe that we could continue the cooperation between Halberg Chronobiology Center and Professor Germaine Cornélissen to finish the international scientific projects as BIOCOS.

We believe this is Professor Franz Halberg's legacy, to be continued by Prof. Cornélissen of Halberg Chronobiology Center University Minnesota, who will continues cooperate with European and other countries. Our chronobiological team of Masaryk University of Brno will, together with Halberg Chronobiological Center in University of Minnesota, answer scientific chronobiological scientific questions and continue Professor Halberg's scientific work.



Figure 2 Professor Franz Halberg, Dr. Othild Schwartzkopff, Professor Germaine Cornélissen in Halberg Chronobiology Center, University Minnesota on May 3-4, 2013 during Symposium (videoconference) in Masaryk University Brno with participation of Professor Kenner and Brno team from the Department of Physiotherapy and Rehabilitation

SOME REMARKS CONCERNING THE CHRONOBIOLOGY OF EARLY HUMAN DEVELOPMENT

THOMAS KENNER

Department of Physiology, Medical University in Graz

In the work of Franz Halberg, the early development of the human fetus, the birth and the further development of babies and children was not so much in the focus of interest. In connection with the research of our group in Graz, Franz Halberg was visiting Graz, and the Department of Physiology of the University in Graz. One publication of this term was presented in Brno (1). Our interest in early development was raised by the pathologic phenomenon of sudden infant death (SIDS). The study of normal and pathologic development brought us in contact with Prof. Heinz Prechtel. In the meantime a research group is existing and the incidence of SIDS decreased markedly during the last years.

The main research about early human development was initiated and developed by H. Prechtel in Groningen. H. Prechtel is now retired and lives in Graz and he is Honorary Professor in the Department of Physiology of the Medical University in Graz.

Main publications can be found in the book (2) edited by Christa Einspieler, Heinz F.R. Prechtel, Arend F. Bos, Fabrizio Ferrari and Giovanni Gioni - with the Title: "Prechtel's Method on the Qualitative Assessment of General Movements in Preterm, Term and Young Infants." Cambridge University Press, 2004.

HUMAN DEVELOPMENT OF MOTOR CONTROL

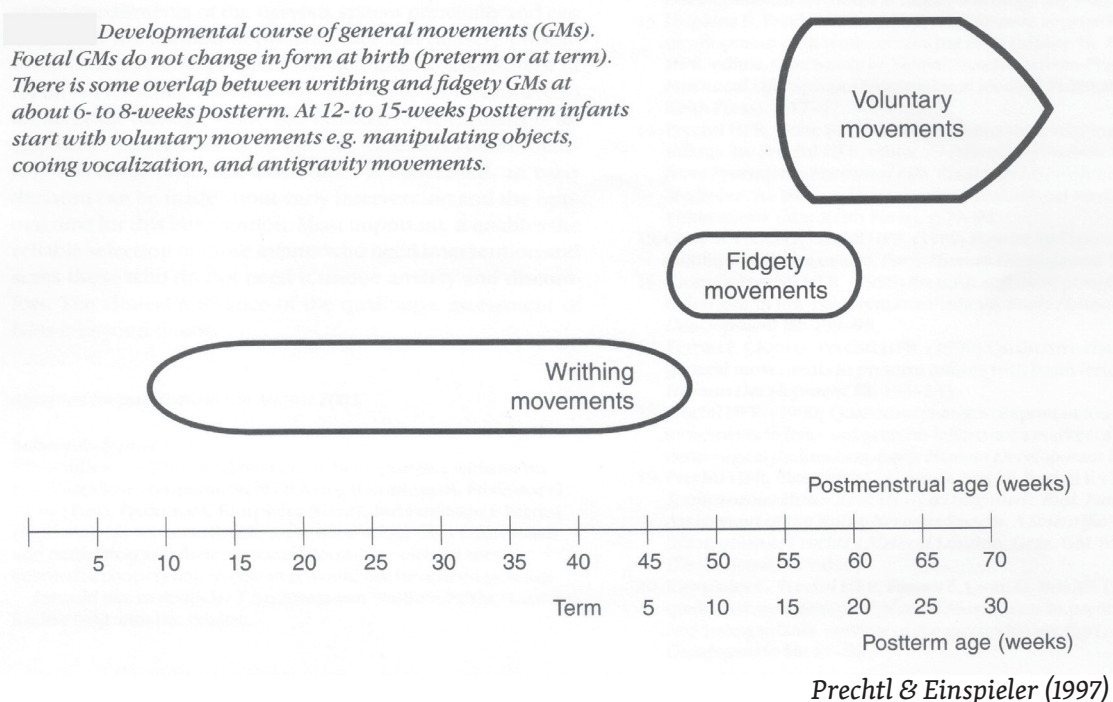


Figure 1 from lit. (2)

On page 10 of the cited book the movements of babies before and after birth are described. The term General movements (GMs) was coined by H. Prechtel in an observational study on spontaneous motility in carefully selected low-risk preterm infants. GMs have by and large a similar appearance from early foetal life until the end of the second month postterm ("term" means time of birth). The GMs are slow and go through the whole body or extremity. About 6 to 9 weeks after birth, GMs with a writhing (slow) character gradually disappear while so-called fidgety (small and more frequent) movements gradually emerge. At

the time of around 20 weeks after birth the fidgety movements disappear and intentional and antigravity movements occur and start to dominate.

In the diagram of the first picture - Fig. 1 - one can see a graphic explanation of the changing pattern of movements. In a rough summary it may be said: *From start on at first slow (writhing) and then faster and faster and finally more and more adjusted to specific needs - including very fast reaction.*

With respect to the so called Sudden Infant Death (short: SIDS, where the final S indicates "Syndrome") the time scale is important. In the first picture Fig. 1, the time scale is presented in weeks, starting with the conception. In the second picture Fig. 2 the time scale is presented in months-intervals and starts with term (birth).

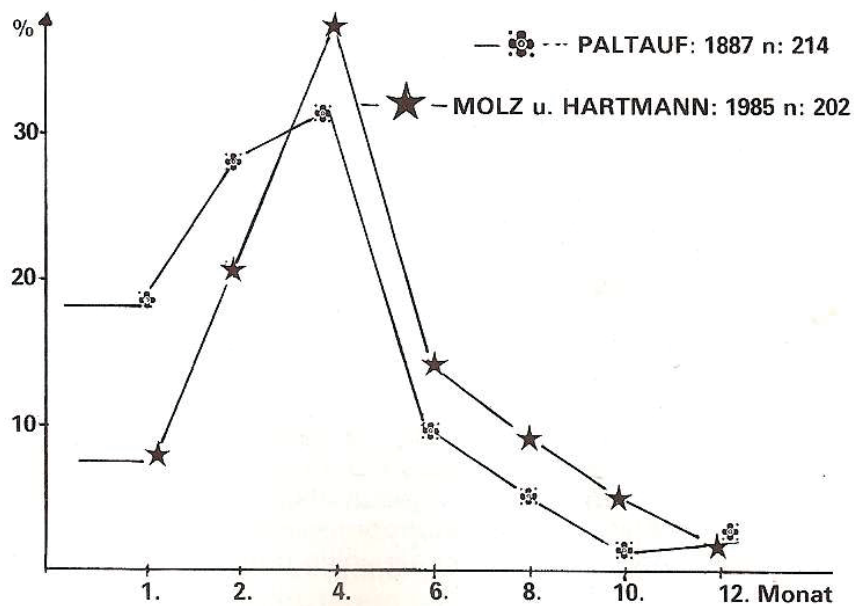


Figure 2 from lit. (3)

In this second picture - Fig. 2 - by Molz and Hartmann (3) the diagram shows on the ordinate the relative numbers in % of the total incidence of SIDS in two publications.

It is noteworthy, that early after birth in the time of slow "writhing" movements the incidence of SIDS is low. Then, with the appearance of fast fidgety movements, the incidence of SIDS increases. The peaks of incidence in the second picture correspond to the time of decrease of fidgety movements.

From an attempt to interpret the modification of the frequency of movements as generated from exiting relatively simple neural networks, the so called **logistic equation** (4) could be used as a model to analyze and simulate generation of movements.

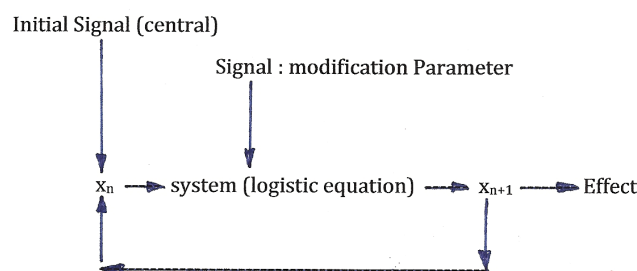


Figure 3 The following sketch shows the basic "structure" of the "logistic equation": The process in this system is initiated from central. One impulse is enough to generate a circular process which as effect can generate (depending on the adjustment by the parameter) periodic processes (slow in one direction "writhing"), periodic fast (may be "fidgety") and - always depending on the parameter - chaotic.

The logistic equation works as a feedback system. A sketch of the basic structure is shown in Fig. 3 at the end of this paper. The “activity” is started by an input signal. The equation can be imagined as describing the activity of a nerve structure network system which modifies the input signal. The output-signal is sent to some effector, and produces at this location an effect, e.g., the contraction of a muscle. However, the same output-signal is at the same time fed back to the entrance of the system. It has the function to modify the next output. Therefore it is obvious that the next output will be different from the first. The result depends on the magnitude of the modification of the signal. It is possible to explain automatic variations of the frequency of the output and other modifications. Under certain conditions such systems may also be able to generate abnormal, chaotic and, therefore even dangerous reactions.

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REMEMBERING A BELOVED TEACHER AND DEAR FRIEND, FRANZ HALBERG (5 JULY 1919 – 9 JUNE 2013) IN APPRECIATION

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Figure 1 Franz Halberg

On Sunday morning June 9, 2013, one of the greatest scientists of the 20th and 21st centuries left us. His close associates also lost a very staunch friend and a mentor who never ceased to inspire. Franz Halberg's passing shy of his 94th birthday leaves a void that cannot be filled.

Over 40 years ago, as a young inexperienced student, I had the good fortune of meeting Franz in Paris at a conference of the Groupe d'Etude des Rythmes Biologiques. That day changed my life. It was the start of an exciting journey in science, when I first discovered quantitative chronobiology (1), then chronomics (2), the two disciplines Franz will be remembered for founding. These new transdisciplinary scientific disciplines could not have come to fruition without Franz's unveiling predictable variations as a function of TIME that occur within the physiological range and his vision that they had far-reaching implications. Franz not only gathered a critical mass of data, he developed inferential statistical methods for their analysis and interpretation, so as to establish a solid foundation for the new science. Details of a rich time structure could thus be revealed, akin to the finer spatial resolution obtained with a microscope. As data accumulated and longitudinal records became available, Franz Halberg's keen observations and methodical scrutiny led him to find periodicities shared between biological systems and their broad environment. Seen (photic) and unseen (non-photic) influences from the Sun and the cosmos led to chronomics in a way reminiscent of discoveries enabled by the advent of the telescope.

Franz Halberg was born on July 5, 1919 in Bistritz, Romania. There, he received his elementary and secondary schooling. Franz received his medical degree from the University of Cluj in Koloszar in 1943. Becoming a citizen of Austria, Franz worked in the Department of Anatomy at the University of Innsbruck from 1946 to 1948 where he studied the adrenal. In 1948, he came to the United States with a World Health Organization fellowship in clinical endocrinology, continuing his work at Harvard Medical School, also holding a position of Assistant in Medicine at the Peter Bent Brigham Hospital in Boston. Franz joined the staff at the University of Minnesota Medical School in 1949. There, his breakthrough experiments led to the important discovery that circadian rhythms are partly endogenous and can be manipulated by environmental synchronizers, notably the lighting and feeding schedules (3, 4). His documentation that biologic rhythms tip the scale between health and disease and even between life and death led him to coin the term circadian (5). Franz's results were widely published, including a 1969 citation classic (1). By 1958, Franz had recognized the important role played by the cell's RNA and DNA cycles. He was first to show that the hypothalamic-pituitary-adrenal system served as mediator of photic inputs (6). Pineal feedsideways were subsequently added, as was the understanding that there are endogenous physiologic networks that respond to the cosmos (7, 8).

Franz's recent work demonstrated that, beyond circadians, many built-in cycles resonate in part with their counterparts in our broad environment. The growing edifice of shared periodicities with bridges across disciplines Franz built (9, 10) addresses wide-ranging applications, from the optimization of individualized health care to concerns for the health of societies. Franz strived to understand how to enhance positive thoughts and emotions as a scaffold for tolerance and love by seeking optimal configurations of the time structured realm of the mind, what he called the chronosphere (11). He was a scholar in the true sense of the word, combining science, philosophy, poetry, and spirituality, laying the foundation of chronobioethics (7).

Franz's legacy is far-reaching. He will not only be remembered for his work in cancer chronotherapy, showing that increased efficacy and lesser undesired side effects can be achieved by timing cancer treatment according to marker rhythms (12). Franz will also be remembered for showing that a calorie acts differently whether it is consumed at breakfast or dinner (4, 13). But first and foremost, his principle of "Primum nil nocere" (above all, do no harm) prompted Franz to advocate the individualization of treatment, guided by marker rhythms, with important applications in preventive cardiology. By screening for abnormal patterns of blood pressure variability (10), appropriate circadian timed treatment more than halved the risk of stroke and other adverse cardiovascular events. Franz's approach to primary prevention, which he called "prehabilitation" aimed at curtailing the need for rehabilitation.

Franz Halberg is regarded as the father of modern chronobiology and its undisputed leader, particularly as it relates to biomedical research and therapy (14). Many trained in his laboratory over the years, including senior investigators and leading chronobiologists. Franz Halberg served for more than 10 years as President of the International Society for the Study of Biological Rhythms, and, after the Society's name was changed in 1971 at its meeting in Little Rock, Arkansas, he continued to serve as President of the International Society for Chronobiology for another 15 years (14). Franz also served as Editor-in-Chief of the journal *Chronobiologia*, published between 1974 and 1994, the then official journal of the Society.

Many worldwide indeed call Franz Halberg their mentor and turned to him for advice, from study design and data analysis to the interpretation of results in the time dimension. In cooperation with colleagues from around the world, Franz authored over 3,500 scientific publications. He treasured the close cooperation with the Brno team. Together, we showed that timing the administration of low-dose aspirin could be optimized (15) and that the best circadian stage for its anti-coagulation action differed from that related to its blood pressure lowering effect (16) in an N-of-6 pilot study (Figure 2). Together, we mapped the biologic week in neonates, demonstrating its partly endogenous nature (17), Figure 3. Together, we learned about Vascular Variability Disorders (18) and their bearing on adverse cardiovascular outcomes (19) (Figure 4), to cite but a few examples of a lasting fruitful cooperation.

CIRCADIAN RESPONSE TO ASPIRIN (100 mg/DAY FOR 1 WEEK) IN HEALTHY WOMEN

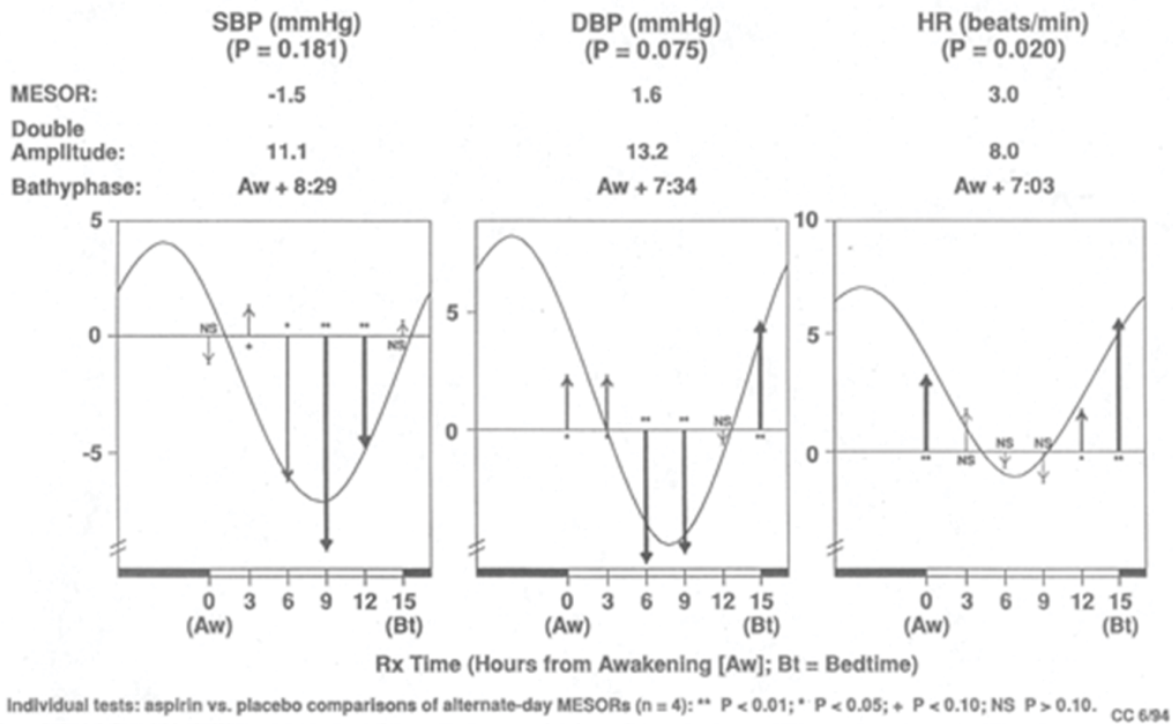


Figure 2 Low-dose aspirin lowers blood pressure when administered in the afternoon but not when it is taken upon awakening or around bedtime.

LARGER PROMINENCE OF ENDOGENOUS (LEFT) THAN EXOGENOUS (SOCIAL; RIGHT) CIRCASEPTAN CHRONOME COMPONENT OF NEONATAL SYSTOLIC BLOOD PRESSURE (SBP)

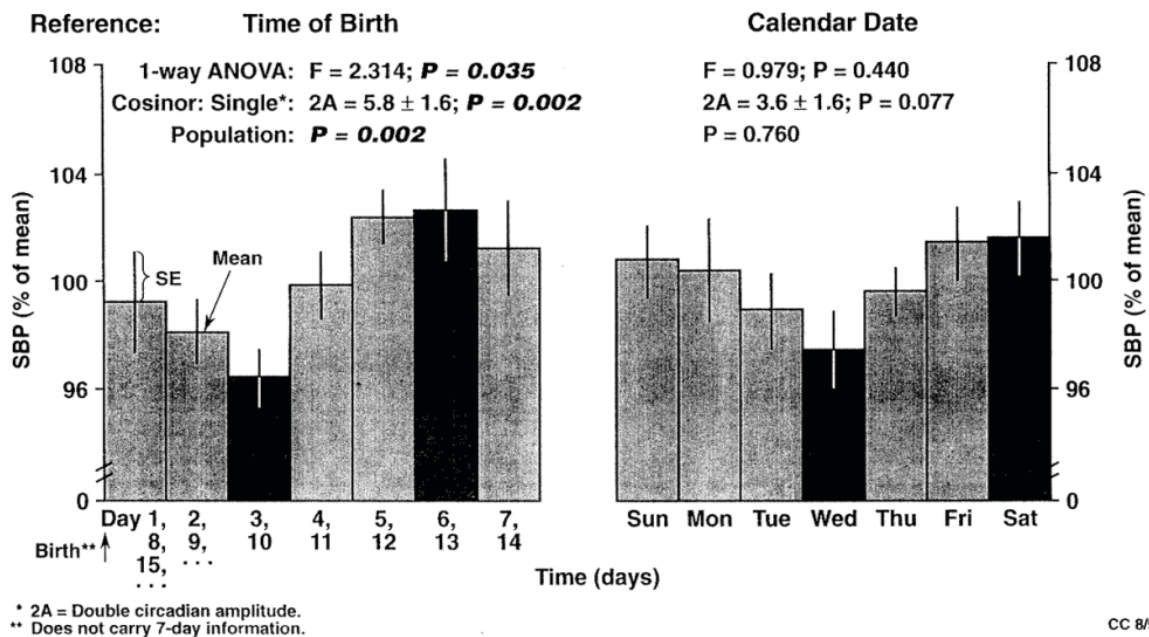


Figure 3 The about 7-day (circaseptan) component in systolic blood pressure of neonates monitored in early extrauterine life is synchronized among different babies by the time of birth rather than by the day of the week, suggesting that developmental age is more important than the social schedule

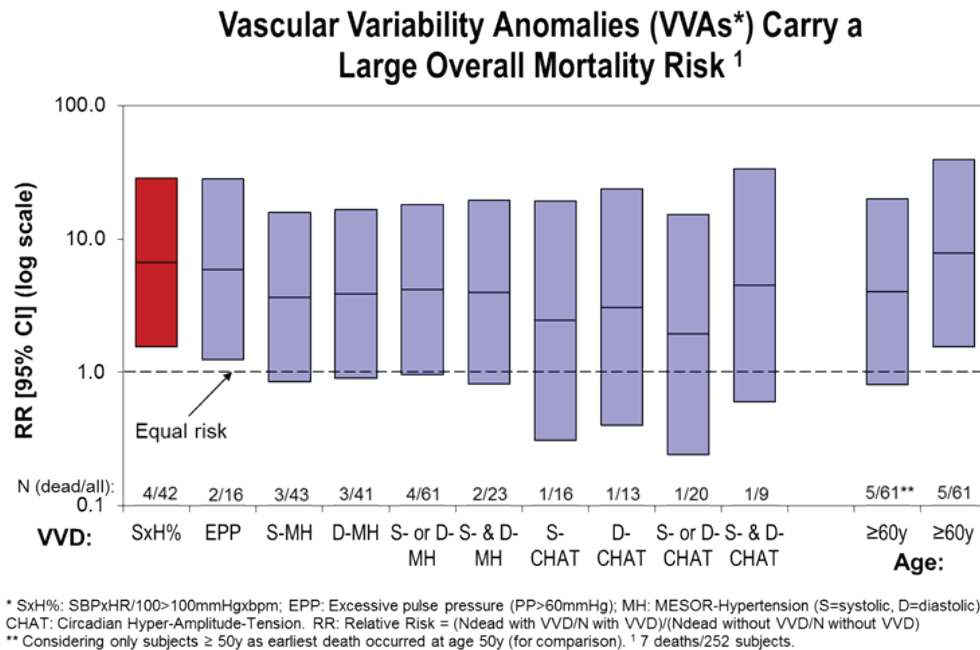


Figure 4 Results in Brno, Czech Republic: a Pulse Pressure product (PPP) above 100 (mmHgxbpm)/100 is associated with a relative risk (RR) of overall mortality statistically significantly larger than one, as seen from the non-overlap of one (equal risk) by the 95% confidence interval (CI) of RR. The risk associated with an excessive PPP is compared with the risk of other Vascular Variability Anomalies (VVAs) or Disorders (VVDs) in the same population.

Minnesota Medicine called Franz Halberg “Father Time” (20), and colleagues in Russia and Azerbaijan honored him as “Lord of Time” (21). Franz’s endeavors earned him numerous awards. Apart from holding professorships in Laboratory Medicine and Pathology, Physiology, Biology, Bioengineering and Oral Medicine at the University of Minnesota, he was a Fellow of the New York Academy of Science and of the American Association for the Advancement of Science. Franz was a honorary member of the Romanian Academies of Science and Medical Sciences. He was also elected Corresponding Member of the French National Academy of Medicine. His Chronobiology Laboratories were officially affiliated with the University of L’Aquila in L’Aquila (Italy), the René Descartes University in Paris (France), and the Faculty of Computer Science at the Autonomous University in Madrid (Spain). Franz received medals from the University of Montpellier (France), the University of Krakow (Poland), the University of Ferrara (Italy), the University of Szeged (Hungary), and the Therapeutic Society of Moscow (Russia). Franz also received honorary doctorates from the University of Montpellier (France), Ferrara (Italy), Tyumen (Siberia), Brno (Czech Republic), L’Aquila (Italy), and People’s Friendship University of Russia (Moscow, Russia). Franz was awarded the prestigious Arnold-Lucius-Gesell Prize from the Theodor-Hellbrügge Foundation. He was an elected member of the prestigious Leibniz Society and of the International Academy of Science. His achievements in the new field of chronomics earned him the O.Yu. Schmidt Medal and diploma for outstanding merits in development of geophysics, the first such award given to a non-physicist.

Until his last breath, Franz strived to introduce timing for diagnosis, prognosis, treatment, and first and foremost prevention into clinical practice. At over 93 years of age and still active 7 days a week in the Halberg Chronobiology Center at the University of Minnesota, which continues his work, he was one of the last two recipients of a lifetime career award from the National Institutes of Health. The impact Franz had in science stemmed not only from his original findings but primarily from his vision of their implications that led beyond a scientific breakthrough to a new way of thinking. Franz’s incredible persistence and intellectual clarity in the face of entrenched thinking in fields that transcend disciplinary boundaries sets him apart as a truly great scientist. As we say farewell with a great sense of loss, we remember Franz Halberg as a trail blazer who leaves a remarkable legacy that will live forever.

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DR OTHILD SCHWARTZKOPFF CHRONOBIOLOGIST, HALBERG CHRONOBIOLOGY CENTER UNIVERSITY OF MINNESOTA, USA

GERMAINE CORNÉLISSEN

Halberg Chronobiology Center University of Minnesota, USA

With great pleasure, we honor Dr Othild Schwartzkopff on the occasion of her birthday this month.



Dr Othild Schwartzkopff was born on 18 May 1922 in Germany and received her medical degree in 1946 at the University of Goettingen. After an Internship at the hospital in her home town (1946–1947), and residencies in surgery (1947–1948) and medicine (1949–1950) in Duderstadt, she joined the Pediatrics Department of the General Hospital in Rheydt/Rheinland (1952–1955), and later the Children's Tuberculosis Institute in Ayrath/Rheinland (1955–1958).

When Othild moved to Canada in 1958, she worked as an intern and later as a resident at the Grey Nuns Hospital and at the General Hospital in Regina, Saskatchewan. Othild completed her residency in 1960. She passed the Licenses Examination in Winnipeg, Manitoba, in 1960. She worked as a General Practitioner in her own private practice in Herbert, Saskatchewan, from 1960 to 1962. From 1962 to 1963, she held the position of a pediatric resident at Vancouver General Hospital. She was licensed in British Columbia. In 1963, Dr Schwartzkopff became a Member of the College of Physicians and Surgeons. She then moved to Sault Ste. Marie, Ontario, where she continued her work as a pediatrician in a group practice from 1963 to 1968.

In September 1964, while continuing to practice in Canada, Othild passed her American Board of Pediatrics in Minneapolis, Minnesota, USA. In 1967, she passed the Basic Science Examination at the Minnesota State Board of Examiners. After passing the examinations of the State Board of Medical Examiners in July 1968, she received her license to practice and moved to Minnesota. Dr Schwartzkopff became a Fellow of the American Academy of Pediatrics (FAAP) in April 1971. From 1968 to 1988, she was in general pediatric practice in St. Paul, Minnesota, USA. During her last years in practice, she held a clinical academic position in the Pediatrics Department at the University of Minnesota. There, as a clinical assistant professor of pediatrics, she introduced second year medical students to the problems they might face in practice.

Throughout her career, Dr Schwartzkopff has volunteered her time and talents in delivering health care in places as varied as the Amazon rainforest, Peru, and parts of Mexico.

In the mid-1990s, Dr Schwartzkopff joined the Halberg Chronobiology Center, where she now serves as a Clinical Director. She already had an interest in the cardiovascular system and chronobiology when in 1945, for her dissertation on "The effects of nicotinic acid and nicotinic acid amide on the cardiovascular system, blood pressure in particular", she measured the blood pressure at about the same time each day, covering usually at least a week on each patient. She thus collected data that are now of interest in a transverse way for looking at about half-weekly and weekly components. As part of the BIOCOS Project, Othild has indeed participated in many studies, with collaborators around the world, as attested by her over 270 publications and her numerous invitations to lecture abroad, notably here in Brno, but also in Austria, China, India, Russia, Saudi Arabia, Slovakia, Taiwan, Turkey and Vietnam, among others. Her message reflects that of the Center, namely to screen for Vascular Variability Anomalies for pre-rehabilitation, while using the information from longitudinal records to learn about influences from our environment near and far, striving for a unified science.

Ad multos annos sanos!

DECADAL AND MULTIDECADAL CYCLES IN THE CARDIOVASCULAR SYSTEM, RELATING TO DIAGNOSIS AND TREATMENT?

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Brno is renowned for Johann Gregor Mendel, who is regarded as the father of modern genetics (1). But Mendel also studied astronomy and meteorology. The majority of his published works were related to meteorology. Broad time structures (chronomes) in us have a strong genetic component which, in turn, entered the genome in response to environmental chronomes, explored meteorologically by Mendel. The more remote environmental origin of rhythms and their less remote genetic aspect both qualify biological chronomes as the legacy of Mendel the meteorologist as well as the geneticist.

The need for coordinated physical and biological monitoring, the topic of a project on The BIOSphere and the COSmos (BIOCOS) to complement genomics, can also be viewed as the legacy of Mendel the meteorologist/cartographer. The mapping of chronomes in organisms and their environment is also associated in Brno and beyond with the work of Jarmila Siegelova. Evidence gathered by BIOCOS suggests that genomes have incorporated more and more of the cycles of the very environment in which they evolved, not only by an adaptive natural selection but also by an integrative evolution (2, 3). Herein, we describe the path from circadian to multidecadal variability, from Mendel's genetics to Siegelova's chronomics, achieved by adding TIME as an indispensable dimension in biology. Chronobiology having emerged from entering the physiological range to resolve lawful variations in time otherwise regarded and random and trivial, it has been described as a microscopy in time (Figure 1).

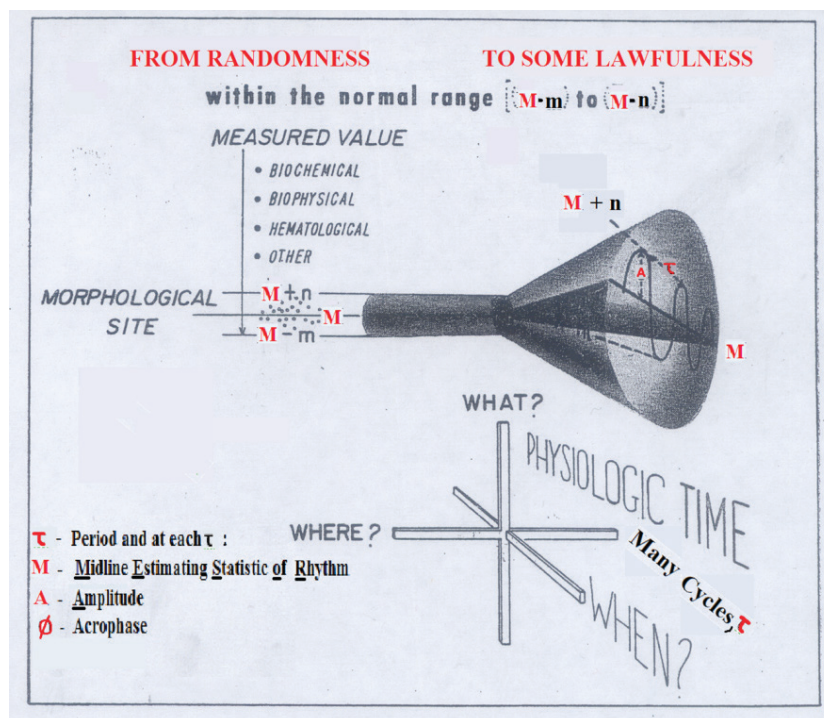


Figure 1 Compared to the microscope enabling a higher spatial resolution, chronobiology achieves a higher resolution in time by entering the physiological range to resolve lawful variations as a function of time. © Halberg.

In 1603, Harvey wrote that the movement of the blood is due to the beating of the heart. In 2013, we add that the human blood circulation reflects the PAST and PRESENT signatures of the cosmos (4). Variability in the count of eosinophil cells (5) led to the coining of “circadian” in 1950. This predictable variation could not have been obtained without splitting the otherwise unexplorable fiction of a normal range invariably applied indiscriminately for either sex at any age. Just as circadians could be resolved by entering the normal range, so can other cycles, as demonstrated herein for the multidecadals.

Just as the atom can be split to release energy (as apparent from the Trinity nuclear test on 16 July 1945), splitting the normal range releases information. It led to personalized spheres of the human mind, or chrono-noosphere (briefly chronosphere), in keeping with a prediction by Stetson that “Perhaps some ... science shall yet evolve, that shall discover that Mind after all is the one persisting reality” (6). With the atomic bomb releasing nuclear energy, we learned what the stars had done and are doing with their atoms. Humans, in turn, changed the passive internal and equally passive external Darwinian evolution into one guided by the sphere of the human mind. We can monitor it on ourselves for personalized surveillance while our emotions and thoughts and the mental accomplishments of a few contribute to a generalized chronosphere, Figure 2.

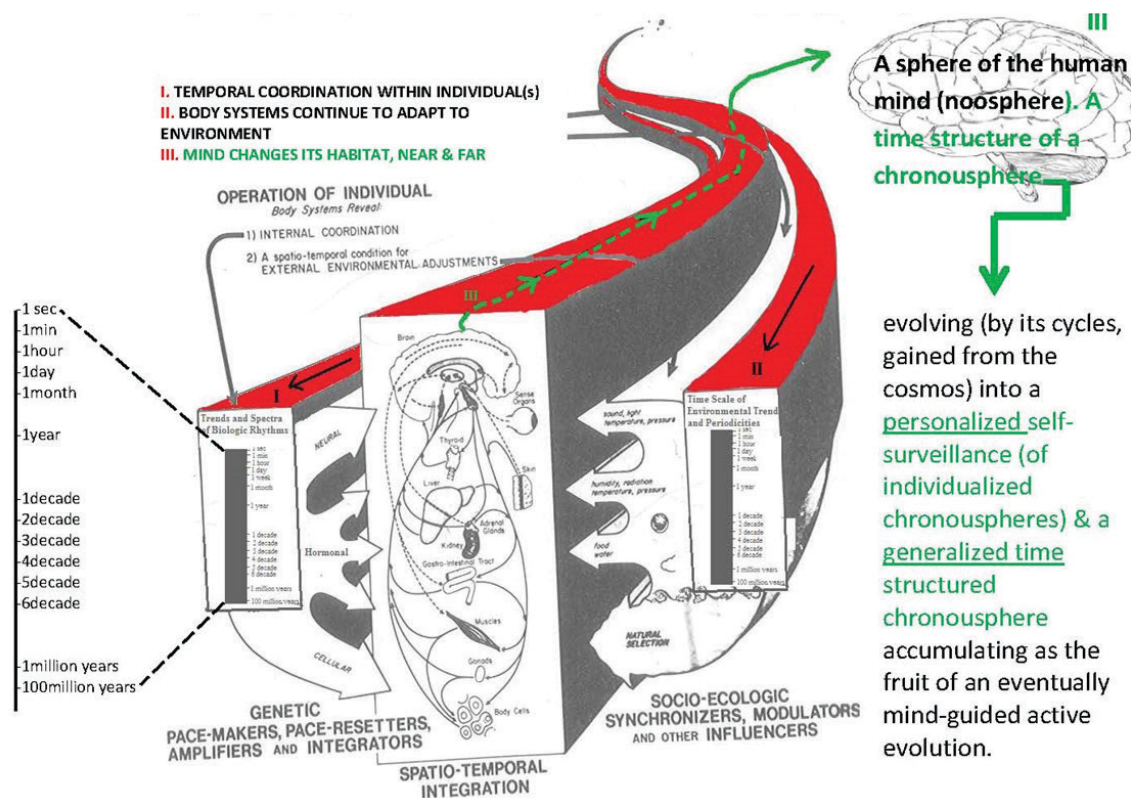
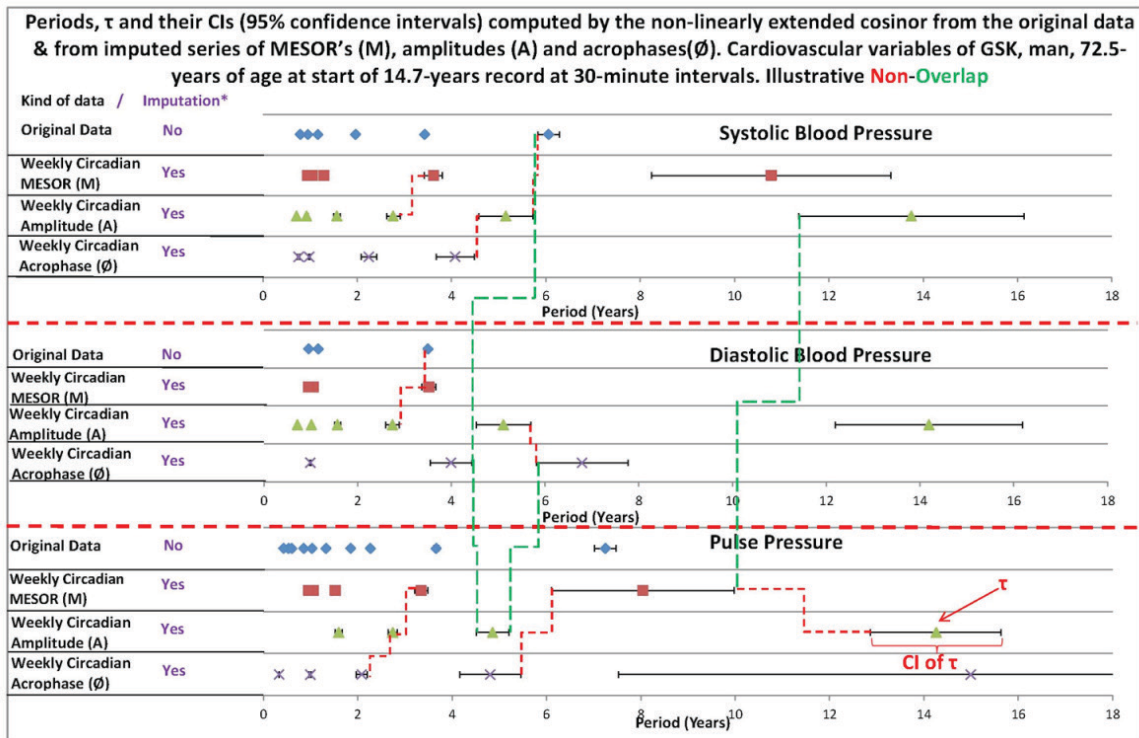


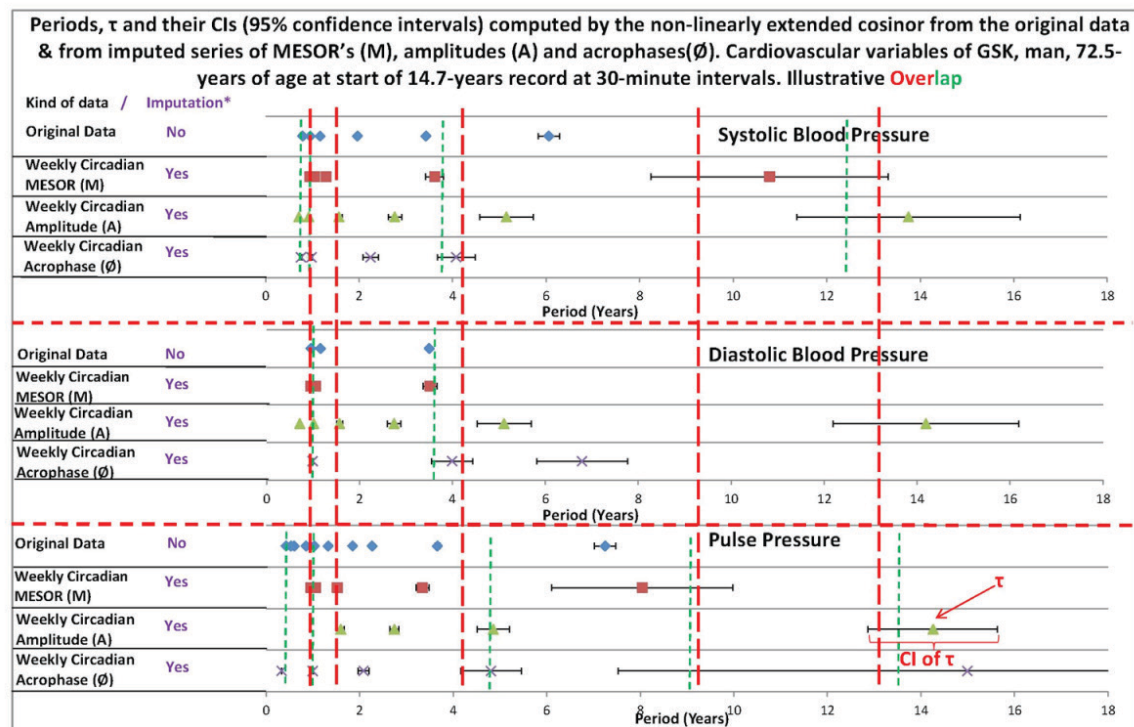
Figure 2 Passive (I & II) versus eventually active (III) evolution. From: adaptations of an organism’s parts to each other (I) and to their environment (II) via hominization by an internally (left, I) and externally (middle, II) coordinated passive evolution with overdue monitoring of individuals and species (chronobiology) and of societies and of their habitats (chronomics); To: a personalized surveillance of individuals’ chronospheres and a generalized chronosphere (right, III) on the maturing time structured internet for resolving interactions of socio-ecologic synchronizers, modulators and other influencers with genetically coded pacemakers, pace-resetters, amplifiers and integrators in a spatio-temporal structure, manifesting itself with a wide frequency range at different levels of integration. I & II drawn in consultation with the late Andrew Ahlgren. © Halberg.

By 1969, rhythms obvious to the naked eye in different frequency regions relevant to different physiological systems and specifically to the nervous system were aligned with a very broad ultradian to multi-decadal transdisciplinary spectrum. We learned that in the same variable of the same person cycles with different periods can be detected and that the 95% confidence intervals of some of their periods overlap across different variables while others do not overlap, Figures 3–6.



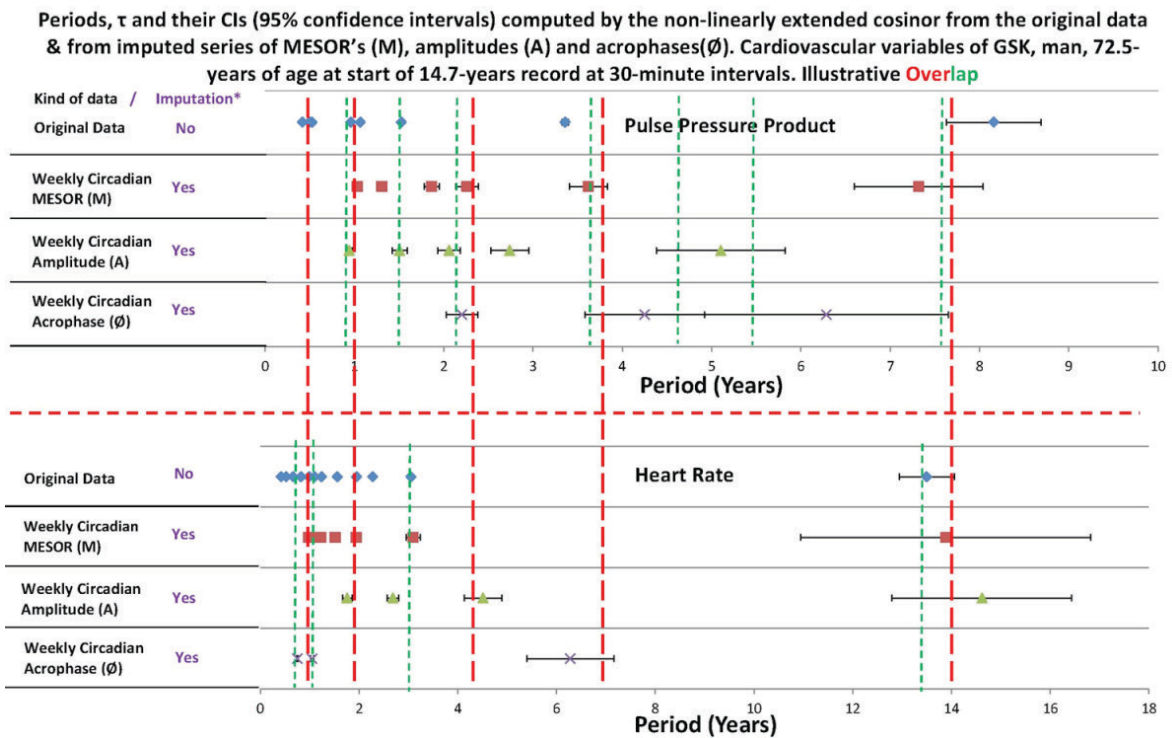
* Intermediate computation of 24-hour rhythm characteristics, in consecutive 168-hour sections of 14.7-years long record. Some conservative CIs (according to Marquardt) are invisible (small). **Non-Overlap** (vertical dashed line) among characteristics within a variable-red; among variables-green.

Figure 3 Example of non-overlapping 95% confidence intervals of components characterizing systolic and diastolic blood pressure and pulse pressure. © Halberg.



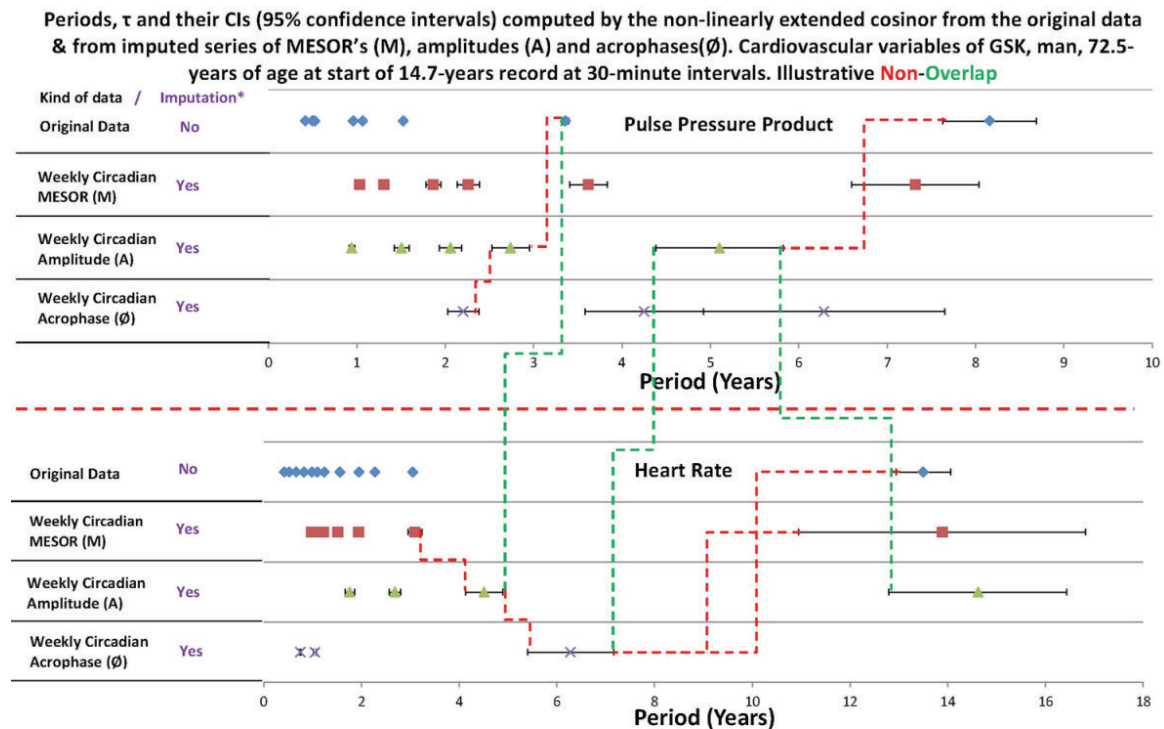
* Intermediate computation of 24-hour rhythm characteristics, in consecutive 168-hour sections of 14.7-years long record. Some conservative CIs (according to Marquardt) are invisible (small). **Overlap** (vertical dashed line) among characteristics within a variable-green; among variables-red.

Figure 4 Example of overlapping 95% confidence intervals of components characterizing systolic and diastolic blood pressure and pulse pressure. © Halberg.



* Intermediate computation of 24-hour rhythm characteristics, in consecutive 168-hour sections of 14.7-years long record. Some conservative CIs (according to Marquardt) are invisible (small). **Overlap** (vertical dashed line) among characteristics within a variable-green; among variables-red.

Figure 5 Example of overlapping 95% confidence intervals of components characterizing systolic and diastolic blood pressure and pulse pressure. © Halberg.



* Intermediate computation of 24-hour rhythm characteristics, in consecutive 168-hour sections of 14.7-years long record. Some conservative CIs (according to Marquardt) are invisible (small). **Non overlap** (vertical dashed line) among characteristics within a variable-red; among variables-green.

Figure 6 Example of non-overlapping 95% confidence intervals of components characterizing systolic and diastolic blood pressure and pulse pressure. © Halberg.

Congruences (continuous vertical red lines) & incongruences (non-overlaps) among cycle lengths, τ , in cardiovascular variables of a man (SBS) η with the τ scale in 4 consecutive sections (from top to bottom, shortest τ left top, longest τ bottom right)

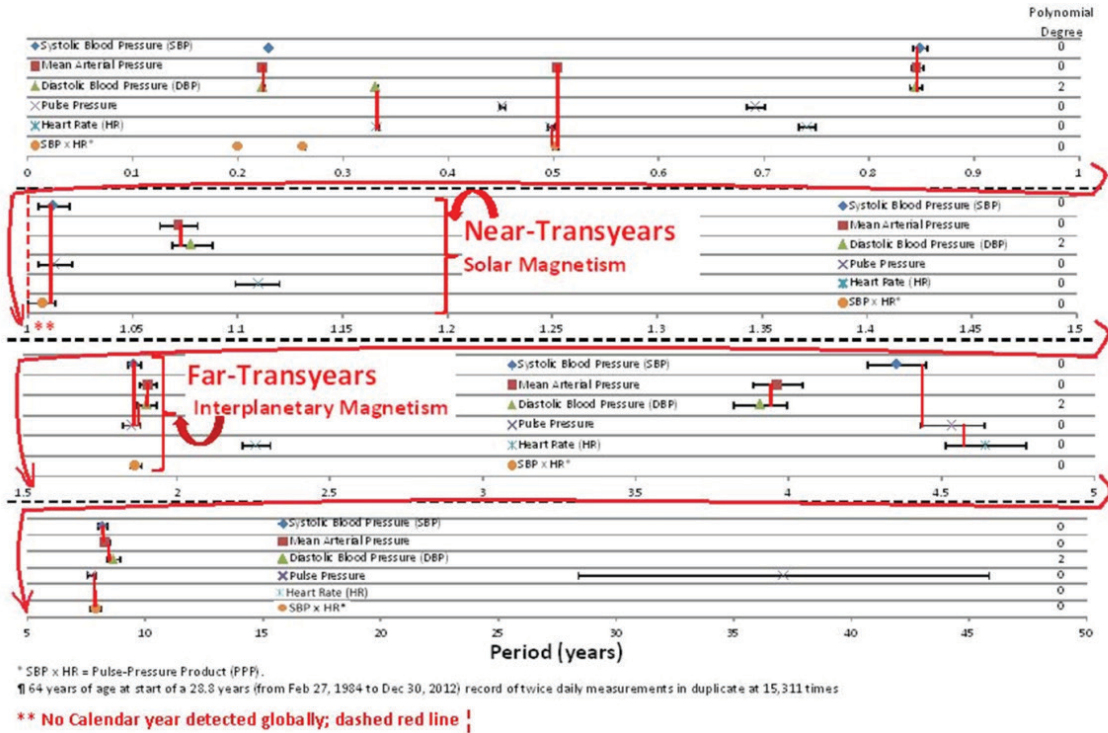


Figure 7 Similarities and differences in cycles characterizing cardiovascular variables self-measured for 28.8 years by a man (SBS). © Halberg.

Congruences (continuous vertical red lines) & incongruences (non-overlaps) among cycle lengths, τ , in the cardiovascular variables of a woman (MIS) η with the τ scale in 4 consecutive sections (from top to bottom, shortest τ left top, longest τ bottom right)

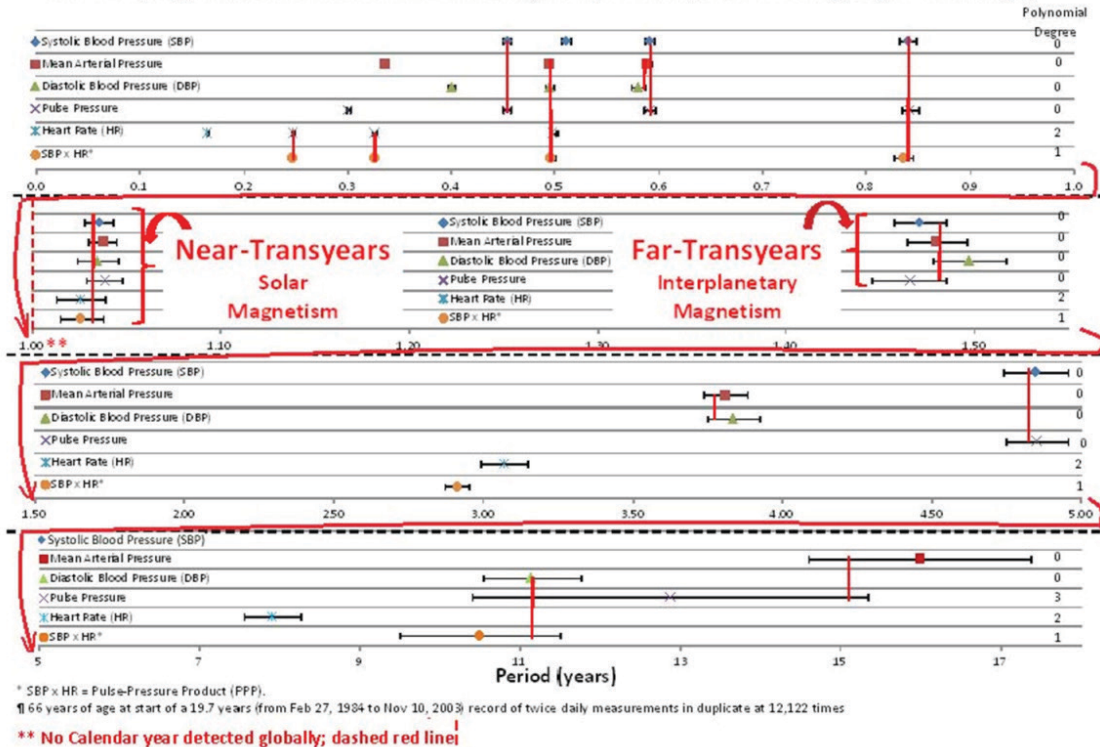


Figure 8 Similarities and differences in cycles characterizing cardiovascular variables self-measured for 19.7 years by a woman (MIS). © Halberg.

As shown in a 28.8-year record, a broad spectrum unfolds, Figure 7. A 0.5-year component in arterial pressure and heart rate is likely a signature in geomagnetics. Near-transyears in systolic blood pressure, heart rate and pulse pressure product may be related to solar magnetism. Far-transyears are also detected. The near- and far-transyears, together with decadals, are also detected in a 19.7-year record, Figure 8. The presence of near-transyears (with a period slightly but statistically significantly longer than one year) illustrates the need to analyze longitudinal records without first stacking the data monthly over a presumed calendar year cycle, as done since the days of General Sir Edward Sabine and Julius Bartels (7).

Cycles with periods clustering around 5 and 10 years are found in longitudinal records of blood pressure and heart rate from several individuals spanning several decades. Cycles with similar periods are also found in anthropometric records at birth (8), Figure 9. Summarizing the periods of the cycles detected in these longitudinal records in a histogram reveals a sharp peak around 10 years, Figure 10.

The foregoing summaries stem from global analyses, that is from analyses of the records as a whole. Because non-photic cycles tend to be non-stationary, complementary local analyses are recommended. In order to gain information about changes in cycle characteristics as a function of time, local analyses include gliding spectral windows and chronobiologic serial sections. Both methods are based on analyses carried out on intervals shorter than the entire record that are progressively moved by a given increment throughout the entire record. It is recommended to use varied interval lengths. Gliding spectra aligned with global spectra are “glocal” in that they provide both a local view of changes with time in a given spectral range and an overall global assessment of all available data.

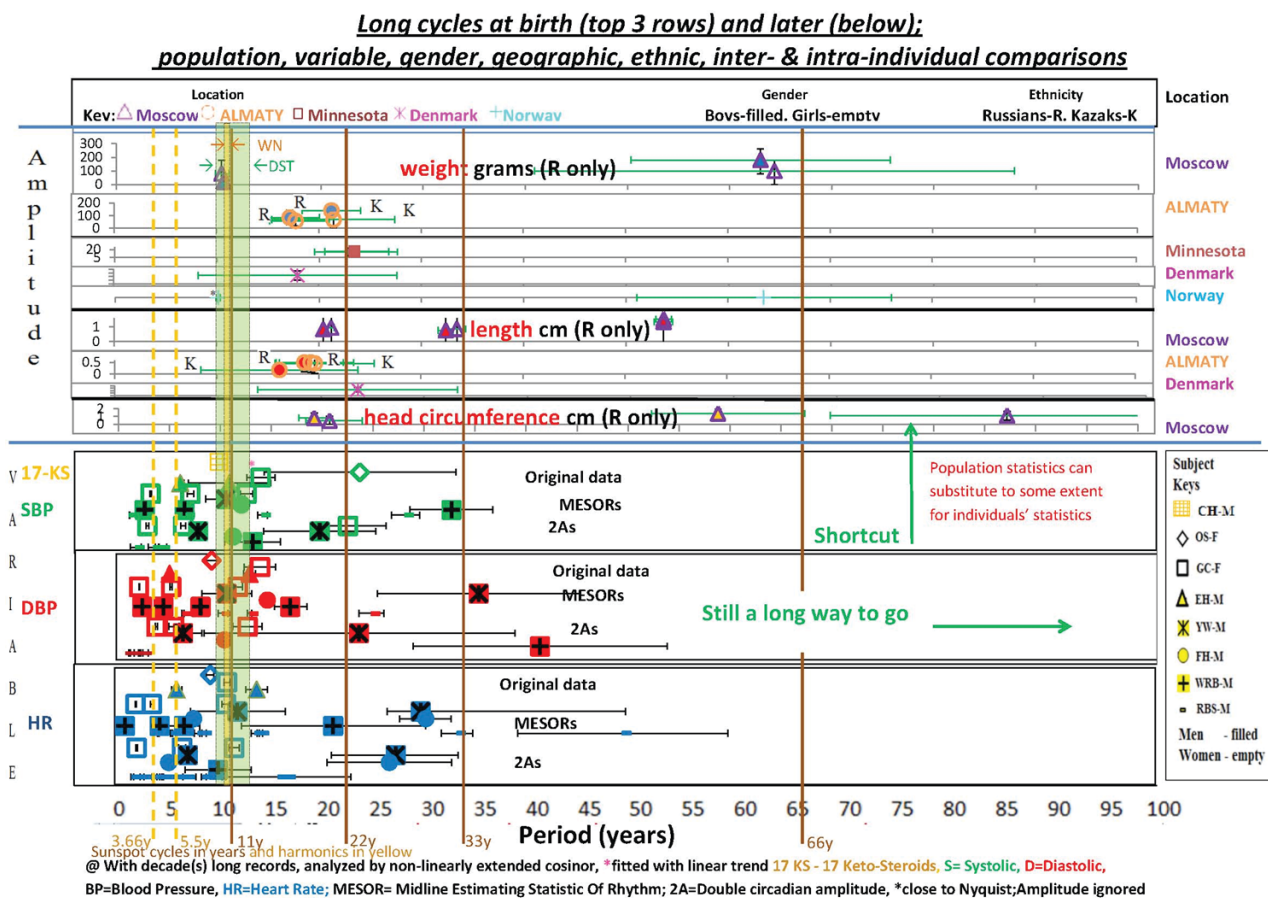


Figure 9 Periods of cycles detected with their uncertainties in anthropometric measures at birth and in systolic (S) and diastolic (D) blood pressure (BP) and heart rate (HR) of 7 bio-medical scientists, including 5 physicians, four of them under hypotensive treatment. Another subject (CH-M) contributed data on the urinary excretion of 17-ketosteroids (17-KS) for 15 years). Note cluster around 10 years with a vertical shaded yellow band indicating Wolf numbers during the prior 100 years with their uncertainty and a vertical shaded green band giving the 95% confidence limits of the period of the equatorial geomagnetic index Dst during the past 27 years. © Halberg.

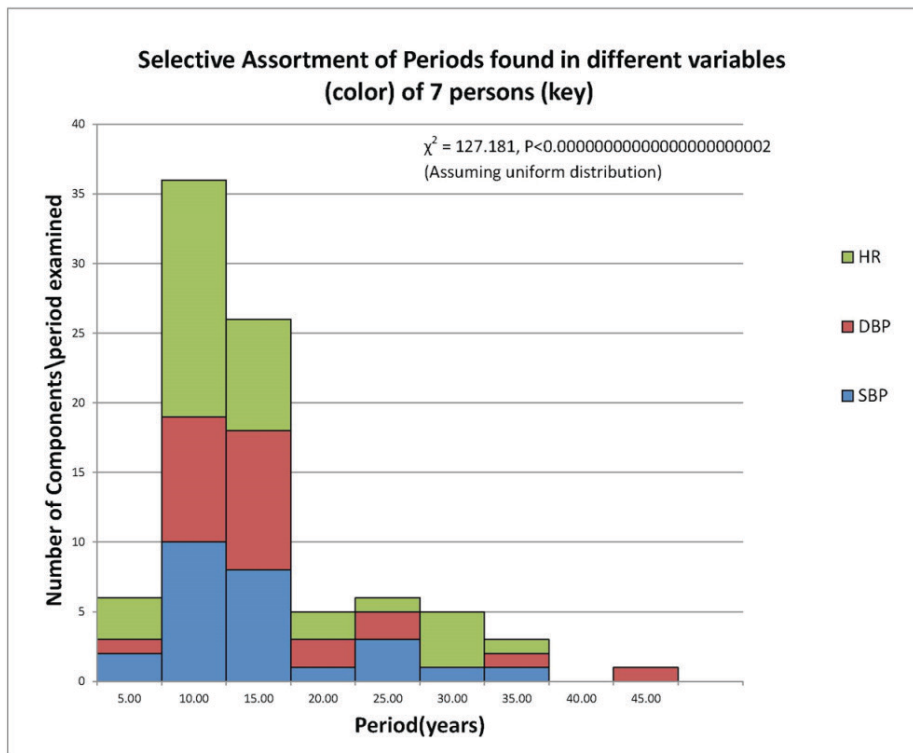
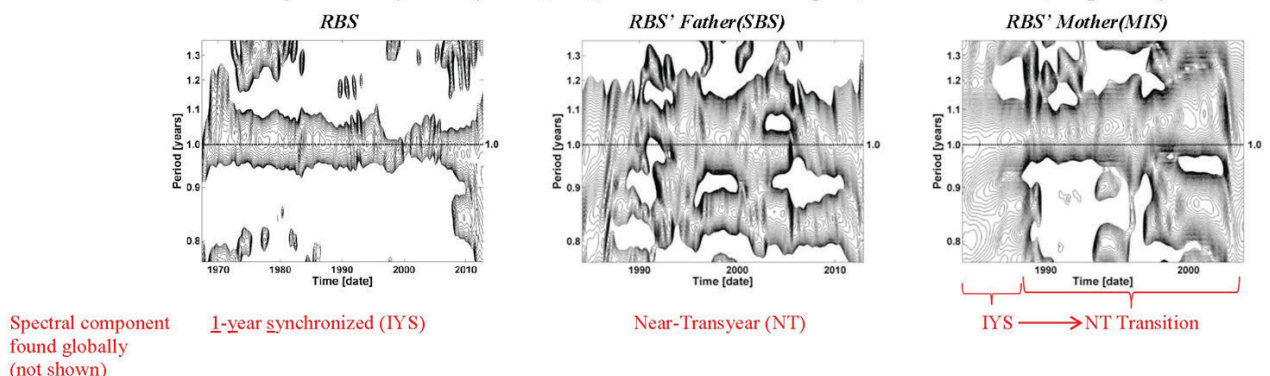


Figure 10 Cluster of periods in the human circulation peaking putatively near the peak of the Horrebow-Schwabe cycle in relative sunspot (Wolf) numbers. © Halberg.

To these “glocograms” (9), local sliding spectrograms (10) were added, as illustrated in Figure 11. It can be seen that lines are really bands when sliding spectra are used to summarize them. Whereas a 1-year synchronized component is seen to characterize systolic blood pressure of RBS (Figure 11, left), a much broader spectral band is observed for his father (Figure 11, middle), and for his mother (Figure 11, right) the period becomes longer than 1 year toward the end of the record.

Spectrograms with 10-year Window Reveal Differing Time Structure in the Paraannual Region of Systolic Blood Pressure Self-measured by a Clinically Healthy Man (RBS) and his Parents During ~45, ~29 and ~20 Years, Respectively*



*Note 1-year synchronized circannual component in RBS (left), near-transyear (also found globally, not shown) in his father (middle), and transition from a calendar year to a near-transyear component in his mother. Results of RBS stem from 5-6 measurements a day as he aged from ~20.5 to ~65.5 years; those of his parents stem from measurements in the morning and evening, as his father aged between ~64 and ~93 years and of his mother between ~66 and ~86 years.

Figure 11 Summary from familial rhythmometry: the systolic blood pressure of the son (RBS; left) is characterized by a 1-year synchronized component, with a band riding on precisely 1-year; that of the father (SBS; middle) and of the mother (MIS; right) show an about-yearly component with its period lengthening as a function of time. Analyses by J Czaplicki (10). © Halberg.

Departure from the 1-year synchronized calendar year has been observed in other instances. To distinguish between circannual and para-annual variations, it is thus important to estimate the period with its 95% confidence interval. Non-overlap of 95% confidence intervals of periods of two or more variables has been used as a criterion of congruence (11). By the criterion of congruence, the estimation of 1 minute by a healthy man more than matched in its association with either terrestrial or solar magnetism the association of terrestrial to solar magnetism with each other (11, 12).

Now that a molecular basis has been documented underlying the circadian system, it is widely accepted that the about-daily variations in physiological functions are partly endogenous and that they can be synchronized by environmental cycles such as the lighting regimen, temperature and the feeding schedule. As organisms evolve in an open environment, the question may be raised whether cycles shared between biology and physics may also be partly inherited, in view of the coperiodisms observed in different frequency regions between organisms and their environment. After all, cycles are essential for life (13)!

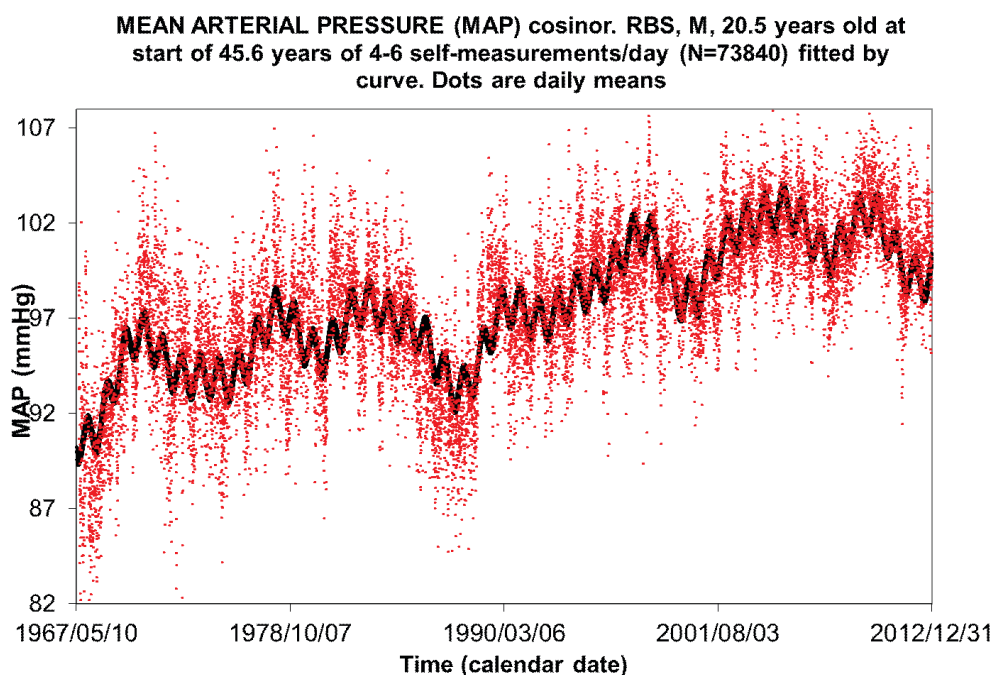


Figure 12 Illustrative example of long record: mean arterial pressure self-measured for 45.6 years by a healthy man.

Data (dots) are fitted with a model determined by the extended linear-nonlinear cosinor.

Periods of cycles thus detected in this and other longitudinal biospheric records spanning decades are summarized in the histogram shown in Figure 13. © Halberg.

As an example of the magnitude of long cycles characterizing vital signs and other variables, Figure 12 illustrates in the time domain a 45.6-year record of mean arterial pressure self-measured about 5 to 6 times per day by a clinically healthy man. Major spectral peaks characterizing biospheric variables recorded over decades such as the data series pictured in Figure 12 have been summarized in a histogram, Figure 13. It includes all periods found in our meta-analyses of the life's work of Alexander Leonidovich Chijevskiy, Raymond Holder Wheeler, Andrew Ellicott Douglas, and, among others, our own. The mega-atomic bombs that sunspots are have acted in a thus far passive evolution, reflected in the circulation of blood with their past and partly present periods. The major peak at Hale's bipolarity cycle of about 20 years is readily apparent in Figure 13's histogram. The solar wind has blown since time immemorial, before satellites recorded it. Solar flares erupted for an equally long passive internal and external evolution of the universe.

As Stetson put it (6), "Mind after all is the one persisting reality". Let us monitor our minds to know ourselves, as implemented already on hundreds of individuals by Jarmila Siegelova and her colleagues in Brno, whereby they erected a monument for the difficult concept of "Know thyself" in a personalized chro-

nosphere (14). The same data reflecting populations and emotions may contribute to a special compartment in the generalized chronosphere that can be moved by emotions. Thus far only a few outstanding minds can teach us about the new transdisciplinary spectrum that reveals cyclicity as the ubiquitous, albeit Aeolian phenomenon. It is important for cardiovascular diagnosis and treatment. It is important for a lot more, including concerns about societal and natural cataclysms (15).

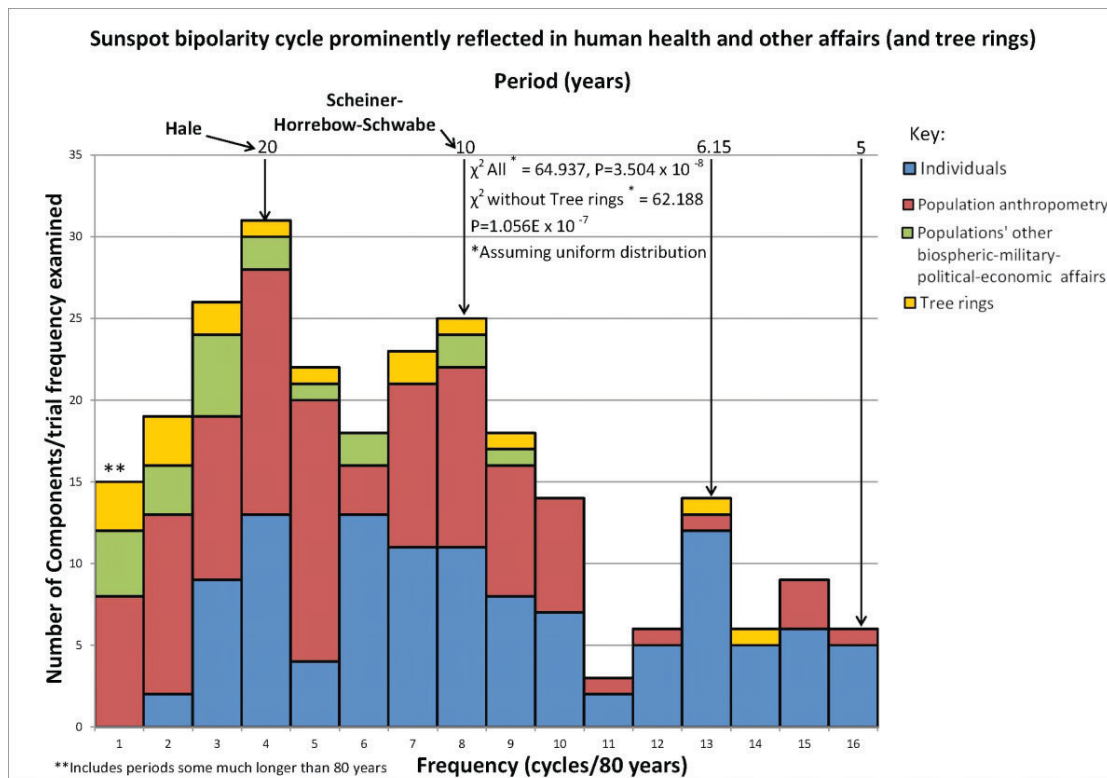


Figure 13 Major cycles characterizing long biological records preferentially assume periods of about 20 and/or 10 years. © Halberg.

Support: University of Minnesota Supercomputing Institute.

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SUNSPOT CYCLES DRIVE THE CARDIOVASCULAR SYSTEM IN A UNIFIED SCIENCE

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Dedicated to Othild Schwartzkopff on the occasion of her birthday.

In 1995, Roederer (1) proposed that cycles of biospheric processes be divided into photic and non-photoc cycles, in line with the nature of those environmental processes. Photic cycles are associated with electromagnetic radiation in the visible frequency range. Non-photoc cycles are related a.o., to corpuscular emissions from the Sun or space more generally, UV radiation, gravity, and geomagnetism. Prominent about the non-photoc cycles are the about 11-year solar activity cycle and about 50-year variations also detected in solar activity and found in a number of biological records (2–4).

Surprisingly, both the about 11-year and 50-year cycles were first reported by economists. Hyde Clarke (1838) was first to report in print an about 11-year economic cycle (5). In that same year, Schwabe (1789–1876) published data clearly showing the cycle, but refrained from writing about periodicity (6, 7). Christian Pedersen Horrebow (1718–1776), a Danish astronomer, son of Peder (Nielsen) Horrebow (1679–1764), whom he succeeded as head of the astronomical observatory associated with the University of Copenhagen, deserves credit for a thorough sunspot data collection between 1761 and the time of his death (16 years), continued by his successor only until 1777 (8). Elsewhere (9), we showed that an about 11-year cycle could be documented based on these early sunspot data collected before Samuel Heinrich Schwabe who started recording sunspot numbers in 1826 and continued to do so for 17 years.

Changes in solar activity, in turn, have been associated with changes in the weather (10), which are thought to influence economic cycles (11). Kondratiev is particularly known for economic cycles averaging about 50 years and ranging from approximately 40 to 60 years. Kondratiev identified three phases in the cycle, namely expansion, stagnation, and recession. Modern modifications of Kondratiev's theory led to the identification of technological cycles such as the Industrial Revolution (1771), the age of steam and railways (1829), the age of steel and heavy engineering (1875), the age of oil, electricity, the automobile and mass production (1908), and the age of information and telecommunications (1971) (12). While Kondratiev was first to bring his observations to international attention in 1925 (13), two Dutch economists had already argued for the existence of such a long cycle by 1913 (14). The presence of an about 50-year cycle in world GDP dynamics detected by spectral analysis recently corroborated Kondratiev's theory (15).

Herein, we revisit the about 11-year and 50-year cycles in economy and illustrate the presence of similar periodicities in biology. About 11-year cycles in merchandise exported to India (1708–1734) preceded those found in the cardiovascular system (16). The about 50-year economic cycle was noted almost two centuries before a similar cycle was reported in the context of preventive cardiology (17). The question is raised whether multi-frequency coperiodisms in cardiology can lead the way toward a unified science.

Solar activity follows an about 11-year cycle. Its period, however, is highly variable from cycle to cycle (18). An about 11-year cycle has been observed in economics as early as 1813 (19). Deduced from authentic documents, and founded upon practical experience obtained in the course of seven voyages to India and China, William Milburn published a table listing the number of ships sent out from England by the Honorable East India Company, with their chartered tonnage, the amount of merchandise and bullion exported, the number of ships lost or taken, and the sale amount of the goods imported by the Company each year between 1708–1709 and 1733–1734 (19).

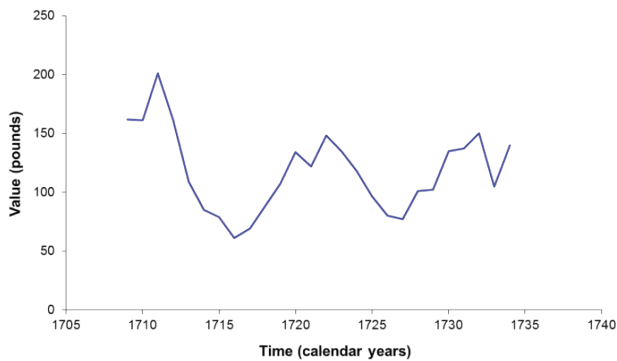


Figure 1 Time course of the yearly values of merchandise exported to India (1708-1734) (19). © Halberg.

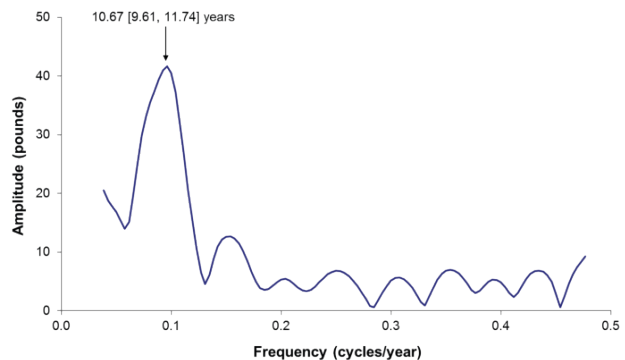


Figure 2 Least squares spectrum of data from W Milburn shown in Figure 1 reveals a large peak corresponding to a period of about 10.7 years. © Halberg.

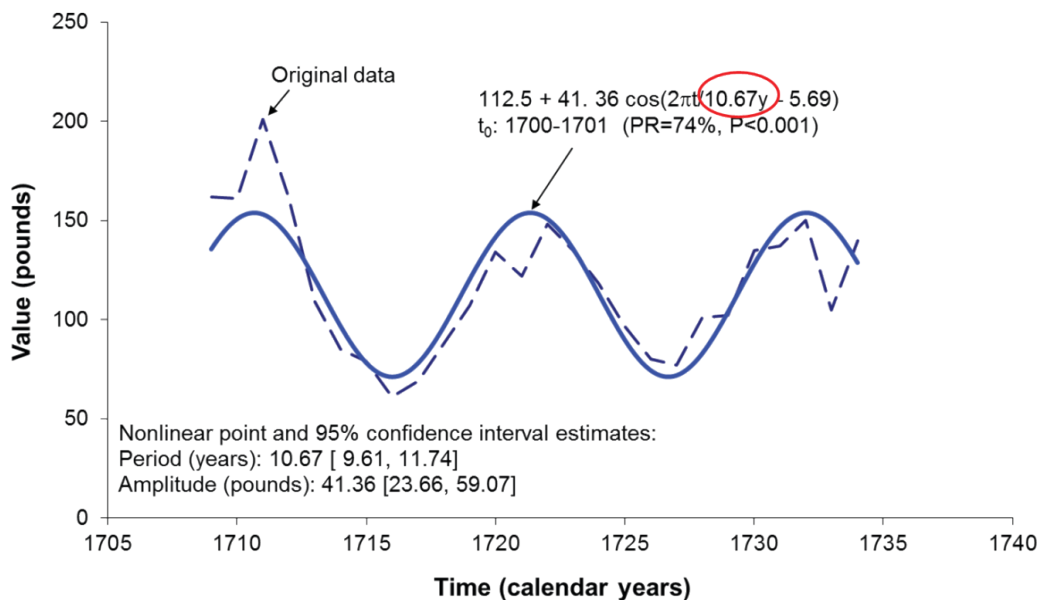


Figure 3 Model derived by the extended linear-nonlinear cosinor (Figure 2) is plotted with the original data (Figure 1). © Halberg.

Some regularity in the values of merchandise exported to India (1708–1734) is readily apparent from Figure 1. A large spectral peak is revealed by the extended linear-nonlinear cosinor (20–22), corresponding to a period of 10.67 years, with a 95% confidence interval (CI) extending from 9.61 to 11.74 years, Figure 2. As seen from Figure 3, the model fits the data well. Other entries published by Milburn (19) presented an increasing trend as a function of time. Accordingly, the data were detrended prior to analysis by the extended linear-nonlinear cosinor, yielding the following results: for the number of ships, in addition to a component with a period of about 9.54 [CI: 6.64–12.44] years, another cycle is detected with a longer period of 17.74 [CI: 6.93–28.54] years of similar prominence; for tonnage, a similar model applies, consisting of two components with periods of 9.90 [CI: 6.62–13.18] and 18.56 [CI: 3.13–33.98] years; for the imports’ sale amount, a component with a period of about 10.20 [CI: 6.58–13.82] years is also detected, together with a component with a shorter period of about 2.357 [CI: 2.165–2.549] years; only for bullion is the about 11-year component not found, the model consisting in this case of components with periods of about 19.44 [CI: 8.44–30.44] and 6.71 [CI: 5.45–7.98] years. Of course, due to the relatively short records, the CIs are quite wide. Major components detected by wavelets are summarized in Figure 4.

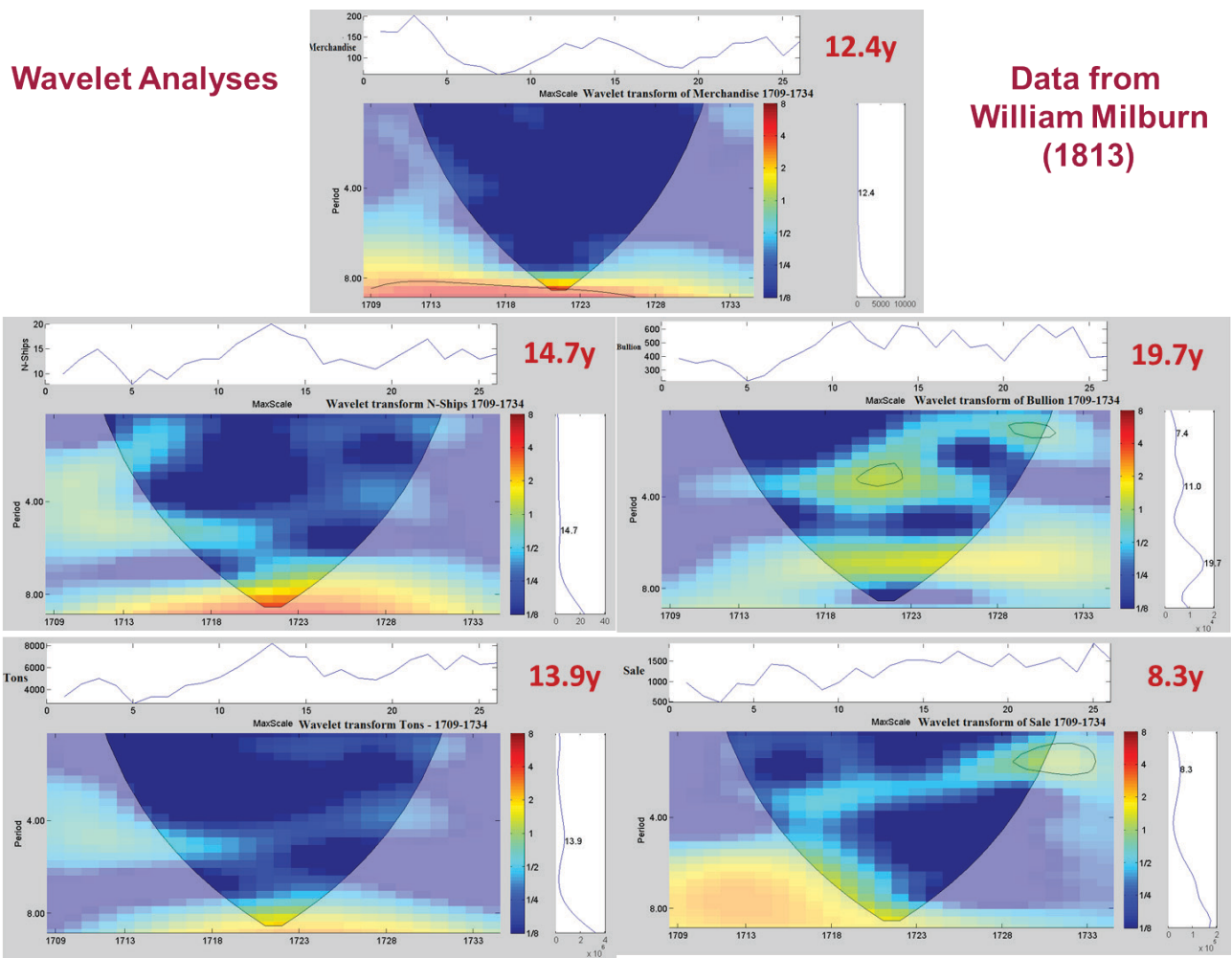


Figure 4 Results from wavelet analysis of the data from W Milburn (19). © Halberg.

In the Railway Register in January 1847 (26: 155), Hyde Clarke (23) already wrote about decadal sequences: “We have just gone through a time of busy industry, and are come upon sorrow and ill fortune; but the same things have befallen us often within the knowledge of those now living. Of 1837, of 1827, of 1817, of 1806, of 1796, there are men among us who can remember the same things as we now see in 1847. A period of bustle, or of gambling, cut short in a trice and turned into a period of suffering and loss, is a phenomenon so often recorded, that what is most to be noticed is that it should excite any wonder or alarm.”

Clarke (23) also wrote about a 54-year cycle (26: 159): “In searching for a period supposed to be of fifty-four years, it became a question whether the period were to be reckoned back from 1846 or from 1847. I ... found that about 1793 a great deficiency of food was felt in France, which aggravated the sufferings consequent on the revolution, but the circumstances of the period of 1793 did not seem to me to determine it sufficiently. I next sought back from 1793 for ... fifty-four years, which led me to 1739 or 1740 as the approximate date. The character of 1740 I found well determined as that of a time of great dearth, and it is so mentioned by Adam Smith, in the Wealth of Nations, Book I. chap. ii, where he says — “The year 1740, however, was a year of extraordinary scarcity.”

Our analyses of the South English Price Index (24) also showed the presence of an about 50-year cycle, among other components with long periods discussed elsewhere (1). As seen in Figure 5, after detrending the data, the estimated 49.7-year cycle has an uncertainty (CI) of 48.4 to 50.9 years. Since around 1720, this component has a relatively stable phase and an amplitude that increases as a function of time, Figure 6.

Solar signatures, such as the about 10.5-year and 21-year cycles are ubiquitous, also in biology (2). It even modulates the circadian acrophase of oxygen production by a population of the giant unicell *Acetabu-*

laria mediterranea (25). Decadals and other long cycles are detected in all longitudinal blood pressure and heart rate records spanning decades that were available for analysis, reviewed elsewhere in this volume (26).

Aeolian (in the sense of intermittent) BEL *, Kondratieff, and other cycles
in a spectrum of the South English Price Index (third row)**

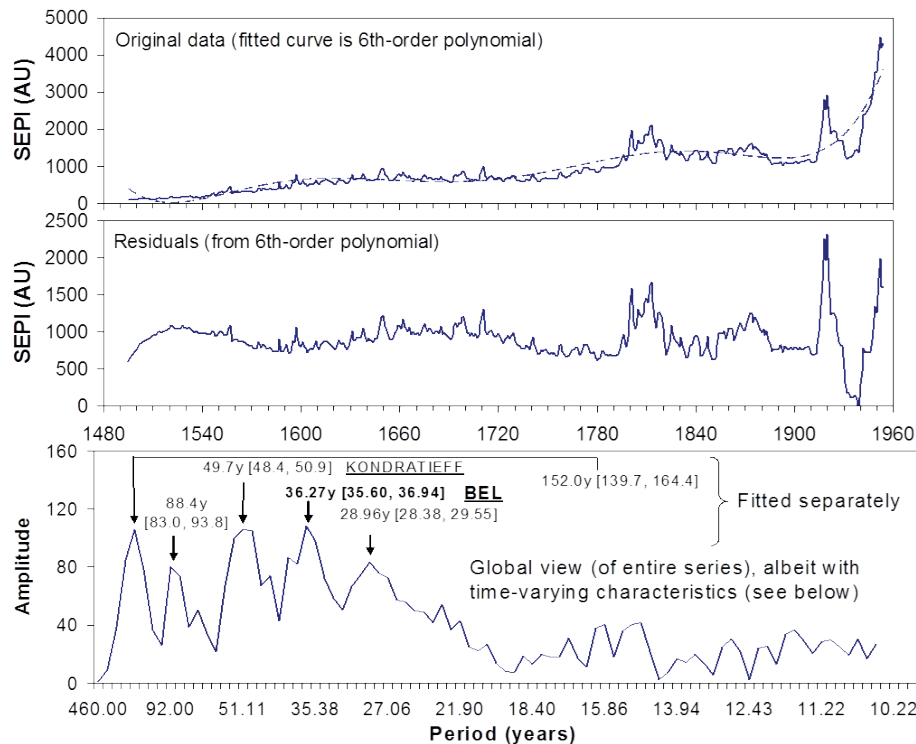


Figure 5 Data on the South English Price Index (24), available from 1495 to 1954 (top), detrended by means of a 6th-order polynomial (middle), are characterized by several long cycles, including an about 50-year Kondratieff cycle, as revealed in the least squares spectrum (bottom) obtained by the extended linear-nonlinear cosinor analysis. © Halberg.

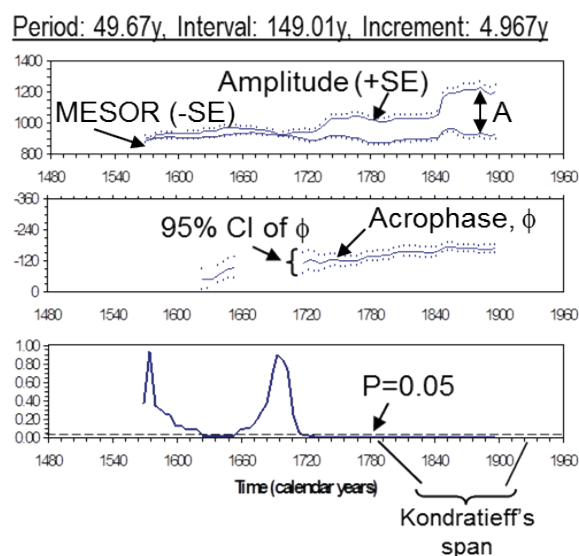


Figure 6 Analysis by chronobiologic serial section of the data on the South English Price Index (24) shown in Figure 5 at a trial period of 49.67 years indicates the increased prominence of the Kondratieff cycle as a function of time (the amplitude becomes larger) and a relatively stable phase since about 1720. © Halberg.

Decadal and other long cycles are not trivial since they also characterize the incidence patterns of major vascular conditions such as myocardial infarctions (Figure 7) (27) and strokes (17, 27, 28), Figure 8. About 50-year cycles, first described in economics, are also detected not only in the incidence of strokes in Minnesota and in the Czech Republic, but also in a number of other data pertinent to human affairs, Figure 9. It is observed in natality in the USA, in anthropometric data in Russia, in homicides in the USA, in an index of international wars, in the incidence of large earthquakes and accompanying tsunamis, as well as in Wolf numbers representing solar activity (2, 4, 29–31).

Slowly assessed, and replicated even more slowly, about 10-year and 50-year cycles have been described for individuals in longitudinal records and in populations contributing transverse and/or hybrid records. The uncertainties of the periods involved, dependent on the length of the time series available for analysis, constitute a major problem in extending the lessons from circadians to long-period cycles. This problem represents an urgent challenge in transdisciplinary science. A repository of data and maps of photic and non-photocycle characteristics derived therefrom is a first step toward a systematic documentation of coproperiodisms linking environmental cycles to cycles in biology and human affairs more generally, in an attempt to gain a better understanding of how humans interact with their environment.

Monitoring vital signs and other physiological variables is facilitated by modern technology. A concerted effort to collect serial data and to analyze them as-one-goes may eventually lead to what Franz Halberg visualized as a “unified science”. Apart from the obvious benefit to individual health, physiological surveillance, combined with existing monitoring by physicists may help improve the health of societies, by enhancing the “good”, reducing the “bad” (criminality, terrorism), and avoiding consequences from natural cataclysms (32).

MORTALITY FROM MYOCARDIAL INFARCTION IN MINNESOTA (1968-1996)*

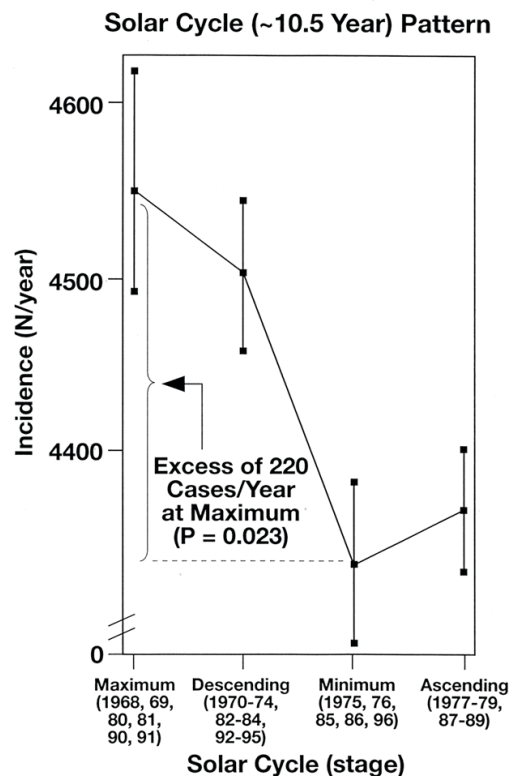
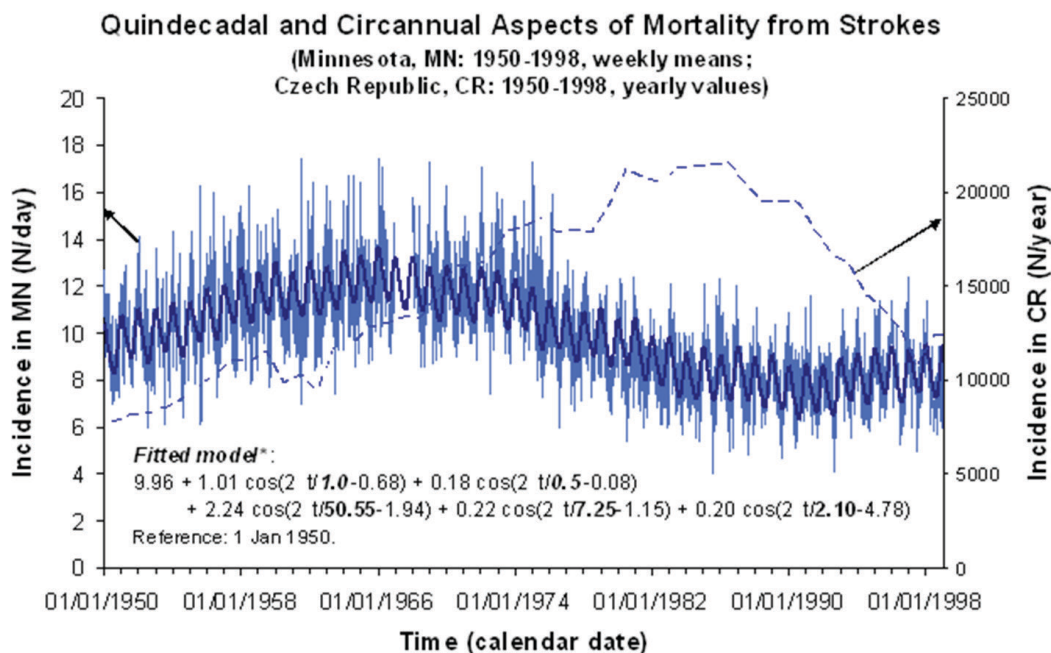


Figure 7 Mortality from myocardial infarction in Minnesota (1968-1996) follows an about 10.5-year cycle, accounting for an excess of 220 deaths per year during years of maximal solar activity as compared to years of minimal solar activity. © Halberg.



* Periods (in years) in bold; italics if fixed, otherwise adjusted by nonlinear least squares fit of composite model.

Figure 8 An about 50-year cycle characterizes the incidence of strokes in Minnesota and in the Czech Republic. Whereas the estimated periods are similar (Figure 9), there is a substantial phase difference, pointing to the need to account for geographic difference when mapping non-photoc cycles. © Halberg.

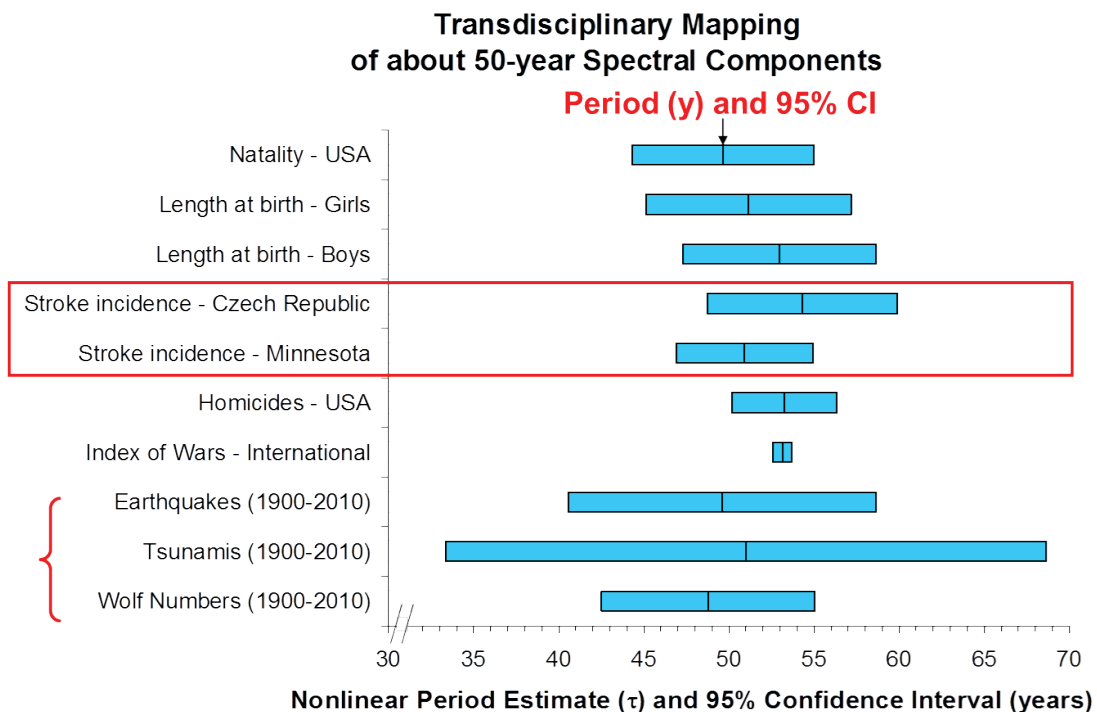


Figure 9 About 50-year cycles characterizing the incidence of strokes in Minnesota and in the Czech Republic, first found in economics, are also observed in natality in the USA, in anthropometric data in Russia, in homicides in the USA, in an index of international wars, in the incidence of large earthquakes and accompanying tsunamis, as well as in Wolf numbers representing solar activity. © Halberg.

Support: University of Minnesota Supercomputing Institute.

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SEVEN-DAY AMBULATORY BLOOD PRESSURE MONITORING: BLOOD PRESSURE VARIABILITY AT REST AND DURING EXERCISE

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**University of Minnesota, USA*

Dedicated to the memory of Professor Franz Halber, M.D., Dr.h.c. multi

INTRODUCTION

Regular exercise increases life expectancy, quality of life and work capability and productivity. European Society of Cardiology, International College of Cardiology, American Heart Association Council on Clinical Cardiology and American College of Sports Medicine call on all population of the world to create a culture of physical activity and health for the prevention of cardiovascular diseases and diabetes mellitus (Singh RB and Indian Consensus Group, 2010, Singh RB et al., 2011, Singh RB et al., 2013).

Usually there is no prescribed time of exercises. There is evidence that incidence of cardiovascular events peaks in the morning around 09:00 to 11:00 (Smolensky et al., 1972, Cornélissen et al., 1994).

In one subject, based on 7-day C-ABPM, time of the evening exercise was associated with the presence of a circadian overswing (CHAT, abbreviation for Circadian Hyper-Amplitude Tension), not found when the same subject exercised in the morning (Homolka et al., 2005, Halberg et al., 2005, Cornélissen et al., 1994). A brief description of the subject results with exercise and circadian timing has been published (Singh et al., 2012).

THE PURPOSE OF THE STUDY

The aim of the study was to compare 24-hour profile of 7-day blood pressure monitoring at rest and during exercise. The further aim was to compare the healthy subject at rest and during exercise and patients with coronary heart disease at rest and during exercise.

SUBJECTS

We examined 21 men, healthy subjects, mean age 29 ± 4.9 years (from 23 to 39).

For exercise training we used bicycle ergometer Kettler, type X7, Germany, 2x during week, constant load 120 W, duration 60 min. Every exercise unit was composed of warm-up period 3 min, load 54 min and cool-down period 3 min.

PATIENTS WITH CORONARY HEART DISEASE

The set being monitored consisted of 20 patients after myocardial infarction in the past history more than 3 months before, of mean age 63 ± 6.5 years and mean ejection fraction of the left ventricle 43 ± 12.3 %.

The patients underwent phase II of cardiovascular rehabilitation (controlled ambulatory rehabilitation program) lasting two to three months with the frequency of three times in a week at the Department of Functional Diagnostics and Rehabilitation of St. Anna University Hospital.

METHODS

In both groups the seven-day blood pressure monitoring was made by using the instrument TM - 2421 of the Japanese firm AD on the principle of oscillometric methods of blood pressure measurement. The regime of measurement of blood pressure was realized 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 (Siegelová et al. 2006).

The average SBP and DBP and their standard deviations (SD) in the given days were determined by the calculation of arithmetic mean of these values. We calculated the 7-day mean for systolic and diastolic blood pressure.

The study was approved by local ethic committee and the patients signed the informed consent.

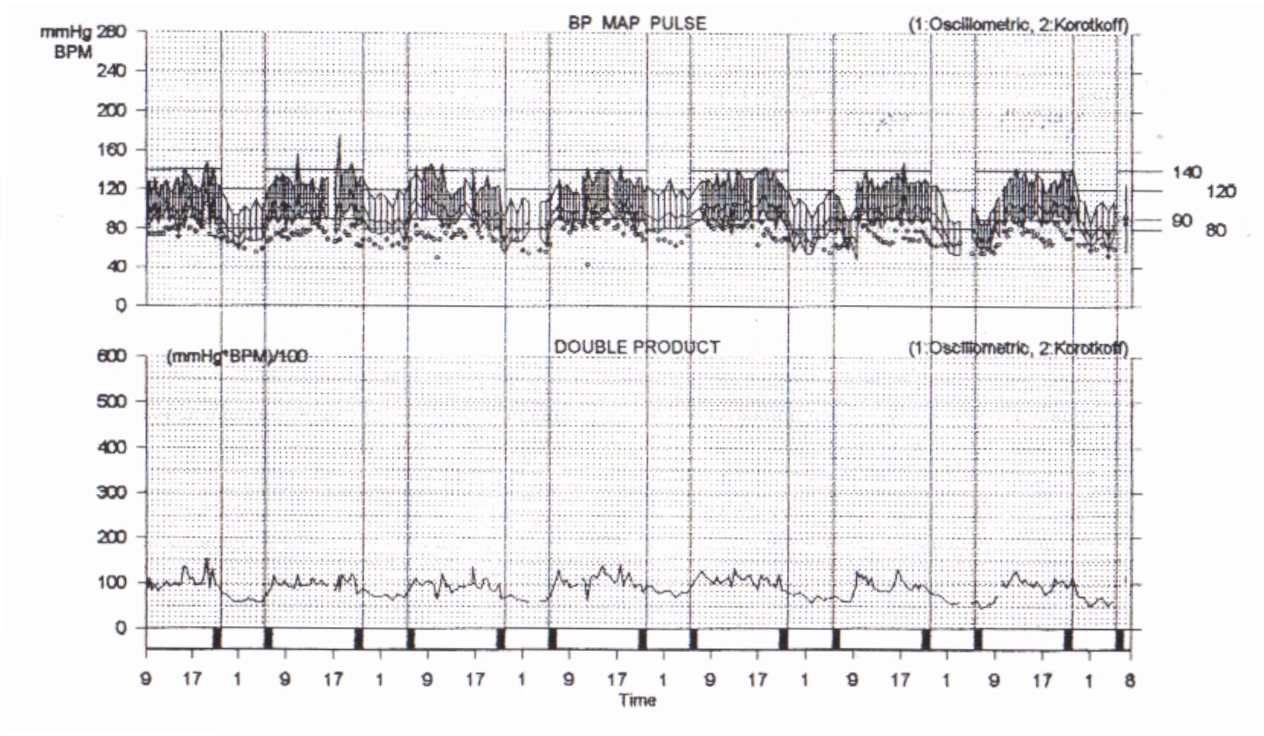


Figure 1

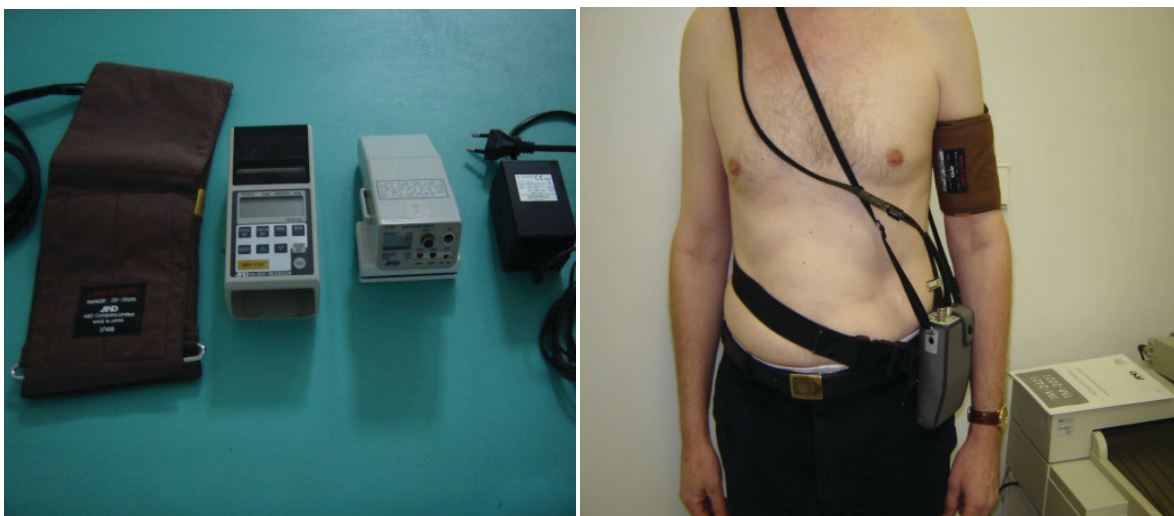


Figure 2

RESULTS

The healthy subjects (men) were ordered according to 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 Fig. 3 at rest and in Fig. 4 during exercise.

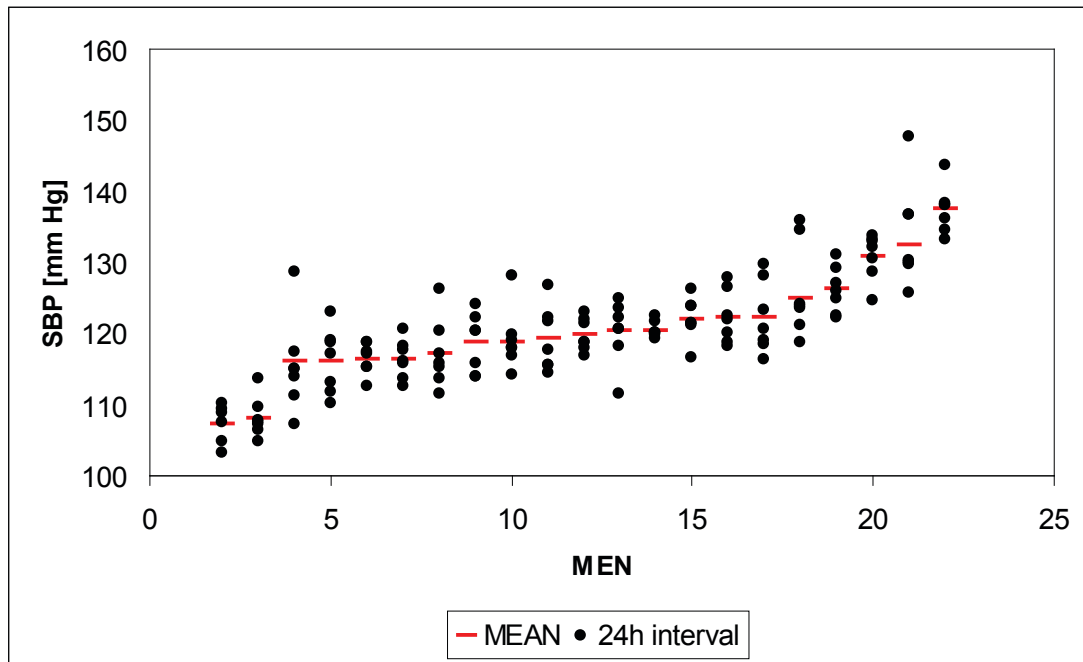


Figure 3 Variability of 24-hour mean systolic blood pressure (black points) and 7-day mean systolic blood pressure (red line) at rest in 21 healthy subjects

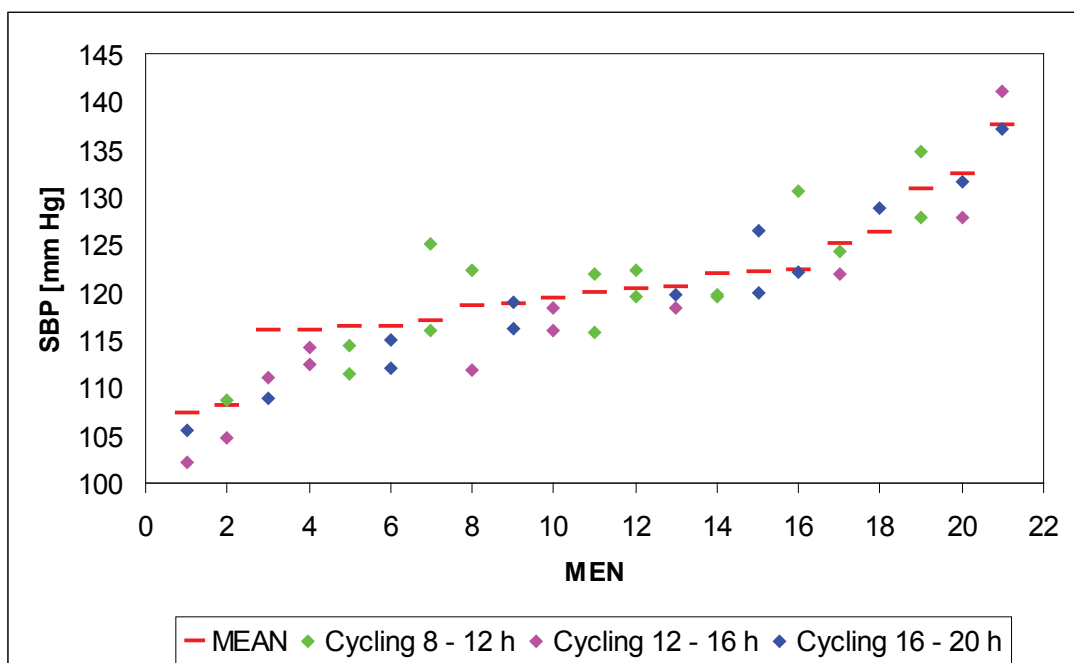


Figure 4 Variability of 24-hour mean systolic blood pressure (points in color) and 7-day mean systolic blood pressure (red line) during exercise in 21 healthy subjects

Variability of one-daytime DBP values during 7-day monitoring is seen in Fig. 5 at rest and in Fig. 6 during exercise.

Mean 7-day DBP (subject No 1: 61 mmHg, subject No 21: 85 mmHg; median value: 70 mmHg).

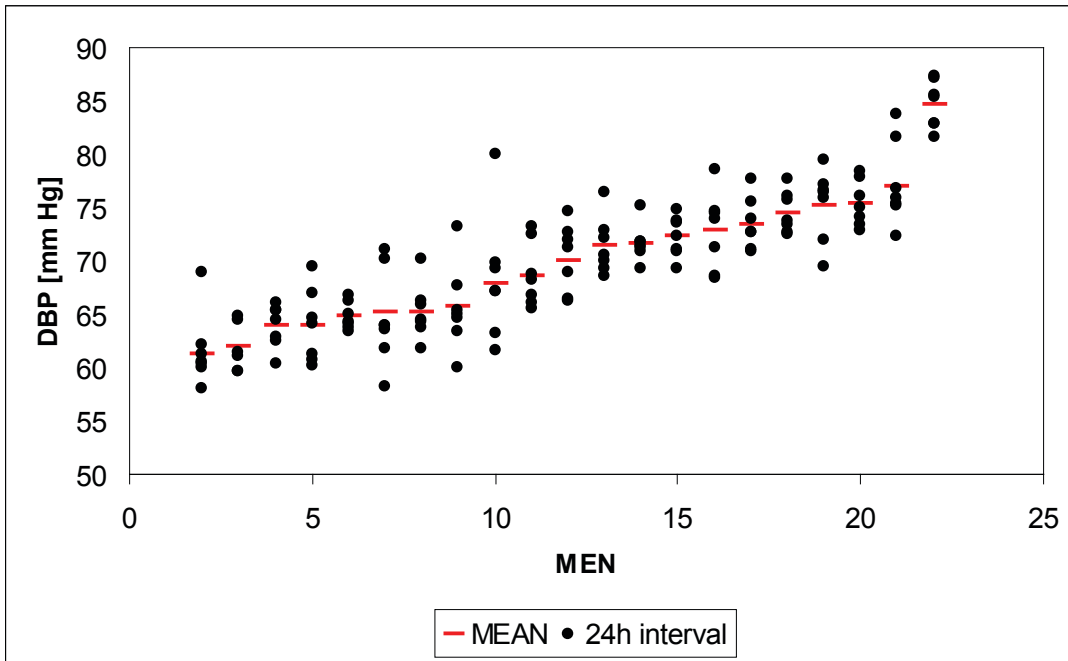


Figure 5 Variability of 24-hour mean diastolic blood pressure (black points) and 7-day mean diastolic blood pressure (red line) at rest in 21 healthy subjects

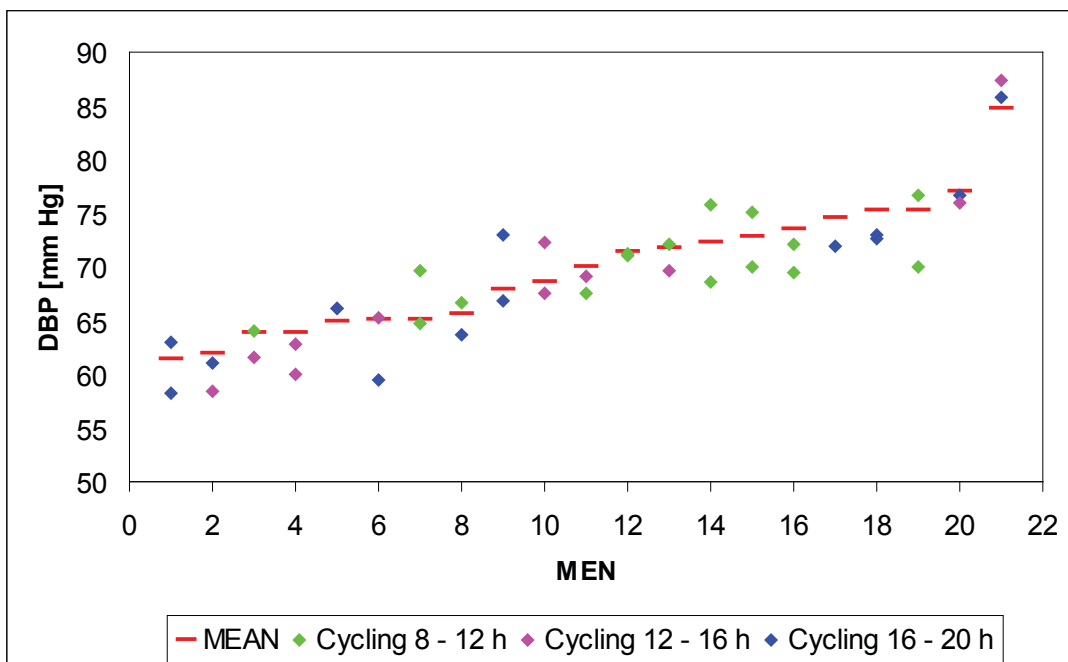


Figure 6 Variability of 24-hour mean diastolic blood pressure (points in color) and 7-day mean diastolic blood pressure (red line) during exercise in 21 healthy subjects

The patients with coronary heart disease (men) were ordered according to mean 7-day SBP (subject No 1: 107 mmHg, subject No 20: 141 mmHg).

Variability of one-daytime SBP values during 7-day monitoring is seen in Fig. 7 at rest and in Fig. 8 during exercise.

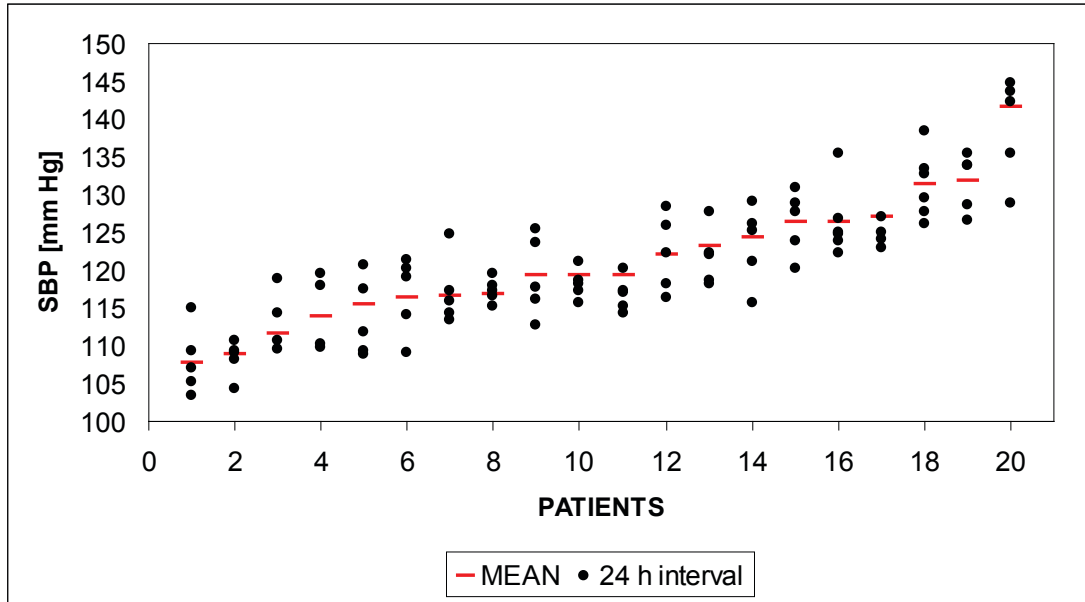


Figure 7 Variability of 24-hour mean systolic blood pressure (black points) and 7-day mean systolic blood pressure (red line) at rest in 20 patients with coronary heart diseases

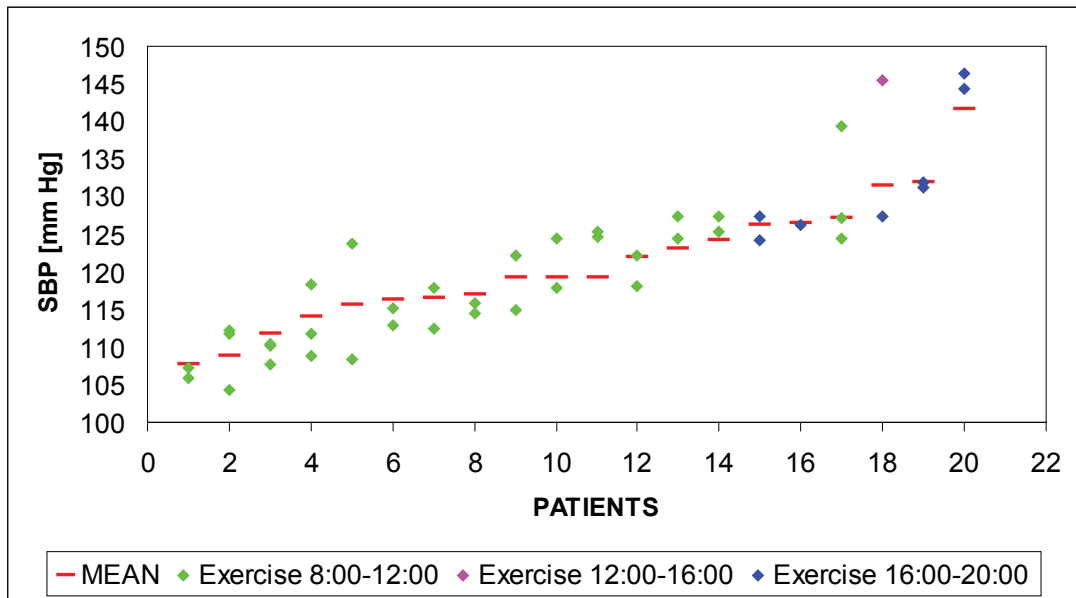


Figure 8 Variability of 24-hour mean systolic blood pressure (points in color) and 7-day mean systolic blood pressure (red line) during exercise in 20 patients with coronary heart diseases

Variability of one-daytime DBP values during 7-day monitoring in patients with coronary heart disease is seen in Fig. 9 at rest and in Fig. 10 during exercise.

Mean 7-day DBP (subject No 1: 66 mmHg, subject No 20: 92 mmHg).

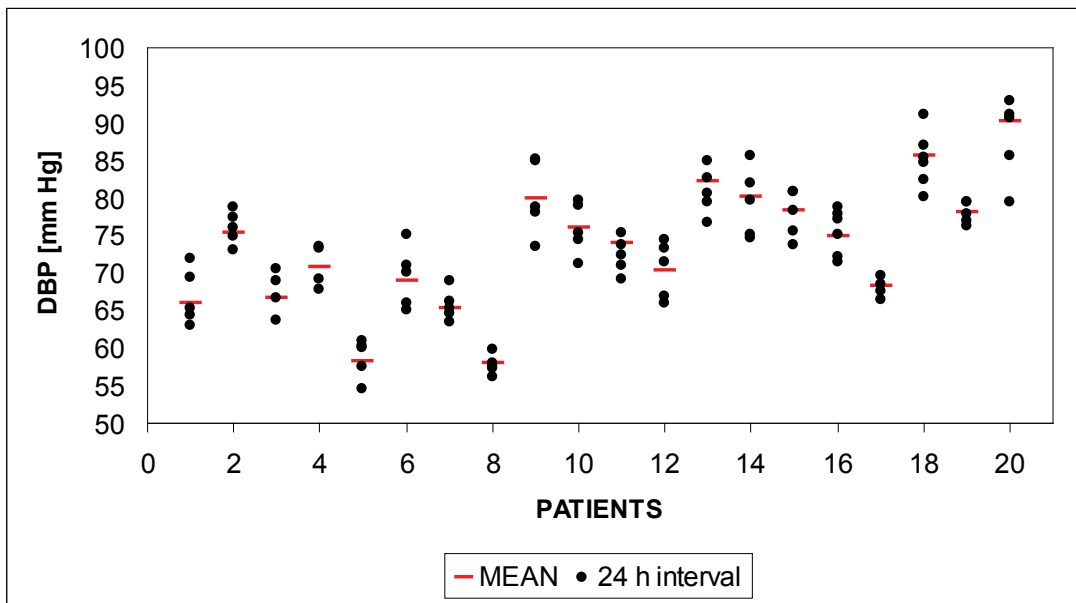


Figure 9 Variability of 24-hour mean diastolic blood pressure (black points) and 7-day mean diastolic blood pressure (red line) at rest in 20 patients with coronary heart diseases

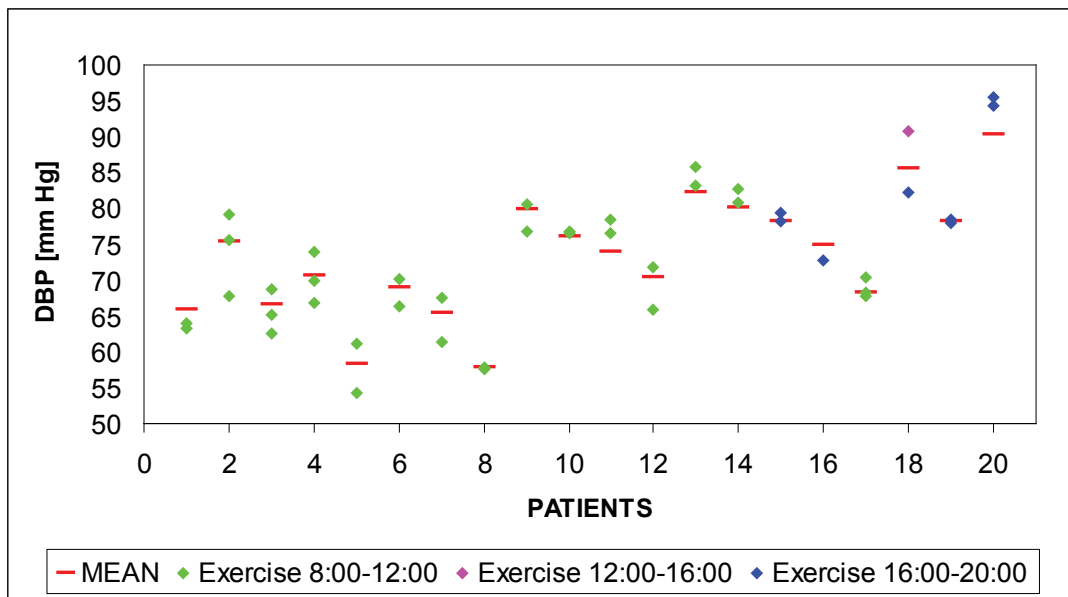


Figure 10 Variability of 24-hour mean diastolic blood pressure (points in color) and 7-day mean diastolic blood pressure (red line) during exercise in 20 patients with coronary heart diseases

DISCUSSION

As the diagnosis of hypertension is generally based on casual measurement of blood pressure in general practitioner office and these values of blood pressure are higher than the values of ambulatory blood pressure monitoring, the table of blood pressure thresholds for definition of hypertension with different types of measurement is included in the Guidelines for Management of Hypertension 2007 (O’Brien et al., 1998, Ohkubo et al., 2002, Hansen et al., 2005, Ingelsson et al., 2006, Mancia et al., 2006).

According to this table the threshold for systolic blood pressure is 140 mmHg in the office or clinic, 125–130 mmHg during 24 hours, 130–135 mmHg during day and 120 mmHg during night.

The corresponding values for diastolic blood pressure are 90 mmHg in the office and clinic, 80 mmHg during 24 hours, 85 mmHg during day and 75 mmHg during night.

The values for home measurement are the same as for ambulatory monitoring during day.

The condition for reliability of diagnosis is low day-to-day variation of night-time and day-time pressure values (Siegelová, et al. 2006, 2011).

Tab. 1 Blood pressure thresholds (mmHg) for definition of hypertension with different types of measurement

	SBP	DBP
Office or clinic	140	90
24-hour	125–130	80
Day	130–135	85
Night	120	70
Home	130–135	85

J Hypertension 2007

Seven-day ambulatory blood pressure monitoring demonstrates large day-to-day variability of blood pressure at rest. Our studies indicate with ambulatory blood pressure monitoring, that a longer monitoring, preferably for 7 days, is recommended (Halberg et al., 2009, 2010, 2011, 2012).

In our presentation we show a large variability of 24-hour profile at rest in 5 days and in 2 days with exercise in healthy subjects and in patients with coronary heart disease.

The variability in healthy subject (day-to-day in 24-hour profile) was presented at rest and during exercise in 21 healthy subjects. During exercise, even when these data were measured only for two days, we observed similar variability as it was described at rest before.

The variability in patients with coronary heart disease (day-to-day in 24-hour profile) was presented at rest and during exercise in 20 patients. During exercise, even when these data were measured only for two days, we observed similar variability as it was described at rest before.

Hypertension is currently diagnosed mostly by means of a single or a few measurements during few consecutive examinations. This practice can be associated with over 40 % false diagnoses due in part to a large variability in blood pressure as such and in response to external factors.

It is clear that 24-hour monitoring is better than a single or a few measurements, but for avoiding misdiagnosis it is not sufficient (Halberg et al. 2009, 2010, 2011, 2012). Our results show that 7-day blood pressure monitoring is the best way for blood pressure real values and it is in agreement with the results of BIOCOS project, carried out under the guidance of late professor Halberg and professor Cornélissen (Halberg et al., 2009, Cornélissen et al., 1994, 2005).

Self-measurement of blood pressure at home can also provide very important blood pressure values that, when averaged over a period of a few days, are more reproducible and predict the presence and progression of organ damage as well as the risk of cardiovascular events better than office values. Home blood pressure measurement for suitable periods can be recommended before and during the treatment also because this relatively cheap procedure may improve patient adherence to the treatment.

The immediate response of blood pressure and heart rate to graded exercise was also circadian stage-dependent in an earlier study. Exercise done by a 46-year old man in the Czech Republic was associated with an increase in the circadian amplitude of blood pressure that was more pronounced when exercise was done in the evening than in the morning, in his case leading to an abnormal circadian pattern carrying an increased cardiovascular disease risk (Halberg et al., 2009, Homolka et al., 2005). Depending on whether the circadian pattern of blood pressure tends to have too large amplitude at the outset or not, exercise should be timed to reduce both long-term and short-term blood pressure without bringing about

Vascular Variability Disorders that may be harmful and associated with a higher risk of a serious ischemic event than MESOR-hypertension (Halberg et al., 2010).

CONCLUSION

From the results we can conclude that 24-hours blood pressure profile at rest and during exercise from day-to-day vary in healthy subjects as well as in patients with coronary heart disease. 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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ABOUT HALF-WEEKLY (CIRCASEMISEPTAN) RHYTHM IN URINARY NEOSPORIN OF HEALTHY WOMAN: METHODOLOGIC MODEL

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INTRODUCTION

As a follow-up on a study of “stress” system dynamics during “life as it is lived” (1), data from a healthy 25-year old woman are further analyzed from a chronobiologic viewpoint. The subject had collected her entire urine over a 63-day span in 12-hour intervals. Neosporin, an immune activation marker, was determined, as was creatinine for the purpose of normalization. Emotional variables (stressors, irritation, positive incidents, anxiety/depression, lack of arousal, performance, complacency, extra-/introversion) recorded concomitantly were also analyzed.

With sampling more frequent than twice-a-day measurements, the about-weekly (circaseptan) rhythm was found to dominate over the circadian variation in negative affect, whereas positive affect in the PANAS questionnaire (2) had a dominant circadian rhythm (3). More prominent circaseptan changes have also been found in depressed elderly citizens as compared to non-depressed controls (4). Circaseptan and circasemiseptan changes have also been documented in blood pressure and heart rate of populations in Minnesota (5), the Czech Republic (6), India (7), and Japan (8).

METHODS

Details about the subject and the chemical determinations can be found in the original publication (1). In their study, the authors (1) modeled the data. Residuals from their model have also been analyzed herein.

Differences between the urinary neopterin determinations of the healthy woman obtained in the morning and evening were computed as were morning versus evening differences in the neopterin/creatinine ratios. A paired t-test assessed the presence of any circadian variation. Their daily averages, morning and evening values were separately analyzed by the extended linear-nonlinear cosinor (9–11). Least squares spectra were computed in the frequency range of one cycle in 63 days to one cycle in about 3 days. Nonlinear least squares (12) were used to estimate the periods corresponding to major spectral peaks with their 95% confidence intervals (CIs).

RESULTS

Figure 1 displays the neopterin/creatinine ratios as a function of time. Differences (PM-AM) between evening (PM) and morning (AM) values are shown in Figure 2. As seen in Figure 3, evening values are statistically significantly higher than morning values (paired $t = 3.605$, $P < 0.001$), suggesting the presence of a circadian variation. With only two measurements per day, estimates of its characteristics cannot be obtained, however. Differences between evening and morning values of the residual values stemming from the model originally published (1) also show larger evening values as compared to morning values (paired $t = 3.145$, $P = 0.003$), suggesting that factors originally accounted for did not include variability related to the circadian rhythm.

Least squares spectra of the morning and evening neopterin/creatinine ratios and of their daily averages are shown in Figure 4. Spectral peaks are readily seen, corresponding to components with periods of

about one month, one week and 5 days, further resolved by nonlinear least squares. In view of the relatively small number of data available for analysis, only two components could be assessed concomitantly with this procedure.

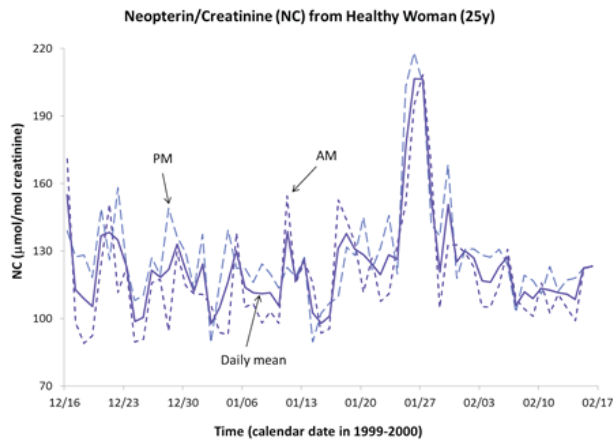


Figure 1 Time course of urinary neopterin/creatinine ratios of 25-year old healthy woman. Morning (AM) and evening (PM) values are plotted together with their daily means. © Halberg.

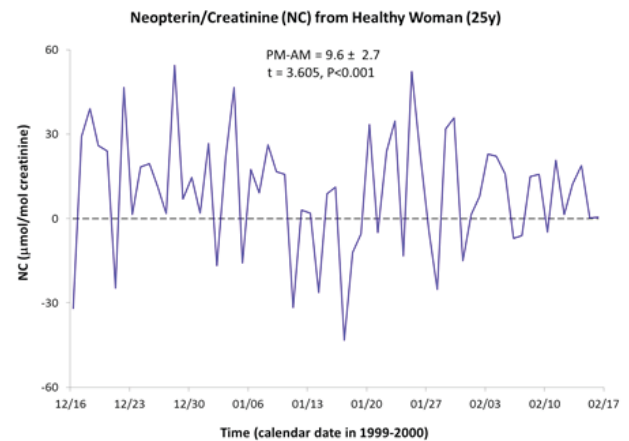


Figure 2 Time course of differences (PM-AM) between evening (PM) and morning (AM) determinations of urinary neopterin/creatinine ratios of 25-year old woman. © Halberg.

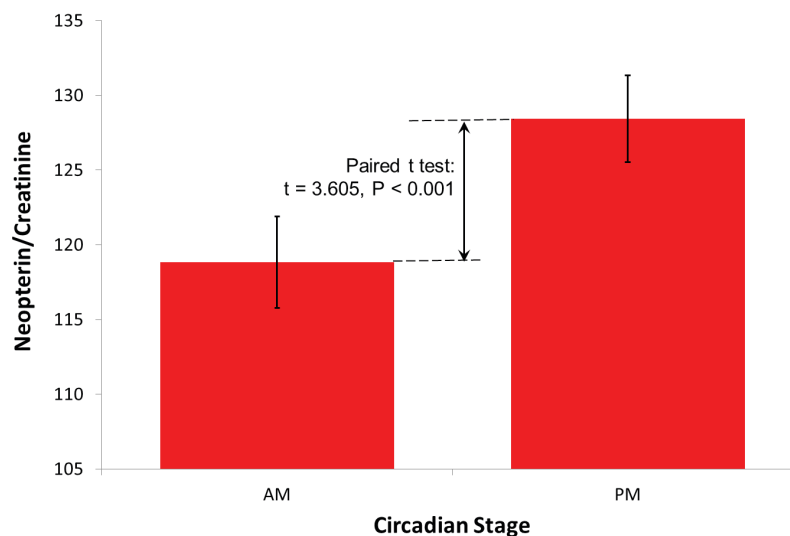


Figure 3 Evening determinations of urinary neopterin/creatinine ratio are consistently higher than morning values, suggesting the presence of a circadian variation. © Halberg.

The about monthly component is found to be statistically significant in both morning and evening determinations, albeit with a slightly longer period of about 47 days for the morning values. The circaseptan component, however, is only detected in the morning data with a CI of its amplitude slightly overlapping zero. Specifically, the morning data can be modeled with a two-component model consisting of cosine curves with periods of 47.6 [CI: 31.4, 63.8] and 6.99 [CI: 6.54, 7.45] days, with corresponding amplitudes of 16.84 [CI: 1.27, 32.42] and 14.22 [-0.75, 29.18], respectively. A similar model applied to the evening data yields estimates of the periods of 35.2 [CI: 22.6, 47.8] and 7.20 [CI: 6.53, 7.87] days, with corresponding amplitudes of 15.41 [CI: 0.19, 30.63] and 10.66 [CI: -5.32, 26.64], respectively. The fact that the CI of the circaseptan amplitude overlaps zero indicates that this component is not statistically significant for the evening values.

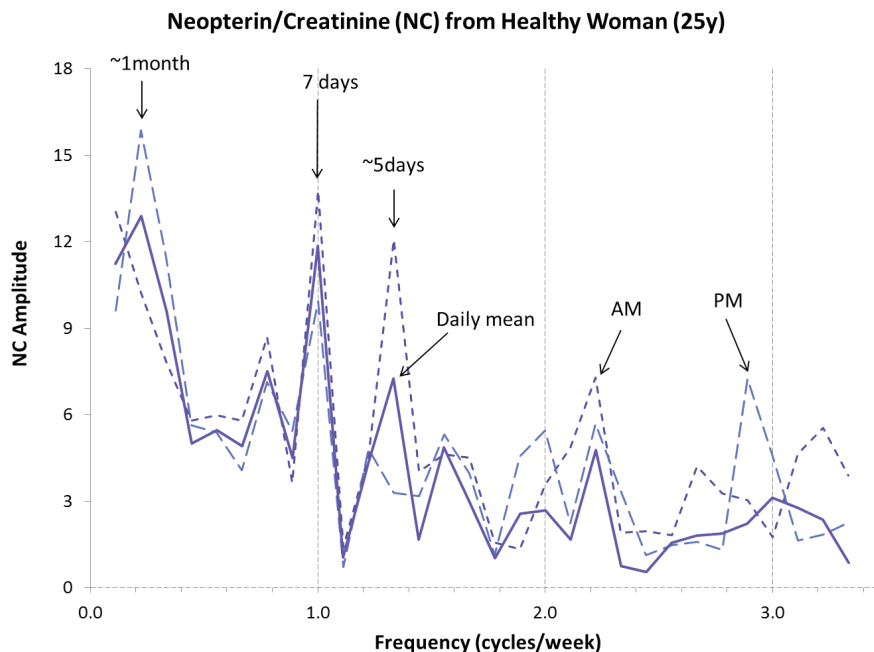


Figure 4 Least squares spectra of morning (AM) and evening (PM) values of urinary neopterin/creatinine ratios of a healthy 25-year old woman and of their daily means. Spectral peaks are observed, corresponding to periods of about one month, one week and 5 days. © Halberg.

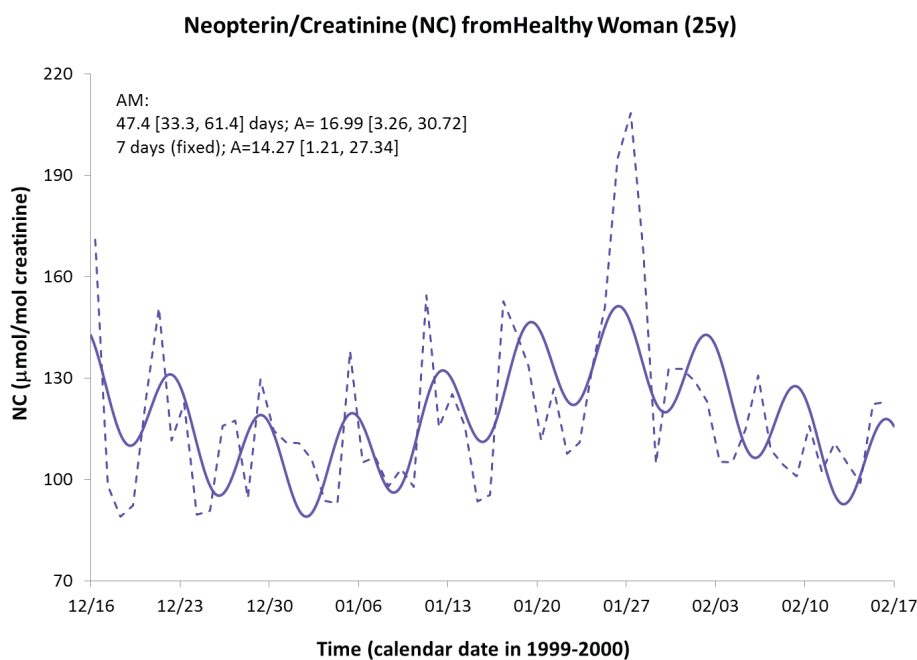


Figure 5 Morning urinary neopterin/creatinine ratios fitted with a 2-component model consisting of cosine curves with periods of about 47 days and 7 days (fixed as it is likely synchronized to the social week). © Halberg.

Since the circaseptan component is likely synchronized to the 7-day social week, its period can be fixed in the model. Using this approach, the model reaches statistical significance for the morning values, the amplitude of both components having a CI that does not overlap zero. The fitted model is shown with the original morning data in Figure 5. In the case of the evening determinations, the monthly variation is detected with statistical significance but not the 7-day component.

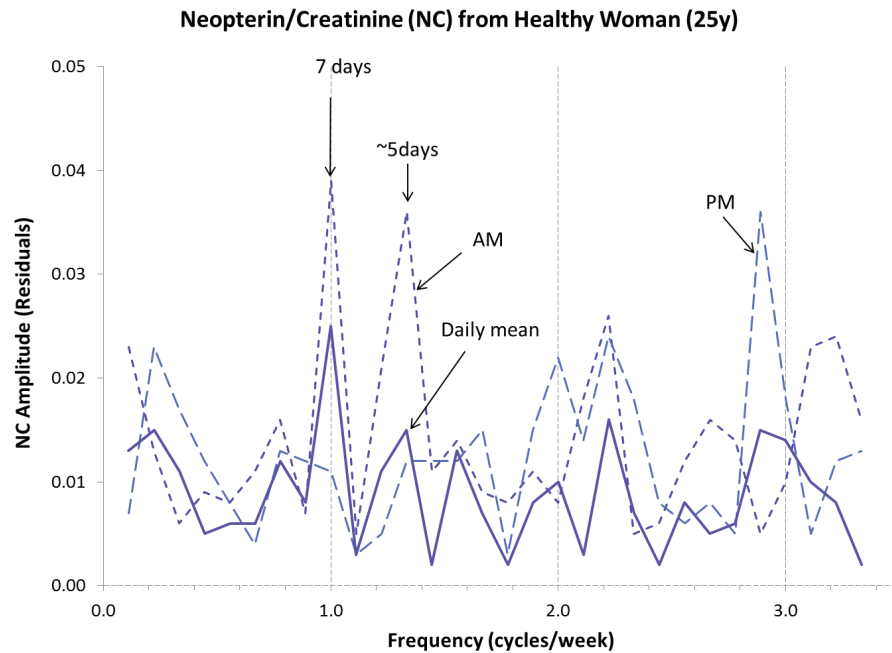


Figure 6 Least squares spectra of morning (AM) and evening (PM) residual values of urinary neopterin/creatinine ratios of a healthy 25-year old woman and of their daily means, after removing model originally derived from the data (1). Spectral peaks at about 7 and 5 days are still observed, whereas the low-frequency component is no longer seen, likely accounted for by the model. © Halberg.

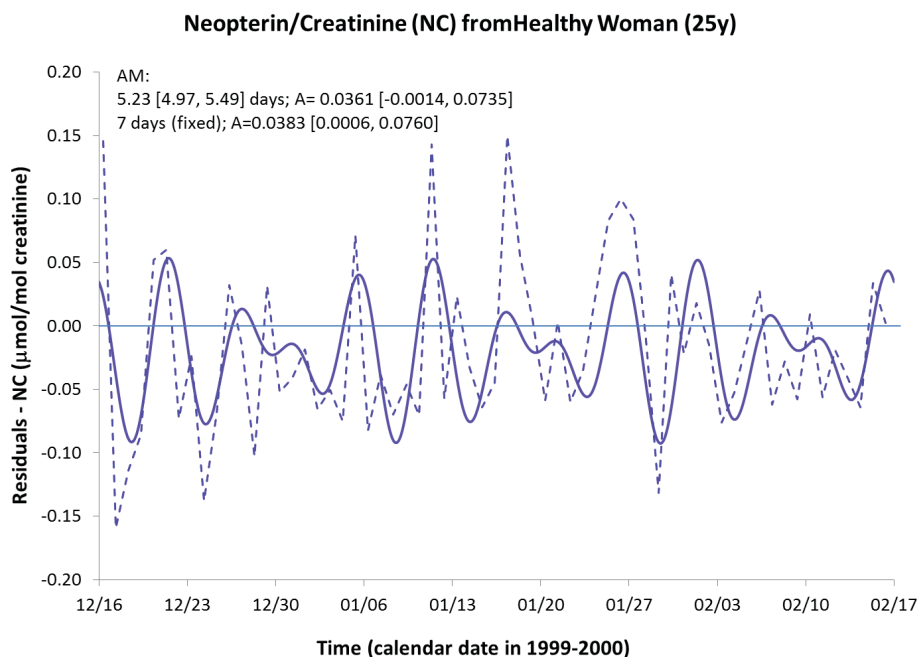


Figure 7 Residuals from original model (1) of morning urinary neopterin/creatinine ratios fitted with model consisting of cosine curves with periods of 7 days (fixed) and about 5 days (adjusted). © Halberg.

Similar results are obtained on the residuals, except that the model used in the original publication (1) accounted for most of the low-frequency changes, as apparent from the least squares spectra of Figure 6. Nonlinearly, the circaseptan component is detected with statistical significance for the morning but not for the evening values when this component is fitted alone. As the period estimate is very close to 7 days (6.99

[CI: 6.60, 7.38]), its period has again been fixed to 7 days in a composite model including the about 5-day component. As seen in Figure 7, the model fits the residuals relatively well, the 7-day component remaining statistically significant, with an amplitude of 0.0383 [CI: 0.0006, 0.0760], and the about 5-day variation reaching borderline statistical significance (the CI of the amplitude only slightly overlaps zero), with a period estimate of 5.23 [CI: 4.97, 5.49] days and a corresponding amplitude of 0.0361 [CI: -0.0014, 0.0735].

Least squares spectra of emotional variables recorded concomitantly did not show a statistically significant circaseptan variation in the morning. Only positive incidents ($P = 0.052$), anxiety/depression ($P = 0.069$), and all stressors ($P = 0.078$) had a 7-day component of borderline statistical significance (P -values not adjusted for multiple testing), suggesting that the weekly variation observed in urinary neopterin/creatinine ratios of this 25-year old healthy woman does not stem solely from her emotional state.

Surprisingly, least squares spectra of neopterin and creatinine analyzed as such rather than as their ratio are characterized by a spectral peak corresponding to a period of 3.5 days, whereas components with periods of about 7 or 5 days are not statistically significant for the morning values, Figures 8 and 9.

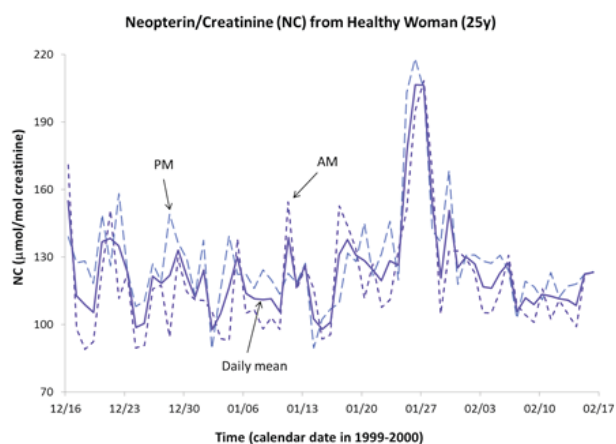


Figure 8 In the absence of spectral peaks at 7 and 5 days, urinary neopterin data (AM) are characterized by an about 3.5-day component. © Halberg.

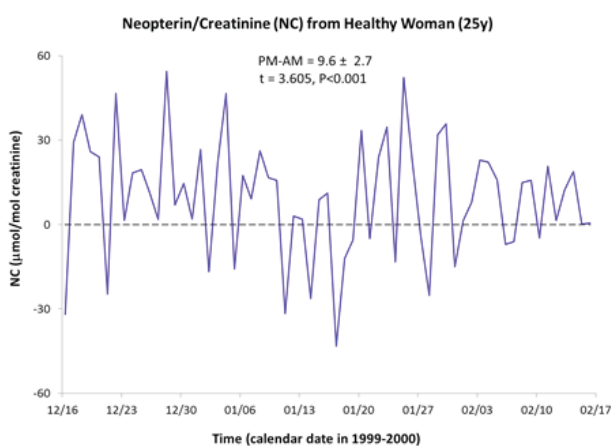


Figure 9 In the absence of spectral peaks at 7 and 5 days, urinary creatinine data (AM) are characterized by an about 3.5-day component. © Halberg.

DISCUSSION AND CONCLUSION

Urine and serum neopterin concentrations are widely used to monitor patients with HIV-1 infection (13). Increased neopterin concentrations have been found in patients with an activated cellular immune response which includes allograft rejection, viral infection and auto-immune disorders as well as various malignant tumors, a higher neopterin concentration being an independent predictor of a shorter survival in patients with several types of cancer (14).

A circadian rhythm has been documented for urinary neopterin in five healthy young men, with a peak in the early morning, around 06:30 and a peak-trough difference reaching 50% (15). This result is in keeping with the statistically significant morning-evening differences found herein.

To summarize findings in the present study, a circaseptan component is detected in the urinary neopterin/creatinine ratio. It is more prominently expressed in the morning than in the evening data. Circaseptan components could not be detected with statistical significance with the sampling used in emotional variables recorded concomitantly. A half-weekly component is only statistically significant ($P=0.045$, not corrected for multiple testing) for positive incidents. When neopterin and creatinine are analyzed as separate variables rather than as a ratio, a half-weekly component is detected rather than about 7- and 5-day components. Circasemiseptans are characteristics of the data analyzed. They can be tested as gauges of strain and compared for their usefulness with the circaseptans detected in their ratio.

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AN ATLAS OF CHRONOMES TO MAP BROAD TIME STRUCTURES

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Dedicated to the memory of Professor Franz Halberg (Figure 1) who first envisioned an atlas of chronomes, with the pledge to endeavor fulfilling our dear teacher's dream.

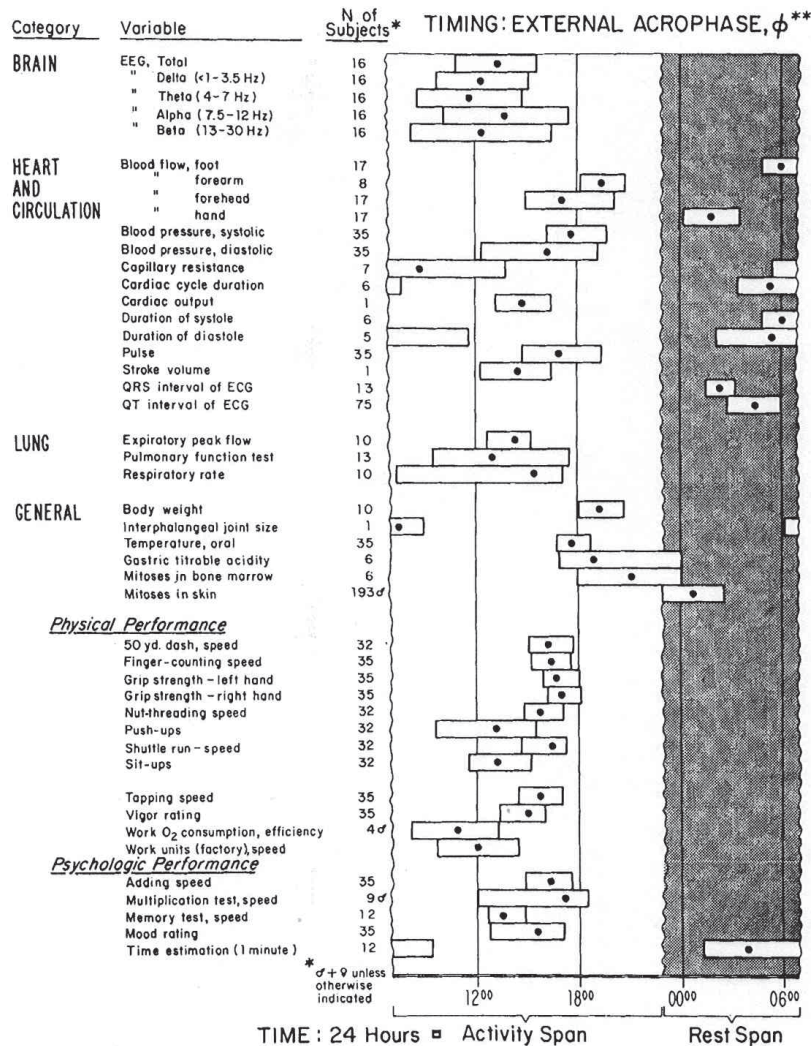


Figure 1 Franz Halberg

WHAT IS AN ATLAS OF CHRONOMES?

An atlas is defined as a collection of maps. Most common are atlases of regions on Earth, but an atlas can also contain other kinds of maps, such as charts of planets, stars, and galaxies. Usually used to find places, such as countries or cities, an atlas generally consists of several kinds of maps, some showing geographical features, others also providing statistics on social, political or economic aspects of each region. Atlases have traditionally been bound into book form, but multimedia formats are getting more popular today as they possess new capabilities such as facilitating searches and providing additional educational materials.

Human Circadian System : Whole Body and Organs



**Cosinor approximation of high values in circadian rhythm. Dots=acrophases; bars = 95% confidence limits. Non-overlapping bars indicate statistically significant differences in timing.

Figure 2 Acrophase chart summarizing peak times with their 95% confidence intervals (horizontal bars) of circadian rhythms in whole body and organs mapped in humans. © Halberg.

Within the scope of chronobiology, the study of non-random changes as a function of time in biology, charts have already been prepared and compiled in several publications (e.g., 1-3). They primarily consist of maps of acrophases (phases of maxima of cosine curves with known periods fitted to data by least squares) shown with their 95% confidence intervals. An example is provided in Figure 2. Circadian (about-daily), circaseptan (about-weekly), circatidal (about tidal or 12.4-hourly), and circannual (about-yearly) charts provide information about times within a day, week, lunar cycle and year when high and low values can be expected to occur. These components all have a well-defined environmental counterpart, serving as strong synchronizers. From a biological standpoint, the environmental cycles are fairly stable as a function of time in terms of the extent to which their periods remain more or less constant.

Compiling information for a host of variables determined in blood, urine, and/or saliva in humans and/or different animal species provides information about chains of physiological events. When acrophase charts report results for one or several variables separately for males and females of different age groups, important gender differences and changes as a function of age come readily to the fore (4). Similar

charts summarizing times when different diseases are more or less likely to occur are also available, their usefulness consisting of knowing when to implement protective measures to shield at-risk individuals, to initiate any needed protective action, and to assure sufficient staffing in clinics and emergency rooms. There are also charts specifically prepared to list times of peak susceptibility or resistance to different drugs. For instance, results from 35 studies on over 5000 rodents indicate that the anti-cancer drug daunomycin is best tolerated when it is administered in the middle of the light (rest) span, whereas cyclophosphamide is best tolerated around the time of dark onset and cisplatin is best tolerated in the middle of the dark (active) span (3), results that can readily be translated for application in the clinic.

An atlas of chronomes should encompass all the above charts. It should also include information about the notoriously wobbly non-photic environmental cycles, which also influence biota (2, 5, 6). In view of the non-stationary nature of the non-photic environmental cycles, an atlas of chronomes should focus primarily on the periods of the cycles, to be estimated with their uncertainties, information about amplitude and phase becoming meaningful only when sufficiently close estimates for the period of a given component can be specified to be compared between biological and environmental variables.

USES FOR AN ATLAS OF CHRONOMES

Long cycles related to solar activity and space weather more generally are not trivial if they can lead to erroneous interpretations and unwarranted decisions. Let us review several scenarios.

- First, observing an increasing trend in blood pressure over several months or years may lead to the decision to treat, when the trend is only part of a longer cycle, as was the case for a 38.5-year physician-scientist (EH), as seen in Figure 3 (7). Another example, depicted in Figure 4, relates to the urinary excretion of 17-ketosteroids (17-KS) by a clinically healthy man (CH): seeing the steady decrease in 17-KS (Figure 4, left), CH considered the need for androgen substitution therapy; the decrease in 17-KS was followed by an increase (Figure 4, middle), both trends being part of a decadal cycle (Figure 4, right) (8).
- Associations between solar activity and/or geomagnetic storms with heart rate variability and the incidence of myocardial infarction, reported in the Russian literature (9), could not always be replicated (10, 11). Results from systematic as-one-goes analyses of important morbidity/mortality statistics in different geographic locations could help resolve some of the controversies. For instance, mortality from myocardial infarction in Minnesota (1968-1996) was shown to follow an about 11-year cycle similar to the solar activity cycle when considering all data covering about 3 solar cycles (6). When data were analyzed separately for each solar cycle, the association could be demonstrated during the first two cycles but not during the third (6).
- A difference in the circadian amplitude of blood pressure, originally detected in school children with versus without a family history of high blood pressure and/or related cardiovascular disease (12), was also found in newborn babies monitored in 1985 and 1986 (13), Figure 5. The finding, however, could not be validated in a follow-up study in 1987-1989 (14). In the absence of a change in the blood pressure MESOR (Midline Estimating Statistic Of Rhythm, a rhythm-adjusted mean) between 1985-1986 and 1987-1989, the circadian amplitude increased slightly, but it did so more and with statistical significance for babies with a negative family history than for babies with a positive family history (14). A possible explanation for the controversial results was obtained from the independent monitoring of newborns over two decades in Moscow, Russia (15), involving decadal cycles modulating both the MESOR and the circadian amplitude of blood pressure. Understanding the origin of the discrepancy is important because a larger circadian amplitude of neonatal blood pressure has also been associated with the intra-uterine exposure to betamimetics, suggesting this treatment may increase cardiovascular disease risk later in life, confirmed in adolescence (16).
- As seen from Figure 6, differences in the characteristics of the about 10-year cycle between babies with a positive or negative family history of high blood pressure illustrate how differences in circa-

dian endpoints between the two groups may change as a function of the stage of the lower-frequency component (15).

- Caution should be exercised in interpreting changes with age in 1-minute time estimation, sometimes used as a gauge of age-related changes in verbal and visual-spatial functions (17). Indeed, depending on whether measurements are taken in the morning or evening, changes in opposite directions can be observed (18). Consideration of the circadian variation in 1-minute time estimation provides an answer to the puzzle, since apart from the MESOR, the circadian amplitude and phase also change with age (18).
- The relative prominence of non-photic cycles has been seen to vary depending on when measurements were taken along the circadian scale (19, 20).

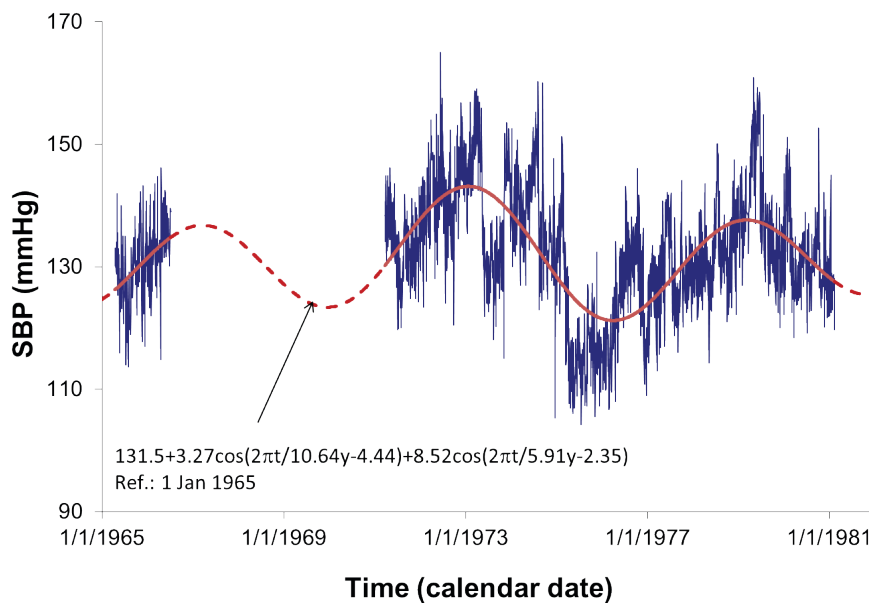


Figure 3 Systolic Blood Pressure (SBP) self-measurements by EH (M, 38.5 years of age at start), averaged over consecutive 2-day intervals, were analyzed by the extended cosinor. The least squares spectrum revealed the presence of components with periods of about 12 and 6 years, resolved by nonlinear least squares. Nonlinear results were used to estimate the fitted model shown with the 2-day means. The increase observed in 1965 appears to be part of a decadal cycle persisting until the 1980s. © Halberg.

Contradictory Correlations of Hormonal Metabolites with Age (I, II) Resolved by Years-Long Cycle (III)

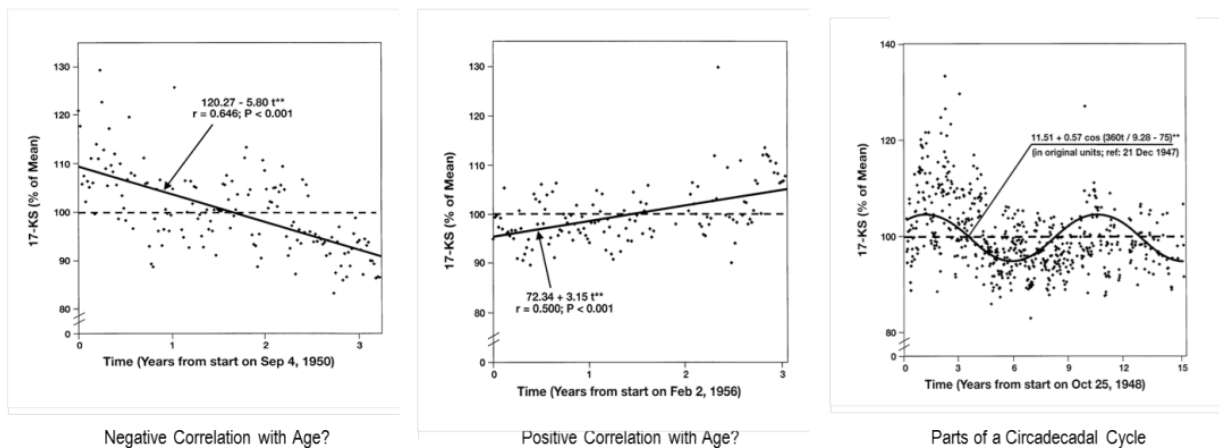


Figure 4 Increasing, followed by decreasing trend for several years each in the urinary excretion of 17-ketosteroids by a healthy man are “short-time” views of a much longer cycle. © Halberg.

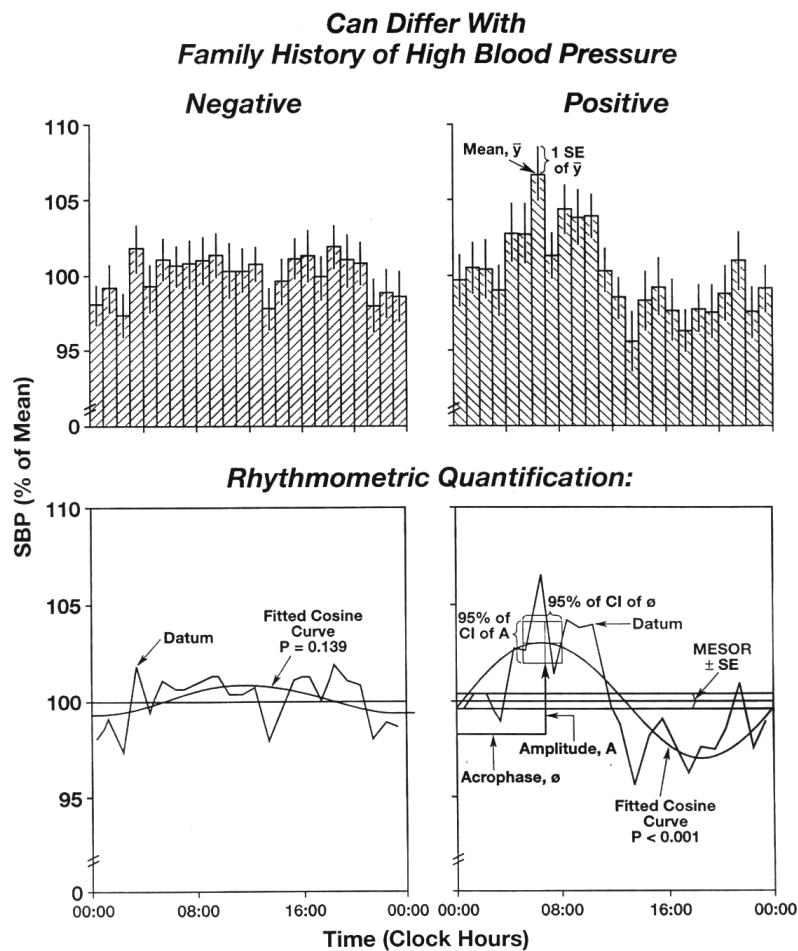
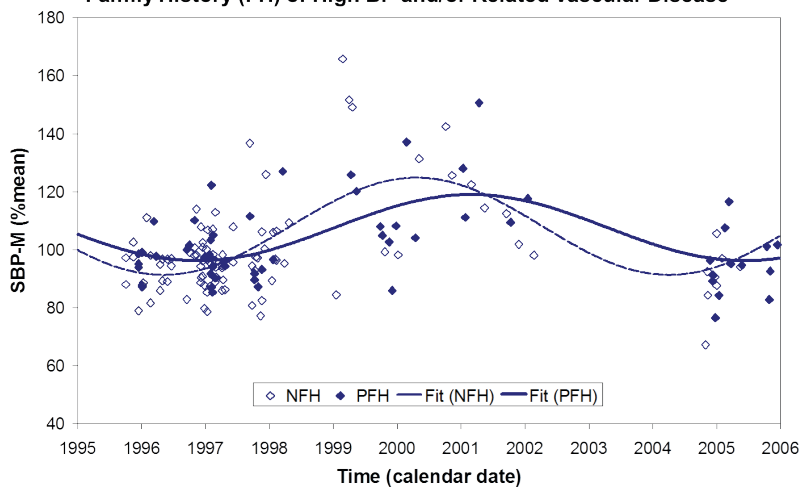


Figure 5 Neonates with a positive family history of high blood pressure and/or related cardiovascular disease have a more prominent circadian variation of blood pressure than babies with a negative family history. Results shown for systolic blood pressure (SBP) monitored during 1985-1986. © Halberg.

Nonlinearly Assessed Circadecadal Period (τ) and Amplitude (A) of Systolic Blood Pressure (SBP) MESOR (M) of Neonates with a Negative (N) or Positive (P) Family History (FH) of High BP and/or Related Vascular Disease



NFH: τ : 7.92 [6.04, 9.79] years; A: 16.75 [9.17, 24.34] %; at $\tau = 10.5y$, $P < 0.001$
 PFH: τ : 8.57 [4.06, 13.07] years; A: 11.40 [3.71, 19.10] %; at $\tau = 10.5y$, $P < 0.001$

Figure 6 An about 10-year cycle modulates the circadian MESOR of systolic blood pressure (SBP-M) of neonates. Differences in its characteristics between babies with a positive or negative family history accounts for the fact that differences in opposite directions can be observed at different times along the scale of the about 10-year cycle. © Halberg.

THE BIOLOGIC WEEK: PARTLY ENDOGENOUS, PARTLY RESPONDING TO SOCIETY AND GEOMAGNETICS

As an illustration of challenges facing the organization of the atlas, let us focus on the about-weekly component. About weekly variations in biology are often viewed as no more than a response to the social week. Whereas the social schedule can be a strong synchronizer of circaseptan rhythms, much evidence has accumulated illustrating that this component has a dual aspect, being partly endogenous while also responding not just to the social week but also to circaseptans in geomagnetics. All these aspects should be represented in the atlas.

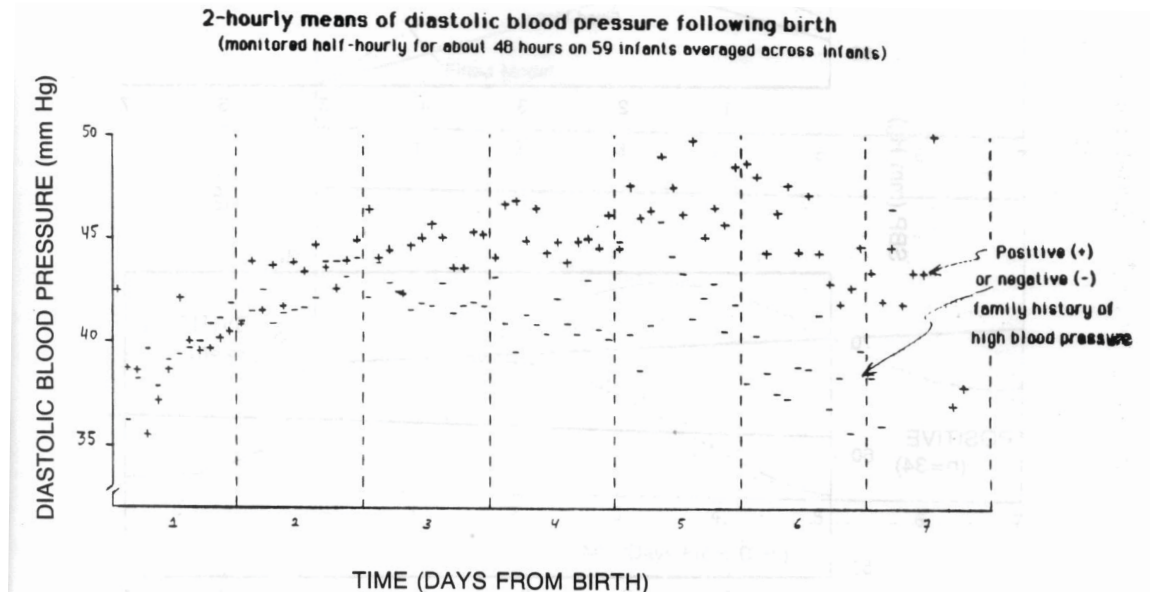


Figure 7 Hint of a circaseptan variation in neonatal blood pressure. © Halberg.

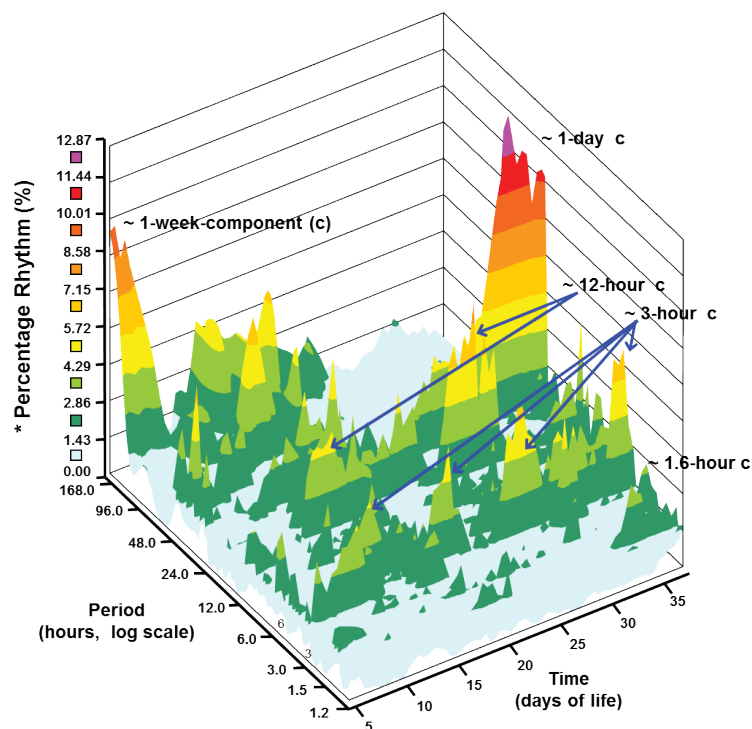


Figure 8 Change in infradian-to-circadian prominence in neonatal heart rate monitored around the clock during the first 40 days of life. © Halberg.

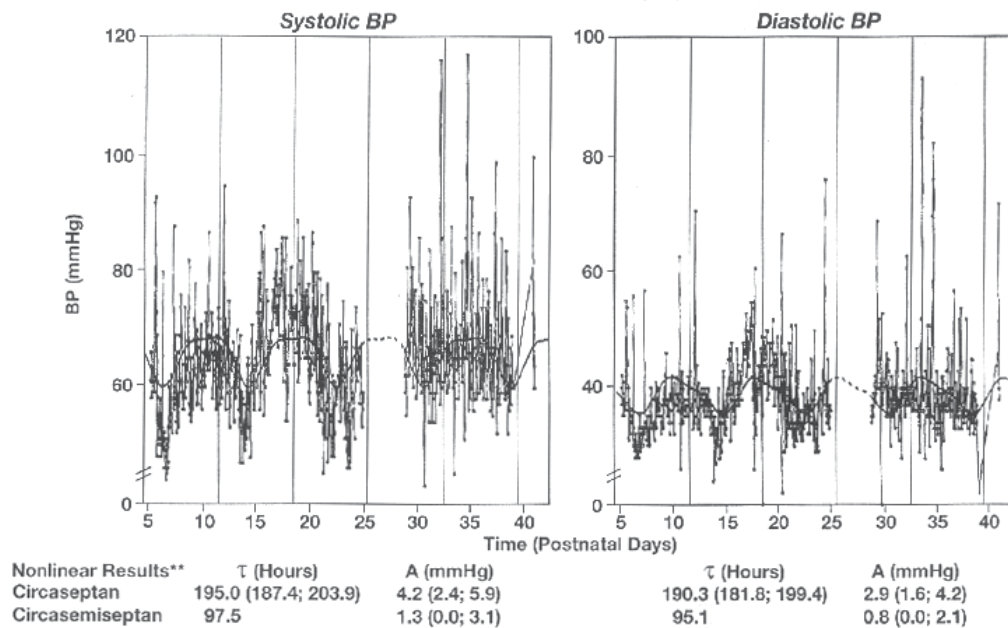


Figure 9 Individual record of neonatal blood pressure illustrates reproducibility of circaseptan variation over more than 3 cycles. © Halberg.

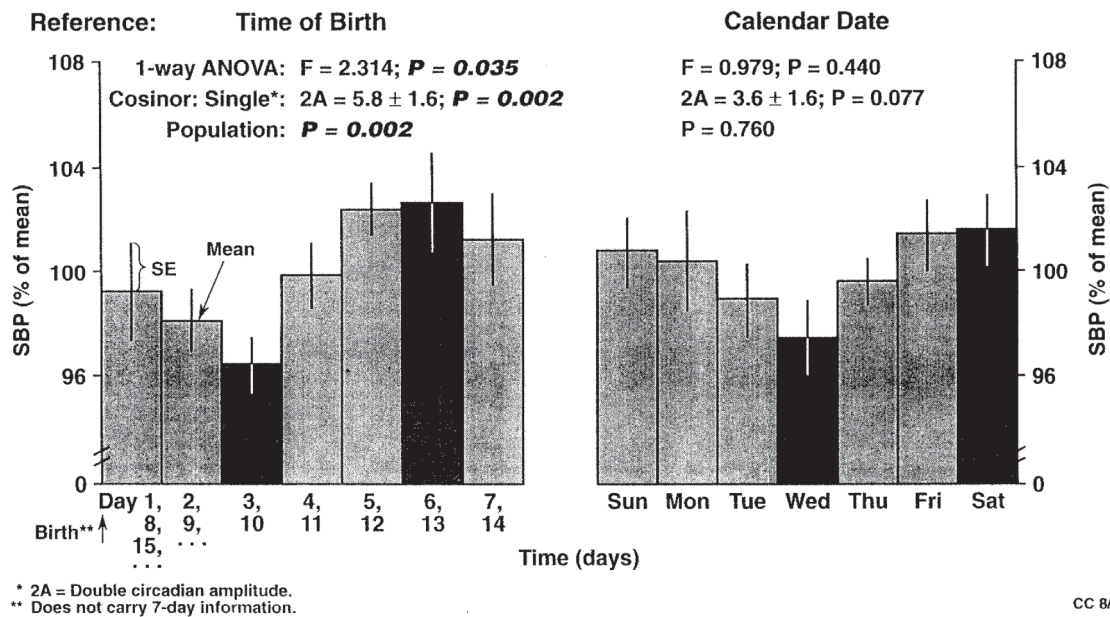


Figure 10 Larger prominence of endogenous (left) than exogenous (societal; right) circaseptan component of neonatal systolic blood pressure (SBP) suggested by stacking the data in relation to the time of birth (developmental age; left) or day of week (society; right). © Halberg.

The prominence of the circaseptan component in neonatal blood pressure was first revealed in hybrid data from a study in Florence, Italy, by the late Brunetto Tarquini, Figure 7 (21). A longitudinal record spanning the first 40 days of life showed that the transition from circaseptan to circadian prominence takes about a month, Figure 8 (22). Records obtained in the Czech Republic by Jarmila Siegelova documented that the about-weekly variation could be reproduced over several cycles and suggested that it may be partly endogenous since the estimated periods did not invariably cover exactly 7 days for all babies, Figure 9 (23). Corroboration came from a summary of records from all babies, Figure 10 (23). Stacking the data by the day of the week did not yield a statistically significant 7-day pattern, but stacking the data by post-natal day did, suggesting that developmental age contributed more to the weekly pattern than any societal schedule,

Figure 10 (23). Additional evidence for a partly endogenous weekly component stemmed from a study on twins monitored in the neonatal intensive care unit at the University of Minnesota (24). Analysis by intra-class correlation showed that the circaseptan period was more closely related between the twins in a pair than among different twin pairs, Figure 11 (24).

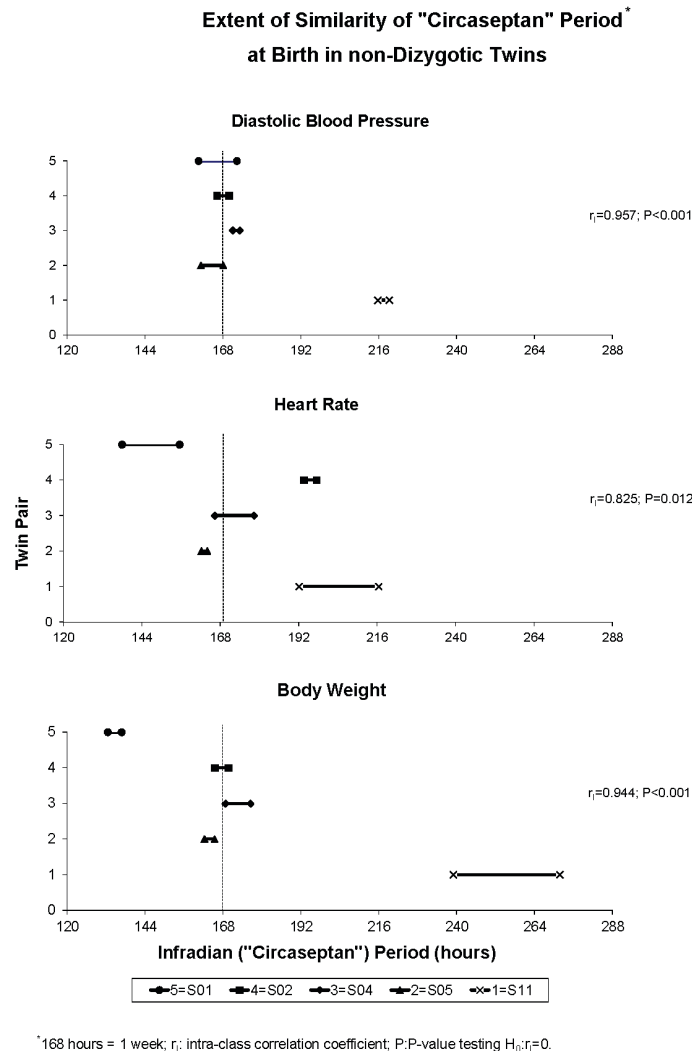


Figure 11 The nonlinearly estimated circaseptan period of diastolic blood pressure (top), heart rate (middle), and body weight (bottom) is more similar between neonates within a twin pair than among twin pairs, as shown by the intra-class correlation coefficient. © Halberg.

Changes as a function of age in the relative circaseptan-to-circadian prominence indicated a resurgence of the about-weekly variation in the elderly, Figure 12 (25). The question may be raised whether this is a common feature of non-photic cycles, since a similar trend with age is found for the relative prominence of transyears versus the 1-year synchronized variation in blood pressure and heart rate, Figure 13 (26).

A spectral peak around one cycle per week is also detected in the geomagnetic disturbance index, Kp, corresponding to the fourth harmonic of the solar rotation period (27). In Moscow, Russia, the circaseptan period of neonatal blood pressure and heart rate, estimated nonlinearly, correlated positively and with statistical significance with the circaseptan period of the local K index monitored during spans matching the neonatal records, Figure 14 (28). These results suggest that early after birth, babies, who do not yet have a strong circadian system, may be more susceptible to geomagnetics. This hypothesis is also in keeping with the about 10-year cycle detected in neonatal blood pressure (Figure 6).

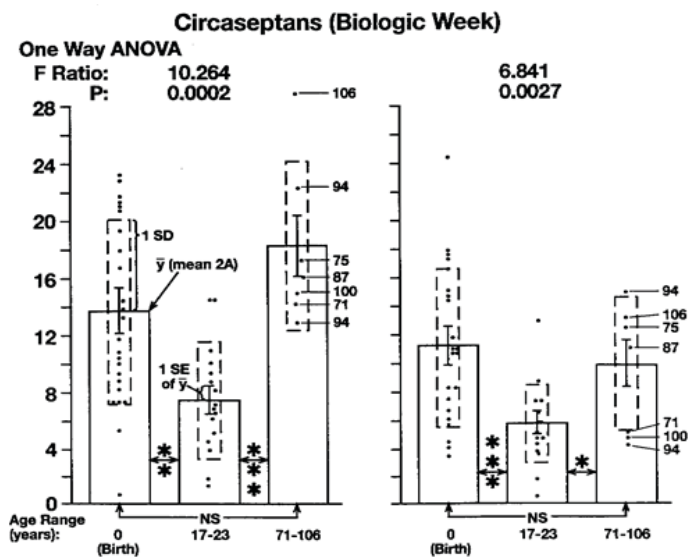


Figure 12 Double amplitude of systolic (left) and diastolic (right) blood pressure is statistically significantly larger in the young and elderly than in mid-adulthood. © Halberg.

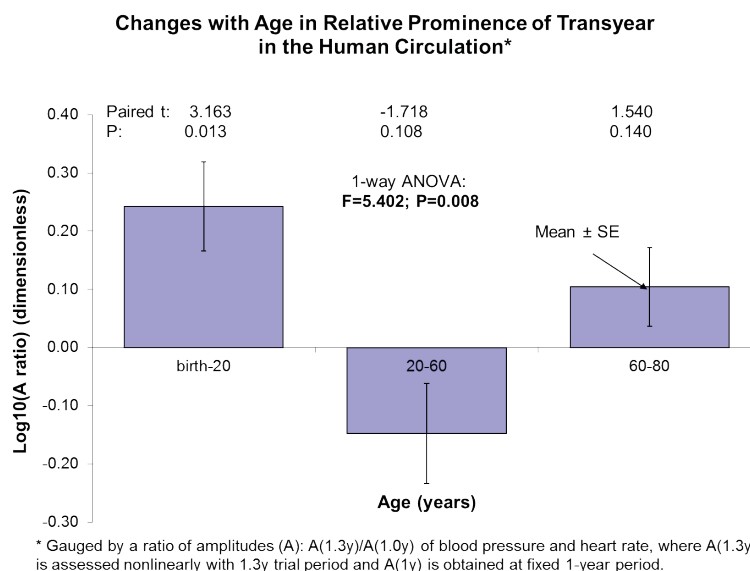


Figure 13 Prominence of a non-photoc (transyear) cycle over a photic (circannual) component early and late in life. © Halberg.

TASKS AHEAD

Cycles with periods of about 5 and 16 months, 10.5, 21, 35, and 50 years, all observed in the non-photoc environment, are also detected in longitudinal records of physiological variables and in patterns of mortality incidence from various causes (2). Thus far, their presence has been demonstrated, and in a few cases, their characteristics have been quantified with a measure of uncertainty. Much more needs to be done for these cycles to become truly useful. They need to be systematically mapped and reported in an atlas that is easy to consult, just as astronomers have started the mapping of stars and galaxies, and unmanned vehicles are exploring the terrain on Mars. Connections need to be made between the presence of non-photoc cycles in the cosmos, how they may be affecting the ionosphere (29) and influence weather on Earth (30), and how these changes can, in turn, have an impact on agriculture (31), nutrition, the presence of pathogens and overall human health (32, 33). The atlas will thus need to organize charts in a way that best conveys sequences of events along a given time scale (i.e., cycle length).

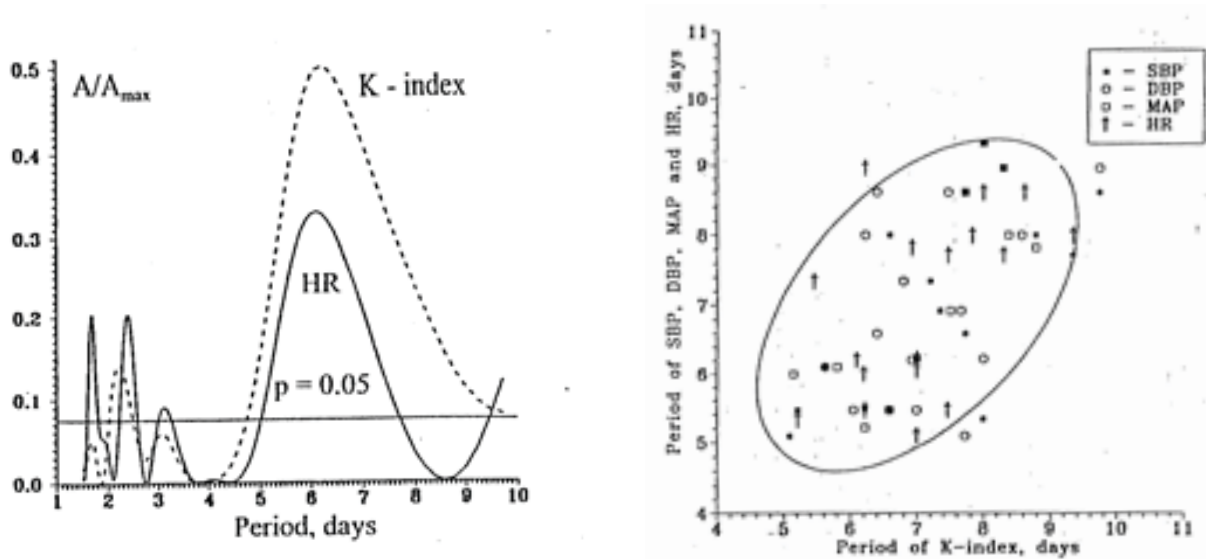


Figure 14 Example of circaseptan spectral peak in neonatal record of heart rate and corresponding index of local geomagnetic disturbance, K (left). Nonlinearly estimated circaseptan periods of neonatal blood pressure and heart rate correlate positively with corresponding estimates of K (right). © Halberg.

Selective geographic assortment of **diphtheria** and **croup** (blue) and **cholera** (red): about (~) 12-year (○), ~ 17-year (□) and longer cycles, including a BEL-cycle (◻).

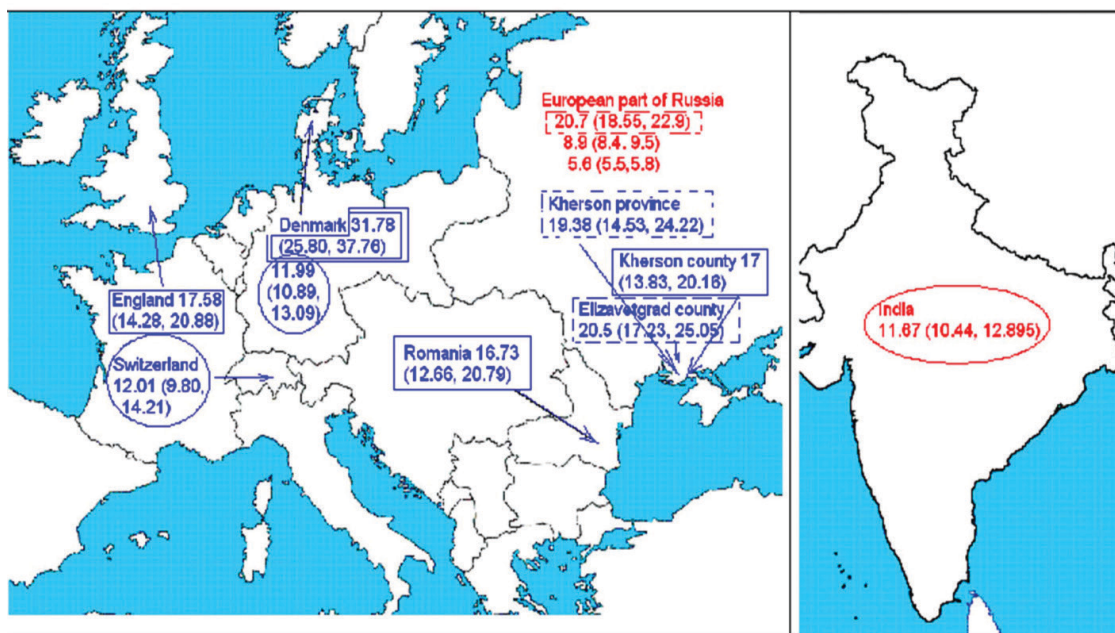


Figure 15 Example of geographic map comparing cycle length of incidence patterns of diphtheria in different countries. © Halberg.

In contrast with the relatively stable 24-hour day and 12-month year, non-photic cycles in the environment related to solar-terrestrial magnetism vary as a function of time. They undergo changes in cycle duration and in their relative prominence. These features can be exploited to go beyond the simple observation of cycles shared between physics and biology (34, 35). They can help our understanding of environmental effects, making it possible to predict the future course of the biological variables (such as the incidence of various diseases) by monitoring cycles in the environment, a task which is facilitated by the availability

online of comprehensive databases on a variety of environmental factors prepared by physicists. The atlas will thus need to include not just a list of cycle characteristics, but also a description of how these cycle characteristics change as a function of time. This feature can be referred to as a “glocality” in time, where “glocal” stems from the combined “global” view of the cycle as a whole, over as long a time scale as allowed by the available data, and a “local” assessment of shorter-term changes in the cycles’ characteristics.

Any geographic differences should also be considered. For instance, latitude dependence was found for an about 21-year cycle in religious motivation (36). The incidence of sudden cardiac death follows a transyear rather than a 1-year synchronized variation in Minnesota and the Czech Republic, but not in some other locations, such as Arkansas (37). A transyear in natality is detected in the Philippines but not in Minnesota, Italy or Japan, where the circannual variation is most prominent (38). Long cycles in the incidence of cholera and diphtheria have been mapped in different geographic locations, Figure 15 (39, 40). Geographic differences are to be expected for oscillations related to solar-terrestrial magnetism as magnetic storms show a strong dependence on latitude. Entries in the atlas will thus need to specify where the data yielding the listed results were collected.

ATLAS CONSTRUCTION CONSIDERATIONS

When considering the actual construction of the atlas, we view it as an “information product” (though not a product that would be sold for profit). To help ensure that we create the atlas in a useful form, we look at examples of other atlases and, to determine some of the presentation details of the atlas, we take some cues from typical product development processes, which generally start out with steps similar to 1) seeing a need or problem to solve, 2) envisioning a product that solves it, 3) specifying the characteristics of the product, and 4) defining the specific form of the product.

We expect our atlas to contain not only a substantial collection of useful chronome “maps” resulting from recent research, but it also might contain charts with different views of the same data, tables of related information, and indexes organized in different fashions, all in a way that is similar to many traditional atlases of maps with their associated geographic and other data.

The desires and needs for the atlas have been clear for some time, and include dissemination of information resulting from research at the Halberg Chronobiology Center and within the broader BIOCOS project in a consolidated form, publishing a reference of information to be used in interpreting results as trends when they actually are part of a cycle with a period longer than the investigation span, and explaining discrepant results when such cycles are not recognized.

The “specifications” of the product characteristics typically come from elucidating examples of the usage of the atlas. These “user scenarios” or “use cases” lead us to a detailed understanding of the audience for the atlas, which in turn should affect how the textual additions to the figures are written. The use cases should also help us refine the list of printed indexes or online search mechanisms to be included.

The atlas to be produced should provide an indispensable guide for short-term as well as long-term studies in view of the fact that cycles with shorter periods are often modulated in their characteristics by cycles with much longer periods. Interest in this kind of endeavor among experienced research-focused chronobiologists and other biologists is evident from work already done in Russia (41-43), where interest in cosmic influences on human well-being has been strong ever since Chizhevsky’s publications (39, 44, 45). The atlas should also interest niches in the fields of space weather, geophysics, meteorology, ecology and environmental sciences, among others.

Considering the multi-faceted aspects of the compendium to be assembled, its scope extends beyond the usual atlas. A better term for it might be an encyclopedic atlas, since educational materials are to be included in the volume. Encyclopedic atlases of the human body, of the world, of wine, etc., can already be found online. By including educational materials, the atlas should be useful to those who work at growing the interest in understanding chronobiology amongst researchers and other people with sufficient education, experience, or reason to be interested.

Use cases also help us recognize what the atlas is not. For example, when we look at a sample list of uses of the atlas:

- construct a model of environment affecting human physiological health to be tested;
- construct a model of prediction of psychological effects to be tested;
- put results of testing a model testing (i.e., research) back into the atlas as a new entry;
- understand effects of environment on physiological measurements;
- correcting misinterpretation of correlations measured at different times, due to unstable (“aeolian”) cycles;
- plan a roadmap of future research projects,

we would notice that we do not expect the atlas to be used as a tutorial for beginner students, and we presume users to have an elementary knowledge of rudimentary math, biology, and physics.

The specific form of the atlas is likely to be two-fold. We would engage a self-publishing company that can make printed copies of the atlas available on an as-needed basis, at the non-profit cost of printing and mailing. An online version would be presented as a collection of HTML web pages that may contain non-displayed meta keywords for web-accessible search engines to index in addition to the visible text on and around the charts themselves. The online version would presumably be updated more regularly than the physical book. Changing online web pages creates something of a referential integrity problem for those who wish to make references to the online form of the atlas in academic literature. We expect that a policy of not removing important information if it becomes outdated, adding instead an explanation of how and why the outdated information has been updated or superseded will be a sufficient solution to prevent references to the online form of the atlas from going out of date.

In book form, the atlas should include references to publications providing additional information about each chart and the origin of the data, together with details about their analysis. Indexing in this case should be key to facilitate searches. Electronically, the charts can be linked to the actual numbers used to generate them. In addition, links can be put in place to the actual data files, allowing other investigators to run independent analyses. Links can also be provided to the original publications.

Whether the atlas is consulted in book form or online, it will be important to provide for each entry in each chart a set of specifications regarding the input data (variable kind, span of observation, sampling rate, location of collection, experimental conditions). Specifications should also be provided for each output, including the period range of interest, and if warranted, corresponding information on the MESOR, amplitude, and acrophase, as well as a list of environmental factors exhibiting coproperiodisms with the given spectral component and variable of interest. A field making use of the conclusion from the study is to be added whenever possible, so that healthcare could take advantage of results on drug interaction or effectiveness, and meteorology could take advantage of cycles observed in a geomagnetic study.

Lessons can already be learned from efforts from Gamburtsev and Nikolaev who with support from the Russian Ministry of Science and the Russian Foundation for Basic Research have published an atlas of natural processes in 3 volumes (41–43). The three books, written in Russian, contain numerous charts, including gliding spectra for viewing changes in dynamics of natural processes as a function of time. They are organized as series of chapters contributed by different authors, presented in different sections dealing first with ideological issues of nature and society development, then with processes in natural and social spheres on different time and space scales, providing results from different investigators and their comparison.

The encyclopedic atlas visualized herein should build on this existing work. Presenting the information in a more dynamic form made possible by tools available online, our encyclopedic atlas should document the following points:

1. Characteristics of cycles with different periods;
2. The existence of coproperiodisms between physics and biology;
3. Similarities in the changes with time in environmental and biological cycles;
4. Differences in environmental-biological associations by geographic location;

5. Encyclopedic entries complementing the charts, drawing conclusions from information presented therein or summarizing results displayed in a set of different charts (as an example, charts related to the biologic week could make the point that different environmental factors influence its pattern at birth, as reviewed above); and
6. Models to predict peaks and troughs to help plan for contingencies, and hopefully for the design of countermeasures.

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APPLICATION OF CARDIO-ANKLE VASCULAR INDEX (CAVI) IN CLINICAL AND EPIDEMIOLOGICAL STUDY

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*Dedicated to the memory of my friend, teacher
and outstanding scientist Professor Bohumil Fišer, Ph.D.*

ABSTRACT

Cardio-ankle vascular stiffness index (CAVI), a blood-pressure independent index of arterial stiffness, is a comprehensive indicator of various conditions, such as cardiovascular or life-style related diseases and aging, as well as unknown factors that enhance development of atherosclerosis. The main advantage of CAVI is the simplicity of measurement in daily clinical practice, its importance in the evaluation of disease grade and cardiovascular risk factors, and its usefulness in the treatment decisions. CAVI could be used also to assess the effects of life-style modification. Until May 2013, CAVI was measured in 3.581 subjects aged 16–70 years (1.657 men and 1.924 women) from the population of the South Moravia region. The strategic aim of this still running study is to provide local standardization of CAVI and to help to establish new international atherosclerosis standards.

Summary statistics of CAVI values (n = 3.581)

N=3581	Mean	95%CI	Median	5-95% quantile
R-CAVI	7.795	(7.741; 7.849)	7.80	(5.20; 10.40)
L-CAVI	7.811	(7.756; 7.865)	7.80	(5.20; 10.40)
average CAVI	7.803	(7.749; 7.856)	7.80	(5.25; 10.45)

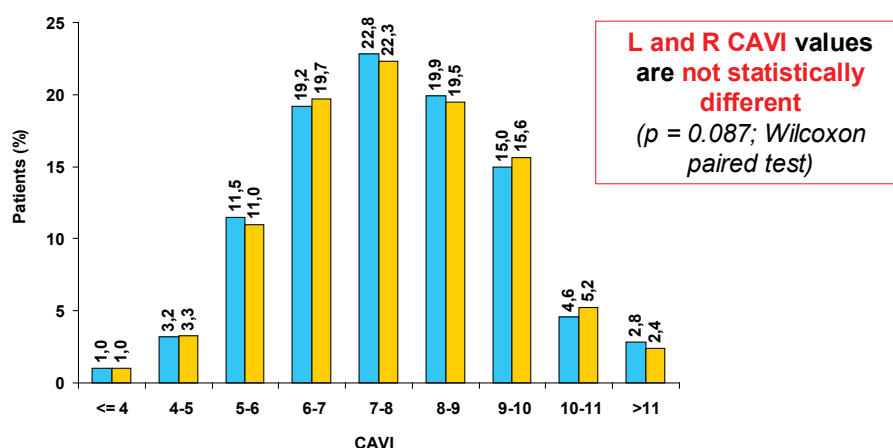


Figure 1

Differentiation of diagnoses based on averaged L and R CAVI

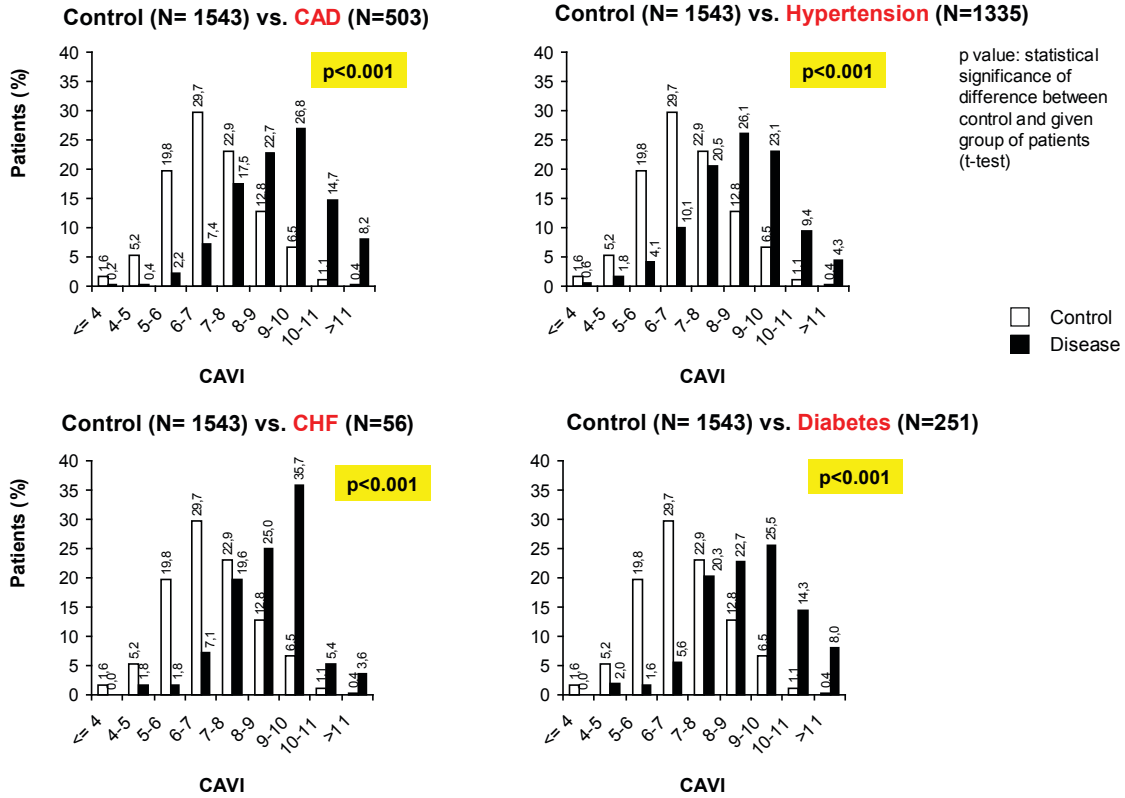


Figure 2

Differentiation of diagnoses based on averaged L and R CAVI

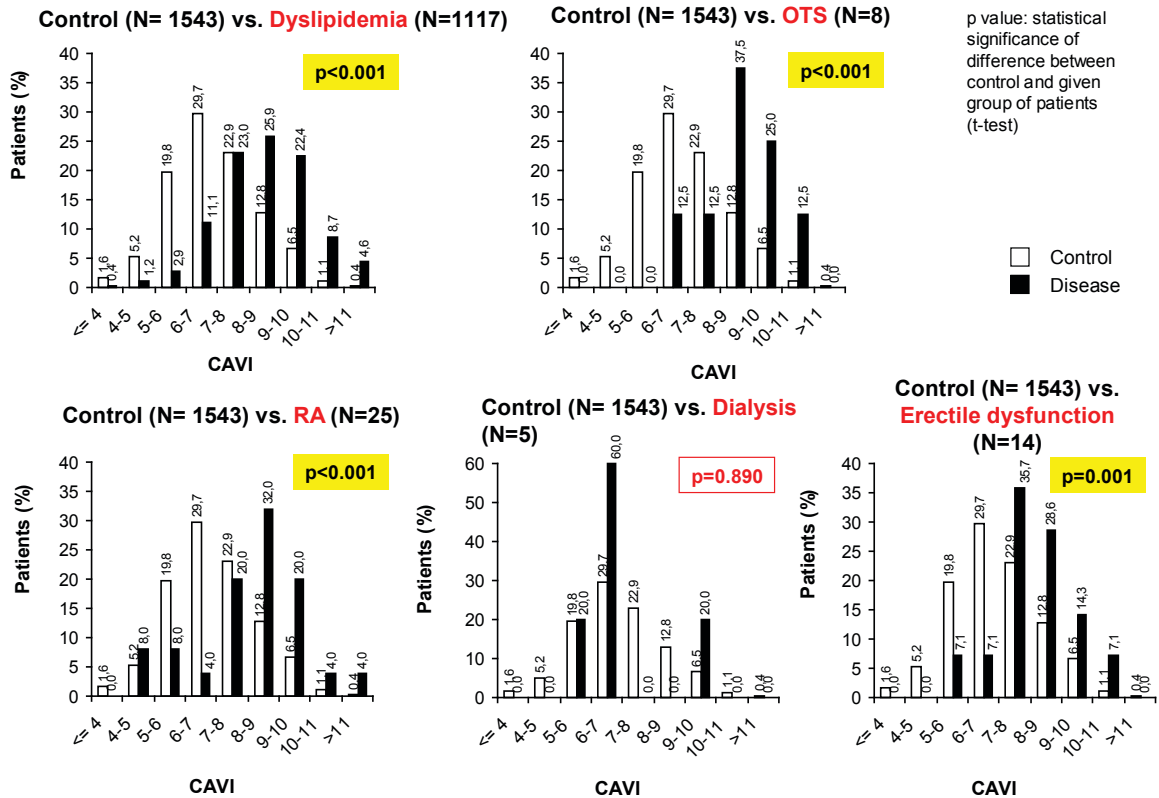


Figure 3

Differentiation of diagnoses based on averaged L and R CAVI

p value: statistical significance of difference between control and given group of patients (t-test).

□ Control ■ Disease ■ mean | 95% CI

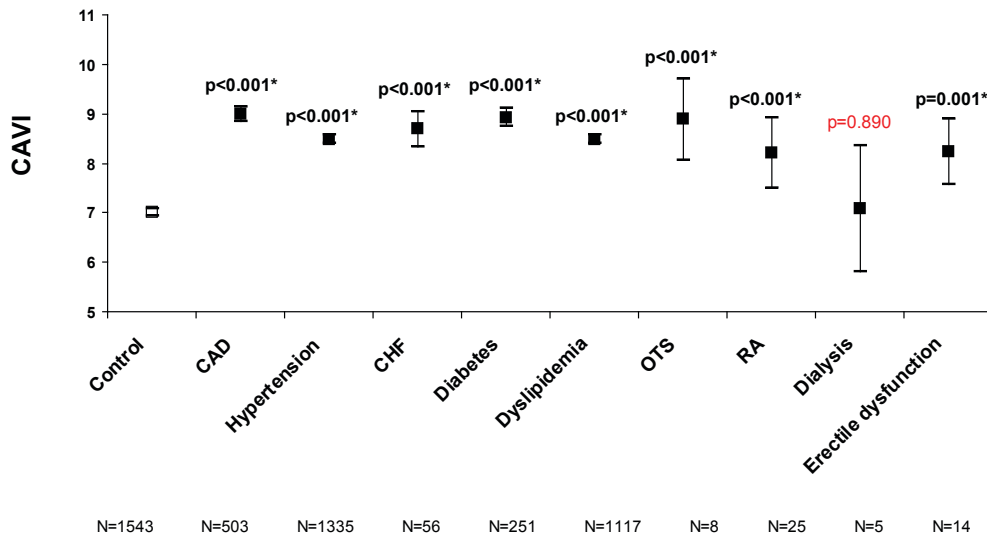


Figure 4

Comparison of calibration datasets between the Czech Republic and Japan

Czech CAVI dataset
(subjects below 20 years were included in the analysis)

Suzuki K et al, Tohoku Pulse-Wave Information, Workshop Jul. 2007

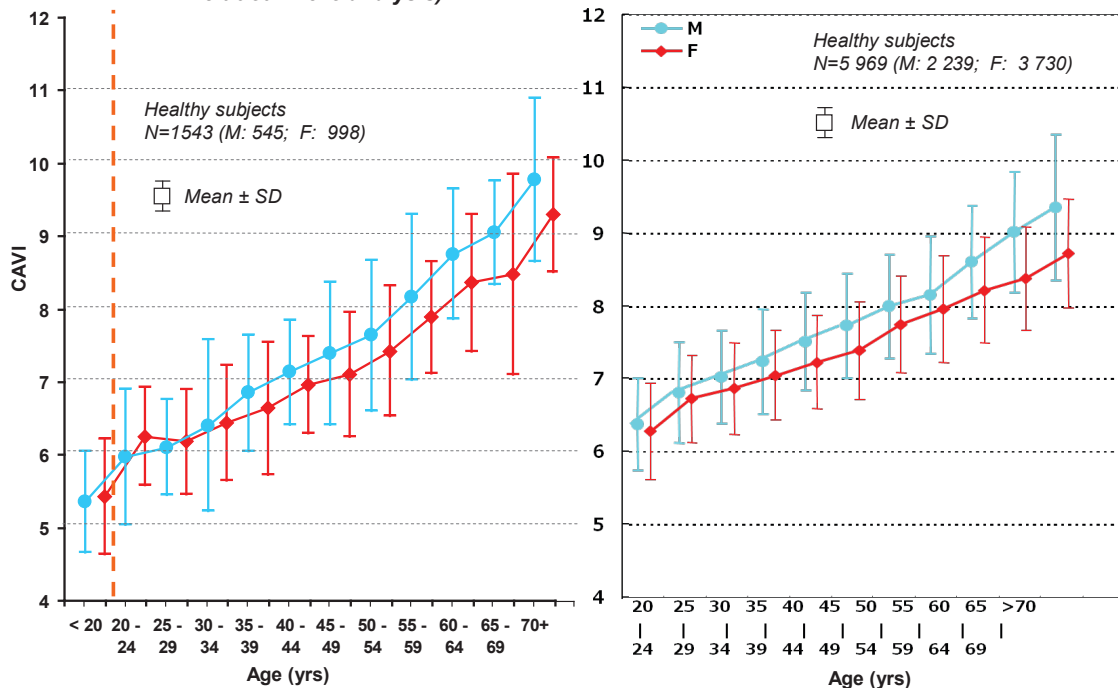


Figure 5

INTRODUCTION

Many studies revealed that high aortic pulse wave velocity is a strong risk factor independent of other known risk factors enhancing the onset of cardiovascular diseases. Vascular, coronary, renal, cerebral, and other organ damage is closely related to central aortic blood pressure and pulse pressure (1). Blood pressure has a great influence on pulse wave velocity and blood pressure greatly varies at the time of PWV measurement, regardless of a presence of hypertension. Recently, a new parameter of arterial stiffness evaluation has been introduced into clinical practice – cardio-ankle vascular index or CAVI (2). Arterial stiffness screening system “VaSera” can evaluate arterial stiffness using the CAVI parameter measured by a simple method which is minimally affected at the time of measurement. The results can be quickly used in the individual evaluation in daily clinical practice and therapeutic procedure. Aortic stiffness expressed by CAVI is a valuable indicator of atherosclerosis, such as cardiovascular diseases, life-style related diseases and aging. This study is a continuation of the long-term CAVI project in Czech Republic focusing on the systematic screening of arterial stiffness in Czech healthy population and people with cardiovascular and other lifestyle related diseases.

PATIENTS AND METHODS

Recruitment of healthy volunteers and patients aged 16–70 years was realized using a campaign in radio and newspapers in close cooperation with different departments from St. Anna Faculty Hospital in Brno.

CAVI MEASUREMENT

CAVI was assessed by the VaSera 1500 vascular screening system (Fukuda Denshi Co., J). CAVI is measured from the beginning of the aorta to the tibial artery above the ankle and covering central elastic artery (aorta) and peripheral muscular arteries (femoral and tibial artery).

STATISTICAL ANALYSIS (IBA, MASARYK UNIVERSITY)

Visualization of data is based on comparative histograms and box-whisker plots. Visual comparison of Czech results with Japanese data uses data description by arithmetic mean and standard deviation. The descriptive summary of L and R CAVI values is based on robust non-parametric statistics, i.e., median and 5th–95th percentile range. The statistical significance of difference between L and R CAVI values was tested by Wilcoxon matched paired test. Statistical significance of differences in averaged values of CAVI among categories of key descriptors was evaluated using one-way ANOVA followed by Tukey post-hoc test; the variables were described using mean and its 95% confidence interval. Comparison of two groups of patients within age category was computed using standard t-test for comparison of two independent samples (with homogeneous within group variance). Spearman correlation coefficient was applied for the analysis of relationship between CAVI and other descriptors.

RESULTS

CAVI was measured in 3.581 subjects aged 16–70 years (1.657 men and 1.924 women) from the population of the South Moravia region. Of that total, 1.543 healthy people were recruited (545 men; 998 women). The rest were subjects with hypertension (n = 1.335), dyslipidemia (n = 1.117), coronary artery disease (n = 503), diabetes mellitus (n=251), chronic heart failure (n = 56), orthotopic heart transplantation (n = 8), rheumatoid arthritis (n = 25), males with erectile dysfunction (n = 14) and patients on chronic hemodialysis (n = 5). Statistical analysis did not show significant difference between right and left CAVI (R-CAVI and

L-CAVI; Fig. 1). Statistical analysis proved significantly higher CAVI value in patients with hypertension, dyslipidemia, coronary artery disease, diabetes mellitus, chronic heart failure, orthotopic heart transplantation, rheumatoid arthritis, and also in men with erectile dysfunction (Fig. 2, 3 and 4). Only in patients on chronic hemodialysis the results of CAVI measurement were without statistical significance but this result can be attributed to too low number of analyzed subjects (only 5 persons). We found a similar CAVI development in Czech and Japanese dataset (Fig. 5). It seems that the distinct increase of arterial stiffness is present in Czech men and women from 50 years of age compared to their Japanese counterparts. Thus, the Czech population over 50 years has a significant risk for development of atherosclerosis.

CAVI IN PROFESSIONAL SPORTSMEN

We also evaluated CAVI in 31 players of one Czech professional ice-hockey team (mean age 27.1 ± 3.31 years). The mean CAVI value in ice-hockey players was 5.77 ± 0.7 in comparison with the healthy standards from Czech CAVI dataset which is actually 6.2 ± 0.8 (difference -0.45). This result could be regarded as a sign of a lower sympatho-adrenergic activity in well trained endurance athletes.

DISCUSSION

Aging is very important risk factor of atherosclerosis. In our study we found that CAVI with age rises by approximately 0.5 in men than women (equivalent to ten years of aging). The present study conclusively demonstrated that CAVI increases not only with age but also in patients with coronary artery disease (CAD), hypertension, diabetes mellitus, dyslipidemia, chronic heart failure, orthotopic heart transplantation, rheumatoid arthritis erectile dysfunction and also patients on chronic hemodialysis. Several authors reported that CAVI reflects the real effects of blood pressure on the properties of arterial wall and development of atherosclerosis is preceded by decreased elasticity resulting from structural changes in the arterial wall (3 and 4). It has been proven that CAVI significantly increases in patients with decreased diastolic function of left ventricle (5). The overproduction of inflammatory and vasoactive substances triggers vessel wall remodeling. One recent study showed that CAVI may reflect global inflammatory reaction of vessels in whole organism - Wakabayashi et al. reported that CAVI rises with increased plasmatic level of CRP, amyloid A, sialic acid, fibrinogen, etc. in diabetes mellitus type 2 (6). Primary prevention of cardiovascular diseases is a priority No.1 in a public health policy of developed and developing countries. The fundamental strategy consists in identifying people in a high risk situation in which preventive measures are effective. Improvement of these predictions in our country will have an immediate clinical and health impact and a short term public effect. The screening based on CAVI parameter is quick, easy and low-cost technique to diagnose arterial stiffness. Higher CAVI values could have a strong preventive effect of interventions in people with symptomatic cardiovascular diseases and it is likely that these interventions will have a protective effect on early risk factors modification and pharmacotherapy in subjects with subclinical disease (7 and 8). Incorporation of the systematic CAVI measurement into regular screening for arterial stiffness may improve cardiovascular risk stratification and increase early identification of patients with high cardiovascular risk. Current knowledge supports the international consensus for risk screening but more future trials are needed to determine whether adding CAVI assessment in the screening strategies would be also cost-effective.

CONCLUSION

In the past 4 years our team made a considerable effort in which is concerning the CAVI measurement and interpretation. We succeeded to collect and publish important and unique data about CAVI in patients with chronic dyslipidemia, chronic heart failure. **Professor Bohumil Fišer, an outstanding Czech expert in cardiovascular physiology, highlighted several times the importance and diagnostic value**

of the CAVI measurement and strongly supported its introduction into clinical practice (9). However, despite the undeniable clinical value, the systematic evaluation of CAVI in clinical practice in Czech Republic is realized only by few outpatient physicians and by only one clinical department in St. Anna Faculty Hospital Brno. Arterial stiffness in the developed countries is strongly influenced by risky behavior (dietary habits, physical inactivity, smoking, etc.) and this type of lifestyle often results in obesity, high blood pressure and atherosclerosis progression (10). Therefore, much more attention should be paid to the early detection of changes in arterial stiffness and to popularize the clinical importance of the diagnostic potential of CAVI in primary prevention.

Acknowledgement: The presented study was realized in the cooperation with Fukuda Denshi Co.,Tokyo, Japan.

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SEVEN DAY AMBULATORY BLOOD PRESSURE MONITORING AND LEFT VENTRICULAR MASS INDEX IN PATIENTS AFTER INFARCTUS OF MYOCARDIUM IN CARDIOVASCULAR REHABILITATION

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Dedicated to memory Professor Bohumil Fišer, Ph.D.

Franz Halberg, Germaine Cornélissen and BIOCOS scientific group, of which we are the members from the beginning, provided strong evidence for the need to account for day-to-day changes in blood pressure and heart rate variables in the similar way as a circadian assessment considers the hour-to-hour variability (Halberg 1953, 1969, Halberg et al., 2000, 2001, Cornélissen et al., 1989).

In our paper dealing with 7-day ambulatory blood pressure monitoring study we described the relationship between age and circadian variations of systolic blood pressure (SBP) and diastolic blood pressure (DBP) (Siegelová et al., 2006).

MESOR – mean values of systolic SBP and DBP were increasing with age up to 75 years, but night-day difference (double amplitude) of SBP and DBP reached the maximum value at 45 years and then decreased (Siegelová et al., 2006). The evidence led to the recommendation of around-the-clock monitoring for 7 days at the outset (Halberg et al., 2002, Cornélissen et al., 2004) to be continued whenever needed, until monitoring for a lifetime becomes more readily feasible.

European guidelines on hypertension management from European Society of Hypertension in 2007, 2009 and 2013 have shown that hypertensive patients have left ventricular hypertrophy due to essential hypertension (Mancia et al. 2007, 2009, 2013).

Left ventricular mass index (LVMI) values, considered as a gauge of cerebrovascular risk, are greatly elevated when abnormal circadian patterns of systolic (SBP) and diastolic (DBP) blood pressure are diagnosed in hypertensive patients. Vascular variability disorders, described by prof. Franz Halberg in Brno Consensus together with the Biocos international participation, showed the risk of chronobiologically interpreted around-the-clock ambulatory blood pressure monitoring and related to outcomes in three different investigations, carried out in the Czech Republic, Japan and Taiwan. Vascular variability disorders include, with an elevated blood pressure (MESOR-hypertension, an excessive pulse pressure, too large a circadian amplitude of blood pressure (Circadian Hyper Amplitude Tension – CHAT), an odd timing of the circadian variation in blood pressure, a too small standard deviation of heart rate (short for deficient heart rate variability). Hypertension characterized by elevated blood pressure increases left ventricular mass. Increase of left ventricular mass in hypertension is dangerous for cardiovascular morbidity and mortality (Halberg et al., 2007, 2011 Cornélissen et al., 2010, 2013, Siegelová et al., 2011).

The relationship between left ventricular mass index (LVMI) and circadian and circaseptan blood pressure values and double amplitude (difference between the increase of SBP and DBP during day time and the decrease of SBP or DBP at night) in patients after myocardial infarction was the aim of the present study. The evaluation of blood pressure variability by 7-day ambulatory blood pressure monitoring in patients with coronary heart disease was the other aim of the present study.

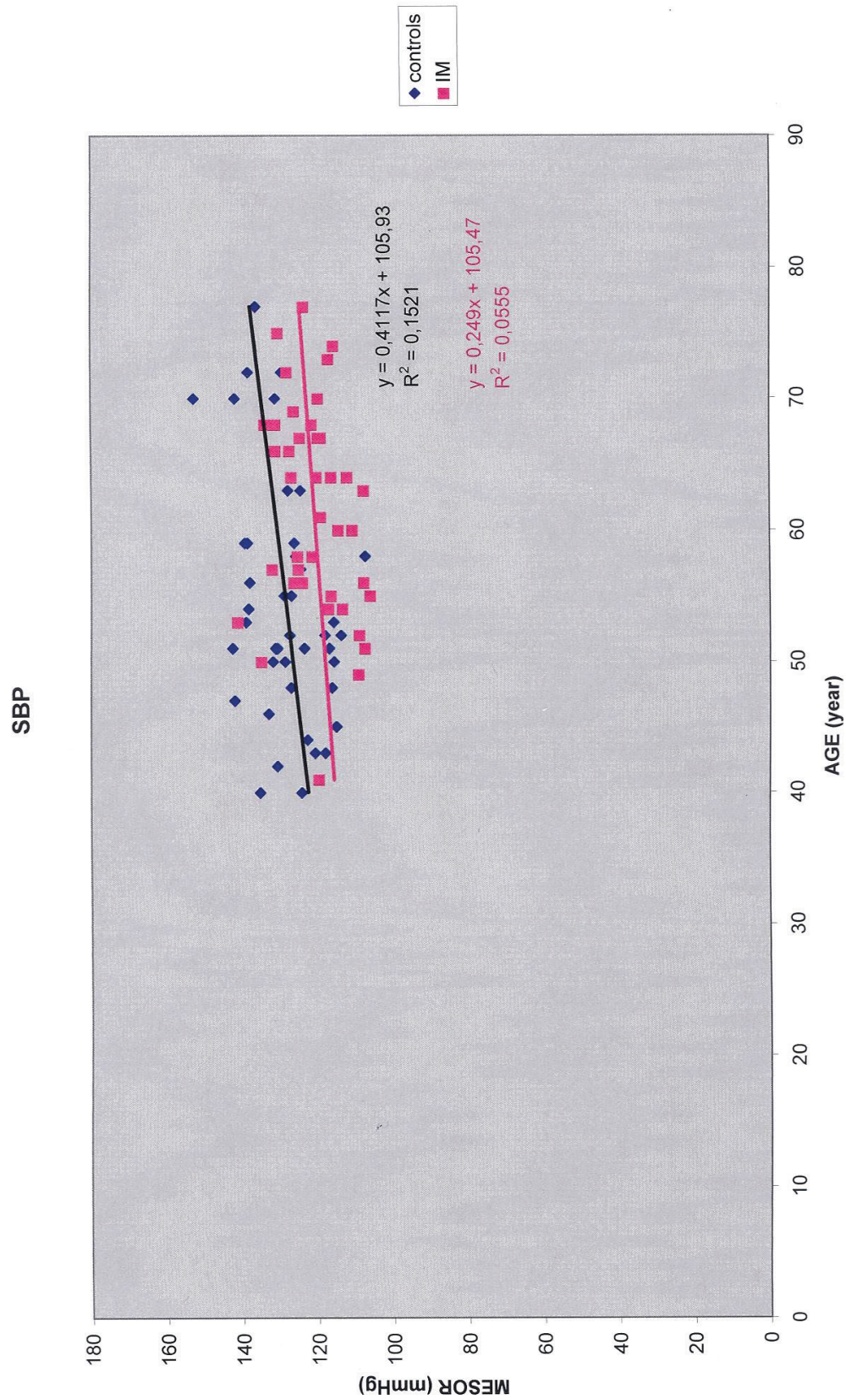


Figure 1 Relationship between MESOR of systolic blood pressure (SBP, mmHg), measured by 7-day ambulatory blood pressure monitoring, and age (years) in healthy subjects (blue) and in patients with coronary heart disease (red).

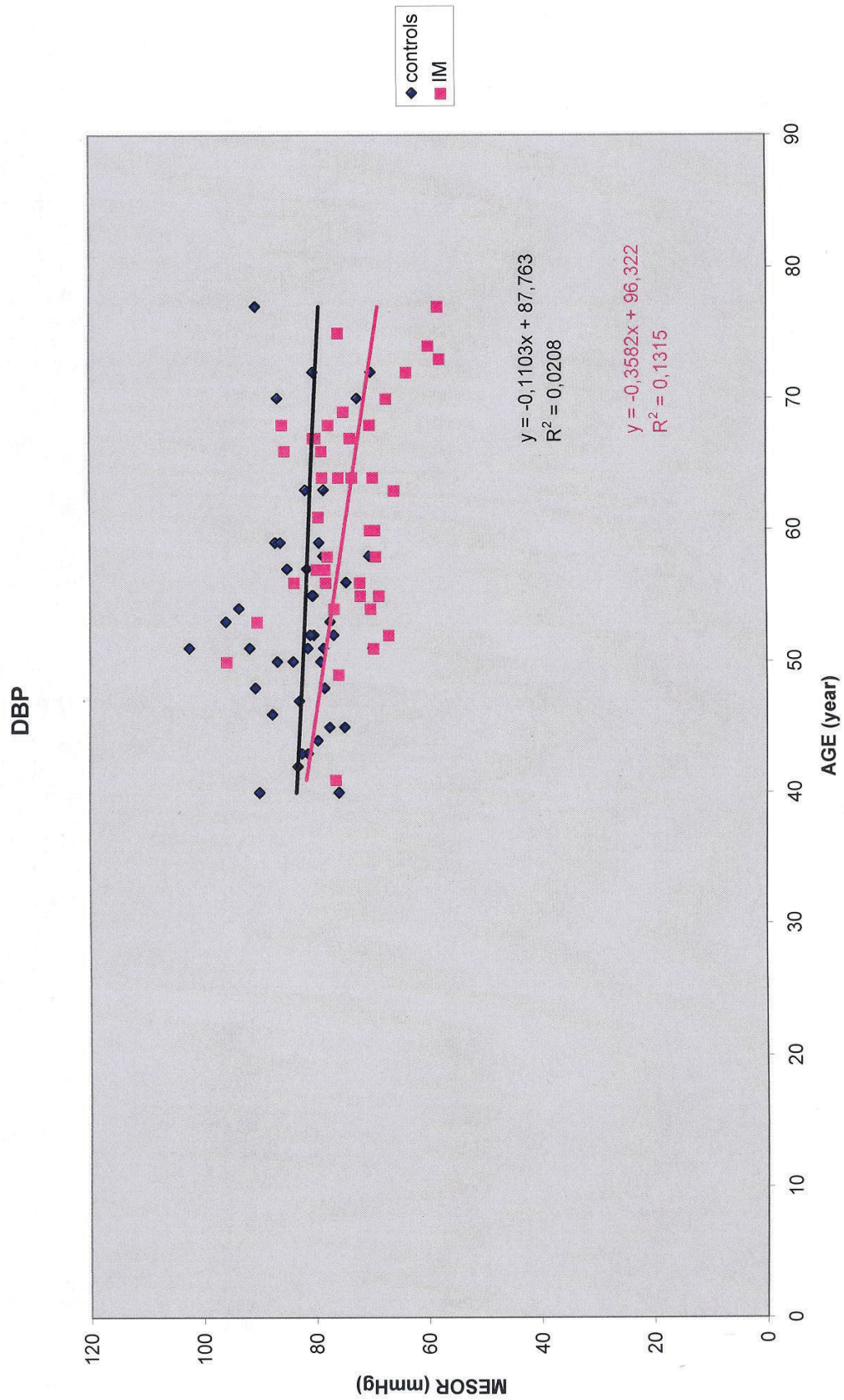


Figure 2 Relationship between MESOR of diastolic blood pressure (DBP, mmHg), measured by 7-day ambulatory blood pressure monitoring for 24 h and age (years) in healthy subjects (blue) and in patients with coronary heart disease (red).

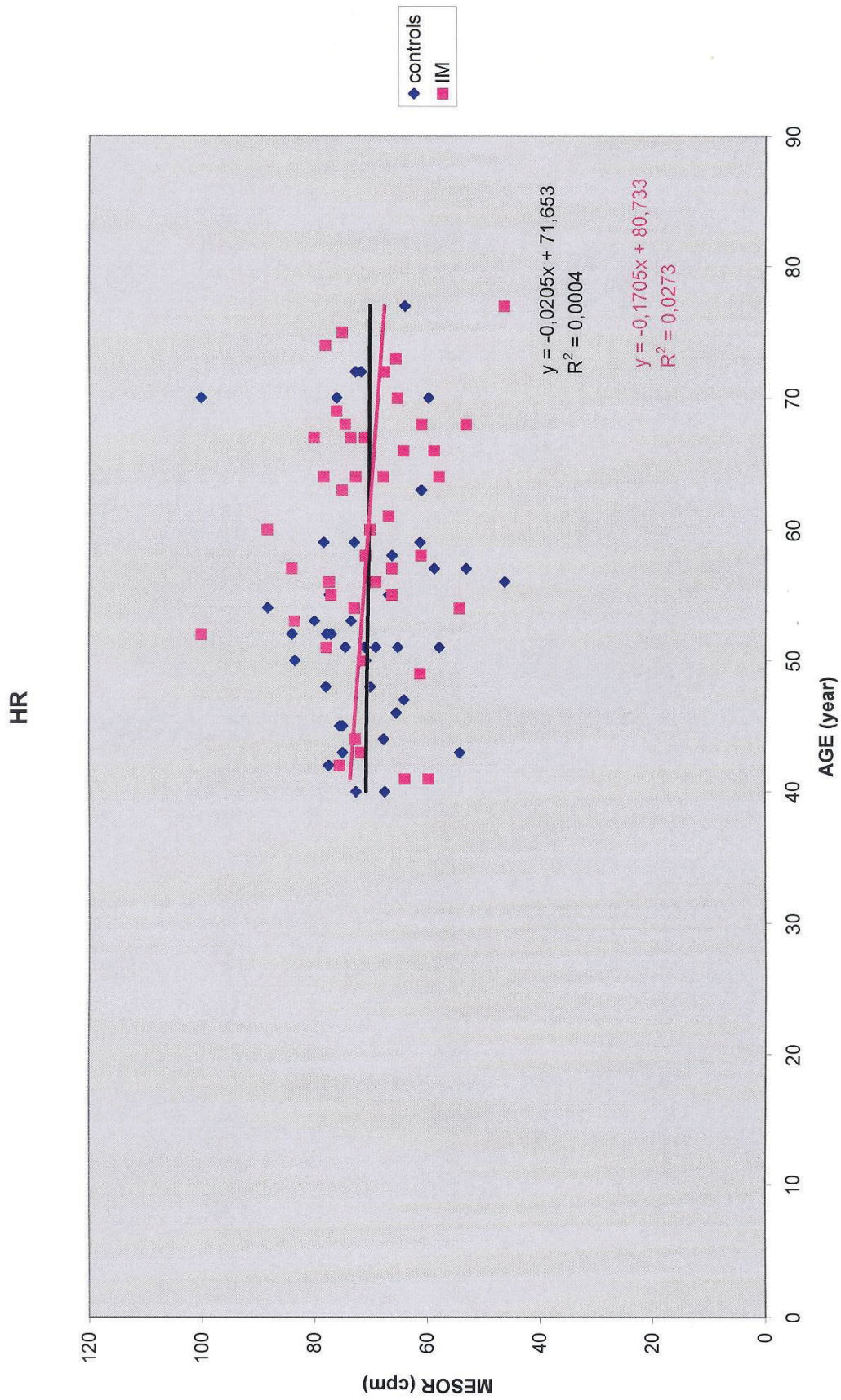


Figure 3 Relationship between MESOR of heart rate (HR, bpm), measured by 7-day ambulatory blood pressure monitoring, and age (years) in healthy subjects (blue) and in patients with coronary heart disease (red).

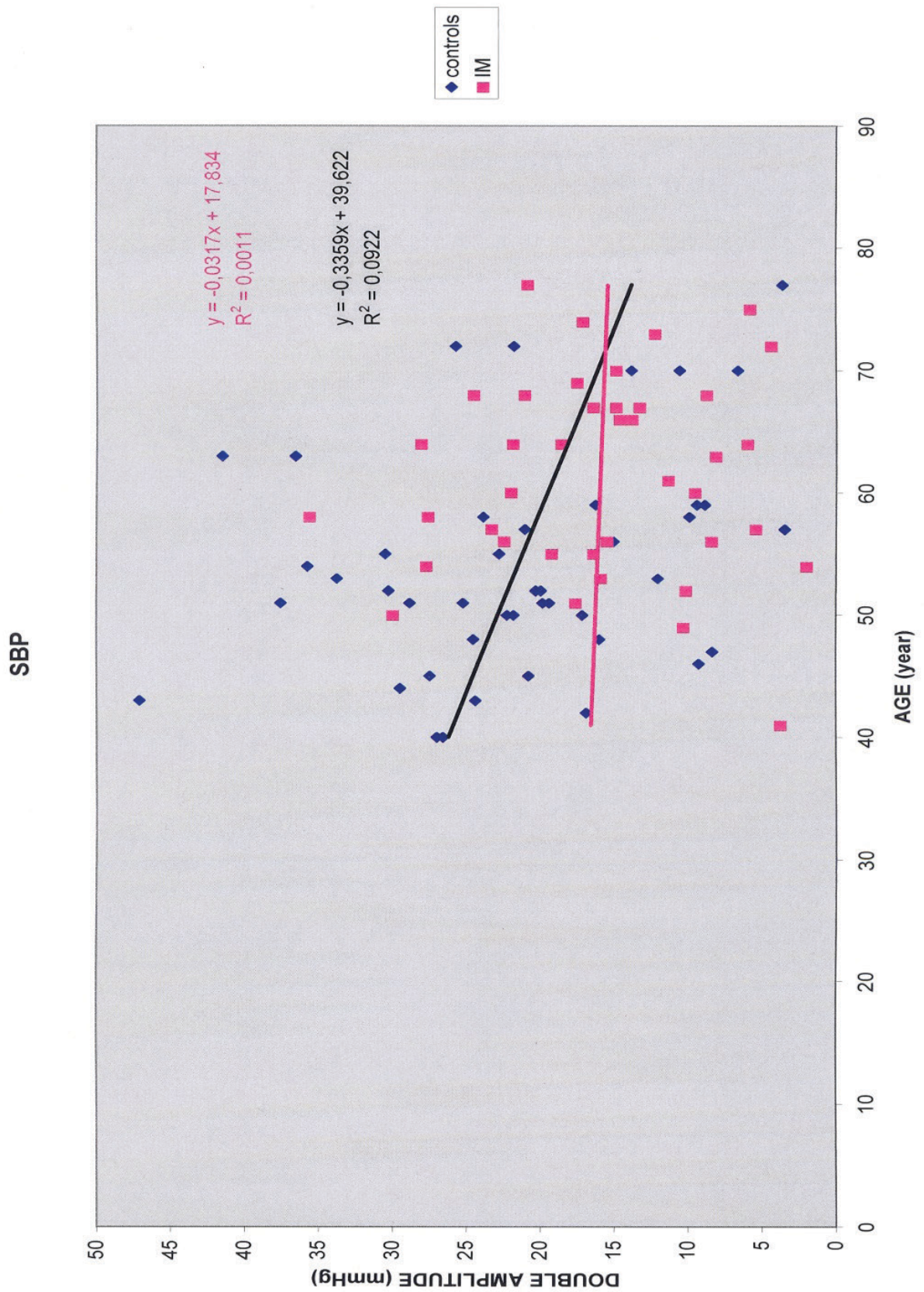


Figure 4 Relationship between circadian amplitude of systolic blood pressure (SBP, mmHg), measured by 7-day ambulatory blood pressure monitoring, and age (years) in healthy subjects (blue) and in patients with coronary heart disease (red).

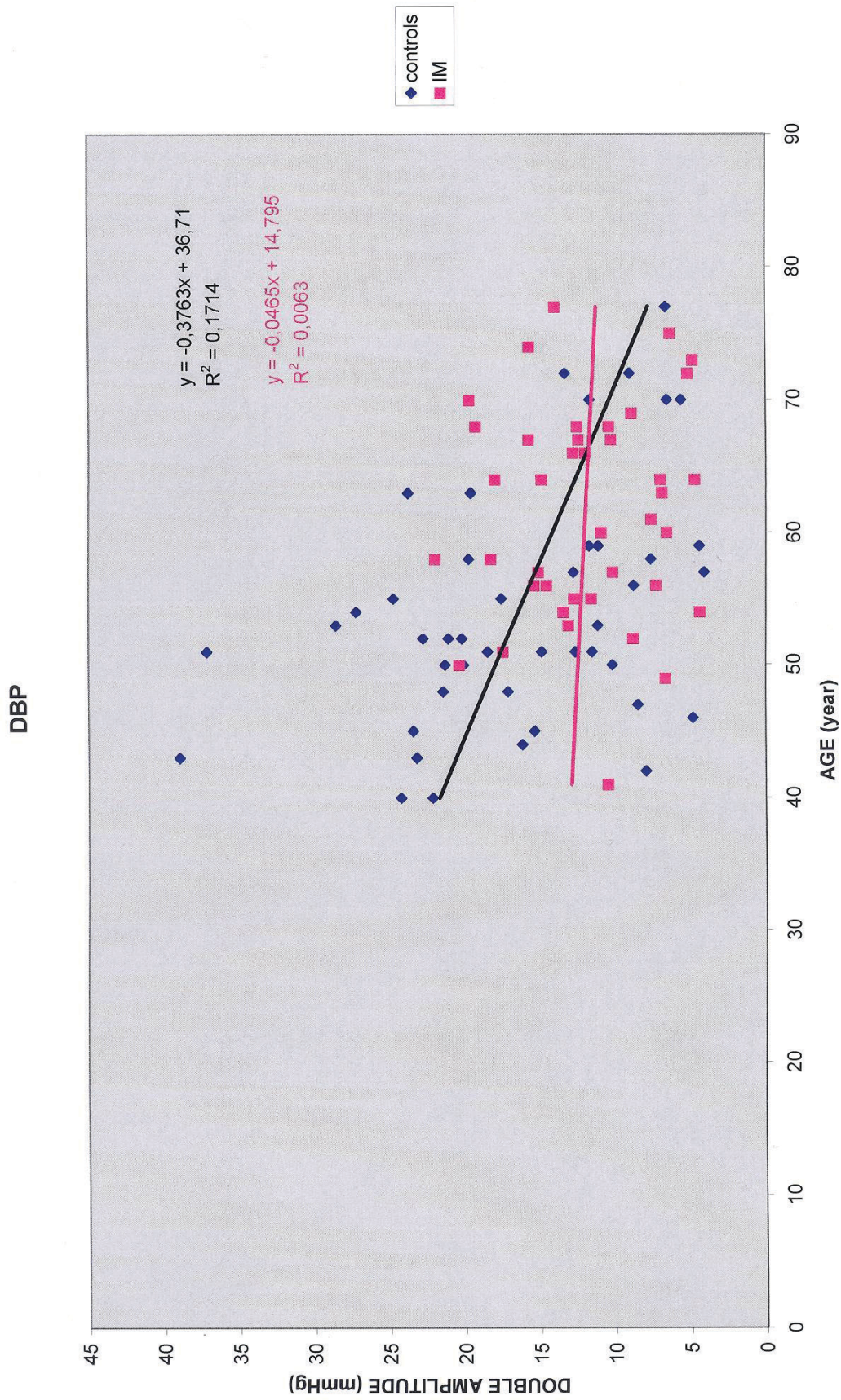


Figure 5 Relationship between circadian amplitude of diastolic blood pressure (DBP, mmHg), measured by 7-day ambulatory blood pressure monitoring, and age (years) in healthy subjects (blue) and in patients with coronary heart disease (red).

METHODS

The set being monitored consisted of 51 patients with ischemic heart disease (IM) of the age $63 \pm 6,3$ years (age between 41 and 77 years) and ejection fraction ($43 \pm 12,3$) %.

The patients were subjected to phase II of cardiovascular rehabilitation (controlled ambulatory rehabilitation program) lasting 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 rehabilitation the patients underwent 7-day ambulatory monitoring of blood pressure. During blood pressure recording they did not interrupt pharmacotherapy (ACE inhibitors, statins, beta-blockers, Ca antagonists).

7-day monitoring of blood pressure was made by means of the instrument TM - 2421 of Japanese firm AD operating on the principle of oscillometric analysis. The instrument measured blood pressure for 7 days repeatedly every 30 min from 5 to 22 o'clock and once an hour from 22 to 5 o'clock. If a value not much probable from the point of view of the instrument setting was recorded, another check measurement was made (Siegelová et al. 2004).

The results were processed by using Halberg cosinor analysis. The data were smoothed by a sinusoidal curve. The mean value of the sinusoid, designated MESOR, and amplitude of circadian fluctuation were determined. Sinusoidal curve was fitted (least square method) and mean value and amplitude of the curve (double amplitude corresponds to the night-day difference) were evaluated every day of monitoring. Average 7-day values of the mean (MESOR) and of double amplitude (2A) for systolic BP (SBP), diastolic BP (DBP) and heart rate (HR) were determined for each subject of both sets.

Left ventricular mass index was calculated from echocardiography from the thickness of septum and dorsal wall of left ventricle.

The study was approved by local ethic committee and the patients signed informed consent.

RESULTS

We evaluated blood pressure by 7-day ambulatory blood pressure monitoring in patients with coronary heart disease.

A significant increase of systolic blood pressure (SBP) MESOR with age was found in healthy subjects ($r = 0.39$, $p < 0.01$), but not in patients with coronary heart disease IM ($r = 0.23$) as is shown in Fig. 1. Diastolic BP (DBP) MESOR was not related to age in healthy subjects ($r = 0.14$) but the decrease of DBP with age in patients with coronary heart disease IM was observed ($r = 0.362$, $p < 0.05$) as is seen in Fig. 2. Mean value of SBP MESOR was higher in healthy subjects C than in patients with coronary heart disease IM (128 ± 9 vs. 121 ± 8 mmHg, $p < 0.01$), as well as DBP MESOR (81 ± 7 vs. 74 ± 7 mmHg, $p < 0.01$). Double amplitude of SBP decreased with age in healthy subjects C ($r = 0.30$, $p < 0.05$) but not in patients with coronary heart disease IM ($r = 0.03$), as is shown in Fig. 4. Similarly double amplitude of DBP decreased with age in healthy subjects C ($r = 0.41$, $p < 0.01$) and not in patients with coronary heart disease IM ($r = 0.08$), as we can see in Fig. 5. Mean values of double amplitude were lower in patients with coronary heart disease IM (double amplitude SBP: 21 ± 10 vs. 16 ± 8 mmHg, $p < 0.01$; double amplitude DBP: 16 ± 8 vs. 12 ± 5 mmHg, $p < 0.01$). Heart rate (HR) was not age-related in both groups, difference in mean values of heart rate was not observed (C: 71 ± 10 , IM: 65 ± 8 bpm). Double amplitude of heart rate was lower in patients with coronary heart disease IM (15 ± 8 vs. 9 ± 5 bpm).

We evaluated circadian and circaseptan values of systolic and diastolic blood pressure and left ventricular mass in patients with coronary heart disease.

The results of left ventricular mass index and circadian rhythm in systolic and diastolic blood pressure are presented on Fig. 6, 7, 8, 9.

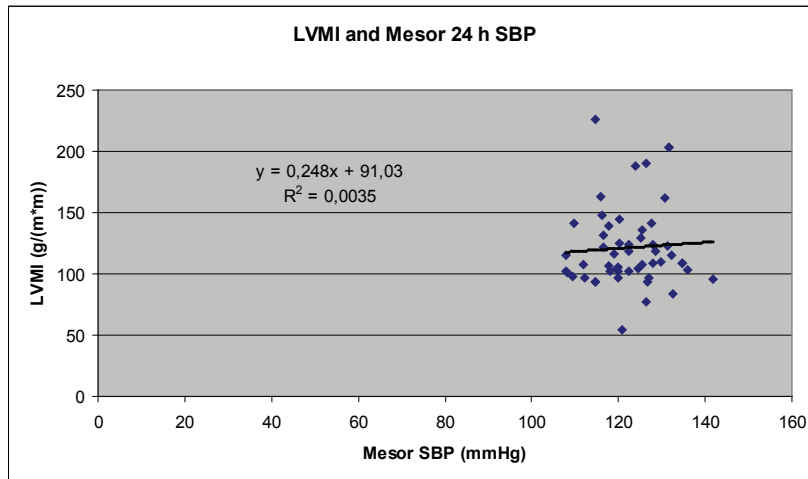


Figure 6 Relationship between MESOR of systolic blood pressure (SBP, mmHg) measured by 7-day ambulatory blood pressure monitoring, 24 h, and LVMI (g/m²m) in patients with coronary heart disease.

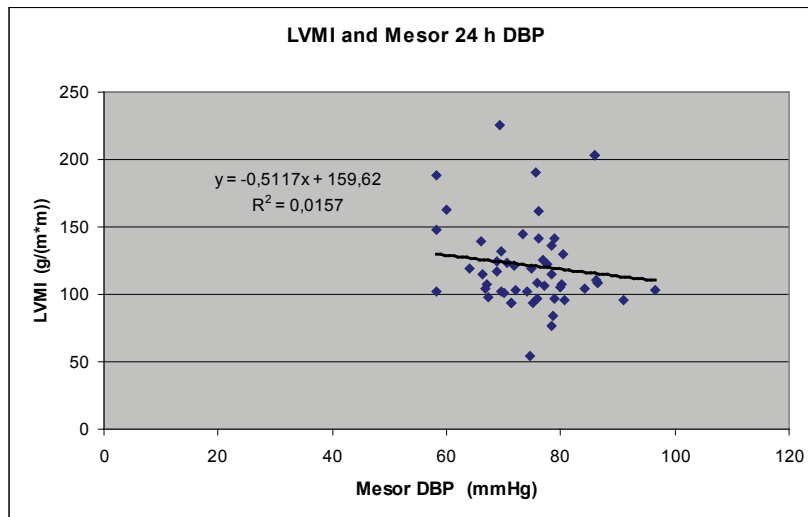


Figure 7 Relationship between MESOR of diastolic blood pressure (DBP, mmHg) measured by 7-day ambulatory blood pressure monitoring, 24 h, and LVMI (g/m²m) in patients with coronary heart disease.

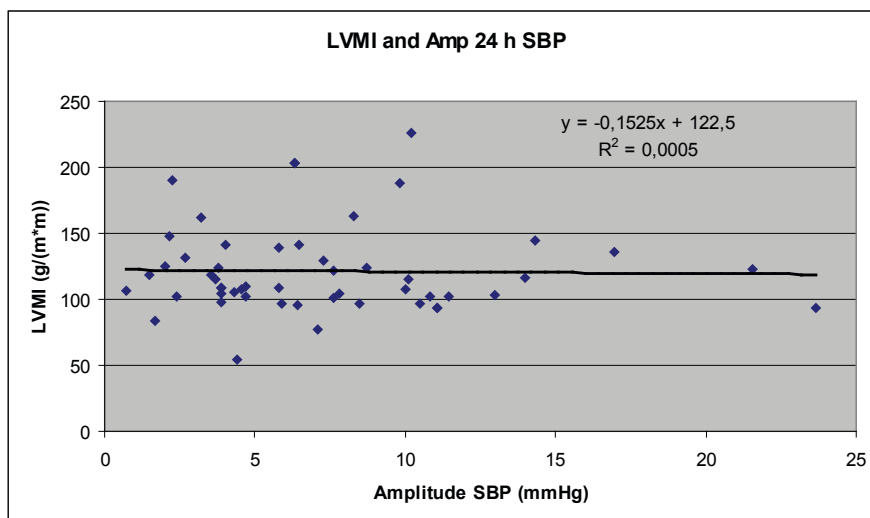


Figure 8 Relationship between circadian amplitude of systolic blood pressure (SBP, mmHg) measured by 7-day ambulatory blood pressure monitoring, and LVMI (g/m²m) in patients with coronary heart disease.

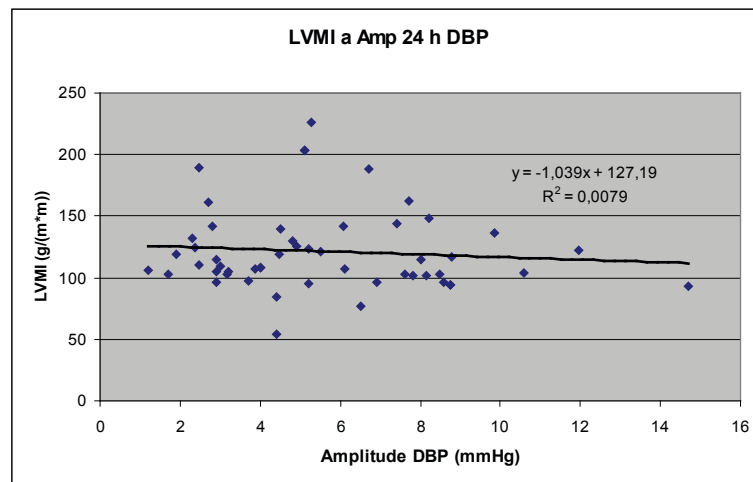


Figure 9 Relationship between circadian amplitude of diastolic blood pressure (DBP, mmHg) measured by 7-day ambulatory blood pressure monitoring, and LVMI ($\text{g}/\text{m}^2\text{m}$) in patients with coronary heart disease.

The correlation between LVMI and circaseptan MESOR and amplitude are on Fig. 10, 11, 12, 13. We have not found the correlation between mean value of LVMI and MESOR and amplitude of SBP and DBP.

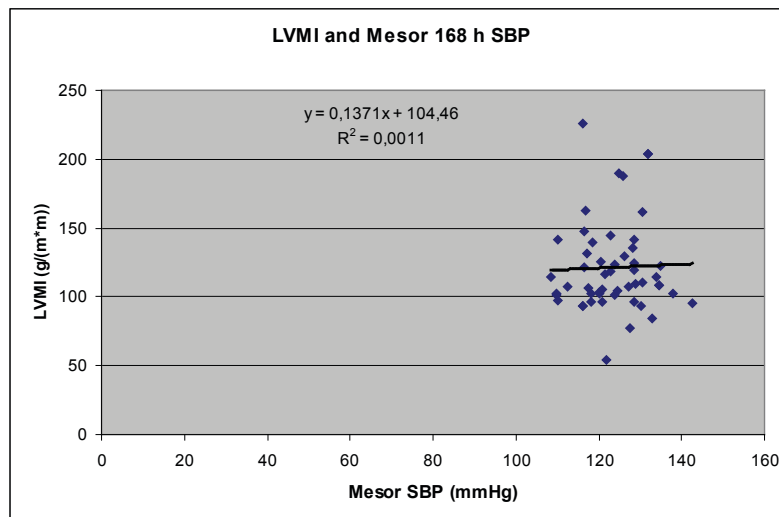


Figure 10 Relationship between MESOR of systolic blood pressure (SBP, mmHg) measured by 7-day ambulatory blood pressure monitoring, 168 h, and LVMI ($\text{g}/\text{m}^2\text{m}$) in patients with coronary heart disease.

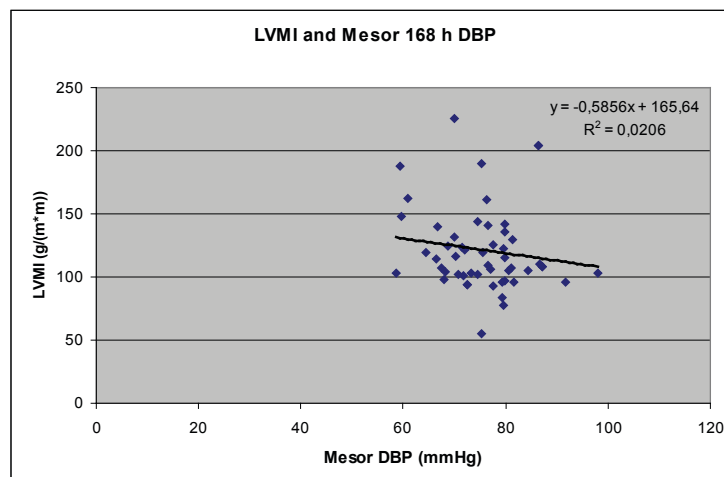


Figure 11 Relationship between MESOR of diastolic blood pressure (DBP, mmHg) measured by 7-day ambulatory blood pressure monitoring, 168 h, and LVMI ($\text{g}/\text{m}^2\text{m}$) in patients with coronary heart disease.

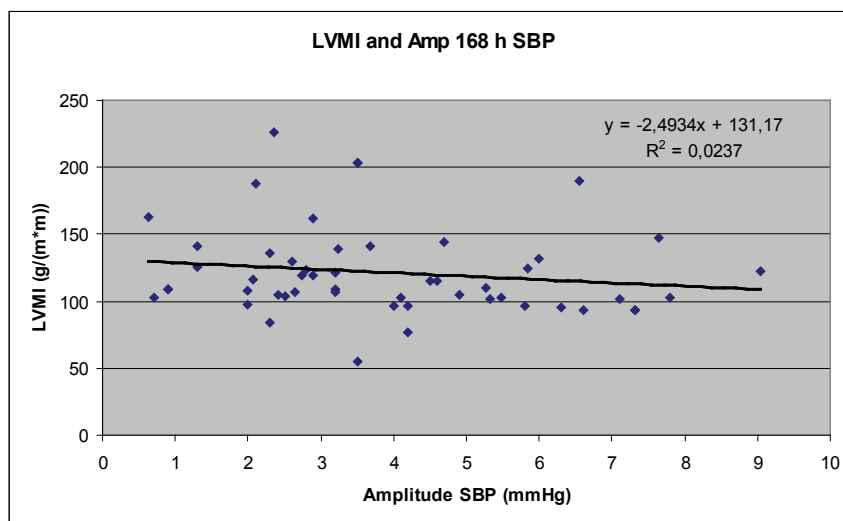


Figure 12 Relationship between circaseptan amplitude of systolic blood pressure (SBP, mmHg) measured by 7-day ambulatory blood pressure monitoring, and LVMI (g/m²m) in patients with coronary heart disease.

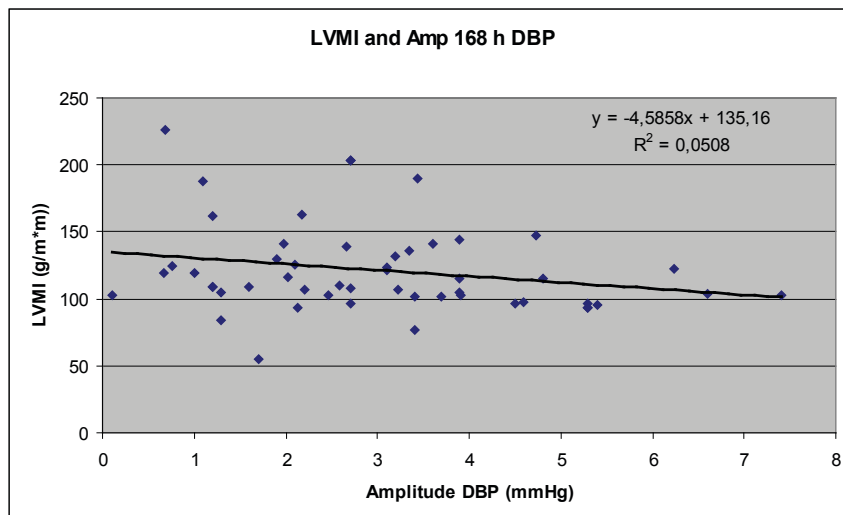


Figure 13 Relationship between circaseptan amplitude of diastolic blood pressure (DBP, mmHg) measured by 7-day ambulatory blood pressure monitoring, and LVMI (g/m²m) in patients with coronary heart disease.

DISCUSSION

There is a growing body of evidence suggesting that time structures in us and around us are intricately interwoven. Most if not all components of variation found in biota are also found in the environment, and vice versa (Halberg et al., 2000). For instance, about daily changes are seen in almost every biological variable under 24-hour synchronized conditions. It has also long been known that the phase of circadian rhythms can be manipulated by changing the phase of the environmental cycles (Halberg, 1969). At least for the case of circadian rhythms, their genetic inheritance has been demonstrated on a molecular basis (Halberg et al., 2002) suggesting that the influence from the environment has been acquired genetically during the course of evolution.

The mapping of chronomes should benefit our understanding of human health and disease in several ways. The study of human chronomes can serve to defined reference values to better define health and to identify pre-disease, so that prophylactic interventions can be instituted as early as possible, preferably before the disease sets in (Halberg et al., 1993, Cornélissen et al., 1993, 1994). The focus is thus put on pre-

habilitation, in the hope that the need for re-habilitation will thereby be reduced (Halberg et al., 2002a,b, Cornélissen et al., 1999).

Several studies (Kumagai et al., 1993, Schaffer et al., 2001) comparing the classification of patients based on single office measurements with that based on ambulatory monitoring for one to seven days suggest that the incidence of misdiagnosis is around 40%, in keeping with the 48% response to placebo in the Australian Therapeutic Trial (Management Committee, 1980, Halberg et al., 1988). Comparison of circadian characteristics from day to day in records spanning at least two days further indicates the shortcomings of monitoring limited to a single 24-hour span (Halberg et al., 1988, Cornélissen et al., 1987, Tamura et al., 1990). Prolonging the monitoring from one to two days reduces the uncertainty in the estimation of circadian parameters by about 35% (Watanabe et al., 1997), whereas further information on the biological week (Halberg et al., 1984, 1995, Cornélissen et al., 1996, Caradente et al., 1994) requires monitoring for at least 7 days, the current recommendation of BIOCOS for everybody at the outset (Sing et al., 2002). It is now widely accepted that prognosis of target organ damage is by far superior when it is based on around the clock monitoring than on single office measurements (Siegelová et al., 2000, 2011, Halberg et al., 2000, Mancia et al., 1996, Mallion et al., 1999).

The mistaken impression that the circadian variation in blood pressure and heart rate is sufficiently stable to be approximated by a single 24-hour profile stems in large part from the use of statistical methods on groups of subjects rather than focusing on the individual patient. Correlation analyses applied to large groups of subjects with a wide range of average values emphasize similarity. Statistical analyses focusing on individual differences observed from one profile to another, however, yield the information more likely to help the patient in need of the treatment (Cornélissen et al., 1987). Several case reports document this point (Cornélissen et al., 1993, 1996, 1997, Halberg et al., 1995, 2002, Mancia et al., 2000). Continued monitoring is the most logical solution.

An important distinction must be made between lessons learned from large clinical trials and their application for the individual patient. Differences and trends uncovered in studies made on groups, even when each subject provides only one or a few measurements, cannot be similarly assessed in medical practice when a decision must be made for treating the individual patient. In order to be able to reach an informed decision for the given patient, serial rather than single data should be collected. When time series are available, it becomes possible to assess risk elevation or the response to treatment for that particular patient.

In our former study we observed the age dependence of the circadian amplitude. Mean values of SBP and DBP were increasing with age up to 75 years, but night-day difference of SBP and DBP reached the maximum value at 45 years and then decreased. This decline of day-night difference was not seen in our patients with heart disease. Furthermore the day-night difference in about 50 years old treated patients was lower than in our about 50 years of age controls. This fact is positive because excessive day-night difference is accompanied with an increased risk for morbidity and mortality.

Comparison of treated patients after myocardial infarction with healthy subjects revealed that the treatment decreased the risk of high blood pressure as well as the risk of high blood pressure variability. The differences could be influenced by the medical therapy.

For a long time, hypertension guidelines focused on blood pressure lowering only. The European Guidelines from 2007 for the management of arterial hypertension developed recommendations based on prevention of coronary heart disease in clinical practice (Mancia et al., 2007, 2009, 2013).

In our study we have not found an increased blood pressure in the group of patients with coronary heart disease and correlation between 24-h MESOR of SBP and DBP and left ventricular mass index, nor between 168 h MESOR of SBP and DBP and left ventricular mass index in treated patients with coronary heart disease.

The values of double amplitude of SBP and DBP in circadian rhythm and circaseptan rhythm were not correlated in treated patients with coronary heart disease.

The evidence of increase of left ventricular mass index is available on the predictive power of cardiac abnormalities as detected by echocardiography because of its ability to more directly and precisely quantify left ventricular mass and geometric left ventricular mass patterns. A retrospective study has recently updated information from more than 35 000 normotensive and hypertensive participants with normal left ventricular ejection fraction (Mancia et al., 2009, Milani et al., 2006).

The increased risk associated with left ventricular mass has been confirmed by other observations. In a prospective study on a cohort of 1652 Greek hypertensive patients followed up for 6 years, echocardiographic left ventricular mass was significantly associated with either a composite of all-cause mortality and cardiovascular events (hazard ratio 1.53) and with stroke (hazard ratio 2.01), after adjustment for major cardiovascular risk factors (Mancia et al., 2009, Tsioufis et al., 2009). A retrospective analysis of 1447 Japanese hypertensive patients who participated in the CASE-J trial showed that cardiovascular events occurred about 2.6 times more frequently in patients with a left ventricular mass index 125 g/m^2 or more (Yasuno et al., 2009, Mancia et al., 2009).

In the PAMELA population, echocardiographic left ventricular mass was associated with a four-fold to five-fold significance increase in cardiovascular morbidity and mortality when data were adjusted for a large number of potential confounders, including office, home and ambulatory blood pressure values. In the PAMELA population, echocardiographic left ventricular mass was associated with a four-fold to five-fold significance increase in cardiovascular morbidity and mortality when data were adjusted for a large number of potential confounders, including office, home and ambulatory blood pressure values. A 10 % increase in left ventricular mass increased the risk more markedly when baseline left ventricular mass was already abnormal but an increasing risk was evident also when calculated from left ventricular mass values within normal range (Mancia et al., 2009, Bomvelli et al., 2009).

In patients with coronary heart disease only a few studies have addressed the usefulness of ambulatory blood pressure monitoring. In most cases a significant relationship was found between coronary heart disease prevalence and either nondipping or increased ambulatory pulse pressure (O'Brien et al., 2013, Fagard et al., 2008).

Ambulatory blood pressure monitoring can also be useful in predicting prognosis in patients with coronary heart disease.

CONCLUSION

In our former study we observed the age dependence of the circadian amplitude. Mean values of SBP and DBP were increasing with age up to 75 years, but night-day difference of SBP and DBP reached the maximum value at 45 years and then decreased.

This decline of day-night difference was not seen in our patients with heart disease. Furthermore the day-night difference in about 50 years old treated patients was lower than in our about 50 years of age controls. This fact is positive because excessive day-night difference is accompanied with an increased risk for morbidity and mortality.

Comparison of treated patients after myocardial infarction with healthy subjects revealed that the treatment decreased the risk of high blood pressure as well as the risk of high blood pressure variability.

Our results showed that left ventricular mass index and blood pressure in patients after infarctus myocardium in contrast to findings in hypertensives are not related to circadian and circaseptan values of diastolic and systolic blood pressure abnormalities.

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THE DUSTY BOXES IN MY OFFICE AND SOME SURPRISING HISTORICAL AND SCIENTIFIC OBSERVATIONS

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INTRODUCTION 1

In connection with the word “historical” in the title, a short personal introductory note: Most Austrians (real Austrians) have some root in one of the countries of the former Austrian monarchy. The father of my mother came from Northern Moravia and had settled long before my time in Vienna. Nevertheless, there must exist some inborn drive or reason, why I love to visit Brno, whenever possible.

INTRODUCTION 2

When I started my work as new chairman of physiology in Graz, my activity had to begin in a provisional location, in empty rooms of an old hospital building which was more or less empty. The construction work of the new building – a few streets away and around the corner – was just in its beginning – and lasted another 5 years. Some old stuff like historic instruments and boxes, books and papers were transferred from an earlier store into the provisional location. During the following years my young coworkers and I started to work and started to teach, to perform experiments and to publish.

After the new building was finished and ready, everything, including historic stuff and boxes had to be transported to the new place. It could not be that some instruments disappeared. The main part arrived well in the new location. Some boxes in which I recognized layers of paper were transported into my new room and stored into a chest.

Only after my retirement I started to wonder about the contents of the boxes.

The observations I made when I opened some of the old and dusty (*zaprášeny*) boxes in my office were surprising.

There were records, from before the year 1900, of arterial pulses (on smoked paper). Among these records I found one, with a note added. “Measured on the radial artery of Dr. Pregl.” This Dr. Pregl had performed with coworkers experiments to study the effect of extract of rat-testicles on the development of force of muscles. Much more fascinating is, that this Dr. Pregl in 1923 received the Nobel-Price for his developments of microchemical techniques. He had moved from Graz to Innsbruck, where he was Chairman of the department of Physiology and where he performed the work on microchemical techniques.

Another unexpected surprise was, that in one box I found about 10 m records (from before 1900!) with ink-writer on paper: arterial pulse and respiration. The analysis of these records and, possibly others which are lost, were published by Dr. Rudolf Klemensiewicz, an assistant who worked as Dozent in the Department of Physiology in Graz. Results were published in “Berichte der kaiserlichen Akademie der Wissenschaften in Wien. Volume 74, 1876” (1).

Now I have to add an additional explanation concerning the topic. About a year or even more a discussion was started among friends in Graz, in Kiel and in Potsdam about the phenomenon of synchronization, particularly between heart beat and respiration. Some day I looked through an old Textbook of Physiology, printed in Vienna 1881 (2), written by the former chairman of Physiology in Vienna, Ernst Brücke. In the chapter about the influence of the oscillations of the respiration onto the arterial blood pressure. In fig. 1 (= fig. 23 in Brücke’s textbook on page 161) one can find an increase of the arterial pressure which starts simultaneously with the expiration. In the text is mentioned, that the experiments had been performed in the

Department of Physiology in Vienna by Chairman Prof. Carl Ludwig and by Dr. Einbrodt, a physician from Moskow, who worked in Ludwigs laboratory.

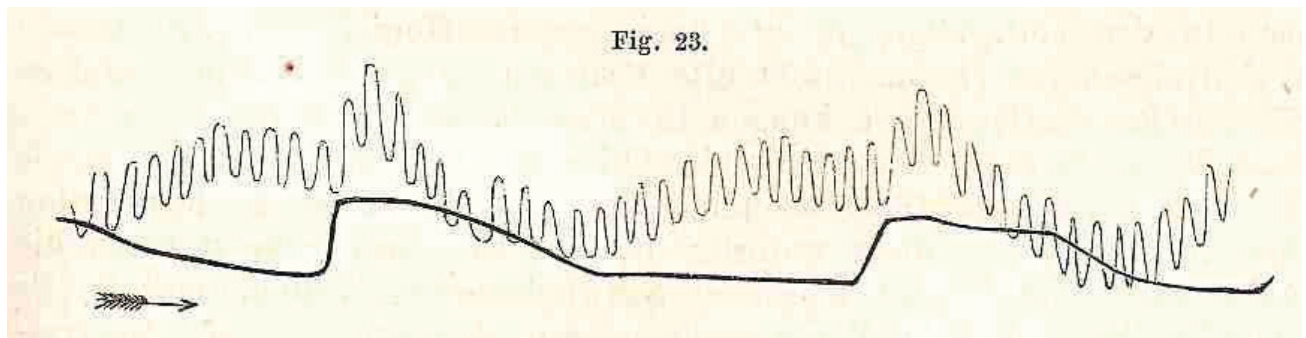


Figure 1 (= fig. 23 from Physiology textbook by Ernst Brücke from 1881).
The synchronization of arterial pulse and respiration can well be seen.

Approximately 30 years ago we had started in Graz experiments on the problem of synchronization with a different technique (3). The procedure which we had developed is explained in the following display (fig. 2) from a record in an anesthetized rabbit. The figure shows in the lower tracing (V_T) the tidal volume and in the upper tracing the time of each breath starting (0 starting of each inspiration) from the lower line to the upper end. Each mark indicates the time (within each breath) when a heart beat (R-wave of EKG) is recorded. Synchronization in this display is indicated, as long as the points, which indicate the location of an R-wave, can be seen as parallel lines. Further studies performed by our group are published in a Book on “Cardiovascular System Dynamics” (4).

The interpretation regarding the interaction and the role of the synchronization of two processes is of great importance. This was already recognized by Steven Hales who was the first to measure arterial blood pressure in a horse, i.e., a warm-blooded animal.

The control mechanisms responsible for the timing of the heart-lung interaction are on one hand tasks of Vagus and Sympathicus. However, it seems, that there are also more direct mechanical interactions between lung and heart.

It can be concluded that even the study of historic experiments can lead to an improved understanding of the desynchronization between heart and lung.

The following summarizing description (5) is based on a translation of papers by Carl Ludwig by J. Schaefer and B. Lohff with a little additional support by T. Kenner:

(5): *Respiratory-related interactions with the heart have remained a challenging physiological phenomenon since more than two and a half centuries. In the course of translating into English the seminal publications of Carl Ludwig and Pjetr Einbrodt – Ludwig’s disciple – we became aware of some aspects of their work that have apparently not been commented on hitherto, but which we believe might be of scientific interest. The arrhythmic effects of respiratory movements which Ludwig had observed in his experiments on dogs and horses and on which he published a paper in 1847 – they were later called respiratory arrhythmia – left him in doubt as to the causes of this phenomenon. Thus it is no surprise that he subsequently undertook further work on this problem, together with Dr. Einbrodt. In the introduction to the resulting paper published in 1860 he wrote:*

“The phenomena which undergo modification as a result of the respiratory movements and which initially come into question with regard to the influence of breathing elude more precise analysis, because they are all composed of different and at the same time always changing elements, the occurrence of which can therefore never be observed individually; the sequence of heartbeats, for example, is well known to be derived from many basic elements, being affected by the excitability of the heart (its muscles, nerves and motoric centres), the degree of excitation of the prolonged medulla (medulla oblongata) and of the vagus nerves, the blood volume of the animal, which can vary over a broad range, the temperature of the blood flowing into the heart and so forth.” (pp. 266, 362)

In order to overcome these experimental handicaps Dr. Einbrodt decided to concentrate on the role of mechanical factors of the respiratory movements. He developed methods to increase or decrease the pressure of the air the animal had to breathe. This procedure led to a greater or lesser degree of compression or decompression of all the organs in the thoracic cavity. As it is written in Einbrodt' and Ludwig's paper:

"... It should be particularly emphasized that during the execution of +RP [= increased respiratory pressure] the respiratory movements can be absent for several minutes without exerting a detrimental influence on the animal or inducing a condition of asphyxia ... There is another reason why the absence of the respiratory movements deserves our attention, namely that this is the only case allowing blood pressure curves to be obtained that are completely free of the influence of respiration, in which each heartbeat is the same as the preceding and succeeding ones and the blood pressure shows only those fluctuations that are dependent on the contraction of the heart." (pp. 272, 368).

Such a statement is quite astonishing in view of the many other influences that may modulate heart rate and cardiac activity, as the authors themselves argue elsewhere in the same 1860-paper. – It had been known since 1845, from work by E. F. Weber, that the vagus nerves exert strong inhibiting influences on the heartbeat. In the following years the mode of action of the N. sympathicus and of various other factors, structures, centers, and receptors became apparent.

How the mechanical influence of breathing affects cardiac activity during respiratory arrhythmia has been the subject of scientific discussions and controversies over a period of more than 150 years and may still be unresolved. Recent publications indicate that cardiac mechano-electric coupling plays an important role.

In the following I return to our experiments on rabbits. The figure 2 shows the interesting variation of synchronization and shows also the fact, that sighs – deep short.

Inspirations – are in most examples followed by a change or variation of the synchronization pattern.

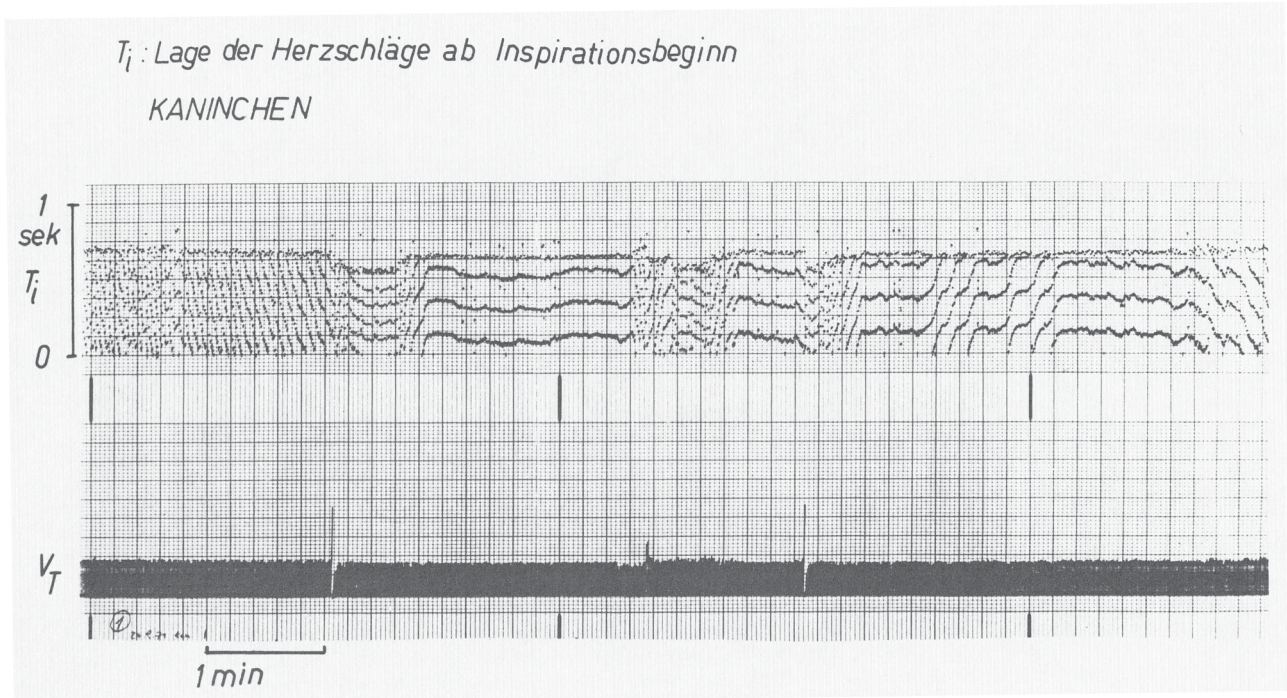


Figure 2 Records from an anesthetized rabbit. For explanation see text

It was approximately in the same time, when I looked at the contents of the boxes, that our group of scientific friends had initiated to work on the application of a mathematically improved description of the evaluation of synchronization (6).

The observation of the more or less unexpected observation of historic recordings has stimulated a search in earlier literature. Some remarks can be found in our publication on the “cardiac phase response curve” (6).

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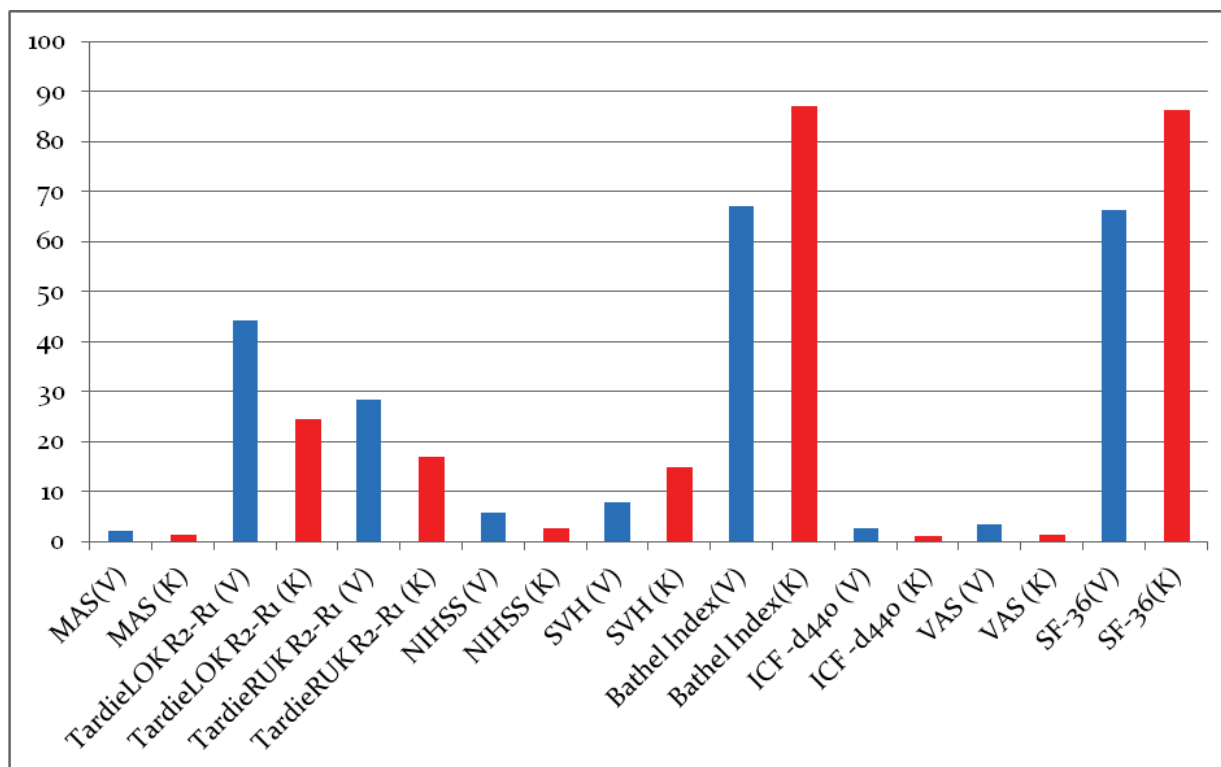
REHABILITATION OF SPASTICITY IN PATIENTS WITH STROKE

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INTRODUCTION

Spasticity is one of the symptoms of the upper motor neuron syndrome after stroke. The main clinical manifestations of spasticity include: reduced muscle strength, impaired targeted motor coordination and isolated movements, increased reflex retrieval, abnormal position of extremities – spastic dystonia, clonus, associated movements – synkinesia and cocontraction (1). Excessive muscle tone along with other symptoms of spastic manifestations significantly impair quality of life in patients after a stroke, reduce patient's mobility, reduce his activities of daily living and self-sufficiency (2). Therapeutic approach to spasticity is an important part of care for these patients. Therapy involves a comprehensive approach including pharmacotherapy (including local treatment with botulinum toxin), physiotherapy, occupation therapy (ergotherapy), physical therapy, prosthetic therapy and possibly psychotherapy, nursing care, regime measures, if indicated also treatment with baclofen pump or surgical solutions (3). The principle in the treatment of mild spasticity is a combination of pharmacotherapy and rehabilitation using physiotherapy on the neurophysiological basis (Vojta reflex locomotion, Bobath concept and proprioceptive neuromuscular facilitation) and relaxation therapy (stretching). As a supplement, splinting is recommended (1).



Graph 1 Clinical scales evaluating spasticity, clinical status, self-sufficiency and hand function before (V) and after (K) six-week rehabilitation.

METHODS

A prospective pilot study evaluates effects of a six-week comprehensive therapy. The 12 patients after stroke with mild to moderate spastic syndrome (Modified Ashworth scale: grade 1-3) were subjected to intensive rehabilitation involving 2× daily physiotherapy and 1× daily occupational therapy (ergotherapy) of the hand, totally 6 hours daily splinting (3 × 2 hours) using a dynamic splint of the forearm and hand (Figure 1), standard antispastic drug therapy (including the application of botulinum toxin). The patients were evaluated at the beginning of the treatment and after six weeks of therapy using standard clinical scales evaluating spasticity (Modified Ashworth Scale – MAS, Tardieu scale), clinical status, self-sufficiency and hand function (NIHSS, Barthel index, ICF-d440 assessment of hand function to fine movements, SVH-score of visual evaluation of the hand, visual algic scale – VAS, SF-36 scale of quality of life).

RESULTS

The results were evaluated before and after a comprehensive six-week therapy. Significant changes were found after a comprehensive therapy, namely improved function of the hand and forearm (SVH, ICF-d440) and the overall condition including quality of life (NIHSS, Barthel index, SF-36). Statistically limit changes were detected in changes of the muscular tonus – spasticity (MAS, Tardieu) (Graph 1, Table 1).

Table 1 Basic statistics (mean value, standard deviation – SD) before and after six-week rehabilitation

	BEFORE		AFTER		p-value
	Mean value	SD	Mean value	SD	p < 0,05
MAS	2.17	0.14	1.38	0.64	NS
TardieLOK R2-R1	44.17	22.73	24.59	13.67	NS
TardieRUK R2-R1	28.34	19.66	17.08	12.98	NS
NIHSS	5.68	2.42	2.59	1.83	SS
SVH	7.92	3.37	14.75	4.01	SS
Bathel Index	67.08	15.62	87.08	21.71	SS
ICF-d440	2.67	0.75	1.08	0.51	SS
VAS	3.5	0.43	1.5	0.68	SS
SF-36	66.25	5.31	86.25	7.92	SS

Notes: NS – statistically non-significant change, SS – statistically significant change

DISCUSSION

Each application of botulinum toxin must be followed by a comprehensive rehabilitation program including physiotherapy, occupation therapy, stretching, splinting, positioning, etc. (4). The most widely used procedures for management of spasticity are represented by pharmacological treatment aimed at inhibiting reflex hyperexcitability. In the last decades, several non pharmacological procedures for treating spasticity have been put forward, including muscle stretching, muscle reinforcement, physical agents and pain management. These procedures may have both neurophysiological and biomechanical effects on the spastic movement disorder (5).

Innovation of comprehensive treatment of spasticity is to use dynamic splints (see our study). These splints are better tolerated by patients and have a better therapeutic effect.



Figure 1 Dynamic splint of the forearm and hand

CONCLUSION

A comprehensive approach can favorably affect the functional state of the upper extremity even at persisting spasticity. In this respect, combination of pharmacological therapy, physiotherapy, occupational therapy (ergotherapy) and prosthetic therapy seems highly beneficial. Treatment of spasticity is a long term process and requires a multidisciplinary approach.

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