MASARYK UNIVERSITY • FACULTY OF MEDICINE
BRNO • CZECH REPUBLIC

NONINVASIVE METHODS IN CARDIOLOGY 2012

Edited by: HALBERG F., KENNER T., SIEGELOVÁ J., DOBŠÁK P.

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Brno 2012

Under the auspices of
doc. PhDr. Mikuláš Bek, Ph.D., Rector of Masaryk University Brno
prof. MUDr. Jiří Mayer, CSc., Dean of Faculty of Medicine Masaryk University Brno
Ing. Petr Koška, MBA, Director of The St. Anna Teaching Hospital in Brno

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

ISBN 978-80-210-6026-5

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PROF. DR. THOMAS KENNER, 80 YEARS OF AGE

JARMILA SIEGELOVA
Dept. of Physiotherapy and Rehabilitation, Dept. of Sportsmedicine and Rehabilitation, Faculty of Medicine, Masaryk University, St. Ann's University Hospital in Brno

Prof. Dr. Thomas Kenner, M.D., Dr. h.c. mult.
Dr. h. c. Universität Jena, 1990
Dr. h. c., Semmelweis University Budapest, 1998
Dr. h. c., Masaryk Universiy Brno, 2000

Prof. Thomas Kenner is exceptional physiologist who focused primarily on physiology of cardiovascular system, covering diverse areas such as aerodynamic properties of arteries, chronobiology of cardiovascular system, pathophysiology and incidence of sudden infant death syndrome, physiology and monitoring of physiological functions in space.

Prof. Thomas Kenner was born in Vienna 29. 9. 1932. He studied medicine at University of Vienna, where he qualified in 1956. From 1956 to 1958 he worked in Dept. of Internal Medicine in Vienna. In 1959 he worked in Max Plank-Institut in Bad Nauheim in Germany. From 1959 to 1965 he was back to Vienna and worked in the Dept. of Experimental Pathology. Since 1963 he is married to Brigitte Hackl and has three children: Bernhard, born 1964, Lukas, born 1965 and Clara, born 1967. In 1965 he started work in Dept. of Physiology in Erlangen, Germany, where he began with University lectures in Physiology, and in 1966 was appointed lecturer in Physiology (habilitation). He continued researching in cardiovascular physiology and from 1967 to 1968 he was a Visiting Scientist in Presbyterian Hospital in Philadelphia and Division of Biomedical Engineering, University of Virginia, and from 1969 to 1971 he worked as Associate Professor, Division of Biomedical Engineering, University of Virginia in Charlottesville, Virginia, USA. In 1971 Prof. Thomas Kenner was nominated for and got „Career Development Award" (NIH). In 1972 he was appointed full-time Professor and Chairman of the "Physiologisches Institut der Universität Graz". He worked as the head of the Dept. of Physiology until 2000, and in October 2000 he retired as Professor Emeritus of Karl-Franzens-Universität, Graz, Austria.

It is very difficult to describe the outstanding scientific, educational and organizational activities of Prof. Thomas Kenner in physiology. The Dept. of Physiology under his guidance flourished and attracted many researchers from different countries. His outstanding capabilities to carry out physiological experiments were were presented and published particularly in the area of cardiovascular physiology and cardiovascular pathology and in clinical disciplines, where his students continued in the experimental scientific work.

From 1989 to 1991 he was nominated Rektor (President) of Karl-Franzens-Universität and from 1991 to 1997 Dean of Medical School of Karl-Franzens-Universität, Graz, Austria. In this period a new building for theoretical Departments of Medical Faculty of Karl-Franzens-Universität was constructed in Graz under his administrative guidance.

His cooperation with other universities in Austria and abroad was renowned internationally, he collaborated with scientific groups from around the world, particularly in the USA and in European countries. Prof. Thomas Kenner won many honors and was member of scientific societies - Austrian Academy of Sciences, Academia Scientiarum et Artium Europaea, American Physiological Society, Cardiovascular Systems Dynamics Society, Deutsche Physiologische Gesellschaft, and Honorary Member of the Hungarian Physiological Society etc. He was nominated Professor honoris causa, University Ljubljana, Slovenia. In1993 he was honored from the Country Styria with "Großes Goldenes Ehrenzeichen des Landes Steiermark".

Prof. Thomas Kenner held many scientific positions, from 1978 to 1981 he was Member of the Life Science Working Group of the European Space Agency (ESA, Paris),

from 1980 to 1987 he was Referee for Medicine in the "Kuratorium of the Austrian Research Fund (FWF)", from 1986 to 1988 he was President of "Cardiovascular System Dynamics Society", from 1985 to 1997 "Curriculum Dean of Medical School of University Graz, Austria". Prof. Thomas Kenner was nominated because of his exceptional scientific work and international cooperation Dr. honoris causa in Germany at "Universität Jena" (1990), in Hungary from Semmelweis University Budapest (1998), in the Czech Republic from Masaryk University Brno (2000).

Prof. Thomas Kenner cooperation with Faculty of Medicine, Masaryk University, Brno, Czech Republic started in 1991. Prof. Thomas Kenner was known in our University as a scientist from the publication about the dynamic of arterial pulses from the year 1968. We met personally for the first time in Prague in 1991 on International Physiological Congress, he was also accompanied by his wife Brigitte Kenner. Then he went to Masaryk University and at the meeting we signed an agreement of cooperation and since this time we were meeting every year once or twice in Brno, where we organized every year one Symposium about Chronobiology at Faculty of Medicine and one Symposium during Medical Trade Fair in Brno. Usually we presented latest scientific discoveries together with Prof Thomas Kenner, Austria, Prof. Franz Halberg, Prof. Germaine Cornelissen, both USA, Prof. Jean-Paul Martineaud, Paris, France and Brno team – Prof. Bohumil Fiser, Dr. Jiri Dusek and me. Sometimes Prof. Thomas Kenner, everytime accompanied by his wife, took also with him his pupils to Brno who presented at Masaryk University their scientific lectures. Prof. Thomas Kenner published some lectures in the journal Scripta Medica and they are included in selected publications. Brno chronobiological team visited also some scientific meetings in Graz and presented results in the area of cardiovascular control in man in health and diseases in Austria.

In 2012, Prof. Thomas Kenner continues his scientific activities, he actively participates in meetings across the world and publishes scientific papers. We are very glad and appreciate very much the long lasting cooperation with Prof. Thomas Kenner. Especially we esteem his friendship and collaboration, his enthusiasm and large scientific knowledge, which are all the time an inspiration for advancing the knowledge of cardiovascular physiology in health and pathology. We have a privilege to have him in Masaryk University as a visiting professor and we wish him many happy returns at the occasion of his anniversary of eighty years.

Ad multos Annos!

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THE FUNCTIONAL EFFECT OF TIME-DELAYS IN CHRONOBIOLOGY AND CHRONOPATHOLOGY

THOMAS KENNER
Physiologisches Institut of the Medical University Graz, Austria

Dedicated to Prof. Dr. Jarmila Siegelova on the occasion of her 70th birthday.

SUMMARY

The field of chronobiology mainly is concerned with rhythms of different frequency, like circadian, circaseptan, circannual etc. (1). Although most periodic events are composed of periods of activity and periods of rest, or of periods of higher and lower activity, it appears that the term delay was so far, until recently, not yet of particular interest.

There are two reasons why a short introduction to the chronobiological and chronopathological aspects of delay appear to be of interest.

The first reason is the fact that a team at the University of Virginia in Charlottesville performed experiments to study the effect of a delay in the control loop of the blood pressure control. The theoretical background of a systems description was worked out and published in 1971 (2). The results of our experiments were published in 1974 (3). These experiments demonstrated, that a delay in the control loop generates instability of the blood pressure in the form of periodic auto-oscillations. An early experiment concerning the control system of the blood pressure control was performed by Hatakeyama (4). He studied effects of the stimulation of the carotid sinus nerves. Already somewhat earlier Guyton and coworkers (5) studied the generation of the so called Cheyne-Stokes respiration, a characteristic form of periodic oscillations of the breathing movements, which is typical for severe cardiac failure. Cheyne-Stokes respiration can also be observed in persons in high altitude, who are not adequately adapted to this situation.

These studies were not yet appropriately recognized. However, the fact must be mentioned, that recently the problem of delay appears to arise more and more interest (6). As usual, results of early studies can now be reproduced with more sophisticated techniques.

A further reason for discussing delay comes from the fact, that this phenomenon plays a role in many fields, like biology, social science, economic science and in many other aspects.

In other words: Delays play an enormous role in chronobiology, chronopathology, in every-day medicine, in everyday life, in society, in economics, politics and in all fields, which have something to do with time.

THE WORD DELAY

The word delay comes from Latin: the first part of the word is derived from de, indicating moving away “from”; then added the word laxare: “to make something loose”, or “to extend something” (7).

One can add the following interpretation: The word DELAY can indicate a *neutral*, or a rather *negative* or even a more *positive* meaning:

- Postponement
  - Detainment (being delayed)
    - Recovery – Rehabilitation

It is of interest, that the term delay is best understood in music. Many of the terms and signs which determine the speed of performance actually determine delays: pause, ritardando, etc.

SINGULAR OR PERIODIC DELAYS IN BIOLOGICAL SYSTEMS

Delay may be a singular phenomenon like the waiting period for the belated arrival of a train or of some person. In medicine, the incubation period means the delay after an infection until the outbreak of symptoms of a certain infection. From the viewpoint of chronobiology or chronopathology the processes, which are going on in an organism during the incubation period are of interest.

EXAMPLE: MITOSIS

As an important example from biology, the process of mitosis, which includes several characteristic delay-periods, can be mentioned (8).

The mitosis starts with the duplication of the chromosomes. After some further delay the chromosomes separate. Finally, the two completely separated daughter cells can be observed.

The further processes – including a resting stage of each daughter cell – depend on the type of cells. In tumor cells, only a short delay may precede the next mitoses. In other types of cells the state of rest may be very long or even permanent. There are indications that cellular cycles are influenced by the main biological clock in the hypothalamus.

Another example is the pacemaker mechanism, which generates the – usually periodic – cycle of excitation and contraction of the cardiac muscle. Similar mechanisms can be found in nerve cells and nerve fibers.

The generation and timing of chronobiological rhythms is based on the sequence of the activity of clock genes and the production and action of clock proteins.

SYNCHRONIZATION

In many examples of delay one can observe the phenomenon of synchronization. The synchronization of two periodic processes requires slight delays in order to permit the adjustment of two or more processes. Synchronization can be understood as the adjustment of two oscillators the frequencies of which are close, but can be forced to become equal. The term which describes this narrowing locking of two frequencies are called Arnold tongues (9). It can be shown that in fast growing tissues such synchronization among mitoses and also synchronization with other periodic processes like the circadian rhythm can be observed (10).

INSTABILITY

Everybody is familiar with the phenomenon of *positive feedback* within the system: microphone – amplifier – loudspeaker. If the location of microphone is too close to the loudspeaker then tremendous loud sound (of a certain frequency) is produced.

Positive feedback may play a role in the generation of instability in certain neuro-muscular symptoms.

Here we discuss the generation of symptoms by delay in the *negative feedback* loop of a control system. Biological and medical examples of interest are: the control systems for the regulation of certain functions, including breathing, blood gases and pH of blood and, finally the control system for the regulation of arterial blood pressure.

INSTABILITY OF BREATHING

Guyton and his coworkers (5) were the first in 1956 to study experimentally the possible generation of instability of the control system for the regulation of breathing. They performed experiments in dogs in order to observe the generation of periodic Cheyne-Stokes respiration, which appeared to be a sign of instability. It was assumed, if the sensors in the carotid bodies and in the brain stem receive the information about pH and pO_2 in the arterial blood not on time but only after a marked delay of time, then the respiration starts to oscillate with a typical periodicity. In their summary (5) they write: "The periodic breathing was induced by inserting a circulatory delay system between the heart and the brain to prolong the transit time of blood from the lungs to the brain. The duration of each cycle of Cheyne-Stokes breathing increased proportionately with the volume of the delay system..." The figures in the cited publication by Guyton and coworkers (5) show the time course of the ventilation in a dog with a delay circuit. Periods of hyperventilation are followed by periods of apnea. The time-period of these oscillations as measured from the time between the maxima of breathing amplitudes ranges between 5 and 6 min.

As already mentioned, also in the paper by Guyton and coworkers (5), the so called Cheyne-Stokes respiration can also be observed in patients with cardiac failure. This fact indicates, that in this pathological condition the blood flow velocity is markedly reduced.

INSTABILITY OF BLOOD PRESSURE

Hatakeyama (4) published 1967 experiments performed in rabbits. He examined the reaction of the blood pressure control system indirectly by stimulation of the carotid sinus nerve. The stimulation of the nerve was adjusted in such a way as to correspond to the estimated reaction of the carotid sinus nerve in response to the direct stimulation of the carotid sinus by blood pressure. Using this indirect technique he observed, that the pressure response to delayed sinus nerve stimulation produced blood pressure oscillations.

In 1974 Kenner and Coworkers (3) published experiments, which demonstrated the generation of instability and auto-oscillations of the blood pressure by time delay in the blood pressure control system of dogs by using a direct pressure related procedure. In our experiments the carotid sinus nerves stayed intact and were not touched.

The procedure of our experiments is described as follows: "Both carotid arteries of anesthetized mongrel dogs were perfused with arterial blood by a servo controlled peristaltic pump. By applying a hybrid computer system to control the perfusion pump, the preparation could be examined under open loop condition and also under closed loop condition. Particularly, the effect of an artificial time delay (1–35 sec) between systemic and carotid sinus pressure was tested. The systemic blood pressure was recorded in the carotid artery close to the aorta. The data were stored in a computer, which was programmed to control a perfusion pump. The blood then was pumped by the servo-controlled pump into the distal part of the carotid arteries where the carotid sinus receptors are located. It was observed, that this procedure generates auto-oscillations of the arterial pressure as soon as the pump action and the blood pressure in the carotid sinus is delayed behind the actual blood pressure. The period of the oscillations is proportional to the artificial time delay.

The following picture demonstrates the described relation between the time of delay and the period of auto-oscillations. It can be seen that there is a linear relation between these time periods.

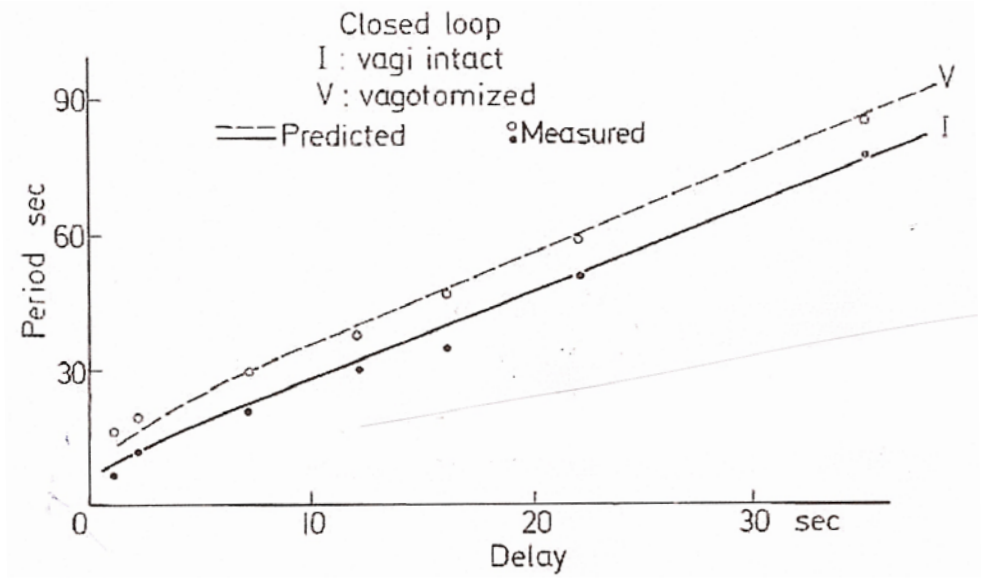

Figure 1. shows the relationship between the period of the auto-oscillations and the chosen time delay. The predicted curves were calculated from open loop data. (Kenner et al. 1974).

TIME AND DELAY AND THEIR ROLE IN ECONOMICS, FIGHT, AGGRESSIVITY

One example, which opens the understanding to further problems of zoology, psychology, epidemiology, population growth and social science, is the model of "predator and prey". Oscillations of the two populations are generated: at first by the reduction of the number of pray through the activity of the predators. Consequently, the number of predators begins to decrease as a consequence of the reduction of the number of pray. The described process finally leads to a decrease of the number of predators, which in turn gives rise to the generation of more and more individuals of prey. So, the process starts again, as described above. It follows a repetition of periodic cycles, which can be described by the so called Volterra-Lotka equations. In this example of periodic oscillations, one component of delaycan be attributed to the time periods, which are determined by the development – the rise and the fall – of the two involved populations.

Delay and "bureaucratic character" as described by Erich FROMM (11):

The following sentences by Erich Fromm show one further problem, which can be attributed to the term "delay". Unfortunately, in our time of growing bureaucracy, such events can by observed quite often.

One could consider the bureaucrat in the post office; and one could observe his small smiling when he – exactly at 5.30 p.m. – closes his office. Consequently, two persons, who were already waiting for half an hour, had to leave. They will have to come again next day.

For this "bureaucrat" it is not important that he closes his office exactly on time – at 5.30 p.m. – but it is his joy to frustrate the two persons by showing them that he has them under control."

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CONTRIBUTIONS TO THE ANALYSIS AND INTERPRETATION OF FORCES INFLUENCING THE PRESSURE-FLOW-RELATION IN ARTERIES

THOMAS KENNER
Physiologisches Institut, Medical University Graz

PREFACE

Each one of the scientific meetings in Brno is a very special event. Not only the beautiful city and its surroundings, and the friendly inhabitants have to be mentioned, but especially the interesting and stimulating presentations and discussions, organized by Professor Jarmila Siegelova. I want to express here my sincere thanks to her and to her coworkers.

FIRST PART: A PERSONAL NOTE

The title of this presentation was chosen in order to indicate that I will try to present the development of ideas related to arterial pulses throughout the time of my learning, when even old-fashioned techniques appeared to be useful.

Shortly after I became a newly promoted Medical Doctor, I worked in the department of Internal Medicine in a hospital in Vienna. In this department I had unexpected possibilities to perform measurements in patients. In a nearly unused room stood an X-ray recorder with a classical screen. Attached to this screen was a device which permitted to focus the view to a certain location of a shadow on the screen, and thus to record movements of shadows, e.g., pulsations of the heart or of the large arteries. The name of this device is “Elektrokymograph”. Today, due to the modern development of computer tomography, this device is obsolete.

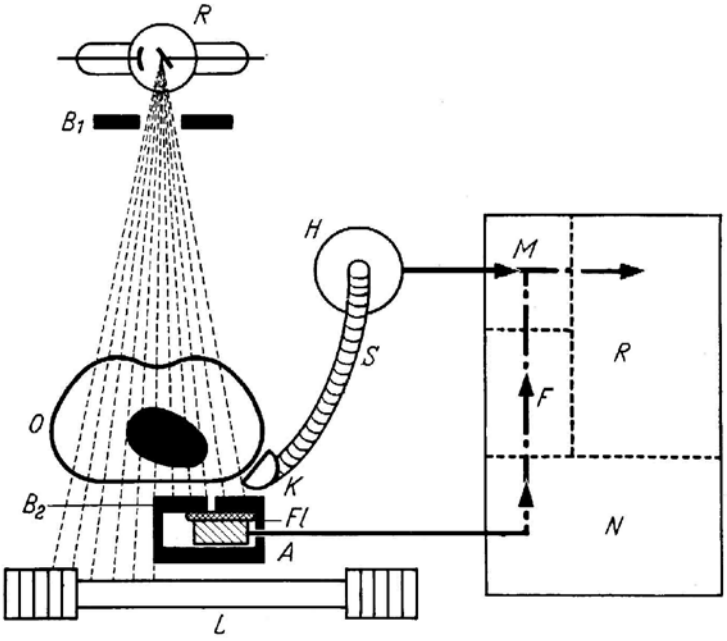


Abb. 1. Schema der Apparatur. *R* Röntgenröhre, B_1 Blende an der Röntgenröhre, *O* Organismus, *A* Aufnahmegerät, Fluoreszenzschirm, B_2 Blende mit Schlitz vor der Photozelle, *L* Leuchtschirm, *N* Netzgerät, *F* Filter, *M* Mischgerät (zur Beimischung des Herztones zur Photokurve), *R* Registriergerät, *K* Kapsel zur Aufnahme des Herzschalls, *S* Zuleitungsschlauch, *H* Mikrophon

Figure 1. from Heckmann (1) 1952

Using this Elektrokymograph, it was obvious, that the pulsations of the pulmonary artery have different shapes in healthy persons and in persons with pulmonary hypertension. Heckmann (1) 1952, Kenner (2) 1959. It also appeared obvious that the shape of the observed pulses represent the pulmonary arterial pressure pulses. It could be concluded, that the analysis of pulmonary arterial pulse shapes can indicate pathological modifications. See Figure 2.

A general description about modeling and analysis of arterial pulses can be found in the book "Grundlagen der Dynamik des Arterienpulses" (3) 1968 and in Kenner (4) (1979).

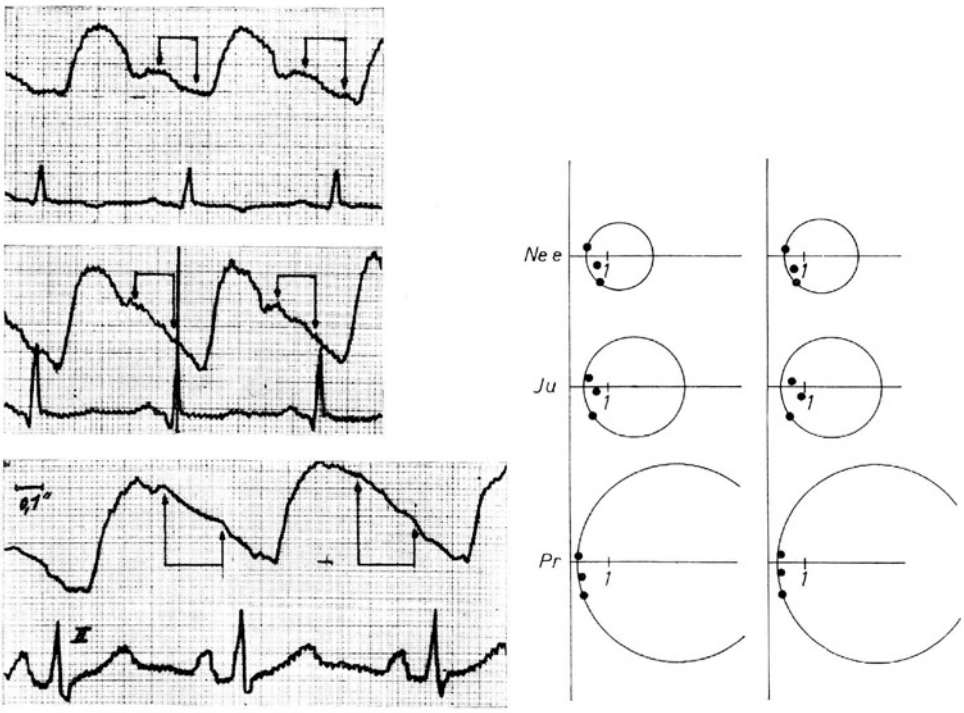


Abb. 2. Ekg. Pulskurven der A. pulmonalis und die dazugehörigen Ortskurven $\mathfrak{W}\,a/z$ von je einer normalen VP (oben), einem Patient mit Asthma bronchiale (Mitte), und einem Patient mit Cor pulmonale (unten). Die Punkte für die einzelnen Harmonischen (1., 2. und 3.) folgen der Reihe nach im Sinne des Uhrzeigers. Die Pfeile auf den Pulskurven zeigen die zentrale Grundschwingung des Pulses.

Figure 2.

At the same time, by chance – I came in contact with R. Ronniger, who just had finished his doctors thesis on recording and analyzing the transmission of arterial pressure pulses. Ronniger (5) 1954. In addition Ronniger (6) 1955 has analyzed and generalized earlier mathematical approaches to calculate the stroke volume from non-invasively recorded arterial pressure pulses. The school of Otto Frank, including Wezler and Böger based their modeling on the socalled Windkessel (air chamber) model.

Ronniger (5) used the transmission equations and the presentation of the pulse transmission in the arterial system in the frequency domaine in then form of a Nyquist diagram. I had the opportunity, to work with him and learn from him in this field.

From a historical viewpoint it is interesting, that already much earlier J. von Kries (7) (1889) had published a book in which he proposed and explained the application of the transmission equations to describe the propagation of arterial pulse waves. As mentioned above, the school of Otto Frank were successfully using Windkessel.

I had the opportunity to work with E. Wetterer in Munich. So I had the chance to study the transmission properties of pressure pulses along elastic rubber tubes in different types of models. The results of our measurements were summarized in our book Wetterer & Kenner (3) (1968).

Figure 3 (from Kenner (4) 1979) shows Nyquist diagrams calculated from arterial pressure pulses recorded in an anesthetized cat. Left row: calculated for the assumption of an homogeneous elastic tube-model. Right row: estimated from recordings from central and peripheral part of the aorta of a cat.

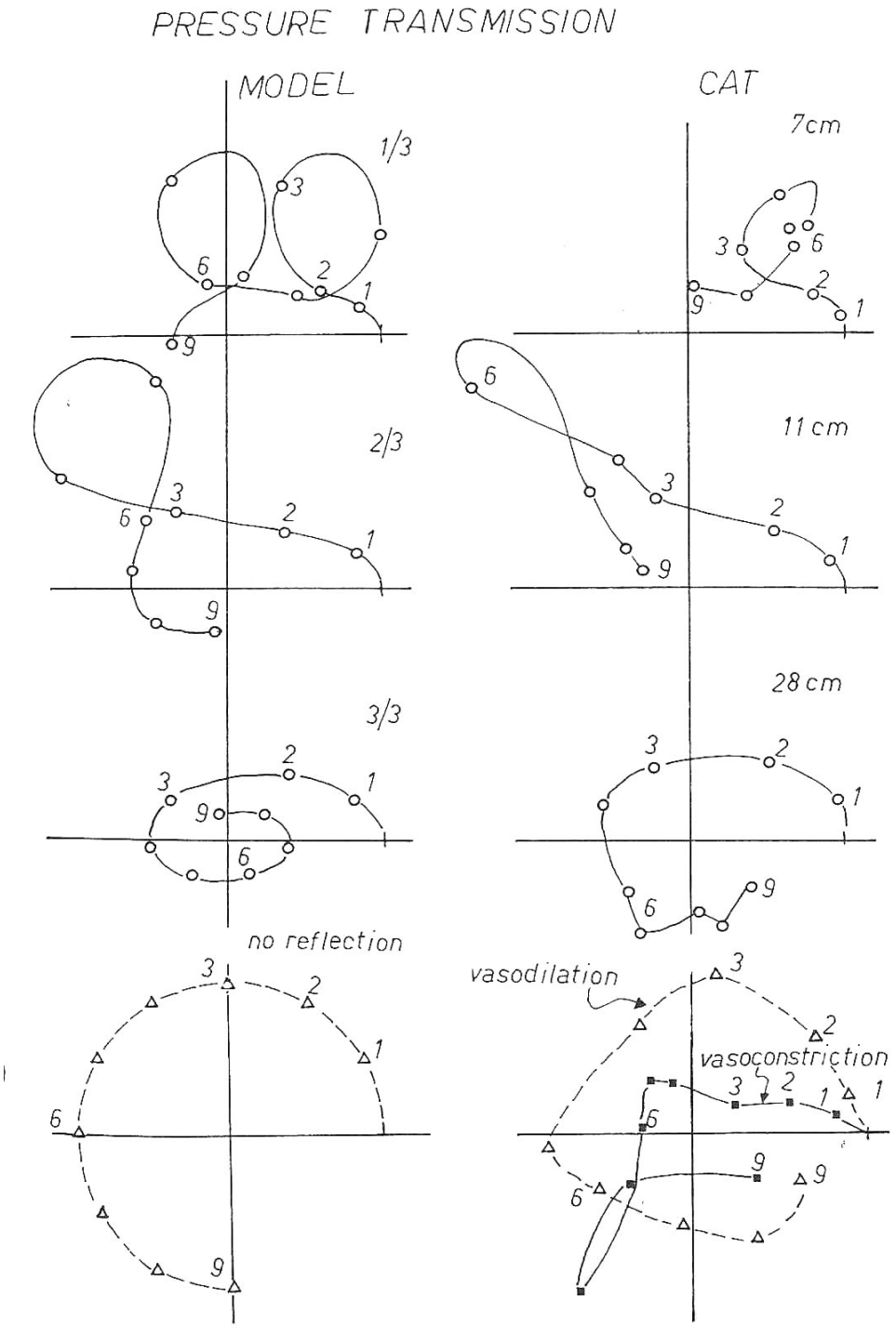


Figure 19. Pressure transmission function plotted as locus diagrams. Left: Measurement in the model showing pressure transmission between the entrance and one-third, two-thirds, and the entire tube length. Right: Measurement in a cat showing pressure transmission between the aortic root and a catheter whose tip is 7, 11, and, finally, 28 cm withdrawn toward the femoral artery. In this final position the reaction to acetylcholine (vasodilation) and to noradrenaline (vasoconstriction) was examined.

Figure 3.

With respect to the pulse wave velocity we have later compared the usual measurement at the front of the proximal and distal pulse wave with a cross correlation technique.

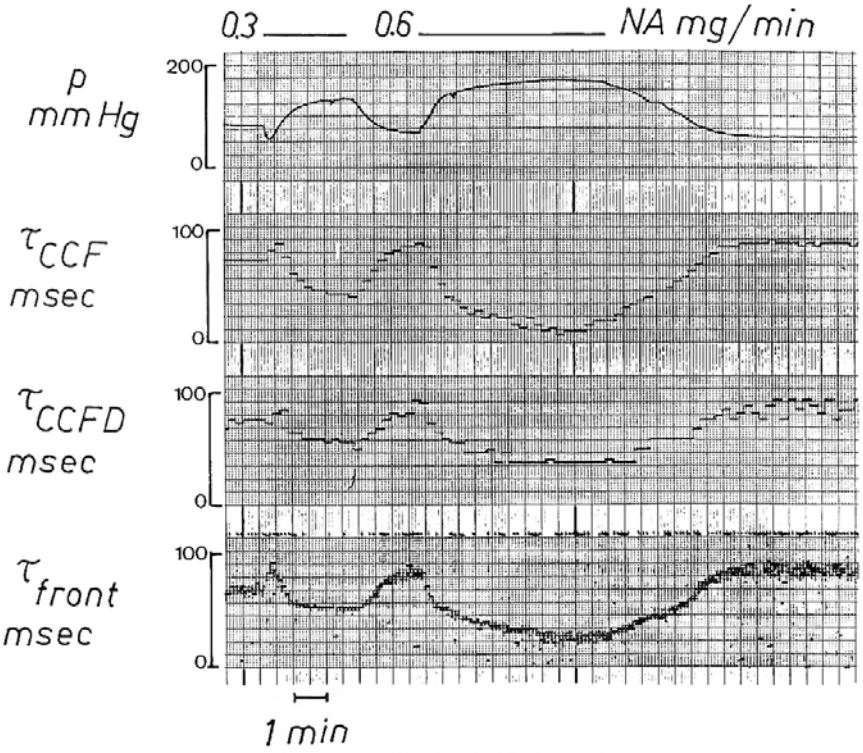


Figure 20. Transmission times between the aortic root and femoral artery measured in an anesthetized rabbit. τ_{CCF} is calculated by cross-correlation, τ_{CCFD} is calculated by cross-correlation of two pulses after differentiation with respect to time. τ_{front} is the transmission time measured at the pulse front. During infusion of noradrenaline there is a more marked decrease of τ_{CCF}. The transmission times are mirror images of the blood pressure.

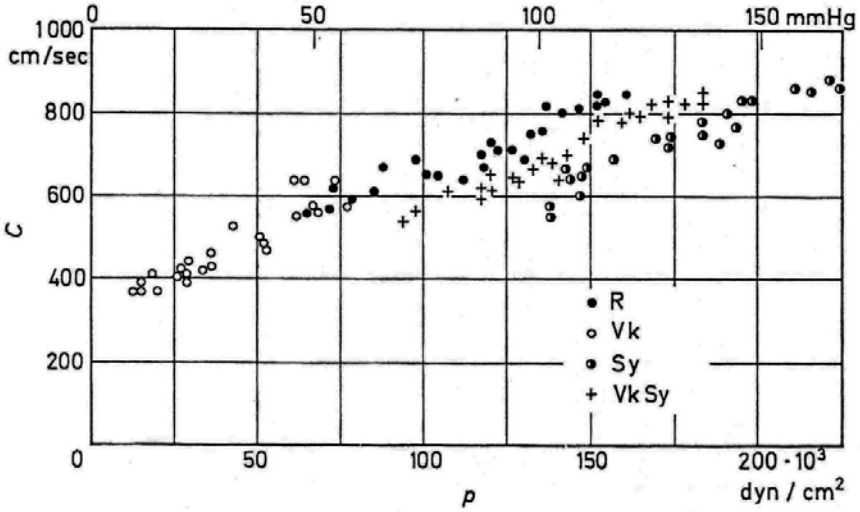
Figure 4.

Figure 4 from Kenner (4) 1979 shows a comparison of the estimation of the transmission time (inverse of pulse wave velocity) through cross correlation of central and peripheral pulse (CCF). For the calculation of the next line (CCFD) the measured data were differentiated versus time (dp/dt) eliminating the effect of lower frequencies. The blood pressure was varied by infusion of Noradrenaline (NA).

Later on, in the department of Physiology of the University Graz, the analysis was computerized and improved und studied in anlmal experiments. At that time we had a very large laboratory computer.

Furthermore, as a development of fast evaluation, the following sequence of steps was programmed: 1. the first step is the simultaneous record of a central and a distal pressure pulse. 2. the pair of simultaneous pulses is picked out. The period is measured. 3. a fast Fourier analysis on the two pulses is performed; then the quotient of amplitudes and the Phase difference are calculated. 4. the final step is the presentation of the resulting Nyquist diagram on the screen. The procedure can be repeated continuously.

Unfortunately we have never tried further development – and especially clinical application. The following picture from Wetterer and Pieper (8) 1953 shows an experiment in a dog. During different procedures, the pulse wave velocity was measured. One can see, that the pressure dependence of pulse wave velocity is markedly influenced by different procedures. R – resting condition, Vk – cooling of vagus nerve, Sy – injection of Sympatol. VKSy – some time after Sympatol during Vagus cooling.



bb. 24.5. Beziehung zwischen der in vivo bestimmten Pulswellengeschwindigkeit *c* der orta und dem Blutdruck (Mitteldruck während der Diastole) bei künstlich mittels Pumpe erbeigeführten periodischen Blutdruckschwankungen an narkotisierten Hunden. — *R* Ruhe- ert. *VK* Zustand niedrigen mittleren Blutdrucks mit gleichzeitiger Vaguskühlung beider- its. *Sy* Zustand unter Wirkung von 60 mg Sympatol. *VKSy* Nachwirkung des Sympatols bei gleichzeitiger Vaguskühlung. (Nach Wetterer u. Pieper, 1953)

Figure 5.

It is remarkable, that the value of the pulse wave velocity does not only depend on the blood pressure, but also on the influence of vasoactive effects.

During the time of my interest in arterial pulses and in the functional importance of arterial elasticity, it seems to me that viewpoints changed markedly. Around the time of 1950, the measurement pulse wave velocity in a patient was considered the result of some rather useless idea.

I enjoy the recent rise if interest. However, I am somewhat critical about the development of an industrial monopoly of a diagnostic language. I am very curious to discuss this matter.

The following figure from the Japanese book by Professor Koichi ONO summarizes in a schematic manner the arrangement of the control mechanisms acting on the cardiovascular system.

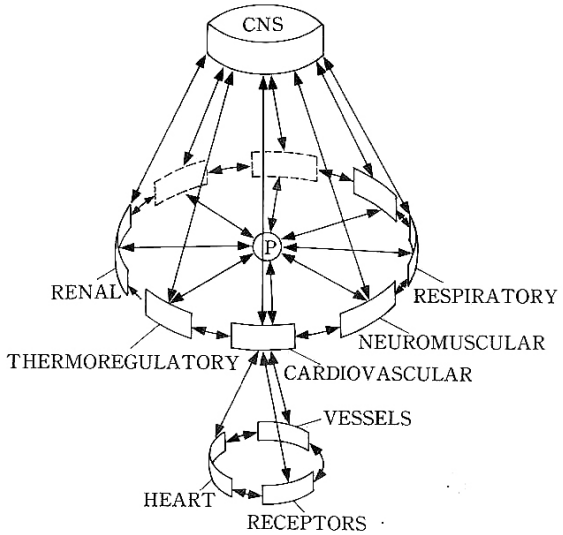


Figure 6.

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SECOND PART: INTRODUCTION

In the first part the description was focused on pressure pulse-pressure and on transmission of pressure pulses. In the second part the relation between pressure and flow will be discussed. In the frequency domain the relation again is shown in complex form as “impedance”.

The pressure – flow relation in the frequency region of heart rate and the higher harmonic frequencies can be called “high frequency”. The “low frequency” region describes the effect of control mechanisms – baroreceptor loop and autoregulation.

With my Japanese friend and coworker Koichi Ono we have participated on studies concerning pressure control and local autoregulation.

During our presence in the Department of Biomedical engineering in Charlottesville, we performed and participated in experiments on anesthetized dogs, where not only the pressure transmission, but also the pressure-flow relation (impedance) was measured.

If one records pressure and flow at the entrance (= input) of the aorta, it can be seen that the peak flow preceeds the peak pressure. From this observation one can conclude that the phase angles of the main part of the input-impedance is negative region of the coordinate system. One example of a Nyquist-diagram of the input-impedance of the aorta of a dog is shown in the following figure (next page), from Kenner 1972.

In the literture all the papers which are related to the discussed topics are listed. Furthermore, in addition, particularly those in which my friend Koichi Ono and I have cooperated are listed.

The last cited paper – regarding heart rate variability and synchronization, will also be discussed in the PPT-presentation.

This important extension of our work, the consideration of time in the sense of Chronobiology, brought many exchanges of ideas with Franz HALBERG and our friends in BRNO.

One of the early ideas, as already mentioned was the observation of heart rate variability and sychronization between respiration and heart beat. Right now it appears that, a as we think about synchronization, the more complex appears the regulation of this process.

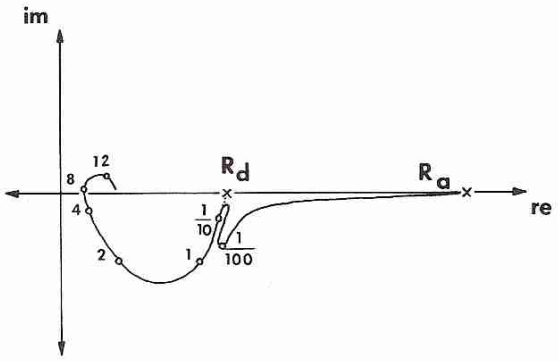

Fig. 8: Nyquist diagram of the input impedance of the aorta of a dog (using data by Taylor (1966*c*). R_a absolute value of the total outflow resistance, R_d differential value of the total outflow resistance. Parameters: frequency in Hz.

Figure 7.

Furthermore, I will mention my friend and mathematician Karl Perktold and a book which he co-edited with P. Verdonck, with the title: "Intra- and extracorporeal Cardiovascular Fluid flow". This book contains aspects which seem worthwhile to be mentioned, and which have also a connection with observations by the late by pathologist Doerr. concerning defects of the aorta,

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AEOLIAN CROSS-SPECTRAL COSMIC COHERENCE ENTERS MEDICINE BY GLOCAL VASCULAR VARIABILITY MONITORING

FRANZ HALBERG[1], GERMAINE CORNÉLISSEN[1], LARRY A. BEATY[2], DEWAYNE HILLMAN[1], SHIYU HONG[1], OTHILD SCHWARTZKOPFF[1], YOSHIHIKO WATANABE[3], KUNIAKI OTSUKA[3], JARMILA SIEGELOVÁ[4]

[1] *Halberg Chronobiology Center, University of Minnesota, Minneapolis, MN, USA*

[2] *Phoenix Study Group, IEEE, Minneapolis, MN, USA*

[3] *Tokyo Women's Medical University, Medical Center East, Tokyo, Japan*

[4] *Masaryk University, Brno, Czech Republic*

ABSTRACT

Health care already changes with emphasis on wellness by recommendations for exercise and a proper lifestyle, notably diet. The effect of these recommendations is not yet assessed in the individual involved, except for the taking of vital signs or at least of a blood pressure (BP) measurement, e.g., before each exercise session, as is also the case in any physical examination. Moreover, exercise, like meals, is implemented at times chosen by convenience, not necessarily pertinence, without concern for the possibility of doing harm to oneself. Hence the next step is the detection of the earliest unwellness, which occurs in the normal range where "physiological" is now equated with "random". Therein, masked for homeostatic thought, lies a new diagnostic and therapeutic realm which can be opened by **c**hronobiologically-interpreted automatic **a**mbulatory BP and heart rate (HR) **m**onitoring (C-ABPM). C-ABPM is of interest in itself for preventive cardiology, since it reveals new diagnoses as vascular variability anomalies (VVAs), and renders old diagnoses made conventionally more reliable (as MESOR-hypertension, an elevation of the Midline-Estimating Statistic Of Rhythm, based on around-the-clock data at least for 7 days and preferably continued until death, as soon as affordable unobtrusive instrumentation is generally available). The recommendation for continuous C-ABPM recognizes several principal, inseparably intertwined contributors to severe cardio- and cerebrovascular disease (CVD), namely the genetics and effects of physical and mental loads upon them that are all best assessed from womb to tomb. C-ABPM yields marker rhythms for vascular and/or other aspects of physiology, including mental functions, and thus provides a quantifiable measure of stress, as a VVA. When a VVA persists in successive 7-day records it becomes a Vascular Variability Disorder (VVD), as an index of strain. When several VVDs persist and accumulate, they become a Vascular Variability Syndrome (VVS). The risk of a hard outcome within 6 years increased from < 5 % to nearly 100 % in a study on 297 patients by Kuniaki Otsuka with hard outcomes. It had a confirmatory follow-up on a much larger number of subjects with a proxy outcome of the left ventricular mass index (LVMI) and was further in keeping with a study followed up for over 4 decades. Some VVDs can be treated, as another study and case reports document. C-ABPM further reveals a new transdisciplinary spectrum with novel infradian (longer than 28-hour) components that contribute to sudden cardiac death, suicide, homicide, terrorism and war, as well as to cycles in church membership and proselytism.

Those who regard the proposition of lifelong ABPM as utopian may realize that we can attach to our health the same attention as we do for security on the road to the tires of our cars when we continuously measure their pressure. This technological opportunity can be made available to our bodies as well as to our automobiles and laboratory animals used for research. By lifelong monitoring, we also gain new objective quantifiable perspectives of how space weather affects us and arrive at new diagnoses in a personalized, a societal and a still broader environmental medicine, that in turn leads to a unified science. Beyond health care, we can start to think globally and act locally in space and can also be "glocal" in time, both with a view of the historical cycles that mold us and in the practice of analyzing time series, such as data from C-ABPM, with repeated passes over them as they accumulate both as a whole at a given time (globally) and further in sections systematically varied in length (locally), with a view of the cycles that characterize them. This requirement of glocality in concept and as an analytical method can be demonstrated, among others, by

the fruits of a glocally-analyzed C-ABPM, yielding a marker for the human mind as well as for the circulation. In so doing, it reveals our intimate associations with our cosmos. In the language of frequencies, the odds ratio for the number of periods shared by human mental function and geomagnetics more than matches that between the magnetisms of the interplanetary field and the earth[1].

1.0 SELF-SURVEILLANCE

Insurance companies are too slowly starting to realize that the current costly, mainly physician-implemented health service to the individual, mostly after the onset of disease, can be complemented by programs for "wellness" not only by good advice and rewards (cost reduction) by those who follow the counsel, but also by an improved, largely self-help-based care with ongoing surveillance and early actions whenever warranted, as needed for everyone. Immediately available, worldwide on a small scale, is a cost-effective C-ABPM system around the clock at 30-minute intervals at all ages, with free analyses from a project on The Biosphere and the Cosmos, BIOCOS (corne001@umn.edu), to all comers. This project constitutes a validation test for an international website recommended by a World Forum on "Natural Cataclysms and Global Problems of the Modern Civilization", held 19–21 September 2011 in Istanbul, Turkey (www.2011.geocataclysm.org) (1), in extending the scope of prior consensus conferences (e.g., 2–4; see 3 for a partial list of earlier meetings advocating C-ABPM). Thus, responses to Sir William Osler's wear and tear, putative harbingers of severe disease (1–4), are detected as gauges of loads (4–8), prompting preventive action. Eventually this task can be implemented on a large scale by an international multilingual analytical and educative website (1, 4), Figure 1, on a larger than the currently ongoing small-scale albeit worldwide endeavor. With emphasis on wellness that is checked so as to act when prevention is needed, we need no longer fly blind to the circadian and the many other variabilities in us and around us, as soon as we have in this generation a computer-savvy family member or friend, or can be assigned to such a person until a system is instituted where such a service can be offered freely, such as in community libraries or pharmacies. In the next generation, everyone can be trained in self-monitoring in earliest schooling (9).

2.0 WHAT CAN BE DONE TODAY

In a forthcoming book for the lay public, aimed to advise patients found to have a BP that is too high or too low, a colleague asked the authors whether he could reproduce Figure 2, published in 1984 (10), as an example of inter-individual differences among 24-hour (h) profiles. At the time of the original publication, we had not yet formulated VVAs or VVDs, Figure 3, that are not generally known, a long series of consensus meetings notwithstanding (1–4) and of course had no reference values for them. Mostly not implemented is the detection of circadian and about (~) 7-day (circaseptan) BP periodicities, documented over a century ago that is immediately available for diagnostic and therapeutic use in 2012. As to diagnosis, let us start by asking: Who in Figure 2 is at the greater risk of a cerebral stroke or other severe cardiovascular disease? The important answer, contrary to current worldwide practice, is: We can't tell, the record is too short. We need a 7-day record as a start and must continue to monitor if it shows abnormality, Figure 4.

In looking at Figure 2 in 2012, some readers who rely on current official guidelines (11) may infer that CH, the 60-year-old man, had a larger swing in BP and may be the healthier of the two. Many more may recognize CH, the subject whose data are shown on the left of Figure 2, as an excessive dipper, a very common diagnosis based on a single 24-h profile, associated with undesirable outcomes, on a population basis (12–15). This majority in turn should not only question a record length of 24 h as a basis of a diagnosis (5, 16–18), Figure 2, but can compare the

1 See definitions at the end, best viewed first.

utility of a classification of dipping with the chronobiologic diagnosis, i.a., of a circadian overswing, CHAT (short for Circadian Hyper-Amplitude-Tension) (19; cf. 4), Figure 3, associated with a high risk of stroke, Figures 5A–C (4). It must be realized that a diagnosis based on the single measurement of BP, Figure 6A–C, like that relying on a single 24-h record, as in the case of Figure 2 and others, is a spotcheck rather than a platinum standard, Figure 7 (2).

2.1 HISTORY SHOWS URGENCY AND FEASIBILITY OF LIFELONG MONITORING, STARTING AT THE DIAGNOSIS OF BP ABNORMALITY [2]

In 1904, Theodore C. Janeway of Johns Hopkins University (20), then the opinion leader, did not wish to see a patient before collecting sufficient data to assess periodicit**ies**. (The plural was justified since by 1880 and 1881 Ignaz Zadek in Berlin had collected sufficiently long time series to document 24-h, 84-h and 168-h rhythms, Figure 8 [21, 22].) In 1974, Frederic C. Bartter, of Bartter syndrome fame, then head of the Hypertension-Endocrine Branch at the U.S. National Institutes of Health (NIH), and later the director of the Clinical Center at the NIH[3], recognized that the reason why his patient was diagnosed differently by two physicians who saw him at different times of day stemmed from circadian changes in BP, Figure 9A. His foresight was later illustrated in the abstract (Figure 9B), with additional evidence accumulating since the availability of automatic BP monitoring, Figure 9C.

Frederic C. Bartter reached the following conclusion after having his patient studied in the clinical center (23; cf. 24): "By conventional standards, this patient is clearly normotensive every morning. Yet the BP determined each day at 6 in the afternoon provides especially convincing evidence that this patient is a hypertensive. ... My plea today [in 1974!] is that information contained in such curves [cosinor fits; see Figures 2 and 3: our addition] become a routine minimal amount of information accepted for the description of a patient's blood pressure. The analysis of this information by cosinor should become a routine. It is essential that enough information be collected to allow objective characterization of a periodic phenomenon, to wit, an estimate of M [the time structure or chronome-adjusted mean, or MESOR] ... an estimate of [the amplitude] A itself, and finally an estimate of acrophase, ϕ [a measure of timing] [Figure 10A] [24] [our addition]. In this way, a patient can be compared with himself at another time [Figure 10B] [25] [our addition], or under another treatment, and the patient can be compared with a normal [Figure 2; our addition] or with another patient" (23).

2.2 WHAT TO DO WITH 24-H CHAT OR WITH OTHER RECORDS COVERING A SINGLE CYCLE

Turning back to Figure 2, by using "clinically" healthy in its title rather than just "healthy", in 1984 (!) we implied that we had no outcome data on the subjects investigated, but were not aware of any abnormality. We still lack outcomes for CH, but have (we emphasize tentative) gender- and age-specified reference standards (RS) for whites, among others (26). We can make a diagnosis of 24-h CHAT (27) specifically in the light of now-available acceptability limits for the 24-h amplitude, still to be improved by restriction to long-lived disease-free individuals. Having diagnosed 24-h CHAT, we must realize the limitations of the record's brevity (5, 16–18). Taking a 24-h profile to assess a single circadian cycle being equivalent to taking the pulse for one second to gauge just a single cardiac cycle was recognized long ago (27)[4]. The analogy of taking the pulse for only one second as assessing only a single cycle can now be extended

2 Dr. Howard Levine, the late head of medical education at the New Britain (Connecticut) General Hospital, and professor of medicine at the University of Connecticut, implemented self-measurements of blood pressure, heart rate and other performance variables, including grip strength, around the clock from the time of a chronobiologic diagnosis of MESOR-hypertension until the end of life from amyotrophic lateral sclerosis, his weakness notwithstanding.

3 Dr. Bartter also self-measured BP around the clock from the time of diagnosis until a fatal stroke.

4 Halberg et al. wrote in 1997 (27): "Even a single heartbeat, however faint, will rule in at least a glimmer of life. The taking of the pulse for only a second or two then provides valuable information as to the merits of further efforts in resuscitation. But if the pulse were routinely taken for only a second or so, a bradycardic athlete in the best of health might be presumed dead!" We paraphrase these authors by stating further that a record of the beating heart for a minute or two may be compatible with diagnosing

to the physiological counterparts of a half-year and of the seasons and to periods shorter than 6 months, the cis-half-year (on this side of the period = cis) or longer than 12 months, the transyear (beyond = trans). Like the 11-year (undecennian) or decadal period of the sunspots, they are all reflected in the human circulation, Figures 11A–C (28–30). Whether it is normal or abnormal, neither a 24-h nor a single 10- or 11-year record can eventually remain the basis of a diagnostic, therapeutic or etiologic decision. In either case, the need remains for further lifelong C-ABPM, and for continued epidemiological data collection and analysis, the purpose of the website in Figure 1. When the 24-h record happens to be abnormal, it constitutes no more than an indication of the urgency of C-ABPM to assess a possibly acceptable physiological response. Reliance on data covering less than a solar cycle length have led to controversy (31, 32) and have retarded recognition of heliobiology in the West, Figure 12A–D (32; cf. 33).

2.3 1-WEEK CHAT

A diagnosis of 24-h CHAT, of an excessive circadian swing, can be physiologically associated, in certain individuals, with events such as the arrival of welcome visitors, Figure 13 (5), or any other pleasant tasks (not necessarily loads) such as giving a party (5) or discussing important-seeming topics with a friend or even with a dear family member or without any obvious reason but perhaps one hidden in space weather (34; cf. 35). When a 24-h cosine curve is fitted to a 7-day series as a whole (rather than to a 24-h profile, as in Figure 2), a few days of CHAT may be smoothed out and the record as a whole may be acceptable, Figure 14A, or at least the number of weeks with CHAT is reduced, Figure 14B (36). On a population basis, the high risk of severe events associated with CHAT, Figures 5A–C, and more so with coexisting VVDs is clearly demonstrated in Figures 15A and 15B (4). A VVA for a single day should invariably prompt, as a follow-up, at least an added 7-day C-ABPM. In a case of fulminating CHAT, Figure 10B (25), this recommendation was not fully implemented, albeit a second short record was even more abnormal than the first. The patient took a conventional stress test instead, which was normal, and hence nothing else was done. Some months later, he returned asking for an implanted BP sensor. We asked why, and he told us that in the interim he had had a myocardial infarction (25). C-ABPM was also ignored in a single case of CHAT during pregnancy but not others. In that case, the systolic BP average (MESOR) was 115 mmHg, Figure 16 (4). In that case, not in others, a premature birth was associated with a partly cost-accounted expense of U.S. $1 million (4).

2.4 "SIMPLER" CLASSIFICATION BY DIPPING CAN MISLEAD

A chronobiologic approach works when a dipping classification can fail (19, 37, 38) or dipping misleads (39) on a small group basis. It seems the more important to realize that dipping cannot be recommended for the diagnosis of individuals, even for 7-day records, it is not equivalent to C-ABPM (4, 40, 41), in keeping with Einstein's "make everything as simple as possible but no simpler".

3.0 CHRONOTHERAPY

When the diagnosis of MESOR-hypertension is made, the dose prescribed is preferably varied, starting with a time preceding the peak by several hours. Hence, the circadian acrophase of BP as a marker preceded by an interval whose length depends on the chronopharmaceutics of the drug(s) involved is a procedure that has yielded a faster desired response, with fewer side effects compared to traditional therapy, Figure 17 (42; cf. 43). If needed, the timing of the drug can next be varied empirically to find the optimum, Figures 18A and 18B (part 2 of 44). This is the more important since the same dose of the same drug in the same patient tested at 6 different circadian stages, for ~1 month at each time (at clock hours after awakening 3 h apart) can induce or enhance an existing CHAT at one test time or at

death vs. life, but it is hardly recommended when a full 24-h record can fail to reveal abnormality that is present during each of 11 subsequent days, and of course vice versa.

another remove CHAT and lower BP, as intended, Figure 19 (45; cf. 46). Sometimes, a single change in the timing of a medication can correct abnormality, Figure 20 (cf. 2). Continued surveillance is indicated, Figure 21 (2). The many millions receiving hypotensive drugs need not fly blind, concerning risks in Figures 15A and 15B, while for security on the road we routinely automatically measure the pressure in automotive tires. Moreover, if we monitor ourselves continuously and automatically, we may learn about a new world of infradian rhythms that reflect physical environmental counterparts and relate to sudden cardiac death (Table 1 and Figure 22), suicide (Figures 23A–D), homicide (Figure 24), and terrorism (Figures 25 and 26). We may even find, on a population basis, the antecedents, Figure 27 (30, 47) as well as the consequences (48) of a tsunami accompanying an earthquake.

4.0 BEYOND CIRCADIANS

Time series collected and accumulating for the goal of self-surveillance, once aligned with physical environmental time series, enlarge the scope of Vladimir Ivanovich Vernadsky's noösphere (49, 50), the sphere of the human mind by a transdisciplinary spectrum of cycles congruent insofar as their periods in us and around us have overlapping CIs (95% confidence intervals) (51–54), Figures 28A-H.

Our inclusion of the moon, i.a., in Figure 28B is in keeping with studies on his own heart (56) by Miroslav Mikulecky, emeritus head of internal medicine and professor of statistics at Comenius University in Bratislava, Slovakia, organizer of meetings on this and related topics (57–61). It is here prompted by the first patient encountered by us who shows the double period of tides (62) averaging 24.8 h, repeatedly in the computer output (not input) of analyses of time series. JF is a woman, 61 years of age at start of a years-long around-the-clock study, including C-ABPM, with a 20-year history of twice-yearly adynamic depression, each lasting 2–3 months. During "downtimes", JF is unable to get out of bed and to keep synchronized with a 24-h periodic sleep-wake schedule. Her sleep pattern scans the hours of the day during her episodes. She self-rated vigor-wellness while claiming sensitivity to the moon. In the first months of the first two adynamic episodes investigated, we found a double tidal period of 24.8 h supporting her impression of selenosensitivity. JF self-measured BP and HR for 5 initial months and for > 16 months thereafter, Figure 28D. At least 2 circadian periods coexist most of the time, Figure 28E. She also collected saliva at 4-hourly intervals around the clock for the determination, in 11,702 assays, of cortisol, aldosterone, dehydroepiandrosterone, estradiol, testosterone and melatonin, Figure 28F, showing multiple recurring circadian endocrine as well as vascular ecfrequentia. Several circadian periods were also present in her outside downtimes during relative wellness (55), suggesting a "wrangling" of the tides with society and (natural and artificial) light. We may speculate whether the tides act via gravity and magnetism, a view shared with physicist-chemist Vladimir Evstafyev (63) and Prof. Mikulecky (their personal communications), acting by mechanisms considered by Friedemann Freund (64). In any event, in JF, this tug of war yields (compromise?) periods between 24.0 and 24.8 h except that during some of the first months of an adynamic desynchronized episode, a precise average double tidal period prevails. The diagnosis in JF of dysfrequentia, visualized by a comparison with an age- and gender-matched control, in Figures 28G and 28H can be made by C-ABPM (but not by self-measurement, a highly motivated JF notwithstanding, in keeping with earlier results [65]).

Cycles in us, such as the physiological week, among others, led to natural geomagnetic near-weeks, Figures 29A and 29B (51). Reports of new cycles by physicists prompted our discovery of coperiodic biospheric signatures of the cosmos such as ~5- or ~16-month-long, Figures 30A–C (34), and other cycles, Figures 31A–C (53, 54). There are further cross-spectral coherences (54, 66–68) and phase synchronizations (68) between endpoints around us, such as Bz, Kp, Wolf number or coronal mass ejection or cosmic rays and urinary variables or the decades-long monitored BP of individuals. Associations are also seen from cross-wavelets and coherence between myocardial infarctions of populations or the incidence of terrorism on the one hand and space weather on the other hand, Figures 32A–D.

We trust that with Figures 33 and 34, among others, a chronousphere [5] emerges, consisting of many infradians with periods longer than 28 h, up to myriadennians (69, 70). For some of the infradian pairs of periods, the disappearance or reappearance of the environmental, e.g., solar or interplanetary component entails corresponding biospheric consequences, Figures 34 (44), 35 (61) and 36 (62). The approach by removal of a gland and replacement of its hormone started endocrinology and eventually chronobiology (71). Investigation seems indicated not only by mapping (51, 54, 71–74) but also by the subtraction and/or addition approach (44, 75), notably for those in health care interested in the effects of space weather (34).

TAKE HOME

In confronting congruent cycles in us and around us, the biospheric cycles when they are coded in our genes, may reflect what goes on and went on outside us from the origins of living matter, more reliably than the relatively recently recorded corresponding physical cycles. The dynamics of the cosmos almost certainly went on for a very long time. The solar wind and its aeolian cycles probably blew for billions of years and left their mark in our makeup. A record of polar lights and sunspots traces only a millennium or less. It can be aligned with time series of helio-, interplanetary, lunar or geomagnetic variables for a much shorter span. Recording by satellites of interplanetary, solar and cosmic variable is still more recent, but there are, of course, physical measures for carbon and other dating. None of them, however, matches in density or length the dynamic information provided by cycles in living matter. The latter phrase aims to use Vernadsky's plea for dealing with life as part of the crust of the earth, as a biosphere turning, with him, Edouard Le Roy and Pierre Teilhard de Chardin, into a sphere of the human mind (Gk noos; hence noosphere) by a directed evolution.

In this context the cycles of the biosphere, mimicking those of the cosmos, constitute another novel way of dating (where we come from and what we encountered on our way to where we are and to where we want to go) and certainly serve to validate, as magnetometers or cosmometers, the relatively recent physical counterparts (52), notably in the human baby (74). This dating by mapping from archaea to man reveals a set of transdisciplinary cycles pervading all disciplines, each a sphere of the human mind (also Attic Gk *nous)*, yielding a novel time structure. We can get much information about such a chronousphere by monitoring ourselves glocally, namely with repeated passes over the accumulating data as a whole (globally), eventually from the womb, and now from where we happen to start, eventually to the "tomb" in the individual, with a view of achieving the same by the monitoring of natality, health, morbidity and mortality statistics for the well-being of populations.

We have learned to deal with excessive heat or cold and now have thermometers to trigger heating or cooling as need be. Similarly, we must deal with excessive or lacking magnetism and other, not always obvious factors that complicate not only physical communications among us (what Stetson [76] and Düll and Düll [77] detected long ago, as the effect of solar emissions). We must also learn to deal with each other toward a desirable not only cross-spectral but also much broader insofar as measurable and manipulable "coherence" with our environment near and far, including space weather. The cosmos affects not only the easily measured "bad" such as sudden cardiac death, suicide,

5 From Gk *chronos* = time, Attic Gk *nous* = mind and Gk *sphairos* = globe. We used "no**u**s" in the portmanteau'd "nousphere" to credit Vladimir Ivanovich Vernadsky, Pierre Teilhard de Chardin and Edouard le Roy, who, i.a., used the derivation of "noosphere" from "noos", recognizing the need for a sphere of the human creative mind or broader culture, courageously extrapolating beyond the sphere of available data (criticized by Hagemeister M. In: Rosenthal BG, ed. The Occult in Russian and Soviet Culture. Ithaca, NY: Cornell University Press; 1997. p. 185–202, yet endorsed with extensive study by Ertel S. Studia Psychologica 1996; 38: 3–22). Cosmism's pioneers as yet did not have the means (computers and satellites) for detecting and documenting the pervading transdisciplinary spectrum of solar, interplanetary, geo- and biospheric cycles and the consequences in the human mind of the aeolian disappearance and/or reappearance of non-photic rhythms.

homicide and war, but also the hard-to-assess "good", as perhaps revealed by church membership (78) and religious proselytism (79), a task of optimization for a budding chronobioethics (80, 81).

In a global coherence initiative, Rollin McCraty and his associates seek a shift from "competition" to "greater cooperation" in a coherent planetary standing wave (82; cf. 83). The "increased power of connected intention and consciousness", also a topic of interest to Michael Persinger's (84, 85) and Hans Wendt's (86) research, should all prompt attempts to find better measures of coherence beyond those used herein from physics and numerical analysis. Perhaps the language of frequencies within them and far outside Schumann's resonances is pertinent, that yielded Figure 23 and remove-and-replace approaches in arriving at Figures 24–26 constitute a step in that direction.

It seems the more important to assess the status quo of information measured as tangible "coherence" with our cosmos, the topic of this paper. From this viewpoint, C-ABPM, while worth implementing for immediate health benefit, once it is aligned with physical environmental monitoring, provides marker rhythm information concerning both environmental magnetism and other nonphotic factors competing with oscillations in the visible range. Patient JF, alluded to herein, is a case in point at the clinical level.

As to mechanisms involved, the physicist and chemist Vladimir K. Evstafyev suggests that while the earth's atmosphere absorbs most cosmic radiation, there is a "transparency window between 375 and 10 MHz" through which radio waves reach the earth's surface and, if of appropriate frequency, bring about spin inversions, as a way to affect chemical reactions (63), a problem also discussed by Waldemar Ulmer as diffusion at the atomic level, modeled further as interaction among quantum mechanical frequency-coupled circuits, as bio-resonance at a very high frequency and resulting in beats at a low frequency fueled by ATP and involving DNA, a speculation based on extensive data (87; cf. 88).

CONCLUSION

The BP cuff in the provider's office must go for the moment to the homes of each individual. In the 1960s and 1970s it seemed worthwhile to plead, as Frederic C. Bartter, of Bartter's syndrome, also did, for moving the BP cuff from the providers' offices to everybody's (including his own) office or other work place by day and home by night. This recommendation holds until a system of C-ABPM became affordably available to everybody. Bartter advocated this as head of the Hypertension-Endocrine Branch at the U.S. National Institutes of Health (NIH), and later as head of the NIH's Clinical Center. In 2012, self-measurements at home have detected an effect of the great earthquake in Japan, proving their possible broader value (48). They confirmed, if not the finding of antecedents (30, 47), at least the consequences of the same quake, found on a small scale yet worldwide in a de facto validation test of an ongoing C-ABPM system, serving for cost-free analyses of self-surveillance data by all comers. This model for a website has now also been proposed by a World Forum on "Natural Cataclysms and Global Problems of the Modern Civilization", held 19-21 September 2011 in Istanbul, Turkey (www.2011.geocataclysm.org). The data collected for the prevention of personal cataclysms, such as a massive stroke, may also be used to attempt an understanding (for countermeasures) of the mechanisms underlying societal disease, such as suicide, crime, homicide, terror and war and natural disasters such as earthquakes and tsunamis, as well as "coherence" or rather mutual understanding and chronobioethical cooperation among people.

DEFINITIONS (1 AND 3–10 ARE BOTH NOUN AND ADJECTIVE)

1. Aeolian. Nonstationary oscillations that appear, may disappear and reappear ubiquitously and/or in limited geo- (or cosmo-) graphic space and time, with changes in period, τ, amplitude, A, and/or phase (ϕ). Many physical as well as biological cycles are aeolian, including among the latter ~24-hour (h) circadians, synchronized with or desynchronized from a 24-h society (socidian and asocidian, respectively). Because of their aeolian nature, some spectral components can be defined only tentatively by the CIs (95% confidence inter-

vals) of their τ. Even this precaution was not sufficient in the case of the BEL, initially defined as a τ with a CI (not the point estimate) of τ covering the range between 30 and 40 years. But then we found CIs nearing (but not reaching) that range that could have been BELs. Hence, some definitions refer only to the CI of τ and not to a point estimate of τ, and others may refer to a "CI near a given range" rather than a CI in a given range, with the limits still to be revised if need be; they are tentative. Biospheric aeolians are not now replicated in the same individual in the case of BEL cycles and have been studied in populations, where some of them are already documented.

2. CI. 95% confidence interval of a characteristic such as period, amplitude or phase.
3. Circadian. Cycle of ~20- to 28-h duration, usually 24-h synchronized (socidian in societal organisms like humans) but even a 24-h synchronized circadian (in circulating endothelin) can disappear and reappear, by the criterion of statistical significance, while it cannot be decided whether it is actually lost or obscured by noise to the point of failing detection. In biology, several circadians can coexist, such as an average τ of ~24.00 h, a socidian corresponding to the societal day, and an average τ of ~24.84 h, corresponding to a luni-solar (double tidal) day (in sleep-wakefulness of a healthy man on a self-selected sleep-activity schedule and of a patient with recurrent adynamic depression).
4. Ultradian. Cycle shorter than 20 h (coined with reference to frequency).
5. Infradian. Cycle longer than 28 h (coined with reference to frequency).
6. Circasemiseptan. Cycle of ~3.5 days.
7. Circaseptan. Cycle of ~7 days.
8. Quinmensal (also cis-half-year). Cycle of ~5 months.
9. Circasemiannual. Cycle of ~6 months.
10. Circannual. Cycle of ~1 year.
11. Near-transyear. Cycle slightly but statistically significantly longer than 1 year (1.00 year < [τ − CI] < [τ + CI] < 1.20 years).
12. Far-transyear. Cycle considerably longer than 1 but shorter than 2 years (1.2 years ≤ [τ − CI] < [τ + CI] < 1.9 years).
13. Horrebow-Schwabe cycle. Cycle with a CI of τ near 11 years (circaundecennian or decadal).
14. Hale cycle. Cycle with a CI of τ near ~22 years.
15. BEL (Brückner-Egeson-Lockyer) cycle. Cycle with a CI of τ near 30 to 40 years (paratridecadal).
16. Kondratiev cycle. Cycle with a CI of τ near ~50 years (quindecadal).
17. Sexadecadal. Cycle with a CI of τ near ~60 years.
18. Congruence (vs. acongruence) classifies sets of τs that, if not identical, are very close to each other in length; "closeness" is defined by overlapping CIs of the τs, introducing objectivity where subjectivity and a lack of indications of uncertainty prevailed for the majority of reports dealing with the many non-stationary cycles, aeolian in space as in time, i.a., in biomedicine, economics and physics, notably in the infradian domain, that characterize our psychophysiology, epidemiology and many other human affairs, and leading to a societal (and thus novel aspect of environmental) medicine.
19. Resonance. The induction or amplification of an oscillation by virtue of interacting natural frequencies (eigenfrequencies) that are similar (approximately or fully identical), within an ever-broader system such as a biosphere, a noösphere and a chronousphere, i.e., $\omega 1 - \omega 2 \approx 0$.
20. Coherence. Stable wave-packet without (or with an extremely small) dispersion of frequencies. Such a physico-chemical state, whether induced or merely reactive or self-sustained, can be stabilized by oscillations with similar frequencies, according to the requirements or conditions for resonance. The non-self-sustained oscillation may break down in the absence of coherence with an external oscillation, whereas the self-sustained one may decrease in amplitude whenever the coherent fraction of the underlying mechanism is subtracted. (In the context of time series, coherence, from cross-spectral analysis, may be used to identify variations which have similar spectral properties [high power in the same spectral frequency bands], if the variability of two distinct time series is interrelated in the spectral domain.)

Support: GM-13981 (FH), University of Minnesota Supercomputing Institute (GC, FH)

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Table 1. Geomagnetic/geographic differences among cycles with periods in the range of 0.8–2.0 years, characterizing the incidence of sudden cardiac death (SCD)1* and myocardial infarction (MI)

Sudden Cardiac Death (SCD)[1]

Site	Span	T, Δt, N	SCD (N)	Period (y) (95% CI)		Amplitude (95% CI)	A (% MESOR)	P-value[2]
				- - - - - Transyear (TY) or Candidate Transyear (cTY) Detected - - - - -				
Minnesota	1999-2003	5y, 1d, 1826	343	1.392 (TY)	(1.173, 1.611)	0.042 (0.00, 0.09)	22.0	0.014
Arkansas	1999-2003	5y, 1d, 1826	273	1.095	(0.939, 1.251)	0.032 (0.00, 0.07)	21.1	0.040
				1.686 (cTY)	(1.293, 2.071)	0.031 (0.00, 0.07)	20.7	0.044
Czech Rep.	1999-2003	5y, 1d, 1826	1006	0.974	(0.856, 1.091)	0.078 (0.00, 0.16)	14.2	0.007
				1.759 (cTY)	(1.408, 2.110)	0.077 (0.00, 0.15)	13.9	0.01
	1994-2003	10y, 1d, 3652	1792	1.726 (TY)	(1.605, 1.848)	0.074 (0.02, 0.13)	15.1	<0.001
				1	(0.944, 1.056)	0.052 (0.00, 0.10)	10.6	0.01
				- - - - - Candidate Transyear Not Detected - - - - -				
North Carolina	1999-2003	5y, 1d, 1826	752	0.929	(0.834, 1.023)	0.069 (0.00, 0.14)	16.9	0.007
Tbilisi, Georgia	Nov 99-2003	4.1y, 1d, 1505	130	0.988	(0.862, 1.114)	0.035 (0.00, 0.07)	40.7	0.007
Hong Kong	2001-2003	3y, 1m, 36	52	0.843	(0.651, 1.036)	(NS)	44.9	0.077

Myocardial Infarction (MI)

Site	Span	T, Δt, N	MI (N)	Period (y) (95% CI)		Amplitude (95% CI)	A (% MESOR)	P-value[2]
				- - - - - Coexisting Year (Circannual) and Transyear (TY) - - - - -				
Czech Rep.	1999-2003	5y, 1d, 1826	52598	1.014	(0.989, 1.038)	2.85 (2.22, 3.48)	9.88	<0.001
				1.354 (TY)	(1.252, 1.456)	1.35 (0.69, 2.02)	4.68	<0.001
	1994-2003	10y, 1d, 3652	115520	0.998	(0.988, 1.009)	3.03 (2.47, 3.60)	9.58	<0.001
				1.453 (TY)	(1.417, 1.489)	1.91 (1.34, 2.49)	6.04	<0.001
				1.15 (TY)	(1.116, 1.184)	1.23 (0.64, 1.82)	3.88	<0.001

*With focus on transyears, with periods longer than 1.0 year (underlined; double underline for near-transyear).

[1] International Classification of Diseases (ICD10), Code I46.1, excluding MI and sudden death of unknown or unspecified cause (except before 1999).

T: length of data series (y=years); Δt: sampling interval (d=day, m=month); N: number of data (including 0s).

Period and 95% confidence interval (CI) estimated by nonlinear least squares. In longer (10-year) series, a near-transyear (cycle with a period between 1.0 and 1.2 years) is detected for MIs in addition to a far-transyear. Brevity of series and lack of ordering statistical significance qualify results from Hong Kong. Note that transyears are found in 3 of 6 locations ($P<0.05$ by linear least-squares) with a relative amplitude > 12 (% of MESOR).

[2] From linear least-squares analyses, not corrected for multiple testing. Amplitude expressed in N/day.

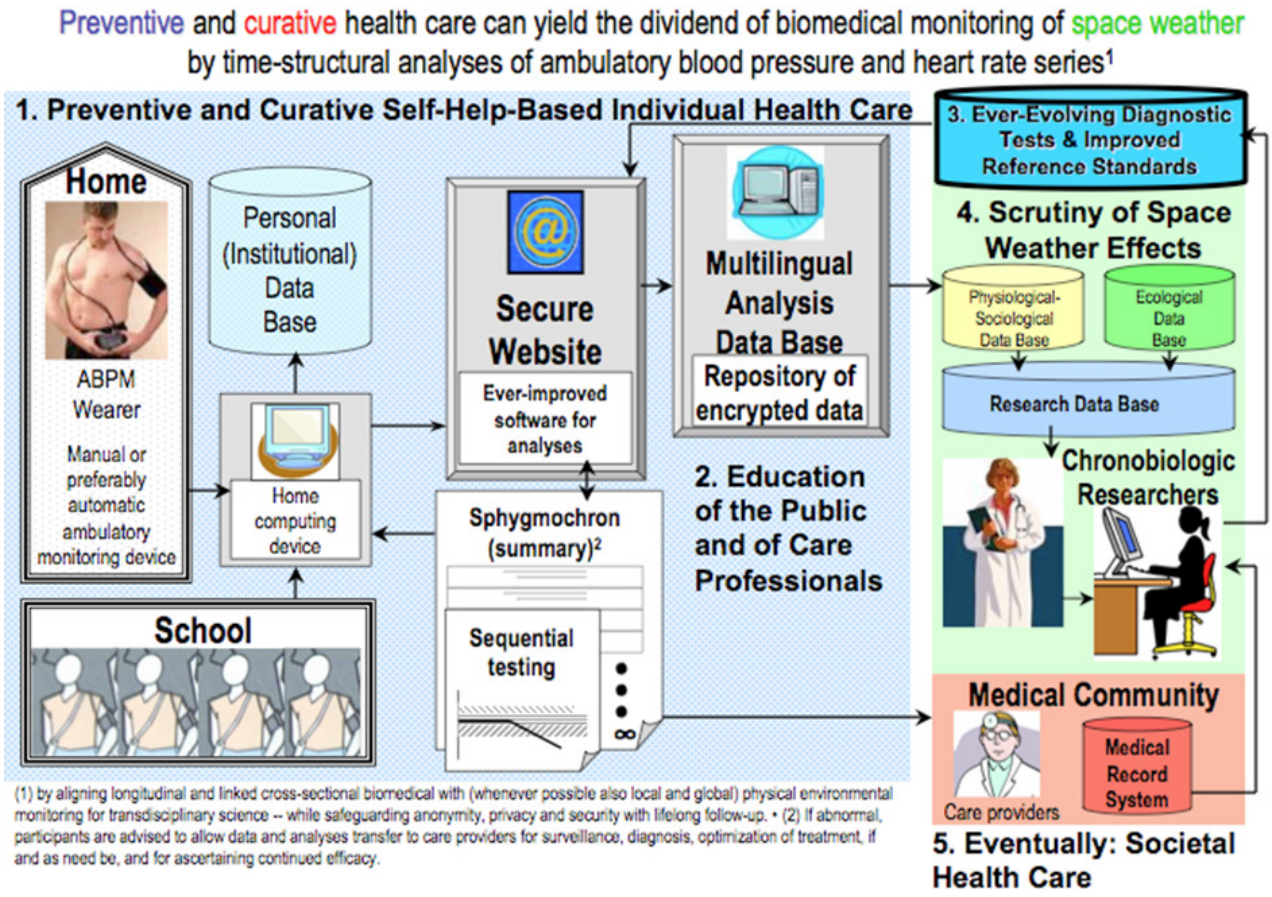


Figure 1. Physiological, other biological, notably epidemiological, and sociological as well as physical and environmental data collection and analyses in the project on The Biosphere and the Cosmos, BIOCOS, are ongoing worldwide on a very small scale, yielding, i.a., the data of this paper and some of those cited from our team. They constitute a validation test underlying a proposal by a World Forum on "Natural Cataclysms and Global Problems of the Modern Civilization", held 19–21 September 2011 in Istanbul, Turkey (www.2011.geocataclysm.org), for a manned international multilingual website, providing analyses for all comers, and saving the data, beyond both the medical community (bottom right) and physical environmental science concerned about space weather effects (upper right), also for the self-surveilling public at large, notably for those interested in science and art, a unified transdisciplinary chronousphere. The Phoenix Project of volunteering members of the Twin Cities chapter of the Institute of Electrical and Electronics Engineers (http://www.phoenix.tc-ieee.org) is planning on developing an inexpensive, cuffless automatic monitor of blood pressure and on implementing the concept of a website (www.sphygmochron.org) for a service providing automatic analyses in exchange for the data that in turn are to be used for refining methods and for monitoring psychophysiological effects of space weather. © Halberg.

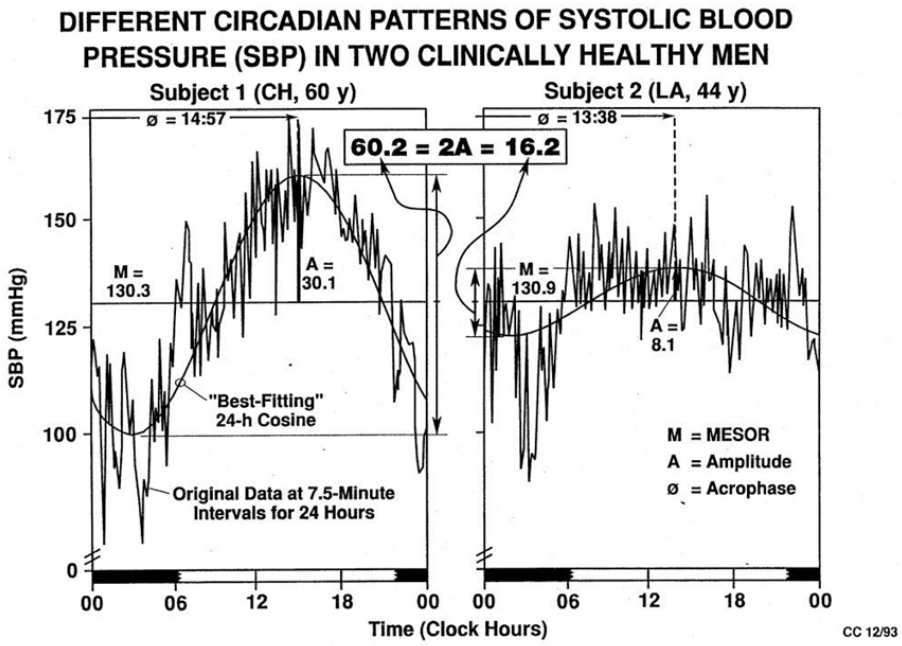
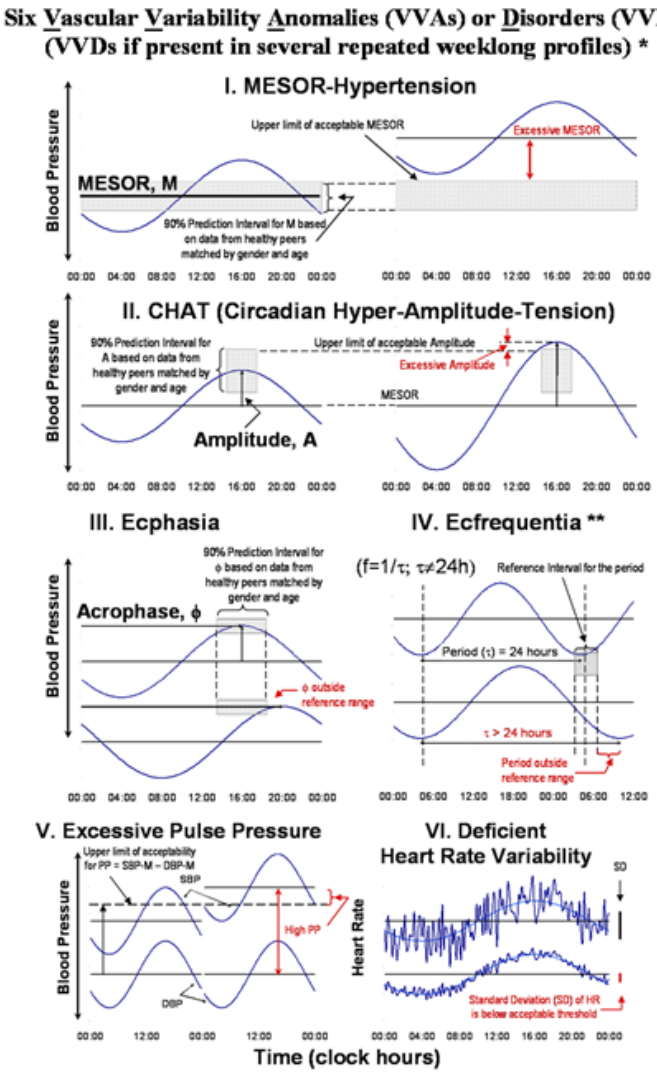


Figure 2. 24-h profiles of blood pressure (BP) variation in two clinically healthy men were described in 1984 (10) as revealing inter-individual differences. In the interim, reference values from clinically healthy subjects with outcomes have demonstrated that a double amplitude of 60.2 mmHg in CH, 60 years of age, is compatible with a diagnosis of 24-h CHAT (Circadian Hyper-Amplitude-Tension, a circadian overswing; see Figure 3) found on occasion in certain individuals as a physiological event (response) under routine conditions. If CHAT persists (is not smoothed out) in the 24-h cosine fit to a 7-day around-the-clock record, the diagnosis of "7-day CHAT", like that of "1-day CHAT", is no more than an indication for further C-ABPM. Two patients whose BP averages (here the MESORs, Midline-Estimating Statistics Of Rhythm) are practically identical differ in terms of their psychophysiology, here gauged by the circadian amplitude of BP. Longer monitoring is indicated to arrive at an assessment of stress or load by a Vascular Variability Anomaly (VVA), or a gauge of strain, a Vascular Variability Disorder (VVD), and thus to assess the risk of developing a stroke within 6 years. As compared to the risk associated with high BP, a risk of systolic CHAT doubled that risk. © Halberg.



* Validated by chronobiologic analysis of around-the-clock 7-day/24-hour records of measurements at 1-hour or shorter intervals, interpreted in the light of time-specified reference standards qualified by gender and age. ** Ecfrequentia: short for frequency (f) alteration (e.g., desynchronization) that can be Dysfrequentia when associated with symptoms and/or persisting in repeated consecutive 7-day records.

Figure 3. Definitions and abstract illustrations of circadian Vascular Variability Anomalies (VVAs), for systolic (S), mean arterial (MA) or diastolic (D) blood pressure (BP) or a combination of the foregoing when the CI (95% confidence interval) of the period, τ, overlaps 24 h for I to III. I to IV are diagnosed by cosinor (10) with reference to gender- and age-specified reference limits (RL) with a CI of the amplitude (A) not overlapping zero and the characteristic(s) M (MESOR), A and ϕ (acrophase) within the corresponding RL:

I. MESOR (M)-hypertension (MH), an elevation of the M above RL, can be S-MH, D-MH, MA-MH or a combination thereof, demonstrated by M, from curve-fitting complemented by stacking along the 24-hour (h) scale by a measure of load, the hyperbaric index and by percentages and times of abnormal values (4).

II. Circadian Hyper-Amplitude (A)-Tension (CHAT), an elevation of the 24-h A above RL, which can also be systolic (S-CHAT), diastolic (D-CHAT), mean arterial (MA-CHAT), or a combination of the foregoing.

III. SBP-, DBP- or MAP-ecphasia (when persisting and associated with illness, circadian dysphasia), an odd timing outside RL of the circadian rhythm of BP but often not of that in HR.

IV. Circadian ecfrequentia, (when persisting and associated with illness, circadian dysfrequentia), one or several circadian periods, τ, with a CI not overlapping RL, represents a 720% increase in risk of ischemic stroke (see last column on right).

V. Excessive pulse pressure (EPP), when the difference in the MESORs of SBP and DBP for adults exceeds 60 mmHg.

VI. A deficient HR variability (DHRV), defined as a standard deviation of HR less than 7.5 beats/minute.

Threshold values remain to be replaced by RL. All RLs remain to be improved by restriction to those of disease-free long-lived peers specified by gender, age, ethnicity and geography. © Halberg.

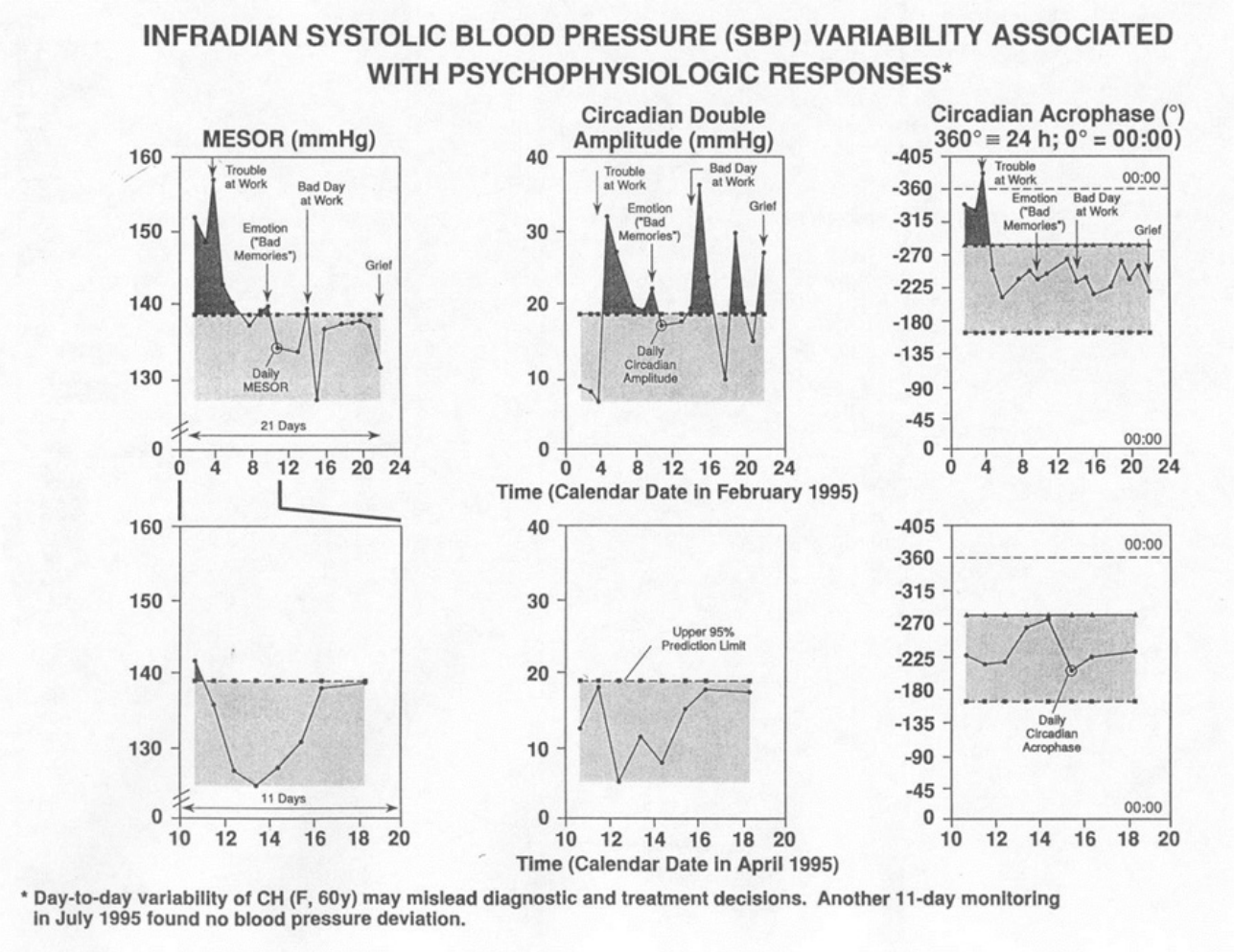


Figure 4. At the start of monitoring, CHF, a woman in presumably good health, was 60 years of age. She monitored her blood pressure (BP) and heart rate (HR) around the clock with a TM-2421 monitor from A&D (Tokyo, Japan). The reliability of the TM-2421 monitor had been documented. This monitor measures BP and HR according to the oscillometric and the auscultatory method. As a rule, with the instrument used, oscillometric readings are more reliable than auscultatory measurements. The monitor gives a beep as a warning to stand still (e.g., if the user is walking or engaged in some other activity) or remain seated or recumbent, as the case may be. After the beep, the cuff inflates automatically, taking and storing a measurement of systolic (S) and diastolic (D) BP and HR. If so set at half-hourly intervals, automatic measurements are taken and stored for up to 2.5 weeks if the instrument is recharged at 3-day intervals, by being plugged into an electrical outlet for several minutes.

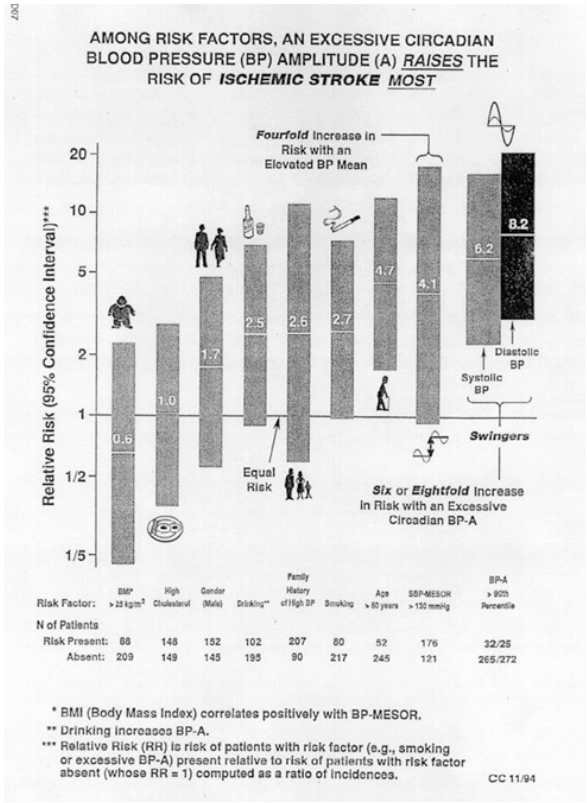
Monitoring sessions were repeated at intervals of weeks or months during 6 years. CHF kept a thorough diary at the time of monitoring, which allowed the association of spans when her BP was found to be deviant with the presence of strong emotions such as grief, conflict and concern, albeit not in association with annoyance by particular measurements. Irrespective of the duration of a given monitoring session, analyses were carried out in repeated scans of the same data for separate subspans of 1. at least 24 h, 2. a week, 3. longer spans, sections of the data such as 4. only nightly readings or 5. readings without those accompanied by a note indicating annoyance by measurement. 6. In particular, interest such as concern for several weeks about a diagnosis of ovarian cancer in her daughter (showing gross abnormality) and 7. including analyses on all her data accumulated at certain times during the 6 years.

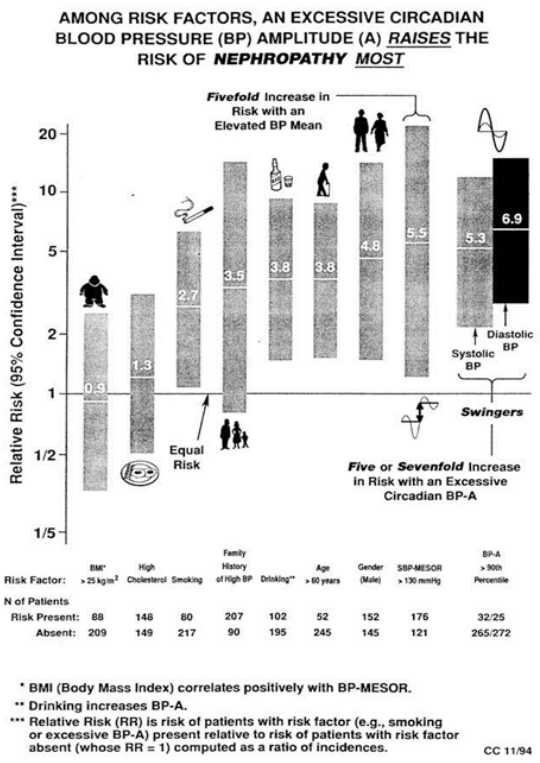
Each data series was analyzed using a curve-fitting and a stacking approach, with analyses of the long series confirming that CHF was 24-h synchronized; the CI (95% confidence interval) of her period, τ, overlapped 24.00 h. A model was fitted by least squares, which consisted of cosine curves with periods of 24 and 12 h. This model for most people accurately approximates the circadian waveform in BP and HR. The parameters are the MESOR, M, a rhythm-adjusted mean; the amplitude, A (of each of the two components), which is a measure of half the predictable extent of change within a cycle; and the acrophase, ϕ (also of each of the two components), a measure of the timing of overall high values recurring in each cycle, were computed. The circadian amplitude and acrophase, together with the MESOR, are interpreted in the light of reference values obtained from data bases on clinically healthy subjects matched by gender and age. These reference intervals are calculated as 90% prediction limits. When the MESOR exceeds the upper 95% prediction limit, MESOR-hypertension is diagnosed; when the circadian amplitude exceeds the upper 95% prediction limit, the condition of CHAT is diagnosed; and when the ϕ or the period lies outside the 90% prediction interval, ecphasia or ecfrequentia, respectively, is diagnosed, as apparent from Figure 3.

In the stacking approach, the data as a whole, averaged over an idealized 24-h cycle, are compared by computer with the time-specified reference limits (derived from data bases obtained independently on clinically healthy subjects). These reference standards are again calculated as 90% prediction limits over 1-h intervals that are displaced by half an hour throughout the 24-h day. The reference values are thus specified as a function of clock-hour, gender and age (for 24-h synchronized subjects only, not for JF in Figure 28D during episodes of depression). CHF's data are compared with the upper limit of standards, called chronodesms. Whenever the subject's data exceed the upper limit of the chronodesm, BP deviation is diagnosed. The amount of time when the data are above the reference limit represents the percent time elevation. The area delineated between the subject's curve when the data are excessive and the upper limit of acceptability delineates the hyperbaric index in the case of BP and the tachycardic index in the case of HR. As an area under the curve, this index has the units of mmHg x h during 24 h for BP and of beats/min x h during 24 h for the case of HR.

The center of gravity of the area of excess is also calculated to represent the time of overall excess, which usually is informative for specifying the timing of treatment administration when it is needed. Cosine fit- and stacking-derived indices were computed for each profile as a whole as well as for spans of about 24 h so as to determine the extent of day-to-day variability in the circadian variation and any deviation in relation to chronobiologic norms. The limitation of a profile of 24 h is seen as intermittent black excesses above the upper limit of the chronodesm in daily summaries in the first record, yet missing (with one initial exception) in the second record, each record covering weeks.

MESOR-hypertension was then detected for the first 5 days but not for the next 16 days in February (top left). The circadian amplitude was acceptable for the first 3 days in February, but was intermittently excessive in February (top middle) but not in April (bottom middle). The circadian acrophase was deviant only at the beginning of the record in February (top right) and is invariably acceptable in April (bottom right). These results suggest the desirability to monitor for much longer than 24 h to obtain a reliable diagnosis. Abnormality can occur while most or all measurements lie within acceptable limits insofar as they are neither too high nor too low on the average. © Halberg.





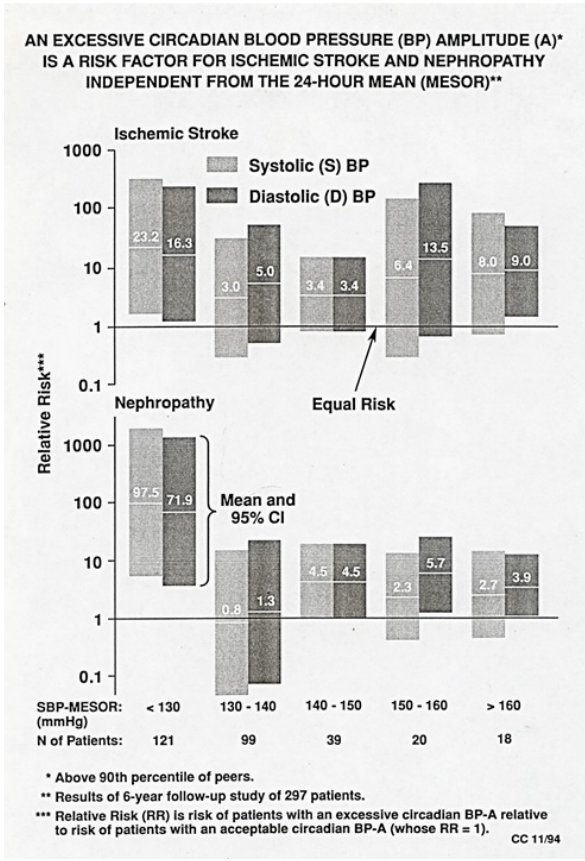


Figure 5A. An excessive circadian amplitude of diastolic blood pressure raises the risk of an ischemic event by 720% (see last column on right). Original data of Kuniaki Otsuka. © Halberg.

Figure 5B. Excessive circadian amplitude of diastolic blood pressure raises the risk of nephropathy by 590% (see last column on right). Original data of Kuniaki Otsuka. © Halberg.

Figure 5C. Note high relative risk at lowest average blood pressure. Original data of Kuniaki Otsuka. © Halberg.

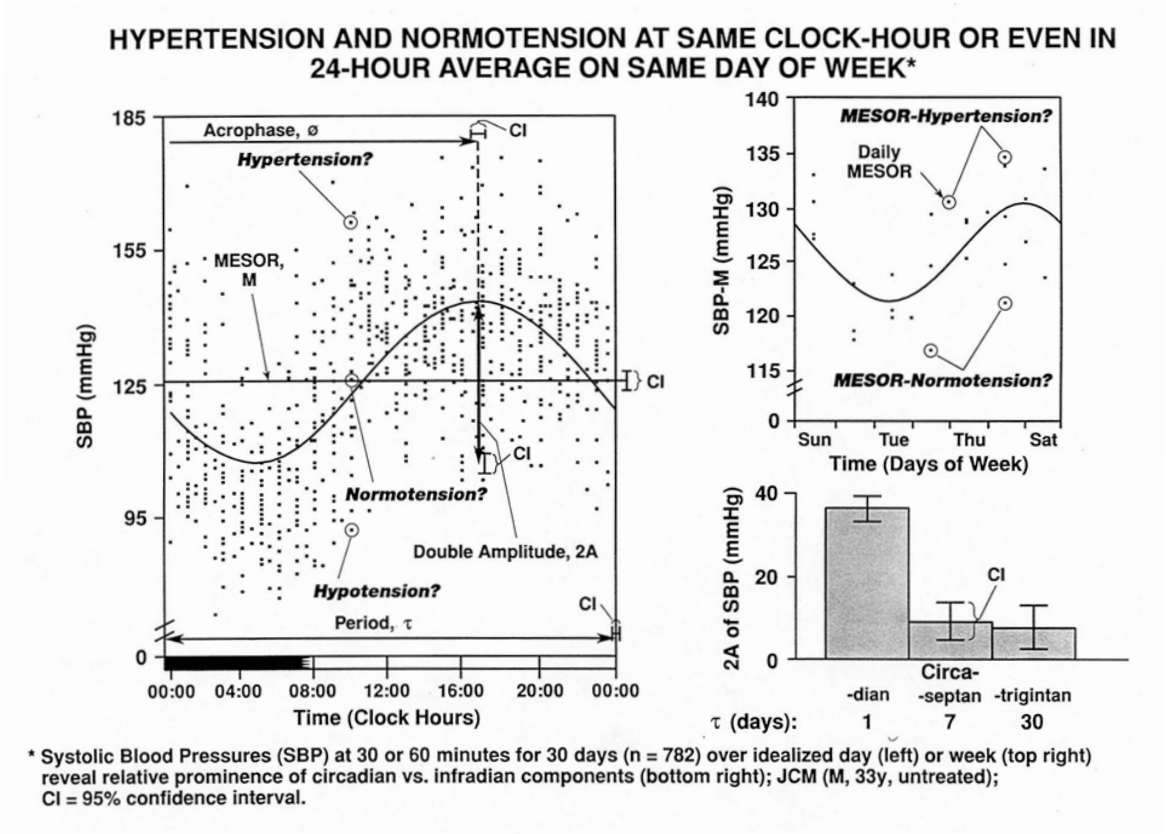


Figure 6A. Need for systematic long-term surveillance by C-ABPM for subject JCM, a clinically healthy neurosurgery resident who had two systolic values of 160 mmHg while giving blood. © Halberg.

A single 24-hour blood pressure (BP) profile: fool's gold, not gold standard*

AUGUST 16, 1994 (N = 13)

CLASSIFICATION FOR BP

SBP DBP mmHg	< 120	120-129	130-139	≥ 140
< 80	15% O	15% N	47% HN	H
80-84	N	N	HN	8% H
85-89	HN	HN	HN	15% H
≥ 90	H	H	H	H

Totals: N = 77% H = 23%

Normotension?

SEPTEMBER 28, 1994 (N = 12)

SBP DBP mmHg	< 120	120-129	130-139	≥ 140
< 80	O	N	HN	H
80-84	N	N	HN	H
85-89	HN	HN	HN	63% H
≥ 90	H	H	H	37% H

N = 0% H = 100%

Hypertension?

STAGES OF HIGH BP

SBP DBP mmHg	< 140	140-159	160-169	180-...
< 90	77% n	23% h1	h2	h3-4
90-99	h1	h1	h2	h3-4
100-109	h2	h2	h2	h3-4
110-...	h3-4	h3-4	h3-4	h3-4

SBP DBP mmHg	< 140	140-159	160-179	180-...
< 90	n	63% h1	h2	h3-4
90-99	h1	25% h1	12% h2	h3-4
100-109	h2	h2	h2	h3-4
110-...	h3-4	h3-4	h3-4	h3-4

* Measurements during simulated office hours (09:00-17:00) with ambulatory monitor by 33-year-old man (JCM) on two different days. O = optimal; N = normal; HN = high normal; H = high in classification of BP for adults age 18 years and older; n = no high BP; h1-h4 = hypertension stage 1-4 in classification of stages of high BP for adults age 18 years and older according to NIH-NHLBI, 5th report of the Joint National Committee on detection, evaluation, and treatment of high BP (NIH Publication No 93-1088). Measurements by ABPM-630 Colin Medical Instruments (Komaki, Japan).

Figure 6B. Sometimes, as in JCM, 23 days of monitoring are not enough for a diagnosis. © Halberg.

Flipping a Coin

Of 230 ambulatory blood pressures (BP) measured automatically during 23 days, about half are acceptable (56%) and half unacceptable (44%)*

CLASSIFICATION FOR BP IN POPULATION

SBP / DBP mmHg	< 120	120-129	130-139	≥ 140
< 80	Optimal	Normal	High Normal	High
80-84	Normal	Normal	High Normal	High
85-89	High Normal	High Normal	High Normal	High
≥ 90	High	High	High	High

(JCM, %/class)

SBP / DBP mmHg	< 120	120-129	130-139	≥ 140
< 80	11	16	14	6
80-84		1	10	10
85-89		1	3	14
≥ 90				14

Total High: **44%**

STAGES OF HIGH BP

SBP / DBP mmHg	< 140	140-159	160-179	180-. . .
< 90	No HBP	1	2	3-4
90-99	1	1	2	3-4
100-109	2	2	2	3-4
110-. . .	3-4	3-4	3-4	3-4

SBP / DBP mmHg	< 140	140-159	160-179	180-. . .
< 90	**56%**	29	1	
90-99		11	3	
100-109				
110-. . .				

* Subject is a 33-year-old neurosurgeon (JCM), right. Interpretation by prevailing criteria (left) of NIH-NHLBI (No HBP = no high BP; 1-4 = hypertension stage 1-4), 5th report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (NIH Publication No 93-1088).
Measurements by ABPM-630 Colin Medical Instruments (Komaki, Japan) from 09:00 to 17:00 during week-days, to simulate office hours.

Figure 6C. Dilemma of JCM persists. © Halberg.

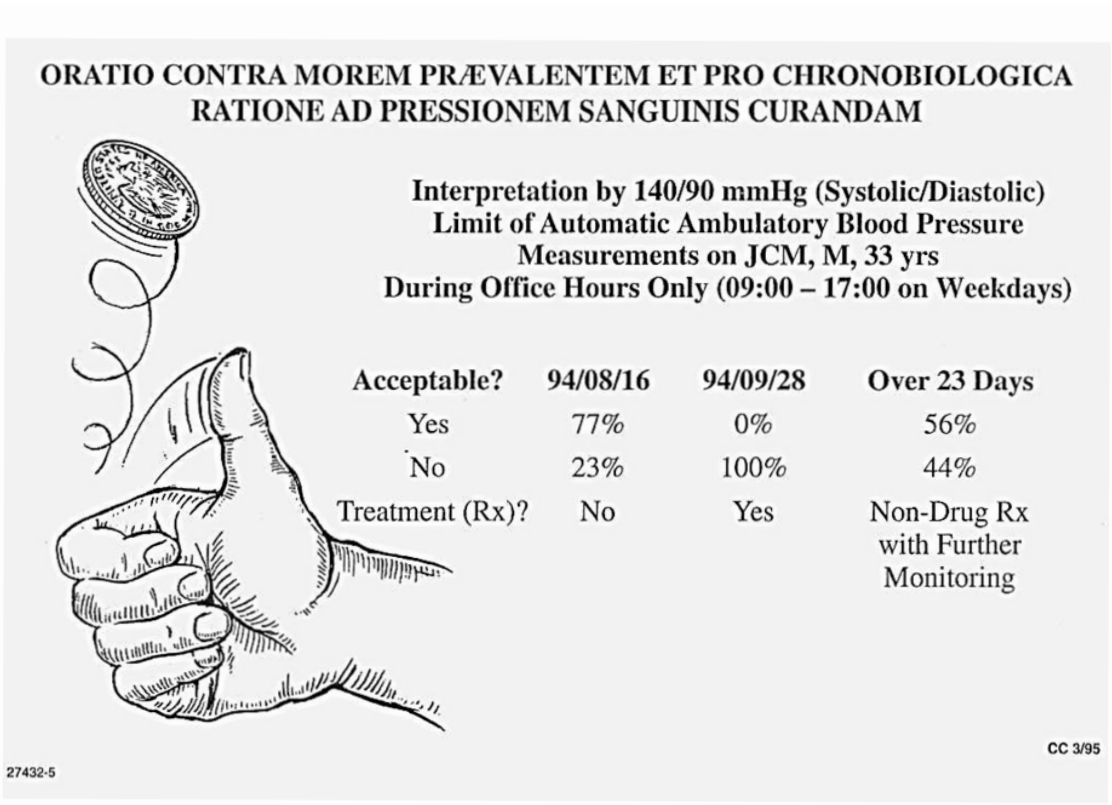


Figure 7. The current gold standard must go, just like THE blood pressure at the provider's office. © Halberg.

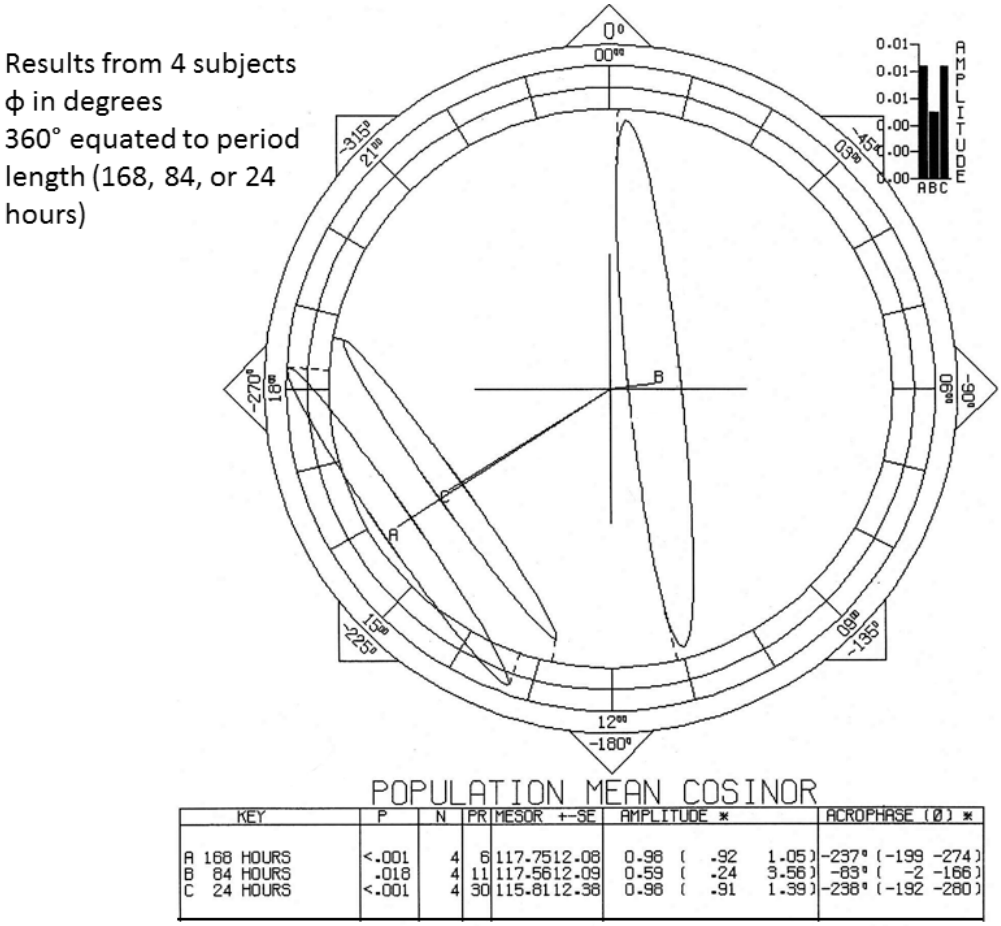


Figure 8. By 1880–1881 Ignaz Zadek had enough data on 4 patients to allow the demonstration by cosinor of daily, half-weekly and weekly rhythms, seen with cosinor diagrams by error ellipses around the tip of vectors that do not overlap the center of the graph (pole) with the length of the directed line indicating the amplitude and its direction the acrophase (24). © Halberg.

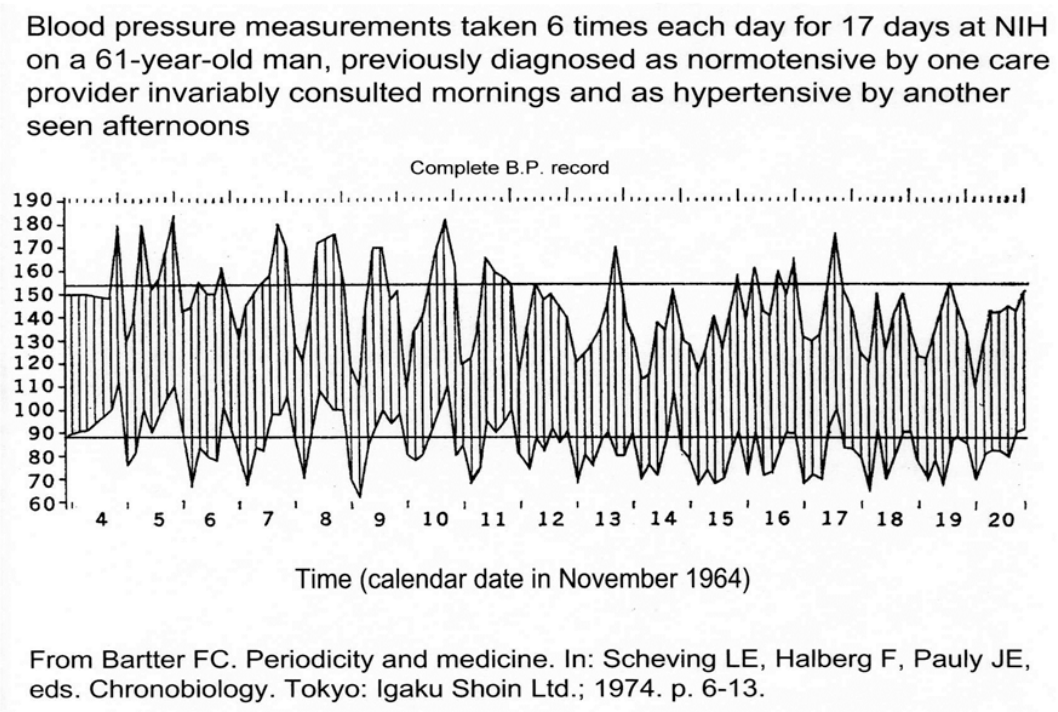


Figure 9A. Blood pressures of Frederic C. Bartter's patient who had been diagnosed as normotensive by one physician seen in the morning and as hypertensive by another provider seen in the afternoon. © Halberg.

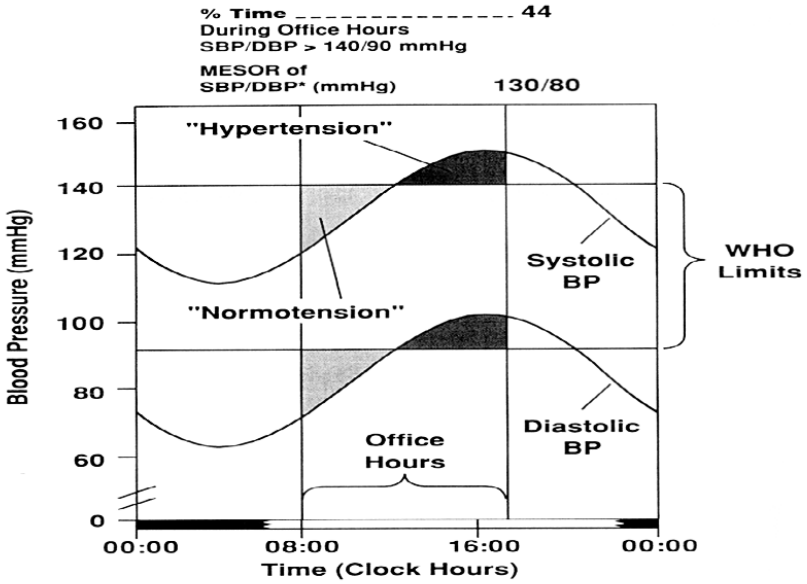


Figure 9B. Limitation of fixed limits for a circadian rhythmic function: fixed (horizontal) limits must go. We are reminded of outmoded laws and guidelines, still on the books in many states, intended to protect horses and mules at a time when automobiles (read chronobiologic monitors) were regarded as noisy toys, imposing obligations on motorists such as "In the event that a horse refuses to pass a car on the road, the owner must take his car apart and conceal the parts in the bushes". © Halberg.

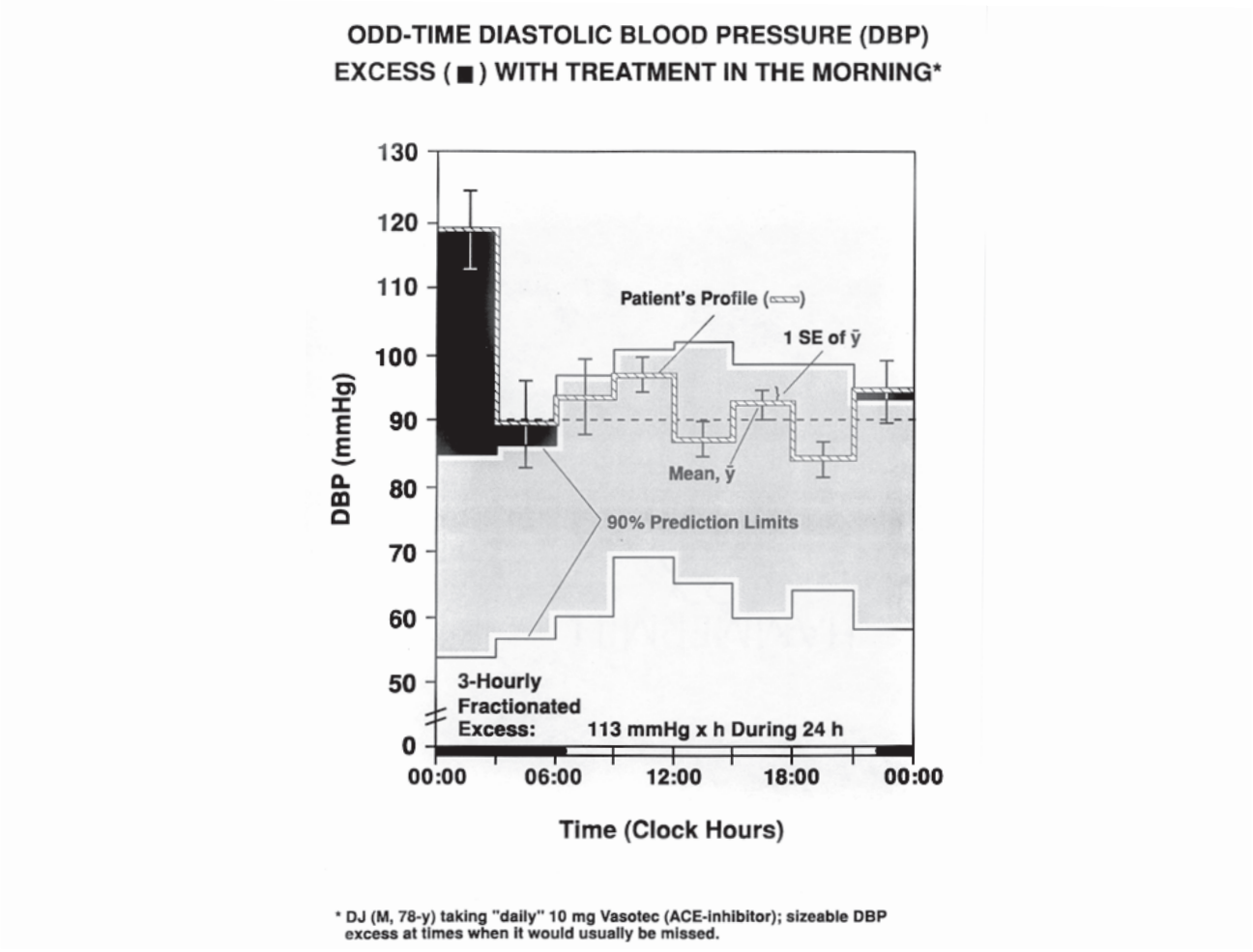


Figure 9C. Daytime office or dense waking self-measurements would have missed very high blood pressures by night. Reliance on office or self-measurements only during waking must go. © Halberg.

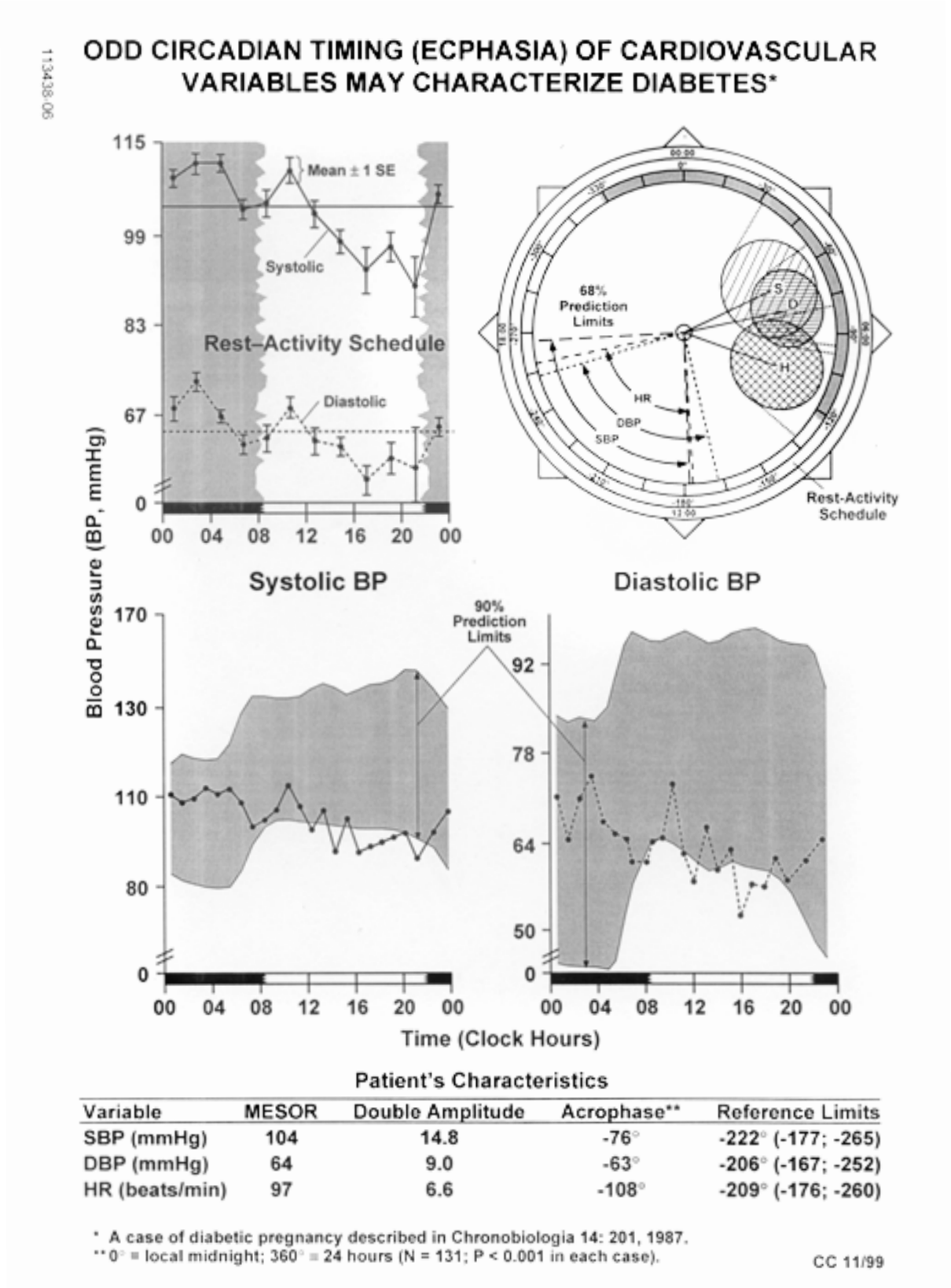


Figure 10A. Circadian ecphasia of cardiovascular variables in diabetic pregnancy. Blood pressure (BP) and heart rate (HR) monitoring of an 18-year-old, gravida 1, para 0, with Type I brittle diabetes treated by an insulin pump during the 23rd week of pregnancy reveals not only a low BP and a high HR MESOR, but also ecphasia (actually a delayed acrophase, i.e., epiphasia) by reference to peer group limits (68% prediction intervals). Results from Maggioni C, Halberg F, Cornélissen G, Work BA. Nocturnal heart rate and blood pressure peaking quantified as circadian ecphasia in a diabetic pregnancy. Chronobiologia 1987; 14: 201. © Halberg.

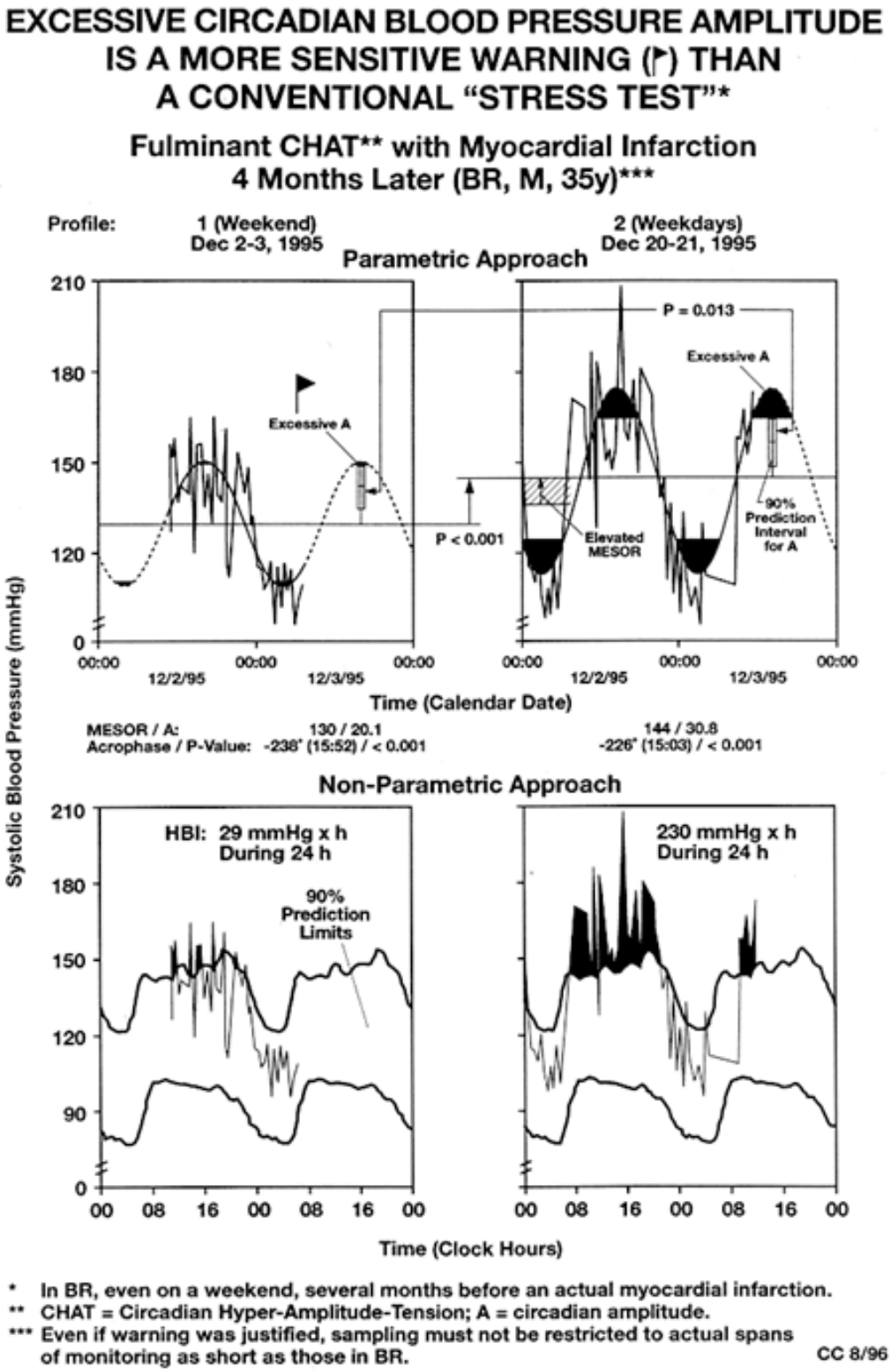
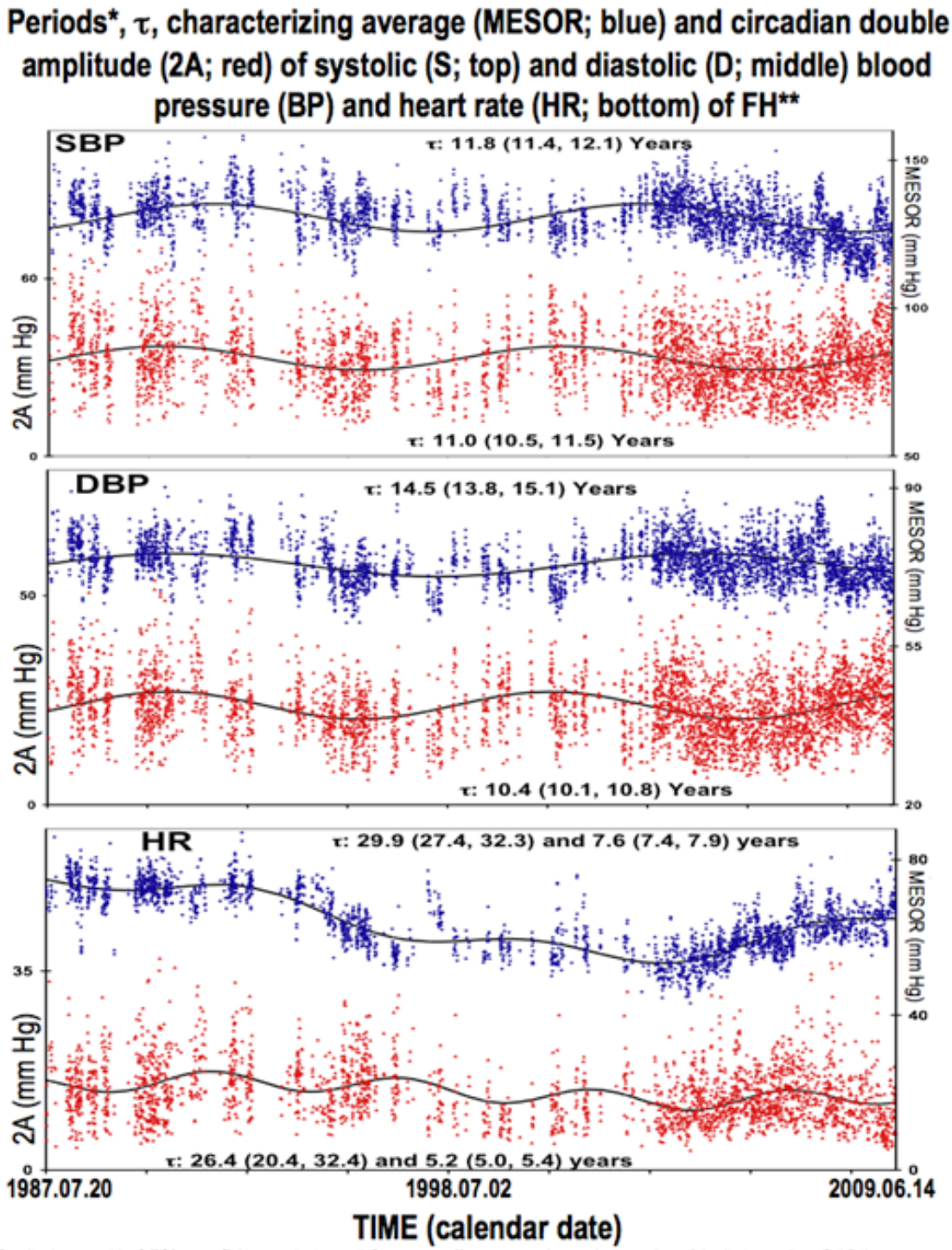


Figure 10B. Presence of CHAT found in two consecutive short records from a 35-year-old man preceded by a few months the occurrence of a heart attack while a stress test, carried out following the abnormal alarming BP monitoring results, found no abnormality. © Halberg.



*Period, τ, with 95% confidence interval from nonlinear cosinor determined in intervals of 48 hours displaced in increments of 24 hours.

**FH, man 68 years of age at start of ~half-hourly automatic measurements with gaps.

Figure 11A. Different decadal and/or multidecadal periods in different variables of the same elderly man (FH) treated with hypotensive drugs. © Halberg.

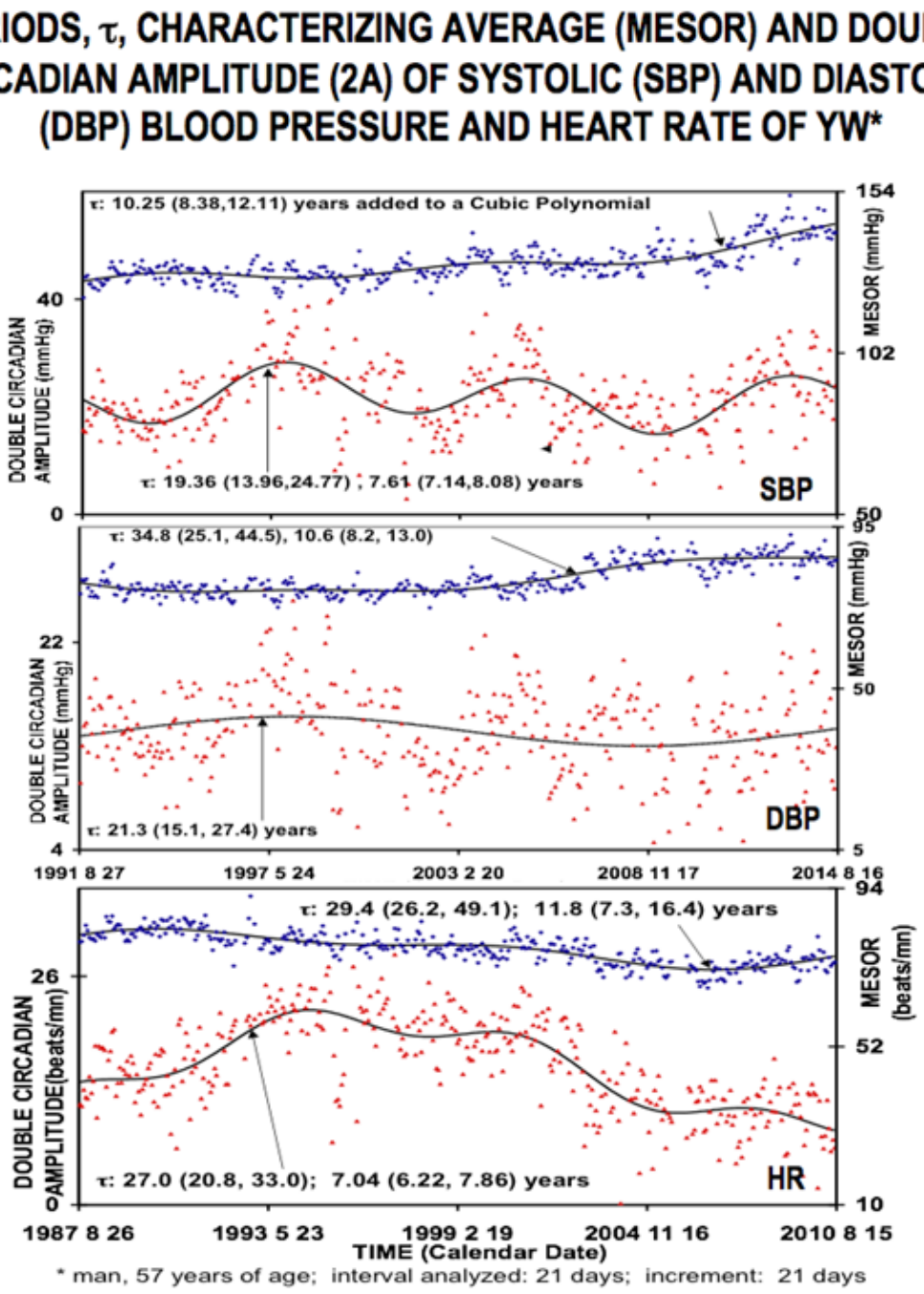


Figure 11B. Different decadal and/or multidecadal periods in different variables of YW, a man untreated for his developing MESOR-hypertension. © Halberg.

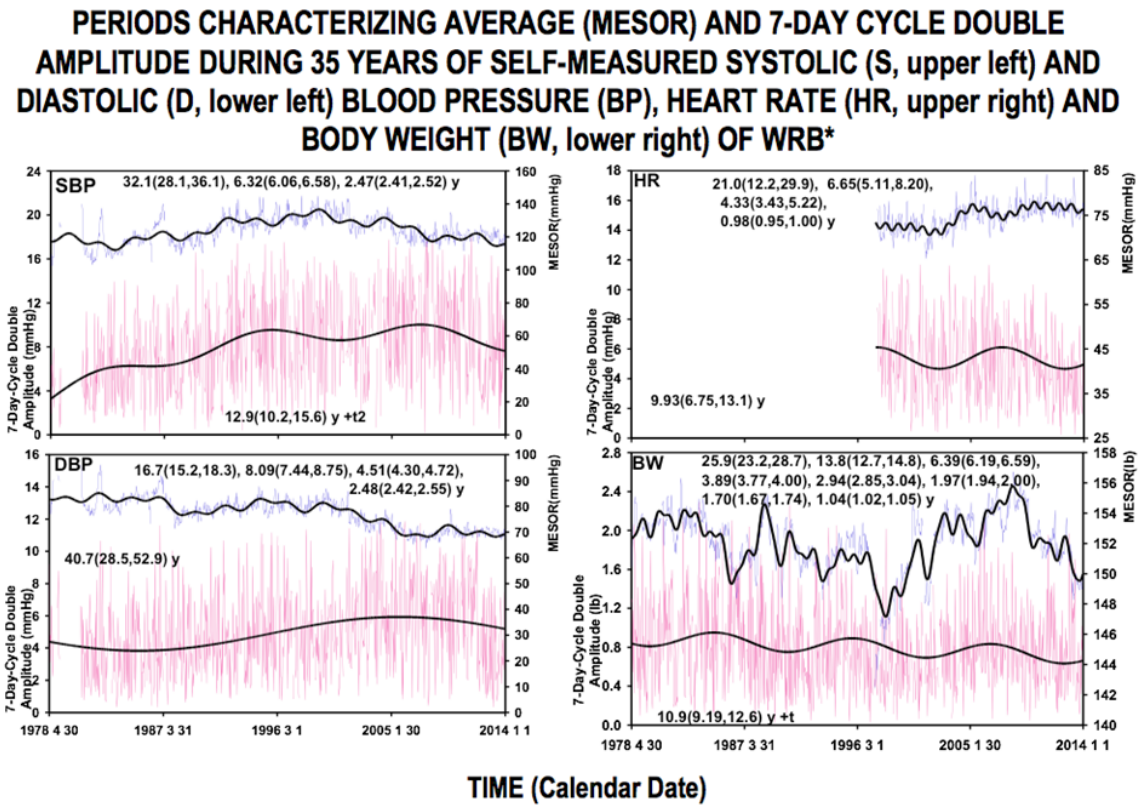


Figure 11C. Different decadal and/or multidecadal periods in different variables of WRB, a man treated for high blood pressure. © Halberg.

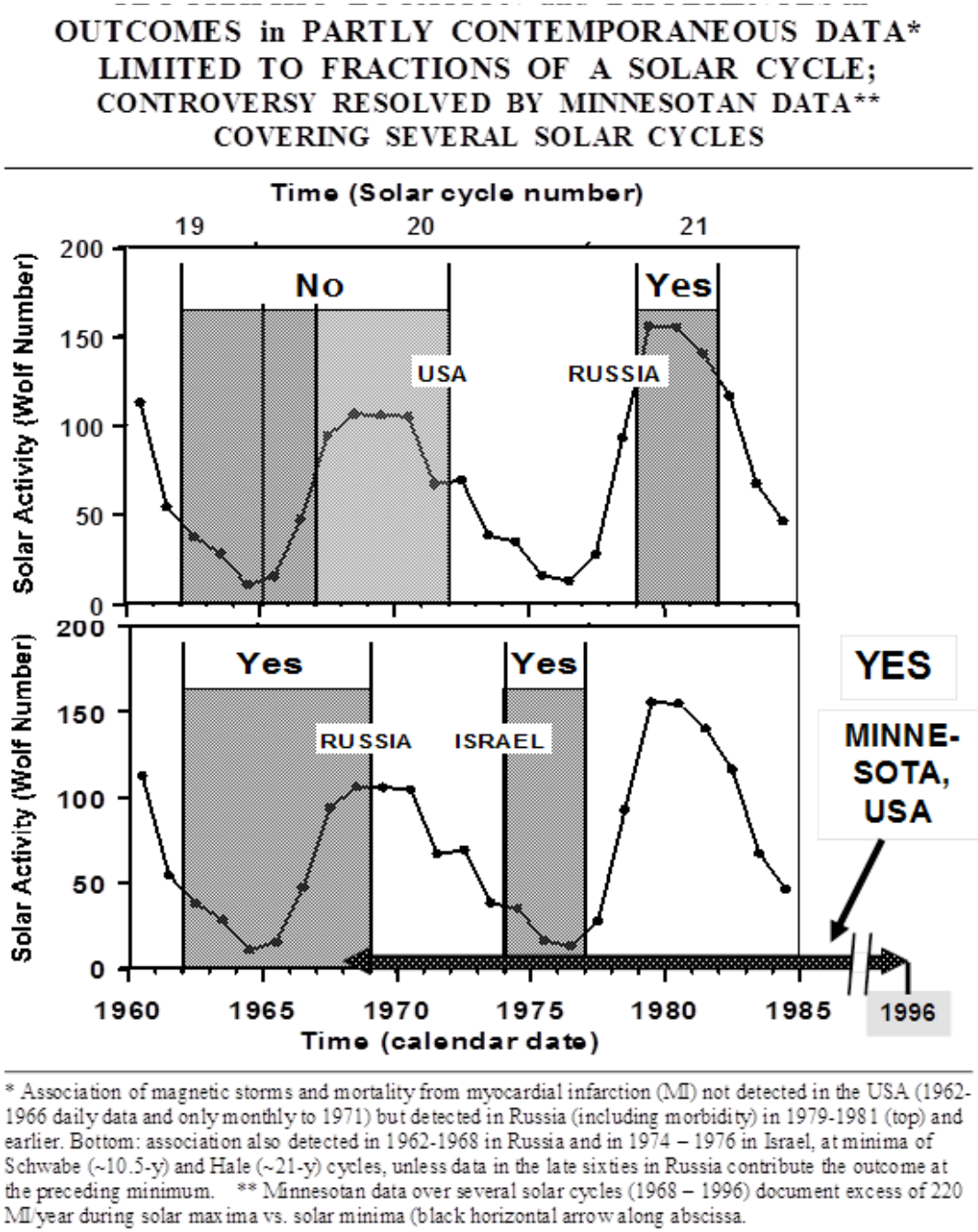


Figure 12A. Geographic as well as temporal differences in the association of the incidence pattern of myocardial infarction and magnetism in the USA, Israel and Russia (where the original studies were done). An excess of death at peak solar activity can be demonstrated in sufficiently (29-year) long series. Time-varying associations revealed by also changing phase synchronizations and coherences readily account for site- and time-specific results. Controversy can be avoided when aeolian time- and site-specific changes are anticipated and documented.

The analogy of a blood pressure measurement over a single circadian cycle comes to mind: such a spotcheck may lead to a lifetime of unneeded treatment (when, in several repeated sessions, the patient was excited and the spotchecks showed a "hypertension", not the "white-coat effect" which in a group examined was hypertension in the morning and hypotension in the evening. A hypertensive patient may be caught on several measurements with occasional normotensive values and hence will not be treated until a stroke or other severe event occurs. Furthermore, an individual with blood pressure overswinging limited to the normal range may not be recognized as being at a very high risk of stroke by limitation of a record to a single cycle. Likewise, studies that cover a single solar cycle may not be conclusive and may miss a relation that can be documented in the same solar cycle elsewhere or over 3 solar cycles (in Minnesota, USA). Taking evidence over a single solar cycle, just like relying on a single circadian cycle, is equivalent to taking the pulse for one second. © Halberg.

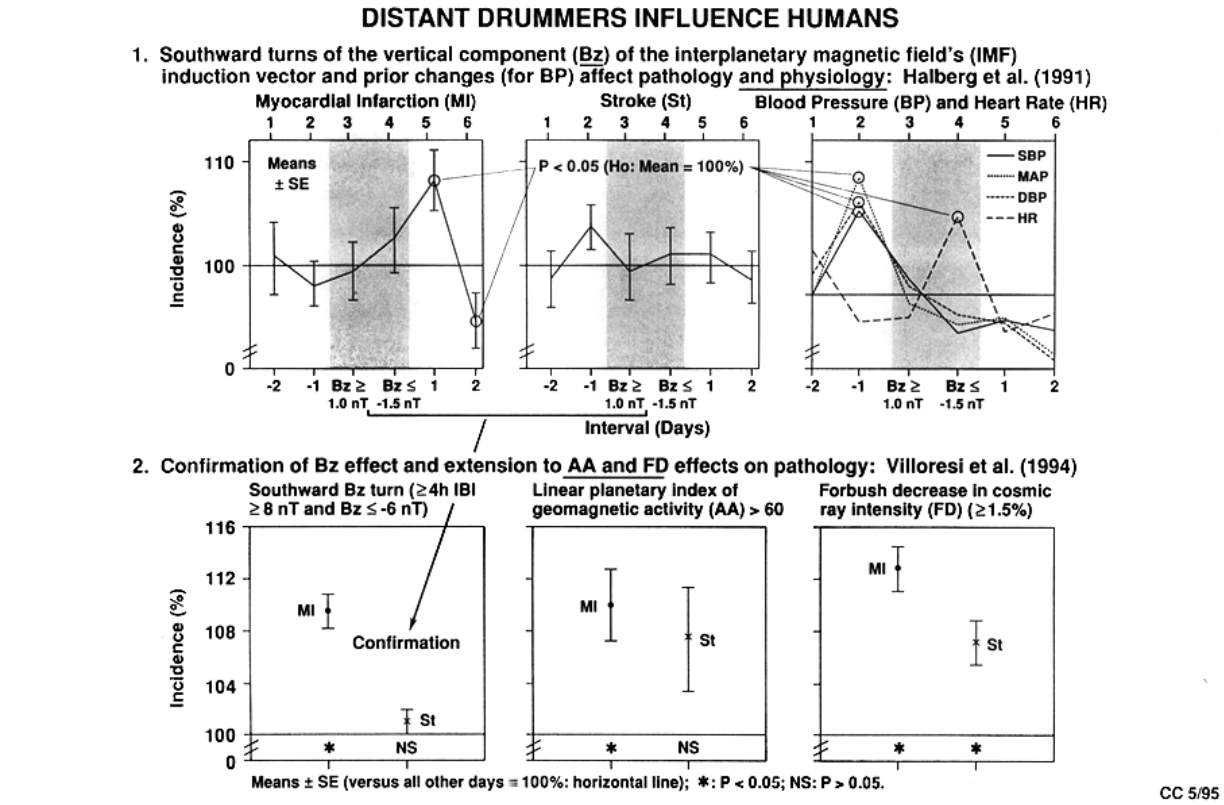


Figure 12B. Meta-analyses in Minnesota on diagnoses made in response to a set of ambulance calls in Moscow (54) are confirmed and extended by Villoresi G, Breus TK, Iucci N, Dorman LI, Rapoport SI. The influence of geophysical and social effects on the incidences of clinically important pathologies (Moscow 1979-1981). Physica Medica 1994; 10: 79-91. © Halberg.

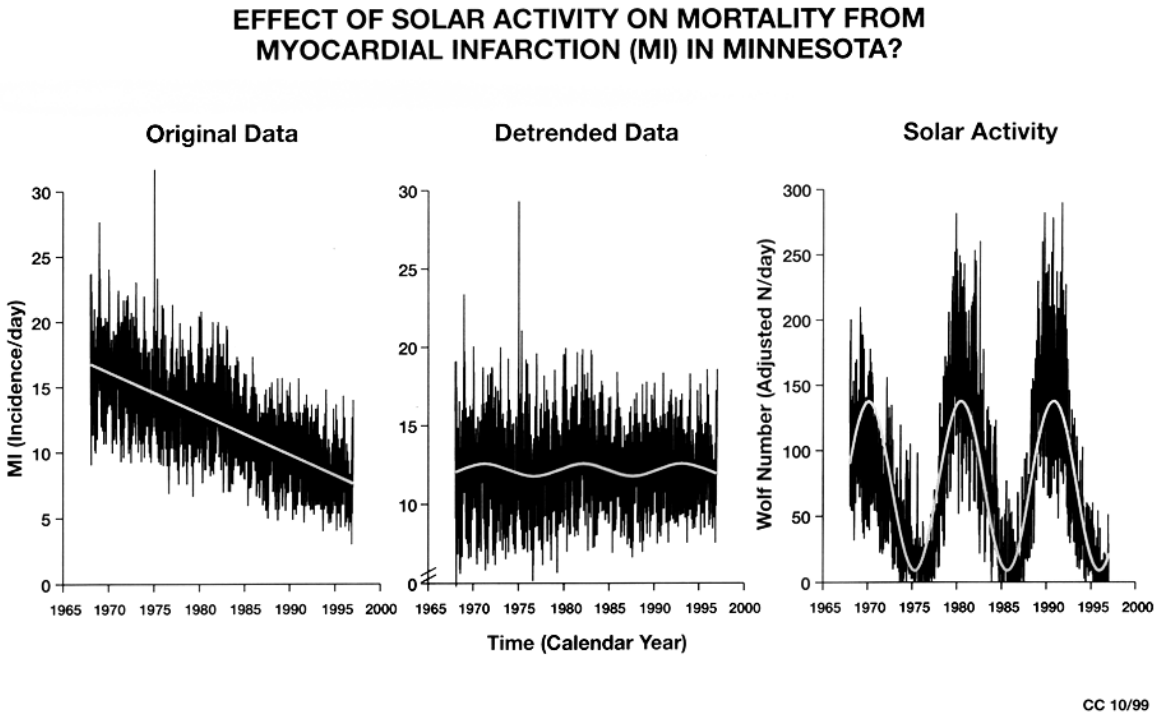


Figure 12C. Demonstration of about 10.5-year cycle in mortality from myocardial infarction in Minnesota (1968–1996) after removal of decreasing linear trend, aligned with about 10.5-year solar activity cycle. Fitted curves represent fundamental component as a first approximation that does not account for the asymmetry of the solar activity cycle considered in Figure 12D. Minnesota data on myocardial infarction and solar activity (see Figure 12A) reveal association of the latter with the former (see Figure 12D). © Halberg.

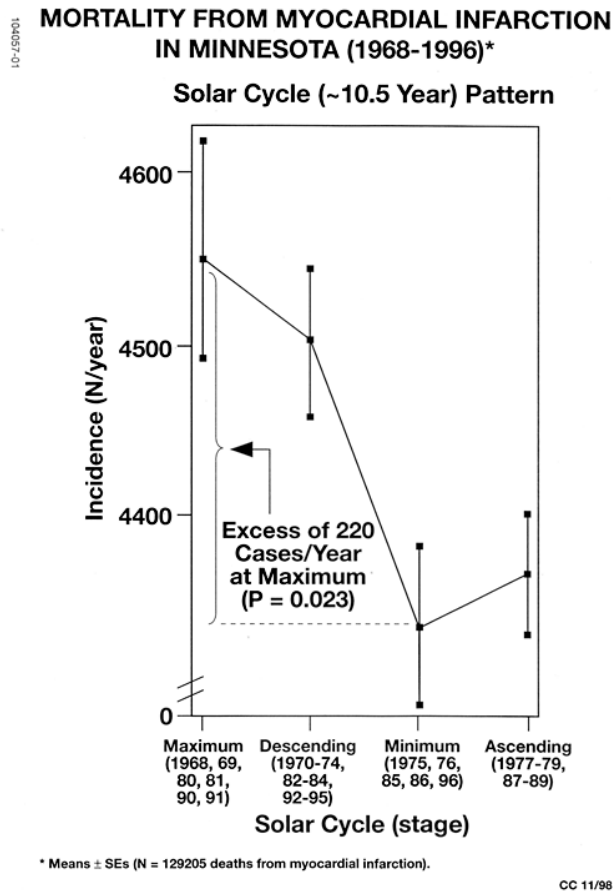


Figure 12D. During years of maximal solar activity, there is an about 5% excess mortality (220 cases per year) from myocardial infarction in Minnesota (1968–1996) as compared to years of minimal solar activity. 29 years of data allow detection of overall mortality from myocardial infarction associated with solar cycle stages. Further analyses in Figures 32B–D. © Halberg.

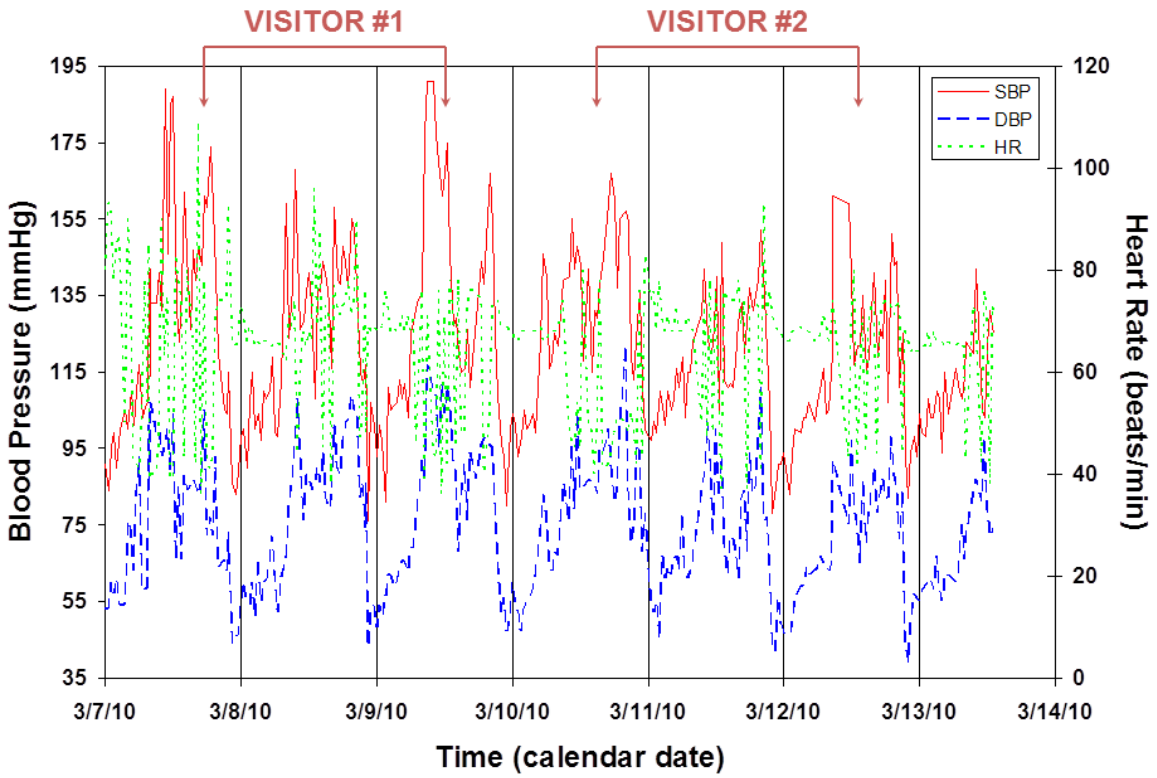
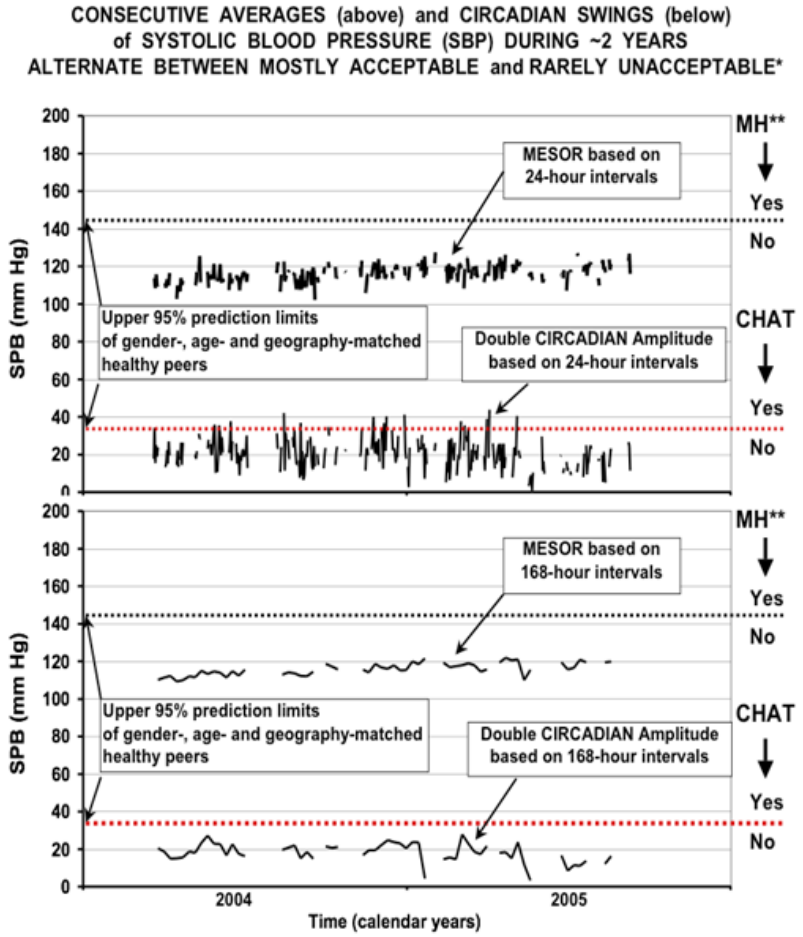


Figure 13. Original data underlie an association of CHAT (fit not shown) with visitors who were friendly, one a prospective collaborator, the other an earlier provider of important data for analysis. FH, an elderly man, was unaware of the fact that the arrival on March 7 of one and on March 10 of the other was preceded by spikes in BP by hours or a day, respectively. All results were within the acceptable range, yet the swing within that range was excessive. CHAT was present while the visitors were around. © Halberg.



*Results from non-overlapping 1-day (top) and 7-day (bottom) intervals in serial sections on half-hourly around-the-clock data; OS (F, 81-82 y) on atenolol treatment. **MH: MESOR-hypertension; CHAT: Circadian Hyper-Amplitude-Tension. When 1-day intervals are used, occasional unacceptable results occur.

Figure 14A. A 24-h cosine fit to 7-day data sections removes the occasional abnormality (bottom) found in analyses of 24-h data sections (top) in an elderly woman. © Halberg.

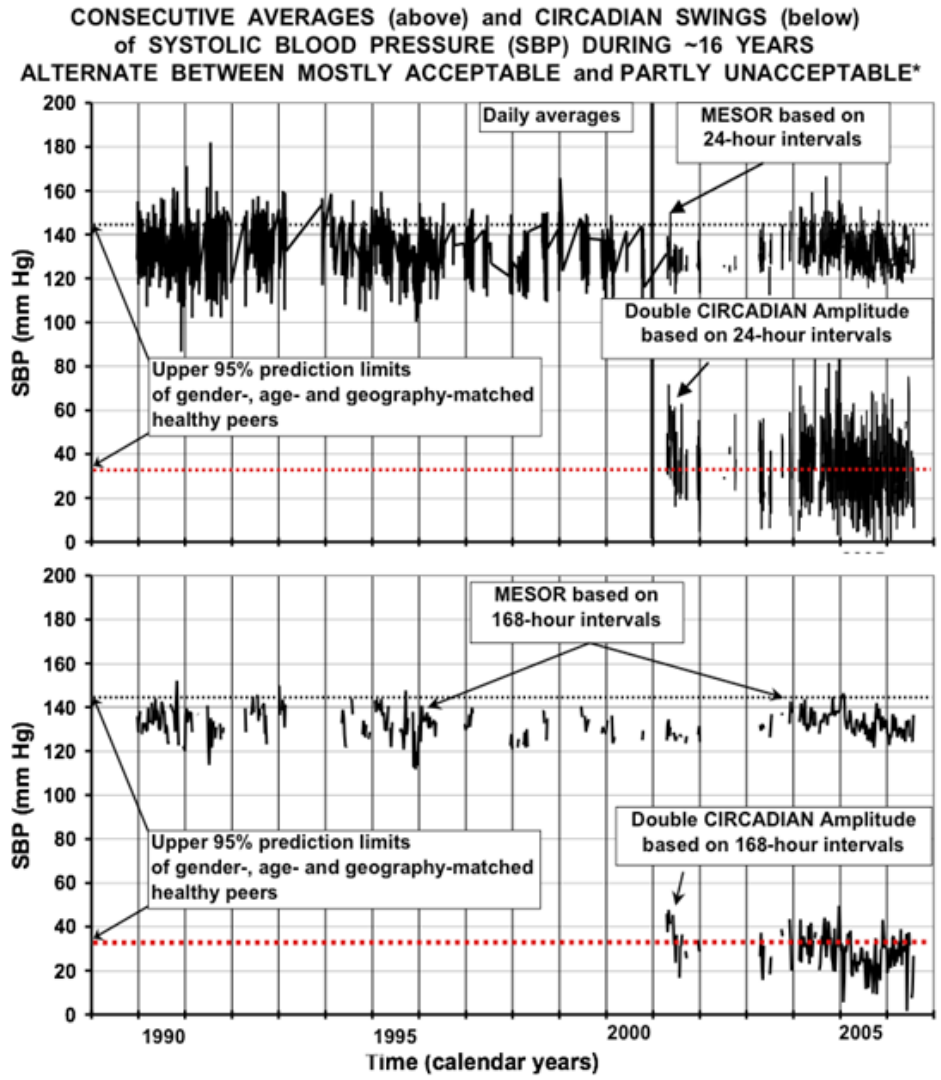


Figure 14B. A 24-h cosine fit to 7-day data sections reduces the extent of abnormality (bottom) found in analyses of 24-h data section (top) in an elderly man. © Halberg.

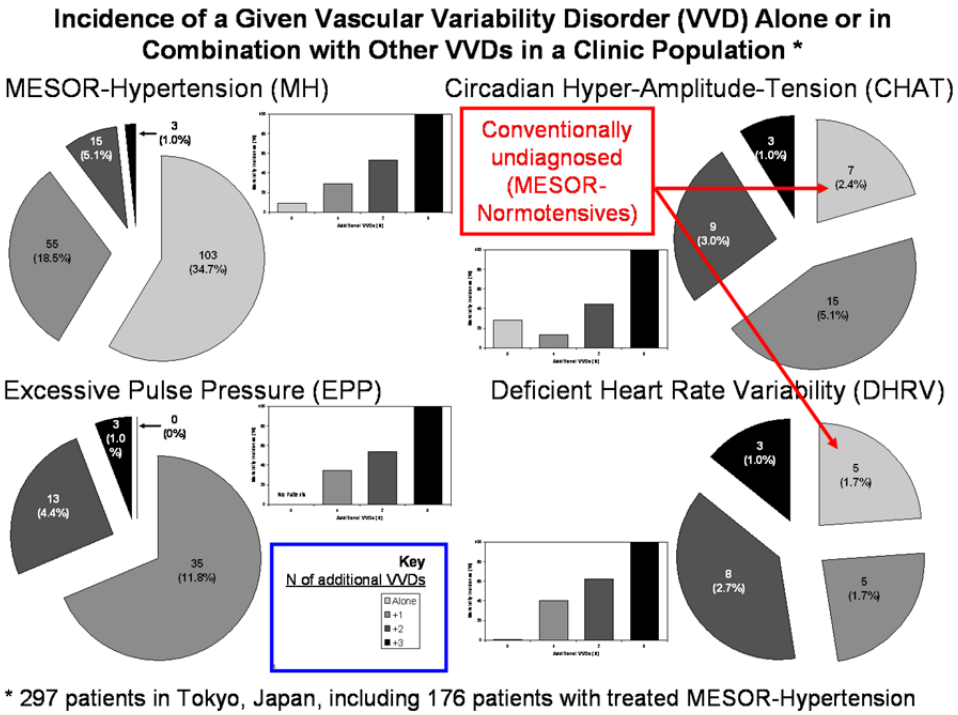


Figure 15A. Percentages of Vascular Variability Disorders (VVDs) or rather Vascular Variability Anomalies (VVAs) and Vascular Variability Syndromes (VVSs) missed in current practice. The incidence of VVDs in this graph is assessed in a clinic population of 297 patients. BP and HR of each subject were monitored around the clock for 2 days at 15-minute intervals at the start of study. Each record was analyzed chronobiologically and results interpreted in the light of time-specified reference limits qualified by gender and age. On this basis, MESOR-Hypertension (MH, diagnosed in 176 patients), Excessive Pulse Pressure (EPP), Circadian Hyper-Amplitude-Tension (CHAT), and Deficient Heart Rate Variability (DHRV) were identified and their incidence related to outcomes (cerebral ischemic attack, coronary artery disease, nephropathy, and/or retinopathy). Outcomes, absent at the start of study in these non-diabetic patients, were checked every 6 months for 6 years, to estimate the relative risk associated with each VVD alone or in combination with 1, 2, or 3 additional VVDs, shown in columns complementing each circular display of incidences of variability disorders.

Earlier work showed that CHAT was associated with a risk of cerebral ischemic event and of nephropathy higher than MH, and that the risks of CHAT, EPP, and DHRV were mostly independent and additive. It thus seemed important to determine the incidence of each VVD, present alone or in combination with one or more additional VVDs. Results from this investigation are summarized in this graph.

Results related to MH are shown in the upper left section of the graph. The 176 patients with MH are broken down into 103 (34.7% of the whole study population of 297 patients) with uncomplicated MH, 55 (18.5%) with MH complicated by one additional VVD (EPP, CHAT, or DHRV), 15 (5.1%) and 3 (1.0%) with MH complicated by two or three additional VVDs. In the latter group, all 3 patients had a morbid outcome within 6 years of the BP monitoring. Ambulatory BP monitoring over only 48 h, used for diagnosis, is much better than a diagnosis based on casual clinic measurements, yet its results apply only to groups. With this qualification, of the 176 patients with MH, 73 (42.2%) have additional VVDs that further increase their vascular disease risk, and that are not considered in the treatment plan of these patients since current practice does not assess these VVDs. This proportion may be smaller in a 7-day record (available for CHAT).

Results related to EPP (bottom left), CHAT (upper right), and DHRV (bottom right) illustrate that these conditions can be present in the absence of MH in as many as 12 (4.0%) of the 297 subjects. Since they do not have MH, it is unlikely that these subjects would be treated from a conventional viewpoint, even though their vascular disease risk can be as high as or even higher than MH. Evidence exists to suggest that treatment of these conditions may translate into a reduction in morbidity and/or mortality from vascular disease. Another lesson from these results is that around-the-clock monitoring of BP and HR interpreted chronobiologically is needed, even in the absence of MH, to detect vascular disease risk associated with VVDs such as CHAT and DHRV, that cannot be assessed on the basis of casual clinic measurements, so that non-pharmacologic and/or pharmacologic intervention can be instituted in a timely fashion before the occurrence of adverse outcomes. Once implemented across the board rather than in selected patient populations, vascular disease could be curbed to a much larger extent at relatively low cost if the monitoring is offered directly to the public and care providers become involved only after detection of a VVD. A website has to be built to interest many people and to provide cost-free analyses in exchange for the data, as is now provided worldwide by the BIOCOS project on a small scale (corne001@umn.edu). © Halberg.

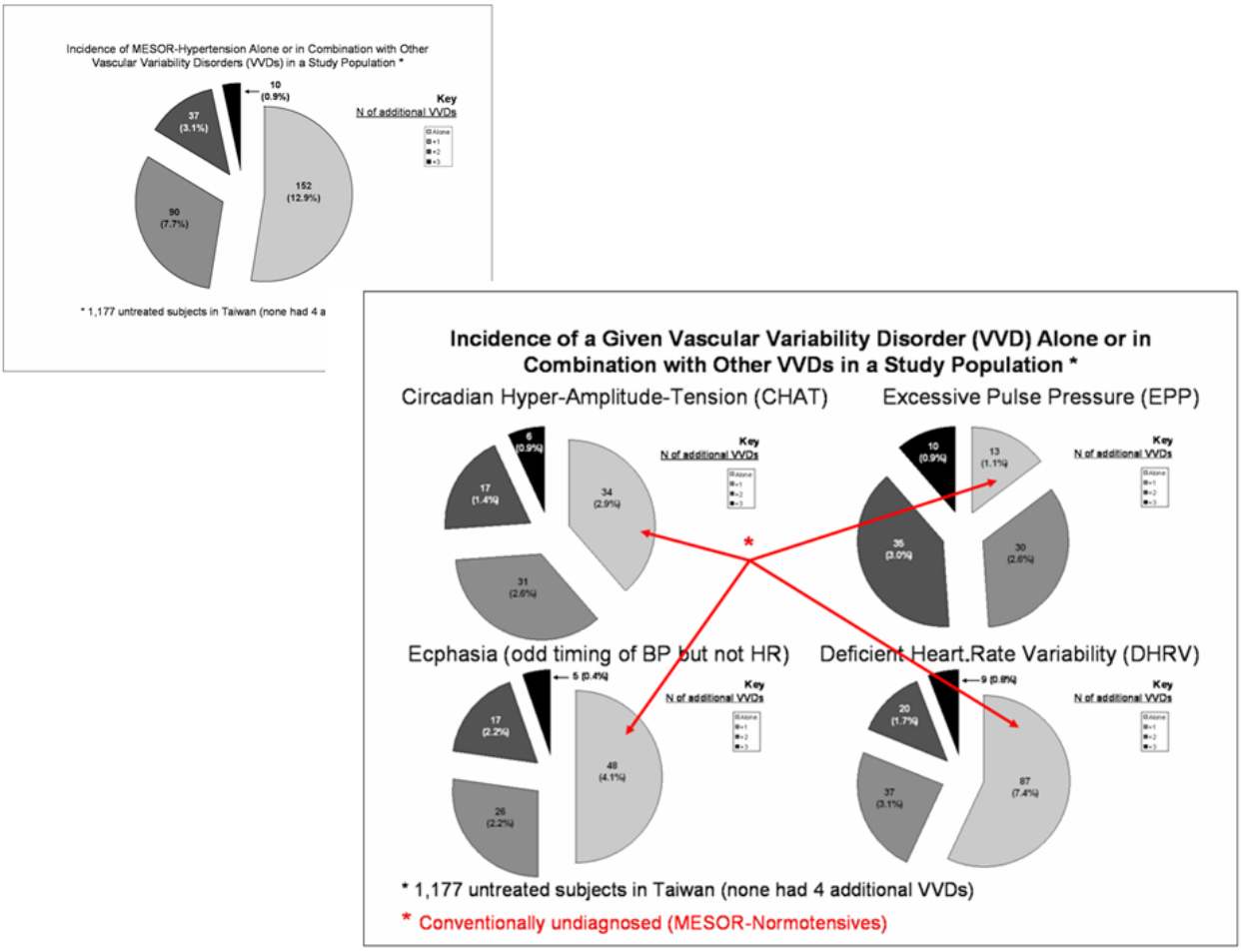


Figure 15B. Single Vascular Variability Disorders (VVDs) or rather Vascular Variability Anomalies (VVAs) (lightest shading) are complicated to a differing extent by one or more added VVDs (darker shading). In this graph, MESOR-Hypertension (MH) is diagnosed in a total of 289 subjects, representing 24.6% of the 1,177 untreated, presumably normotensive subjects included in the study. Among these 289 subjects, as many as 137 (47.4% of those diagnosed with MH) have at least one additional VVD that is not part of the current screening but increases the vascular disease risk beyond that associated with MH alone. The four graphs illustrate that VVDs other than MH occur in the absence of MH in very few patients with Excessive Pulse Pressure (EPP) and in more patients with Circadian Hyper-Amplitude-Tension (CHAT) and in yet more with ecphasia and in 87 patients with Deficient Heart Rate Variability (DHRV), that is for a total of 182 subjects, representing 15.5% of the study population. In this study, BP and HR data available hourly for only 24 h were complemented by an assessment of the left ventricular mass index as a surrogate outcome measure. In addition to MH, EPP, CHAT, and DHRV summarized from another earlier study, ecphasia was assessed. The great limitation of a record covering only 24 h is not overcome by the relatively large study population of 1,177 subjects not treated with antihypertensive agents, yet results in keeping with those obtained in a clinic population of 297 patients suggest that MH is to be recognized as a VVD and that its risk can be very greatly increased when other VVDs combine into Vascular Variability Syndromes (VVSs) that escape current diagnostics. © Halberg.

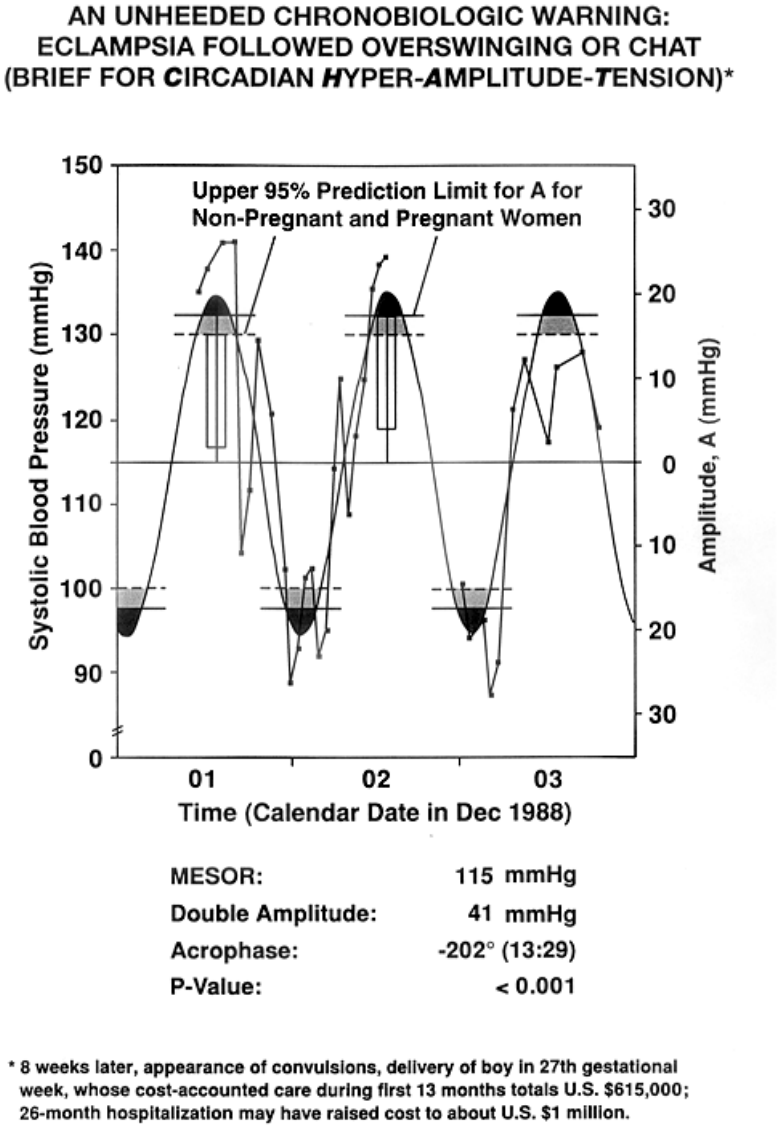


Figure 16. By sole reliance on the average blood pressure (of 115 mmHg systolic), disregarding our strong advice for bed rest and treatment in view of CHAT, a particular obstetrician did not prevent a very premature delivery -- with a partly cost-accounted expense of $1 million -- which happened to be avoided in all other deliveries in an NIH-sponsored study in which chronobiologic advice usually resulted in bed rest and/or drug treatment without incurring major cost. © Halberg.

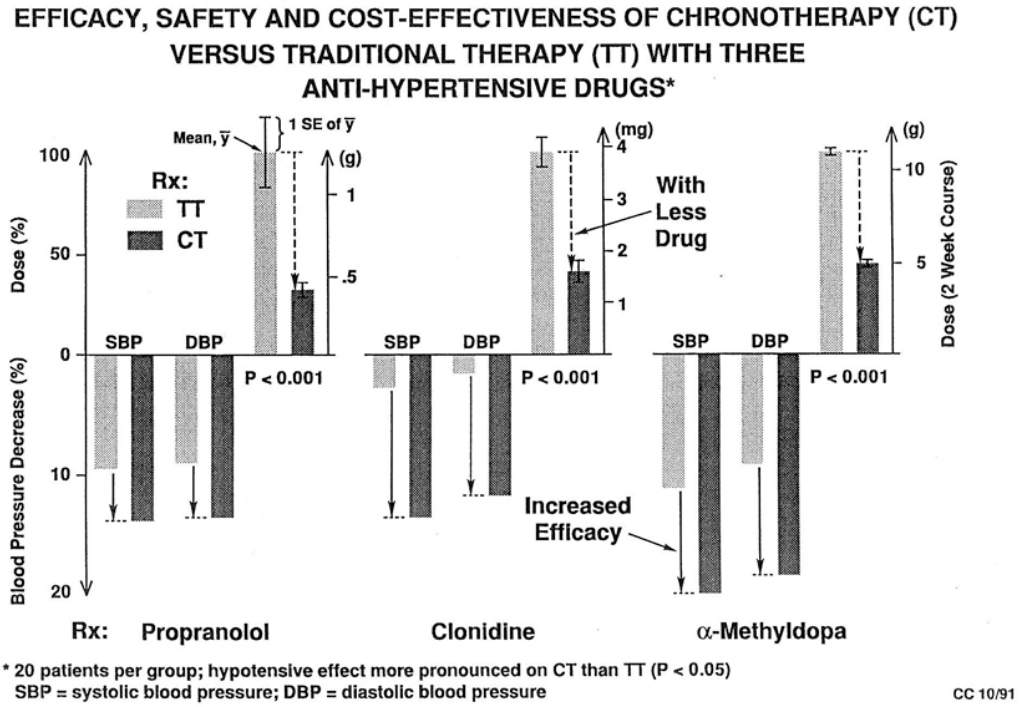
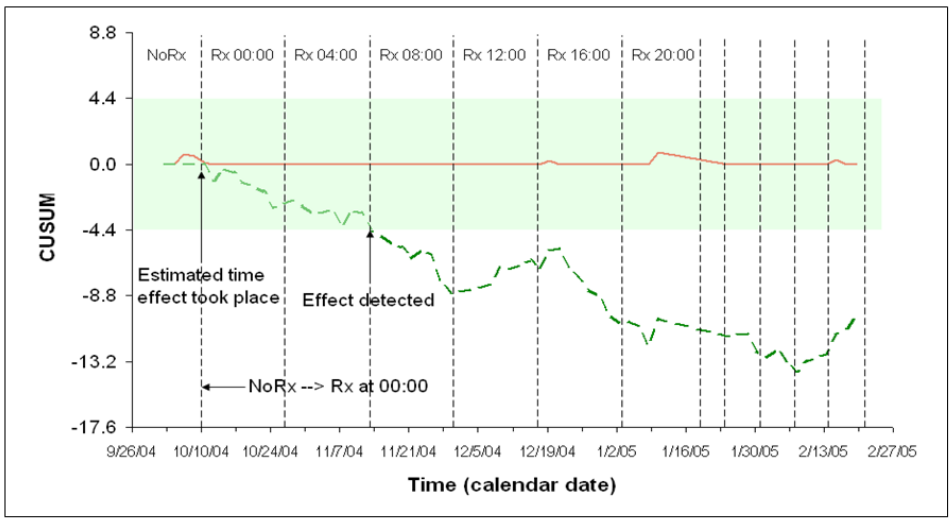


Figure 17. The chronocardiologist Rina Zaslavskaya was first to demonstrate a longer desired effect, by comparison to conventional therapy, by timing hypotensive treatment prior to the circadian peak in blood pressure, on a group basis, with less drug and fewer complications. Minnesotan meta-analysis. © Halberg.

MONITORING THE MEAN SEEMS SUCCESSFUL

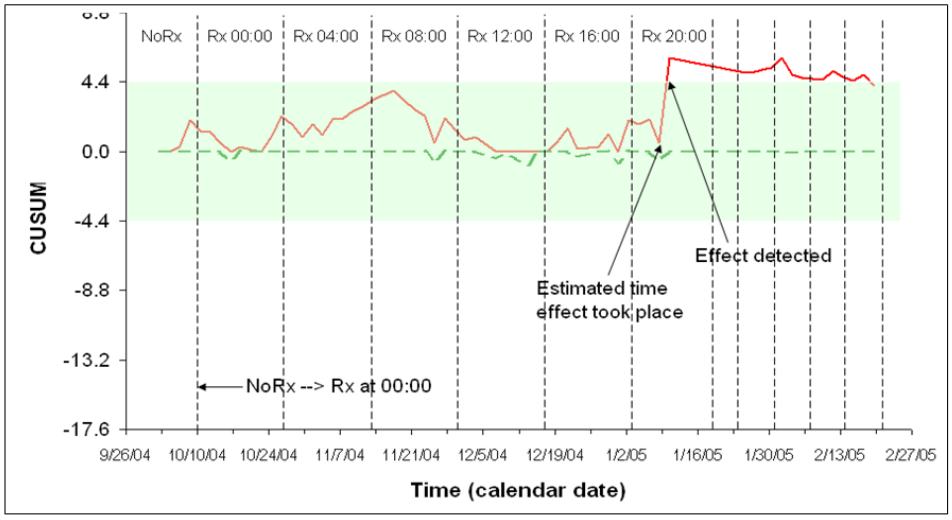


BUT WHAT HAPPENS TO THE AMPLITUDE?

(J Appl Biomed 2006; 4: 73-86)

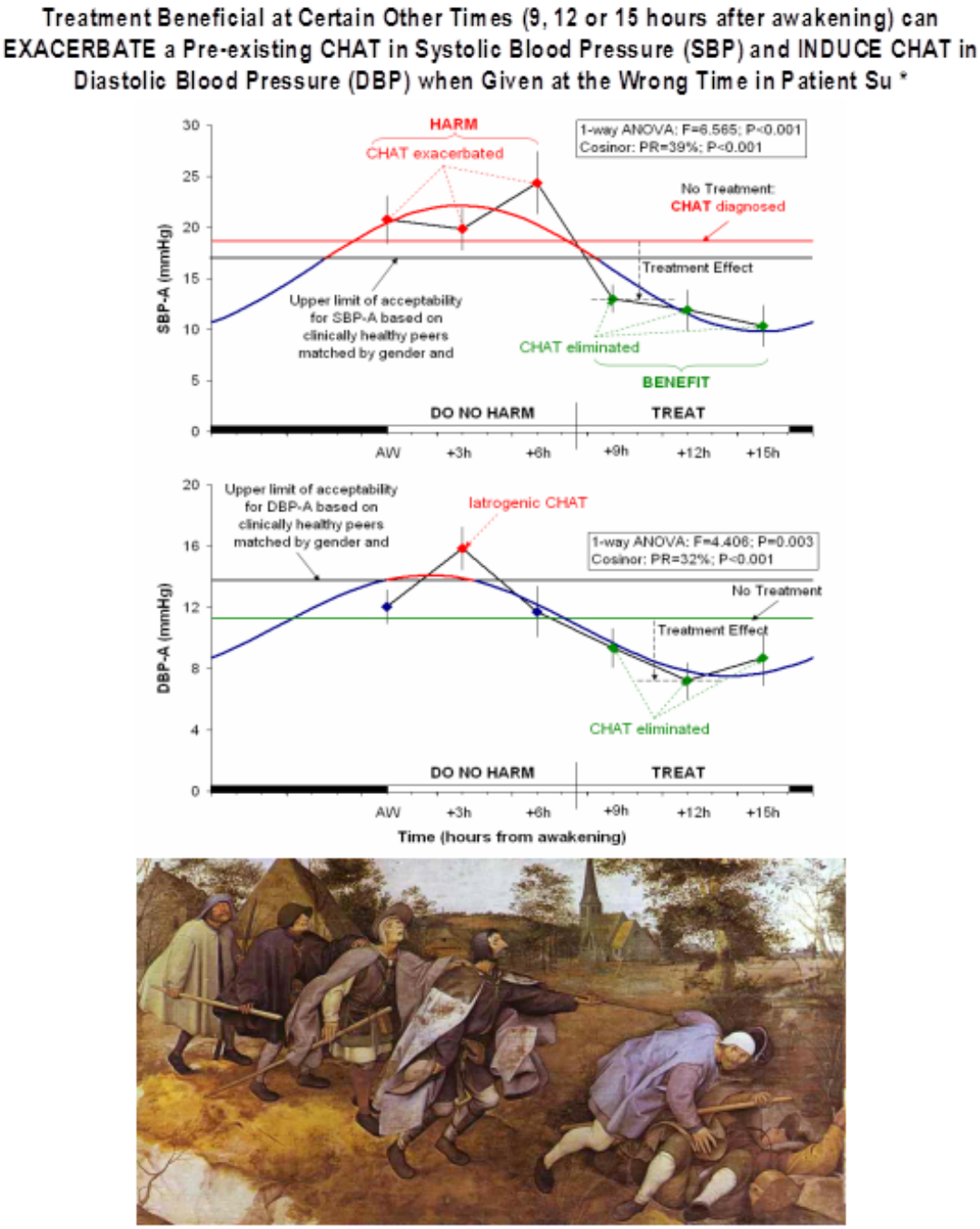
Figure 18A. Changing timing of medication (ΔRx) during consecutive spans shows efficacy of treatment. An empirical approach to chronotherapy: immediately after diagnosis, one should ascertain that the treatment is effective. Optimization of treatment effects by timing can be achieved for the individual patient by systematically changing, e.g., advancing the time of treatment. Successful treatment of MESOR-hypertension assessed by a self-starting cumulative sum control chart. To optimize his hypotensive treatment (Rx), a just-diagnosed 24-year-old individual (TT) switched his Rx first every 17 days by 4 h and then mostly at shorter intervals. Note statistically significant decrease in MESOR, evidenced by the breakout outside the decision interval of the negative CUSUM line. With continued Rx, the blood pressure MESOR leaves the decision interval, indicating a statistically significant decrease in overall blood pressure. © Halberg.

MONITORING THE CIRCADIAN AMPLITUDE



SHOWS AN OTHERWISE SILENT PUTATIVE LARGE RISK

Figure 18B. Changing timing of medication (ΔRx) during consecutive spans shows risk of iatrogenic CHAT (Circadian Hyper-Amplitude-Tension). An empirical approach to chronotherapy: immediately after diagnosis, one should ascertain that one does not induce CHAT by inappropriate timing of anti-hypertensive medication. In this 24-year old man (TT) who advanced the time of treatment by 4 h every 17 days initially and at shorter intervals thereafter, treatment in the evening was associated with iatrogenic CHAT, raising the question whether the risk of MESOR-hypertension may not have been traded for the even higher risk of stroke that CHAT represents. Iatrogenic CHAT, induced by treatment at 20:00 daily, was silent to office visits. TT may have traded benefit (lowering of the MESOR of blood pressure) for something worse (circadian overswinging of blood pressure). This danger applies to some hypertensives (who tend to have a large circadian amplitude of blood pressure) to whom treatment time is not specified by the care provider, as was the case for TT (or is specified for bedtime). A few others who took hypertensive medication at bedtime were also found to have CHAT. The figure also shows the assessability of otherwise undetected harm by as-one-goes sequential analysis. © Halberg.



* Su, M, 66y, treated with Losartan (50 mg) and hydrochlorothiazide (12.5 mg). Each point represents 1 week of half-hourly around-the-clock monitoring after ~1 month on a given treatment time. After this graph was completed, treatment at AW+15h yielded a SBP-A of 10.36 ± 2.09 mmHg and a DBP-A of 8.69 ± 1.85 mm Hg. By cosinor, a circadian stage-dependent response to treatment could be shown to account, with statistical significance for both endpoints, for 39% and 32% of the overall variance, respectively.

Figure 19. A popular drug, if prescribed without personalised surveillance, can induce a Vascular Variability Disorder (VVD) such as Circadian Hyper-Amplitude-Tension (CHAT). A change in the time when the drug is taken can make the same dose of the same drug in the same person beneficial or vice versa. At one administration time (before noon), Hyzaar induces CHAT in diastolic blood pressure and exacerbates a preexisting CHAT in systolic blood pressure (red). At another time of administration, Hyzaar eliminates a pre-existing VVD (green). These opposite effects were found in tests at six medication times, each administered for about a month, with half-hourly surveillance of BP during the last week of each span. These differences occur as a function of the timing of the drug's use along the scale of 24 h. Original study of Yoshihiko Watanabe. © Halberg.

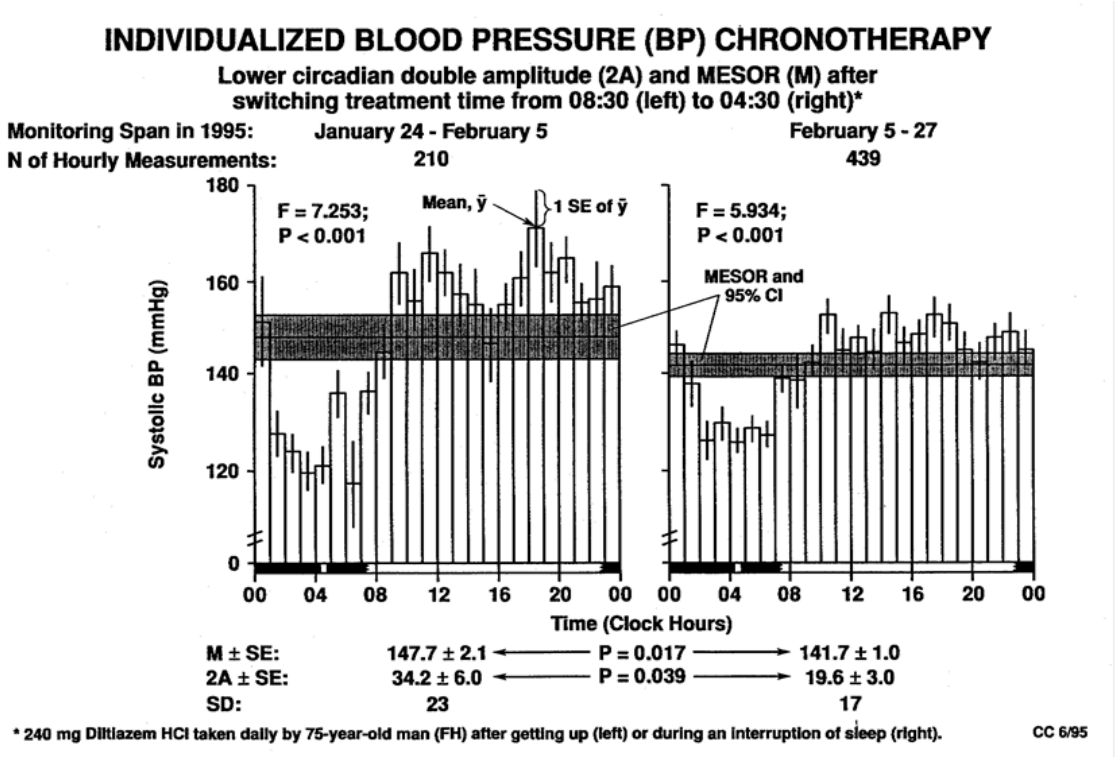


Figure 20. The usefulness of a chronobiologic approach is supported by the demonstration that treatment with antihypertensive drugs can be optimized by timing. The same dose of the same drug can have different effects on the MESOR and circadian amplitude of the same patient's blood pressure when it is administered daily at a different circadian stage as seen by the naked eye and documented by parameter tests. © Halberg.

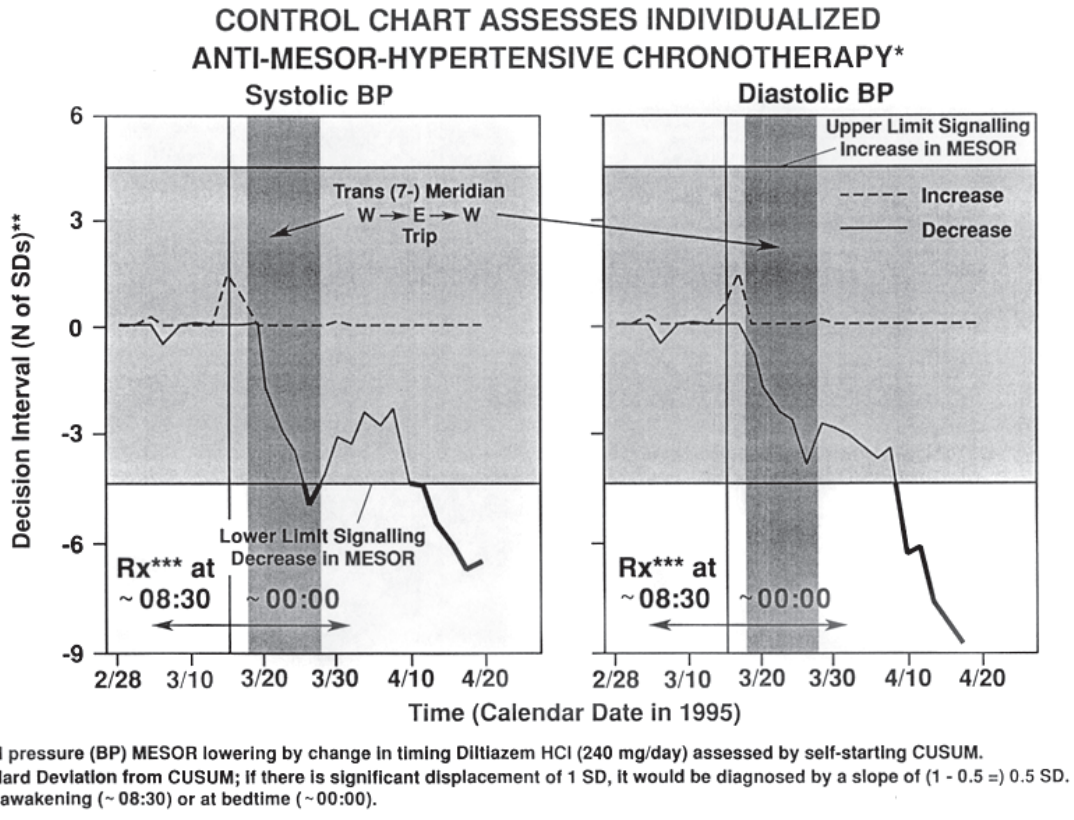


Figure 21. The chronobiological approach includes inferential statistical methods for the rigorous assessment of intervention effects applicable to the individual patient, e.g., detecting whether the lowering in the MESOR of systolic (left) and diastolic (right) blood pressure can be associated with the time when the change in treatment timing was instituted. © Halberg.

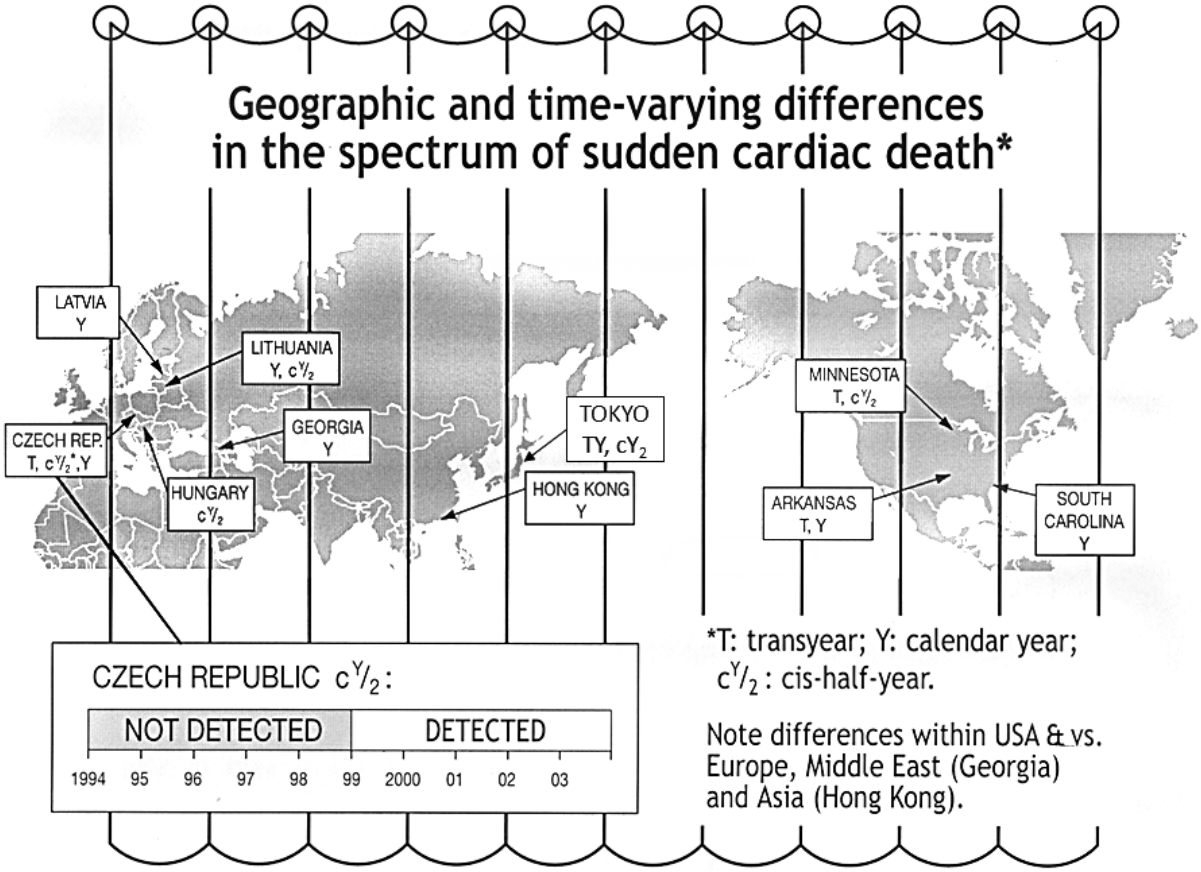


Figure 22. A curtain of uncertainty, because of limited available data, hides any time- and geographic (geomagnetic or dip-magnetic) site-specificity of various spectral aspects of sudden cardiac death. Thus, we find a transyear (T) in Minnesota with a cis-half-year (cY/2) and both a calendar year (Y) and a transyear in Arkansas and the Czech Republic: at the latter site, a cis-half-year, corresponding in length to an also-transient period of hard solar flares, is detected after but not before 1999. Whether other geographic differences in sudden cardiac death may also relate to any magnetic latitude deserves scrutiny. It is noteworthy in any event that cardiac arrhythmias can also transiently reveal a transyear or a cis-half-year, each in a different solar Schwabe cycle stage.

Note site-specificity in the frequency domain displayed by patterns of sudden cardiac death worldwide. Time-specificity is seen at bottom left in the Czech Republic. Rhythms (spectral components) with one or several widely differing periods are found even when focusing solely upon the USA. (A phase difference of changes mirroring a didecadal [Hale sunspot bipolarity] cycle in newborns' body weight in Minnesota vs. Denmark is documented by millions of cases; it shows that the local setting on earth, while depending upon input from the sun, also plays a major role.) © Halberg.

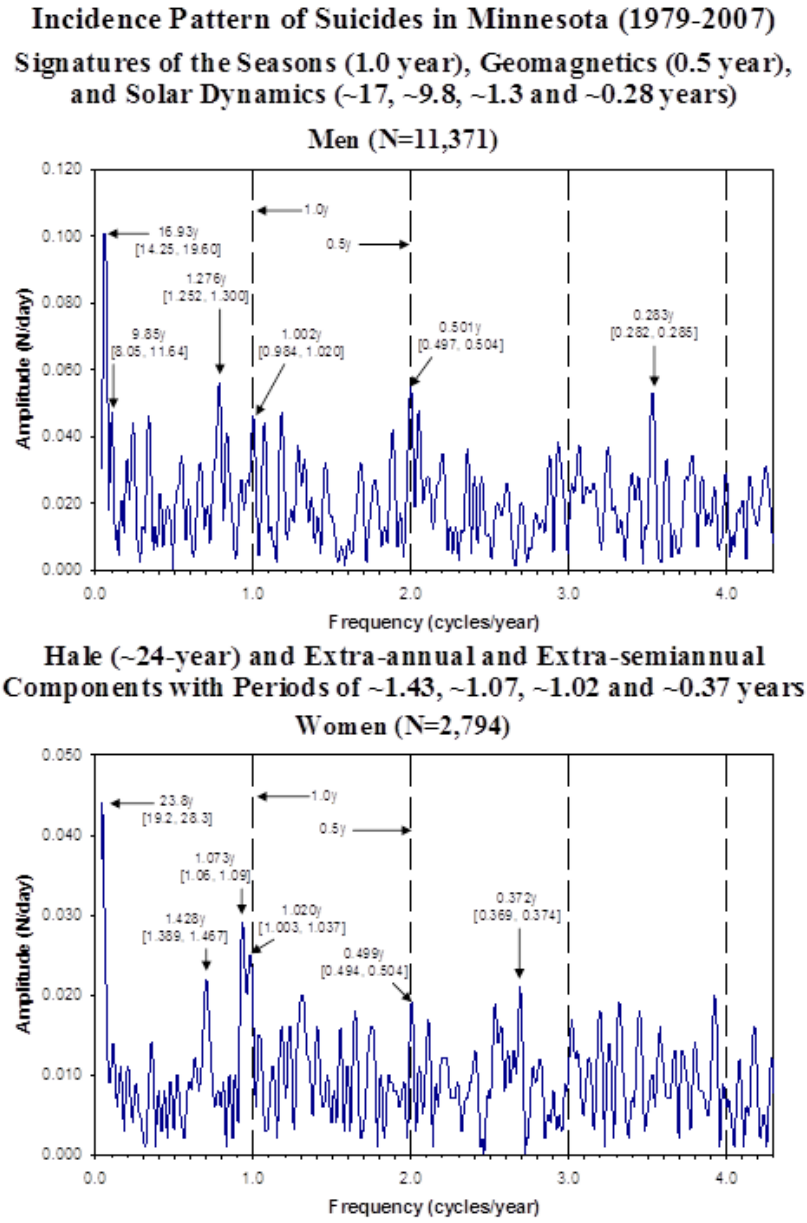
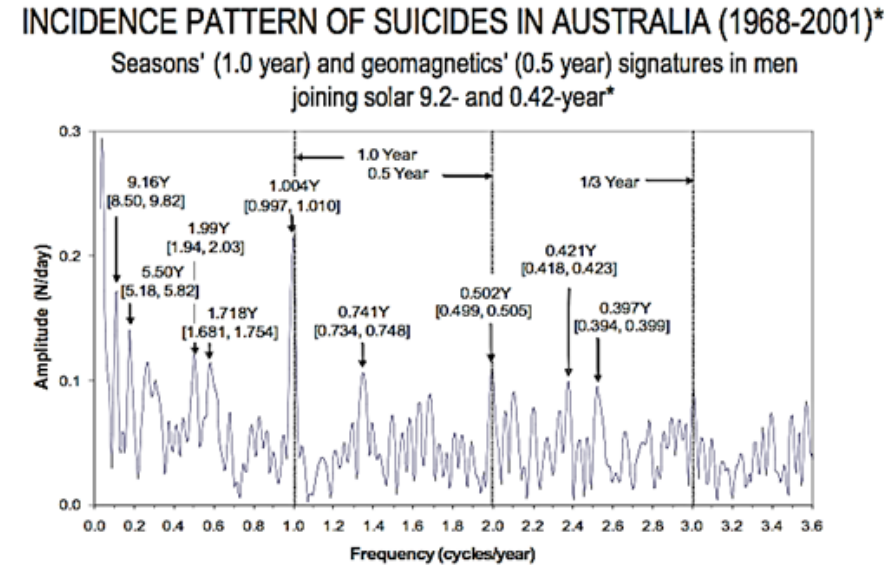


Figure 23A. Daily incidence of suicide by day of death in the two genders in Minnesota (1979–2007). In addition to a circannual and circasemiannual variation, a far-transyear is detected by least squares spectra, with a slightly different period in males (~1.28 years) and females (~1.43 years). A near-transyear is detected in females but not in males. © Halberg.



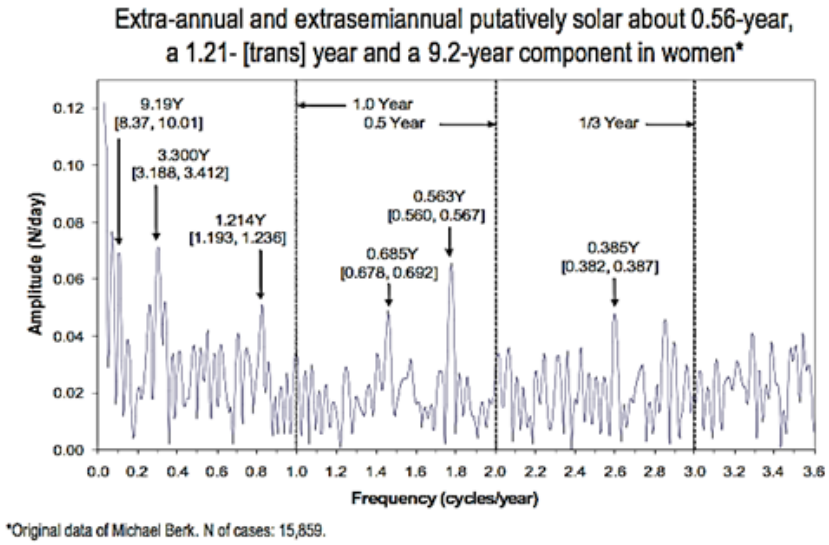


Figure 23B. Suicides in Australia by day of death and gender. The circannual component is prominent in males but not in females. A far-transyear is detected for both genders, albeit with different periods. © Halberg.

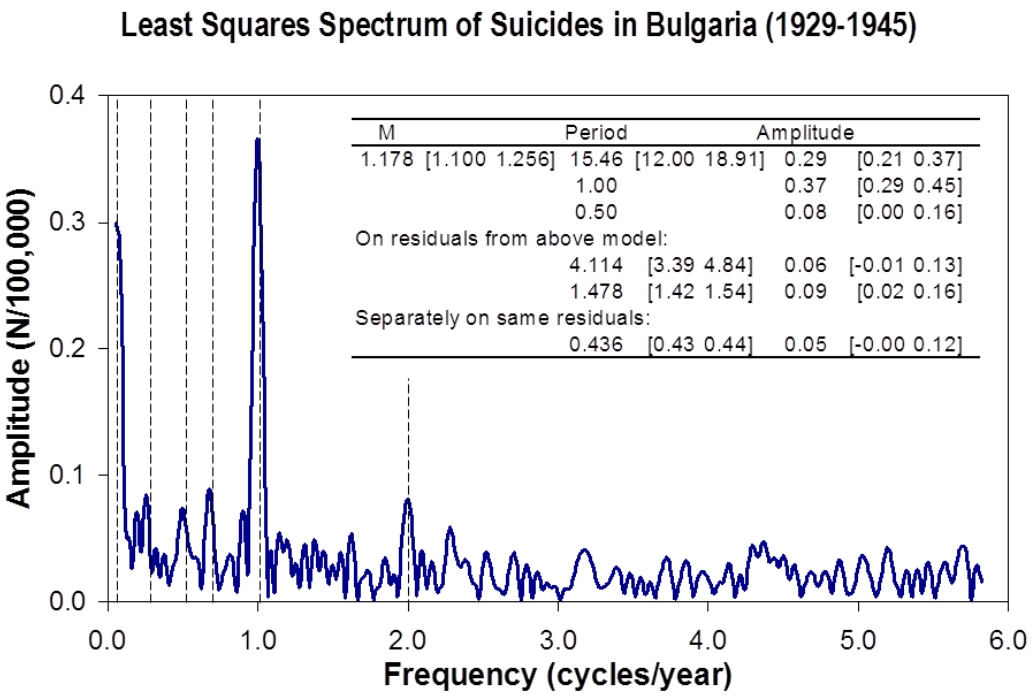


Figure 23C. Suicides in Bulgaria by day of death. In addition to the prominent year, the half-year, a transyear and a cis-half-year are also detected. © Halberg.

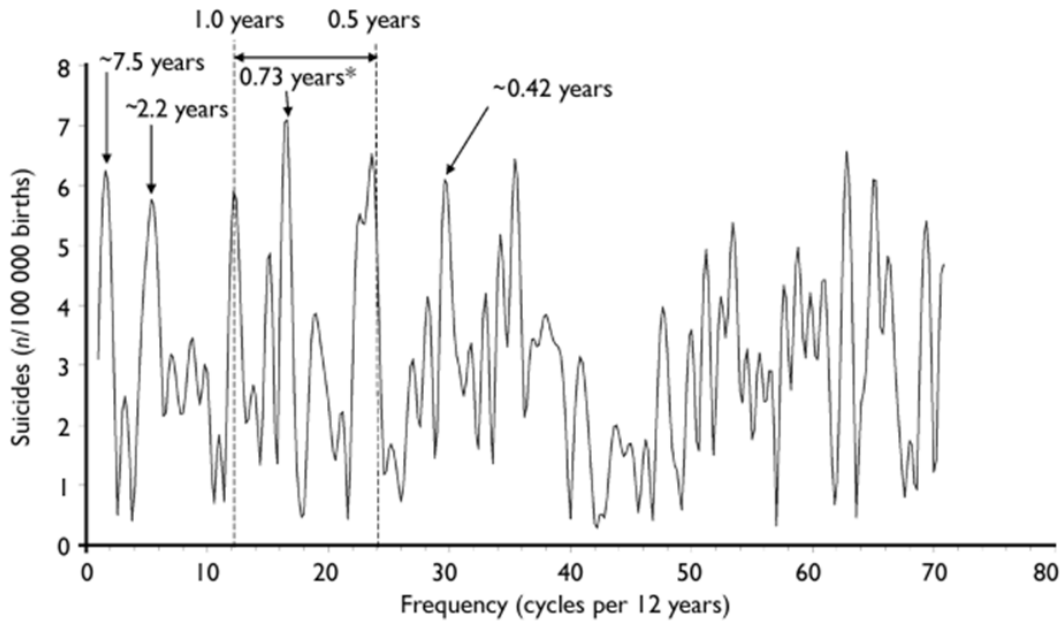


Figure 23D. Suicides in England and Wales by day of birth reveal a different spectrum without the transyears found in Minnesota by day of death. © Halberg.

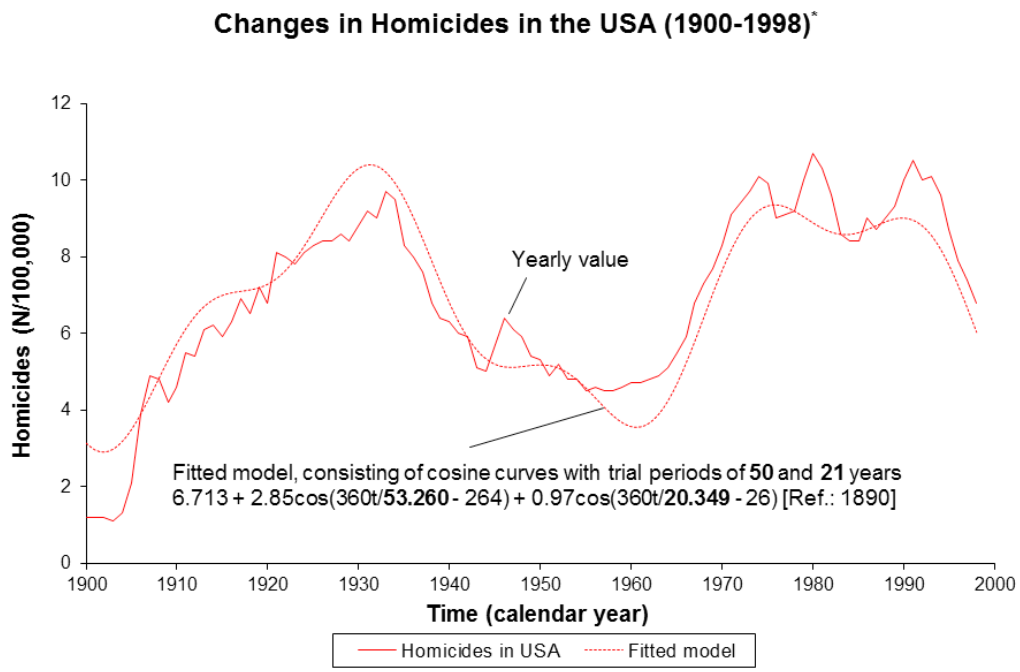


Figure 24. The Kondratiev and Hale cycles are mirrored in US homicides. © Halberg.

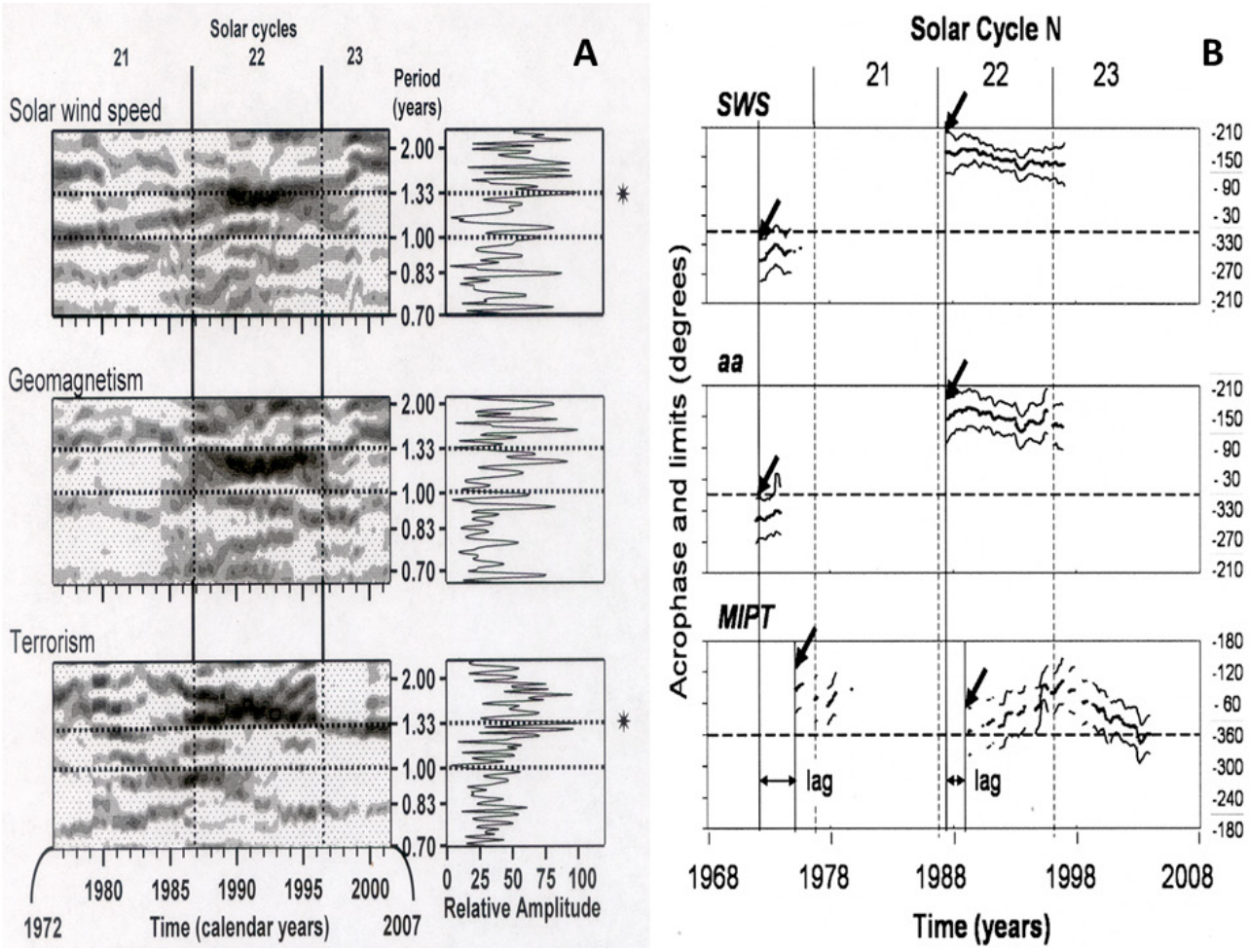
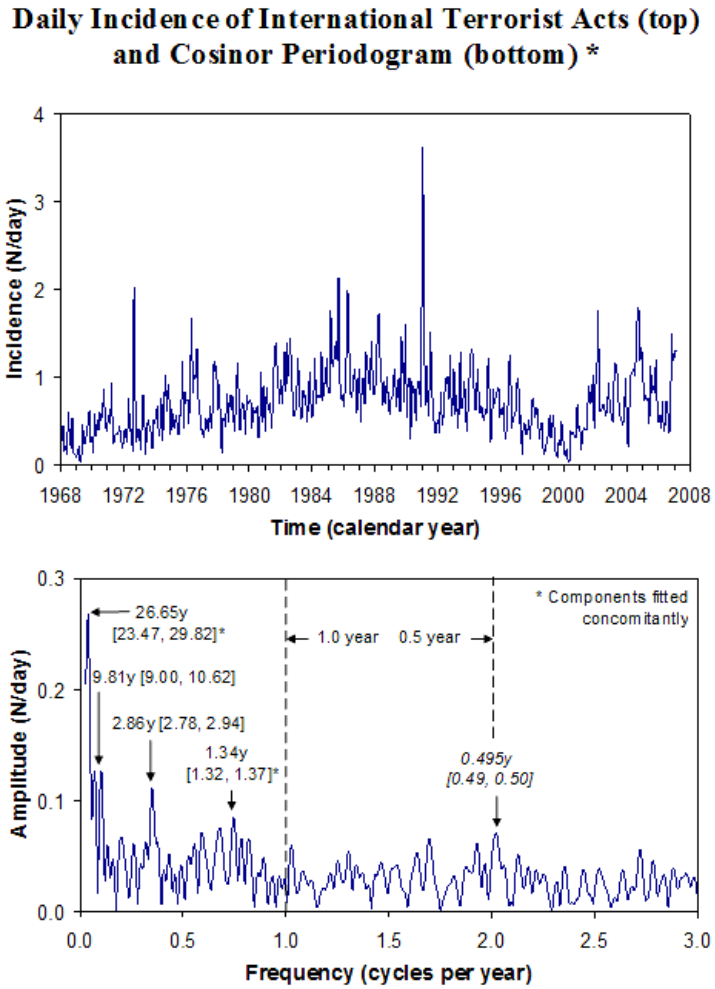


Figure 25. A gliding (local, left) and aligned overall (global, right) spectral window (A, left) show similarities in the para-annual region, a transyear around 1.33 years in solar wind speed (SWS, top), the antipodal geomagnetic disturbance index (aa, middle), and in the incidence of terrorism in the MIPT's (Memorial Institute for the Prevention of Terrorism) 39-year-old database (bottom). Phases of a chronomic serial section is shown for the transyear at the average period among the three variables (B, right). The transyear is observed to be particularly prominent in all three variables during solar cycle 22, as seen from the darker shading at a frequency of one cycle in about 1.33 years. Changes with time of the phase of the transyear component indicate further that statistical significance for terrorism relatively shortly follows (with only a lag) that in solar wind speed and geomagnetism and that it may persist after statistical significance is lost for the two environmental variables. Despite some expected wobbliness, the transyear appears to be relatively stable in all variables during most of solar cycle 22. The fact that a predictable cycle characterizing the incidence of terrorism is also present in the physiology of individuals renders it amenable to monitoring by a population marker rhythm for further scrutiny and for the eventual design of rational countermeasures against undesirable effects of the cosmos. Gliding spectra prepared by Prof. George S. Katinas. © Halberg.



* From February 1968 to March 2007, daily incidence computed from monthly totals (adjusted for differences in the number of days per month). Data from MIPT Terrorism Knowledge Base (http://www.tkb.org/).

Figure 26. In data then available from the Memorial Institute for the Prevention of Terrorism's (MIPT) Terrorism Knowledge Base (1968–2008) (http://www.tkb.org/) (top), a transyear of ~ 1.3 years is detected in the absence of a calendar year component. © Halberg.

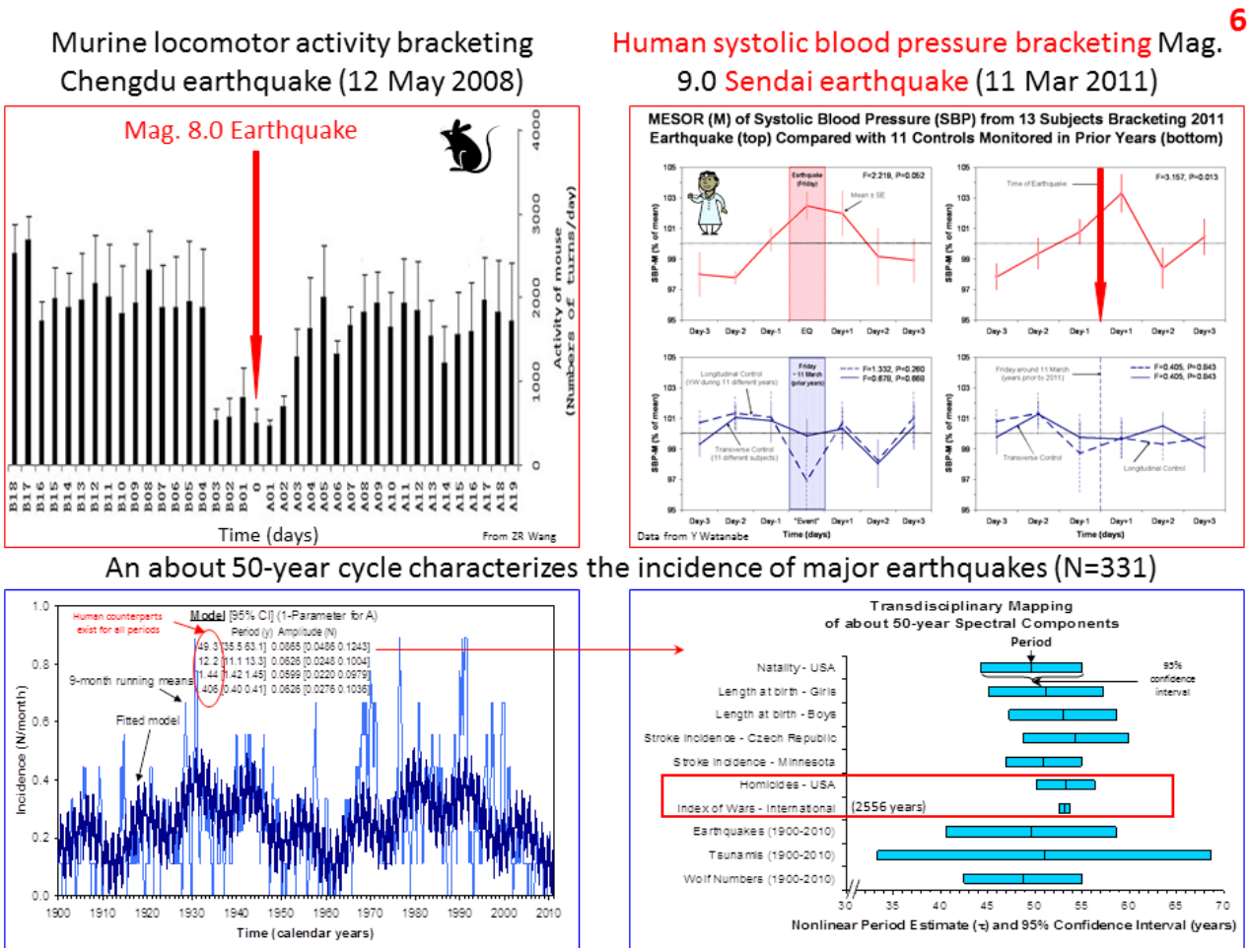


Figure 27. Proposed biospheric contributions to the understanding, if not prediction of earthquakes. Upper left: Locomotor activity of some of the mice telemetered around the clock was statistically significantly decreased starting 3 days prior to the magnitude 8.0 earthquake in Chengdu, China on 12 May 2008. Upper right: Human systolic blood pressure started increasing 2 days prior to the magnitude 9.0 earthquake in Sendai, Japan on 11 March 2011, documented on the basis of weeklong records of around-the-clock ambulatorily obtained data from 13 Japanese. Similar records from longitudinal and transverse controls differ in their time course, suggesting that the trend observed before the earthquake was related to it rather than being a feature of an anticipated weekly pattern. Lower left: The monthly incidence of major earthquakes since 1900 is characterized by the presence of cycles with periods of about 49.3, 12.2, 1.44, and 0.41 year(s), given with their uncertainties in parentheses. Lower right: The prominent about–50-year cycle is also documented in physiology, pathology, societal upheavals and space weather. Nonlinearly estimated periods are displayed with their 95% confidence intervals shown as the length of corresponding horizontal bars. © Halberg.

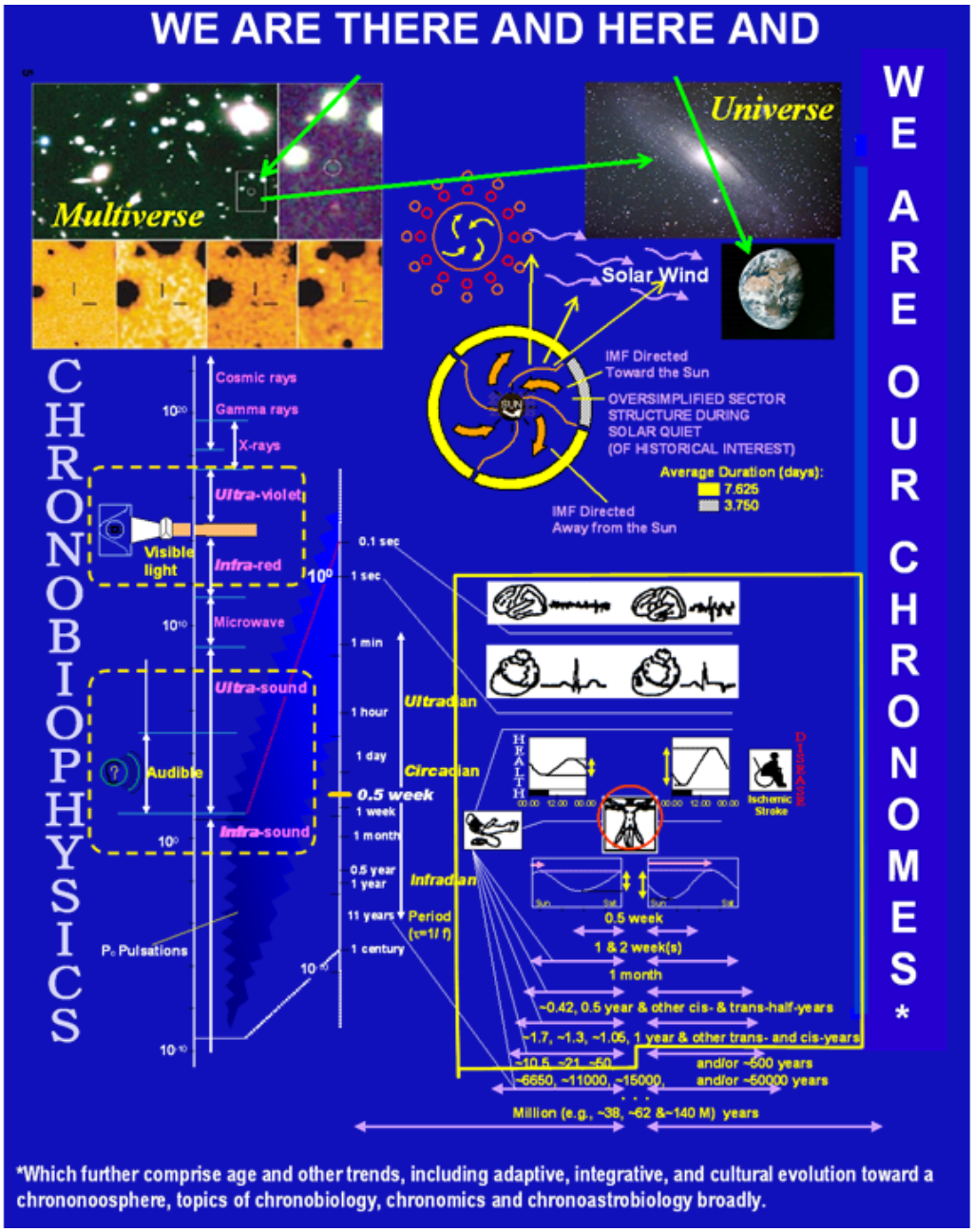


Figure 28A. Frame on lower right half lists some components of the transdisciplinary set of cyclic components found in the bio- and/or in the litho-, hydro-, atmo-, iono-, helio-, magneto- and cosmospheres, underlying a time-structured sphere of the human mind (Attic Gk *nous),* the chronousphere. © Halberg.

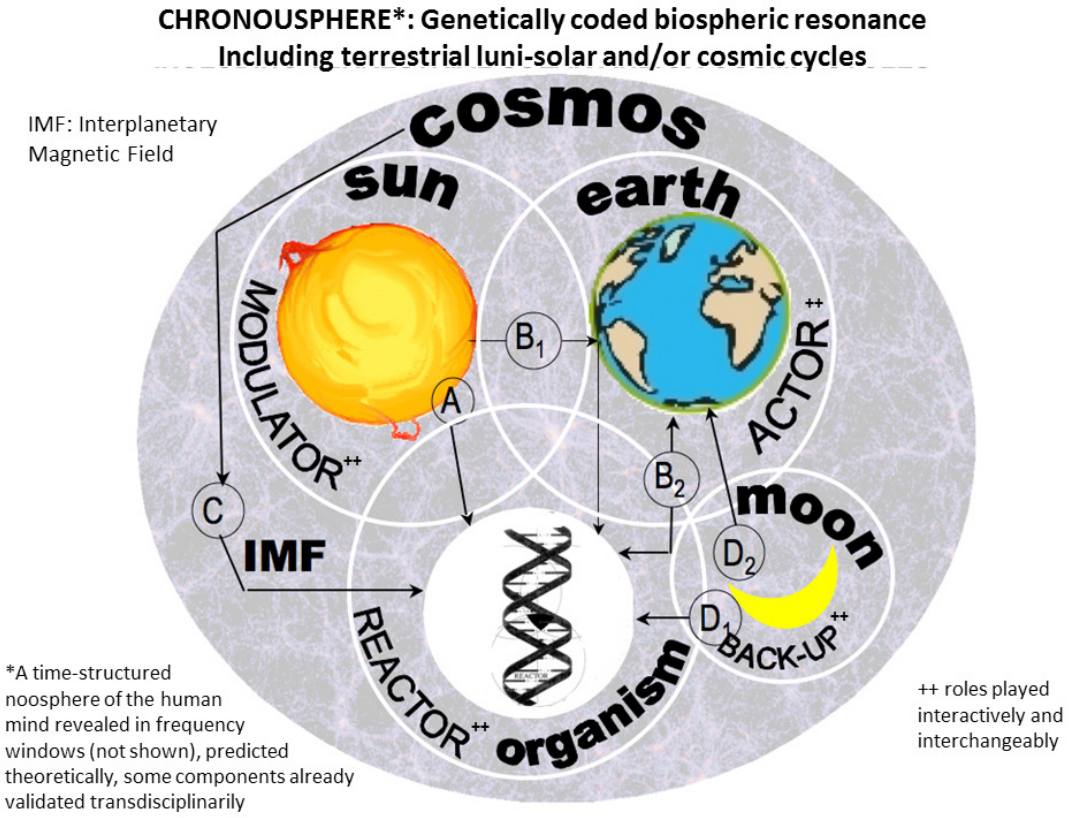


Figure 28B. Signatures of the cosmos with validated statistical significance of anticipated periods characterize: a. dozens of decades-long time series of human blood pressure and heart rate; b. other physiology and psychology, including human mental functions; c. religious proselytism; d. suicide; e. sudden cardiac death; f. terrorist activity for the past 39 or 41 years; g. 2,556 years of international battles compiled by Raymond Holder Wheeler; h. military expenditures for training in non-medical science; i. degrees earned; j. Gallup Polls; and k. political and military actions in nearly 200 years, meta-analyzed from the much broader treasure of data compiled by Alexander Leonidovich Chizhevsky. While chance can never be ruled out, it would be further greatly reduced by systematic lifetime monitoring of physiology in health, of pathology and disease, notably in archives to separate effects of sun, tides and earth, many of which are beneficial. Other effects such as extreme cold and heat or extreme light can be met by countermeasures such as housing, heating and air conditioning. The task remains to develop countermeasures to those nonphotic effects that can be documented as harmful. While the earth is the immediate actor, and for that action the sun is the modulator, the biosphere reacts directly, yet sometimes selectively to only one (or both) terrestrial and lunisolar factors, the tides, as well as natural and artificial light competing with each other under certain circumstances, as seen in patient JF, Figures 28C–G. There may be other more subtle effects of synchronized human action upon the earth. Effects of the moon, contributing about two-thirds of the tides, are thus also demonstrated, Figure 25C–G. The roles of actor, reactor and modulator are continuously changing. In the greenhouse effect, organisms are the actors, as shown by a double-headed arrow (B_2). Original compilation by Mary Sampson. © Halberg.

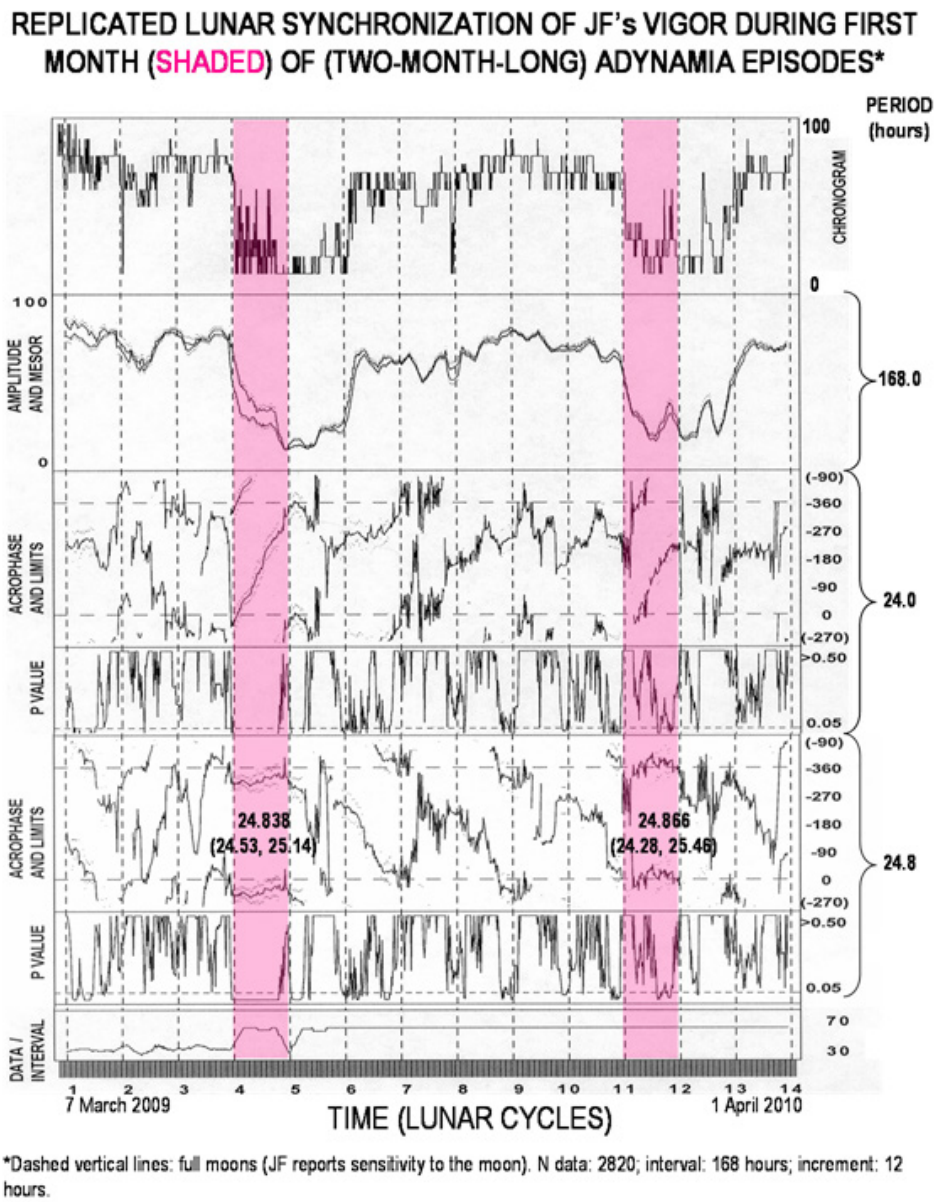


Figure 28C. Chronomic serial section of self-rated vigor-wellness of JF, a woman 61 years of age at start of study during the first 14 lunar months of investigation, revealing extreme changes in vigor and mostly a lack of statistical significance of 24.0-h (row 4) and 2.48-h (row 6) cosine fits. Lunar cycles 4 and 11, the first months of the first two episodes of depression investigated, are characterized by a delaying acrophase in lunar cycles 4 and 11 when a 24-h cosine is fitted and is anticipated by a horizontal time course with a 24.84-h cosine fit in rows 3 and 5 respectively. Each first month of an adynamic episode in nonlinear analyses is characterized by a 24.8-h period twice in succession, never found by us earlier (also further in other variables of JF during adynamic episodes). © Halberg.

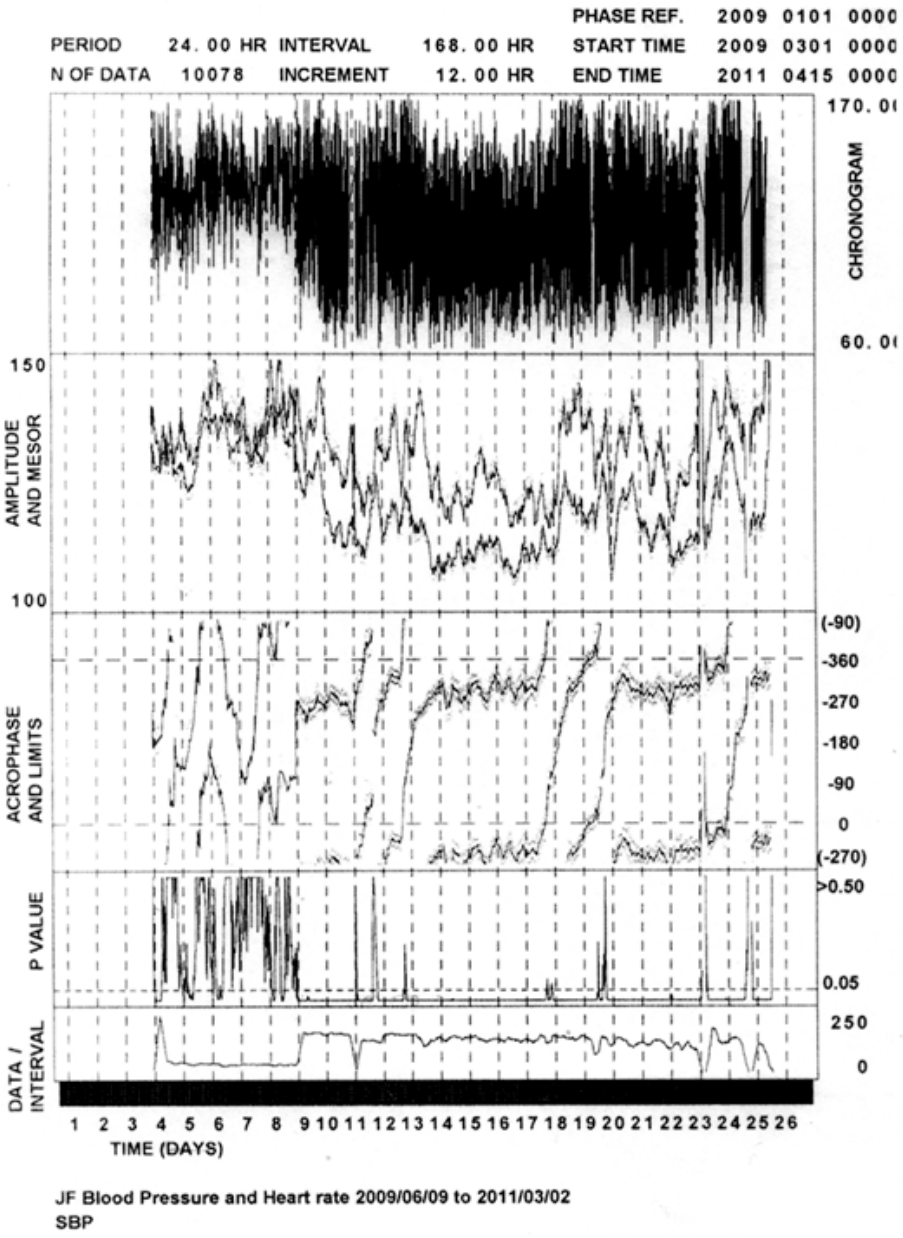


Figure 28D. Self-measurements of systolic blood pressure of JF, from lunar cycles (vertical dashed lines) 4 to 8 inclusive, followed by automatic monitoring in lunar cycle 8. Original data on top reveal lack of lower values during rest/sleep. The lower curve is the second row of the circadian average (MESOR), which is higher during measurements restricted to wakefulness. The circadian amplitude, the distance between the two curves in the second row, is small and not statistically significant, as seen from the penultimate row of P-values for rejection of the zero 24-h amplitude assumption in cycles 4-8. Note acrophases in row 3, shown with 95% confidence interval when statistical significance is reached, i.e., as soon as automatic measurements start in lunar cycle 9 to the end. Their time course continues in alternation horizontally (during wellness) and upward diagonally (during adynamia), thereby indicating a changing dominance between the 24-h synchronized and desynchronized circadian variation. © Halberg.

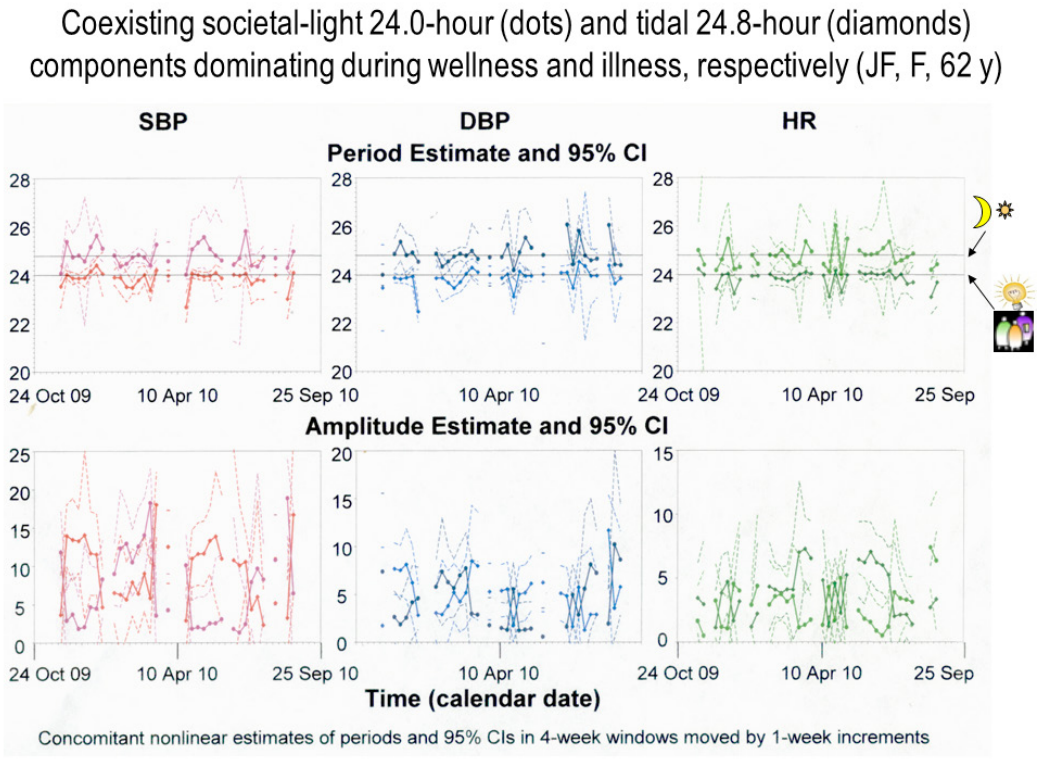


Figure 28E. Competition of 24.0-h and 24.8-h periods in JF's blood circulation with 24-h periods during spans of wellness and longer periods during illness. © Halberg.

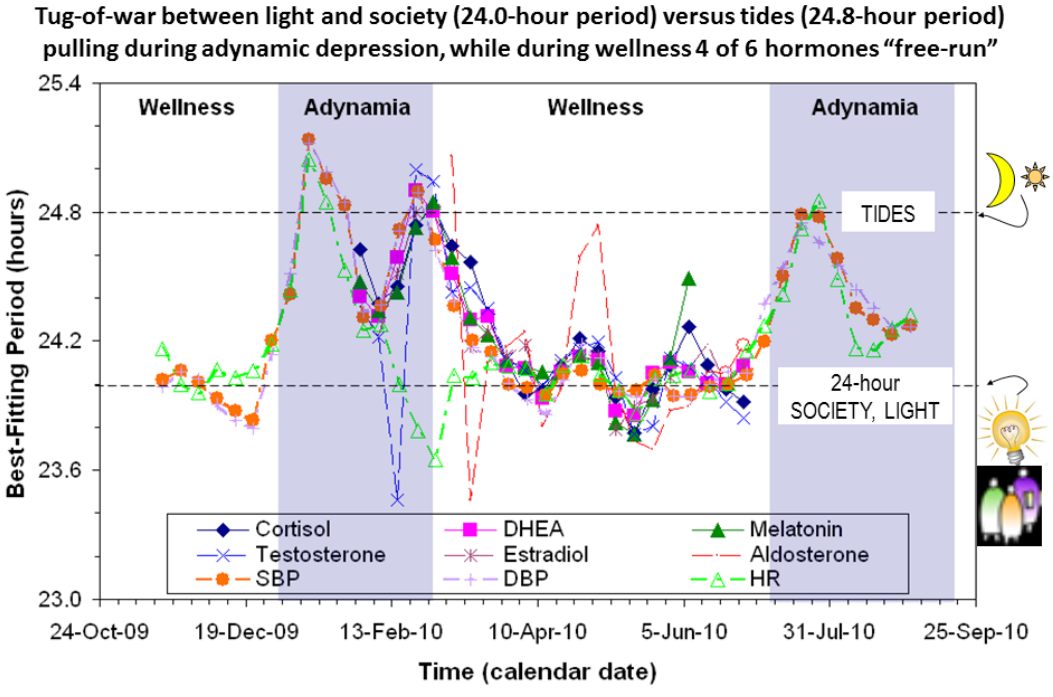
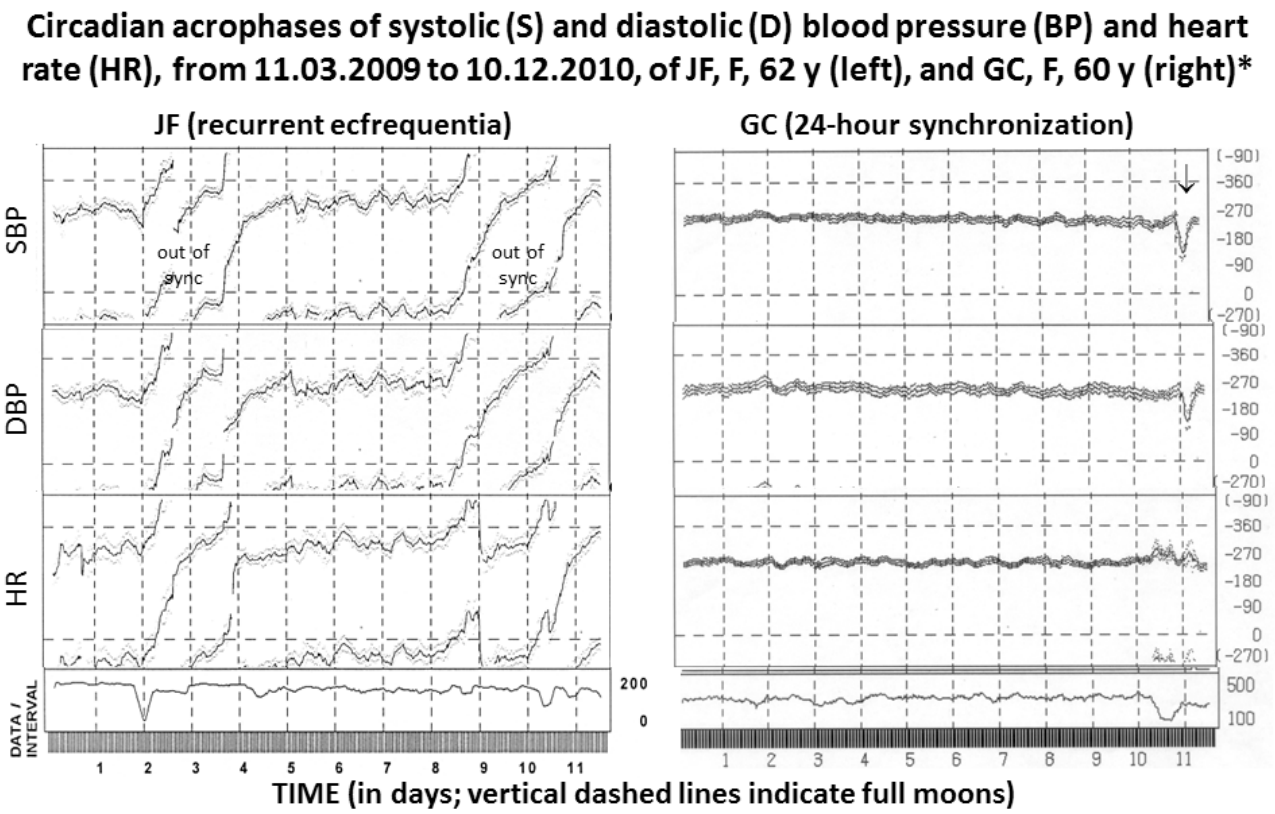


Figure 28F. Competition of 24.0-h and 24.8-h periods in JF's endocrines with 24-h dominance during wellness and the tides pulling most during illness. © Halberg.



*Fit of 24-hour cosine curve to data in 168-hour intervals, displaced in 12-hour increments for consecutive analyses. Acrophases are doubly plotted (left) when nearing midnight, indicated by horizontal dashed lines at 0° and 360°. More or less horizontal time course = 24-hour synchronization. ↓: brief transmeridian round trip across 8 time zones.

Figure 28G. C-ABPM monitors circadian ecfrequentia of JF (left) by comparison to a gender- and age-matched control, GC. © Halberg.

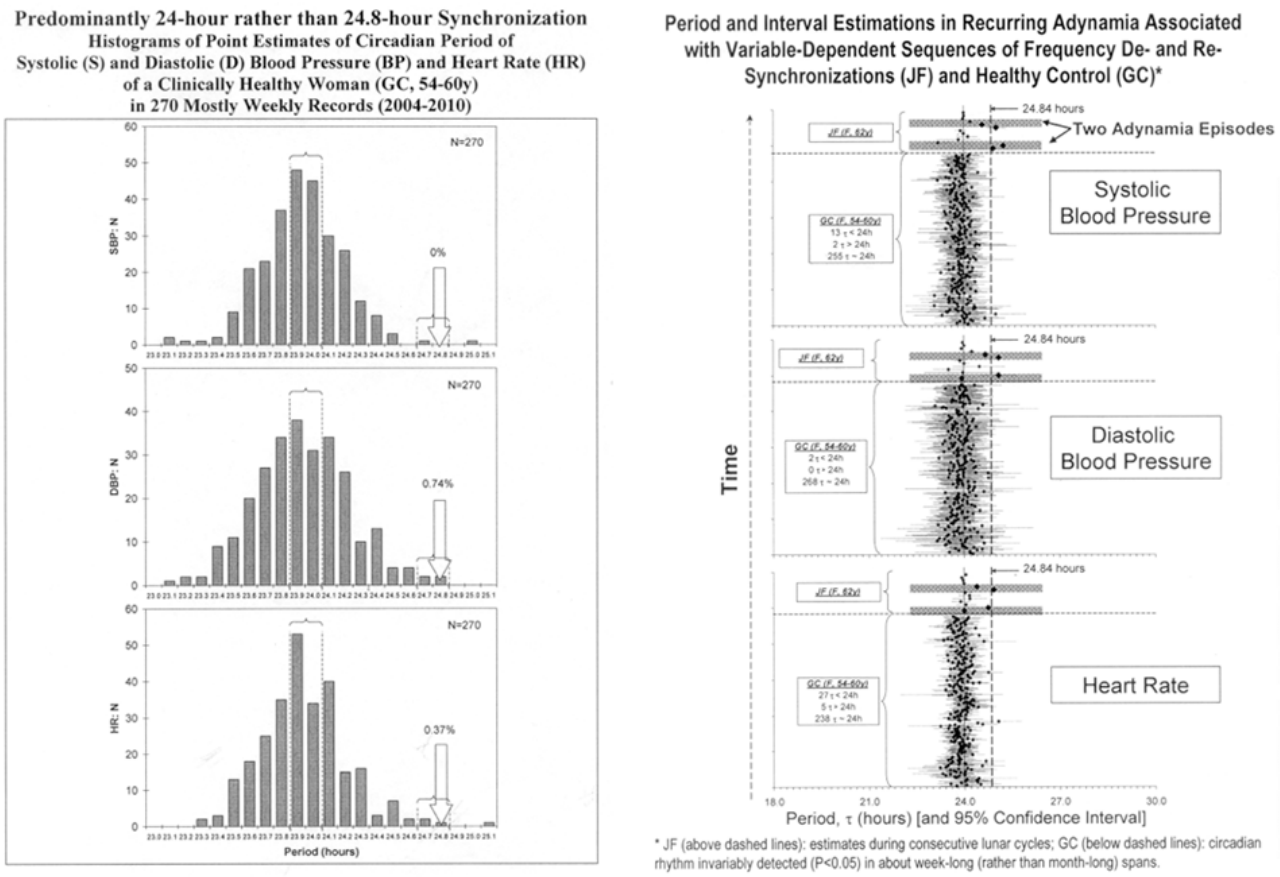


Figure 28H. Distribution of period estimates, τs (histograms on left, individual results on right, shown with their 95% confidence intervals) displayed as a function of time (upward) along the ordinate for a 54–60-year-old woman (GC), based on around-the-clock ~24-h/7-day records at 30-minute intervals. Monthly summaries of a patient's (JF's) τ and CI during "downtimes" (shaded) and outside such episodes of loss of vigor are shown (right, top of each section). The first winter adynamia (shaded) is characterized for SBP by two consecutive τs longer than 24.8 h for JF, a finding not seen in GC. For all three of GC's variables, desynchronized τs are rare, and are absent in a sequence, while in JF's second upper adynamic episode, based on automatic measurements, desynchronization from society is the rule: the CIs of τs invariably fail to cover 24 h. © Halberg.

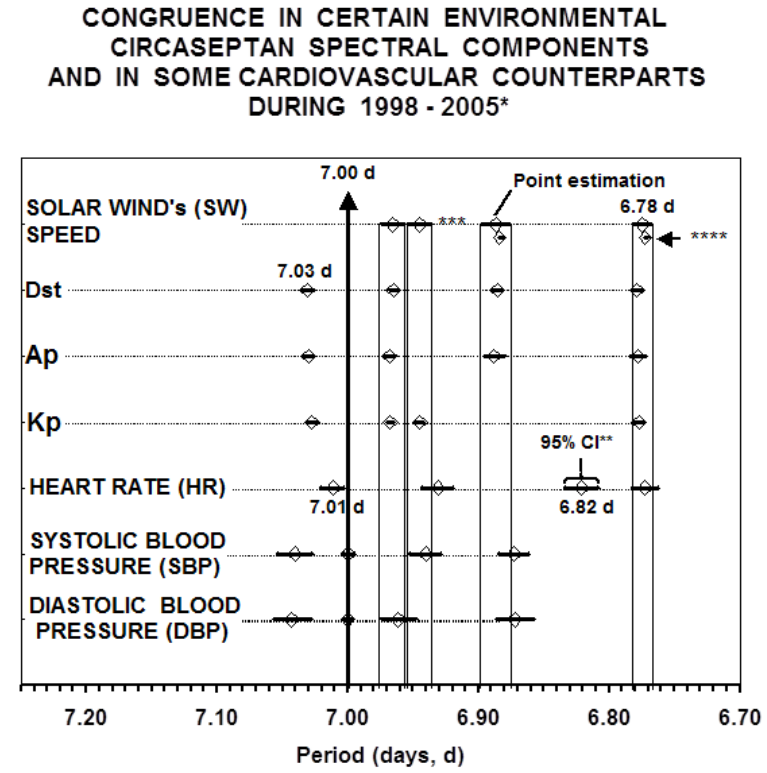
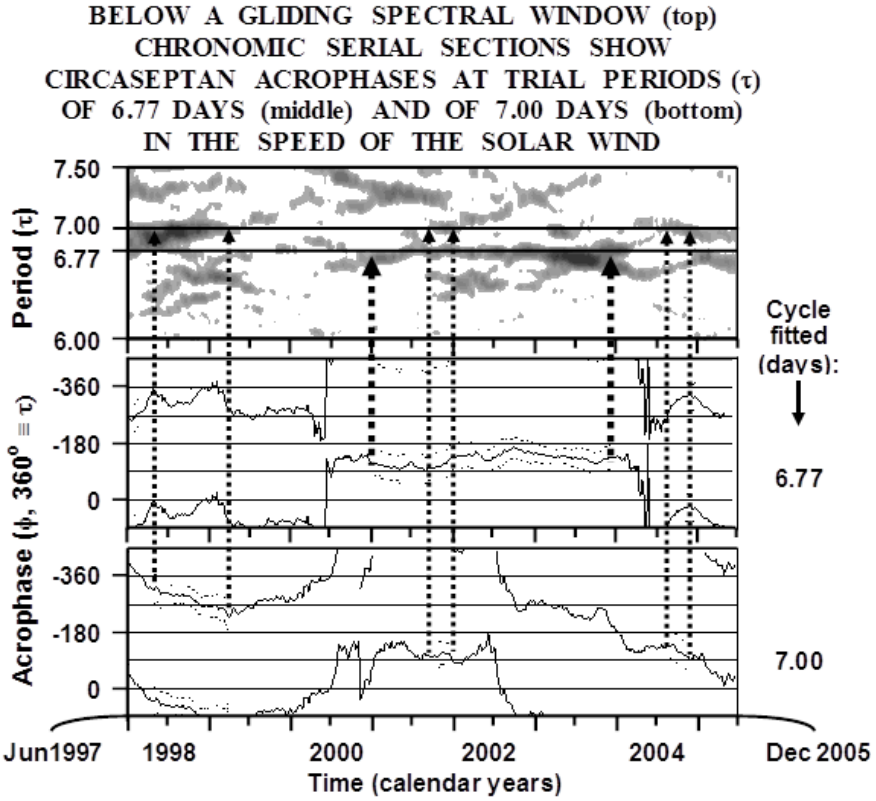


Figure 29A. Selective transdisciplinary congruence in the spectral region around one week. © Halberg.



Data from http://omniweb.gsfc.nasa.gov/html/ow_data.html.
In gliding spectral window, interval = 1 year, increment = 1 week; shaded areas show percentage of rhythm (from 1.2 to 6.8 %). Statistical significance seen as 95% confidence intervals of ϕs shown as dots bracketing curves (middle and bottom). Reference time: 00:00 on Dec 21, 1997. Dotted arrows indicate correspondence between circaseptan components in the phase (middle and bottom) and period (top) domains. 23-rd solar cycle began in May 1996, its maximum was in Apr 2000 and the cycle still continued descending after the end of record.

Figure 29B. Combination of gliding spectral window (top) with special focus on the behavior of two selected periods (middle and bottom), with the time course of the phase validating the 6.77-day period by a more or less horizontal trajectory of phases in only part of the record, but invalidating a precise 7-day periodicity since no dots bracket any horizontal time course of phases, and the small initial section with dots shows a gradual advance. © Halberg.

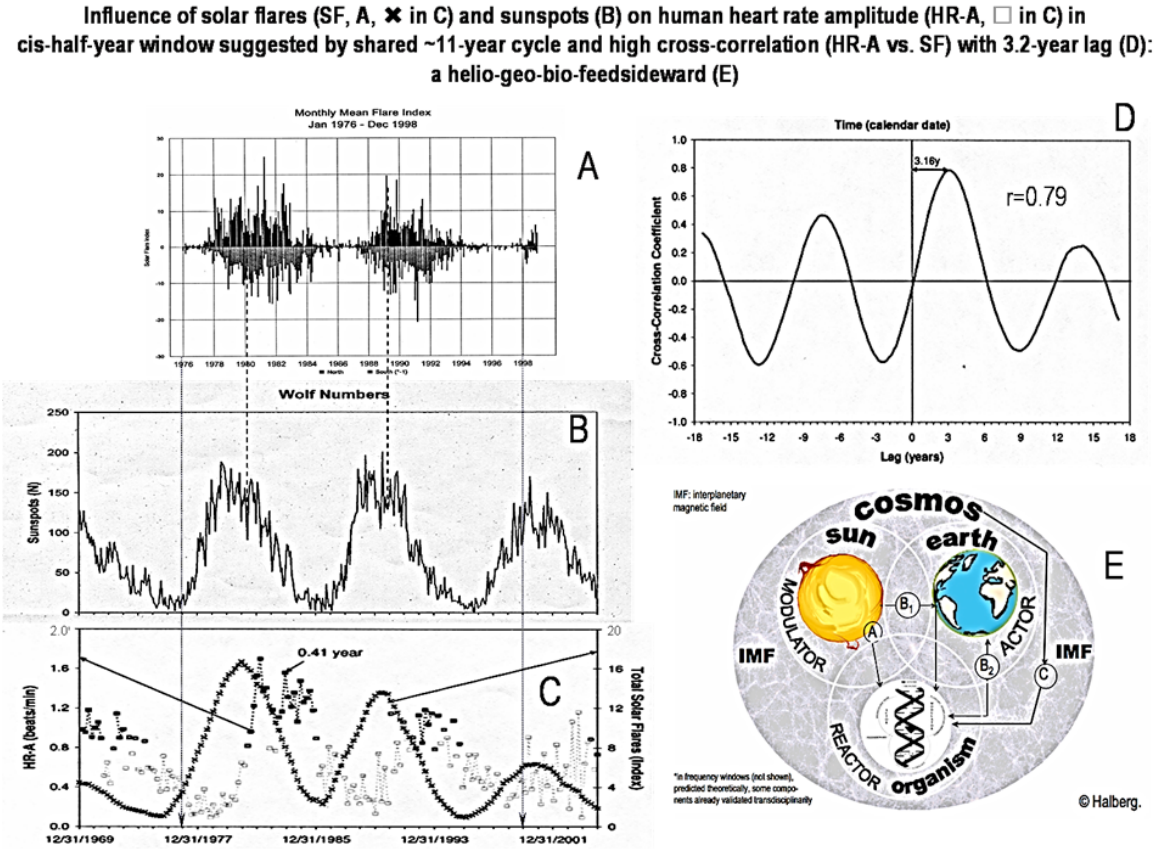


Figure 30A. Waxing and waning of the aeolian ~5-month (~0.41-year) cycle in solar flares (top), sunspots (middle) and with a lag in the heart rate of a clinically healthy man (RBS). Concomitant changes in sudden cardiac death incidence not here shown. © Halberg.

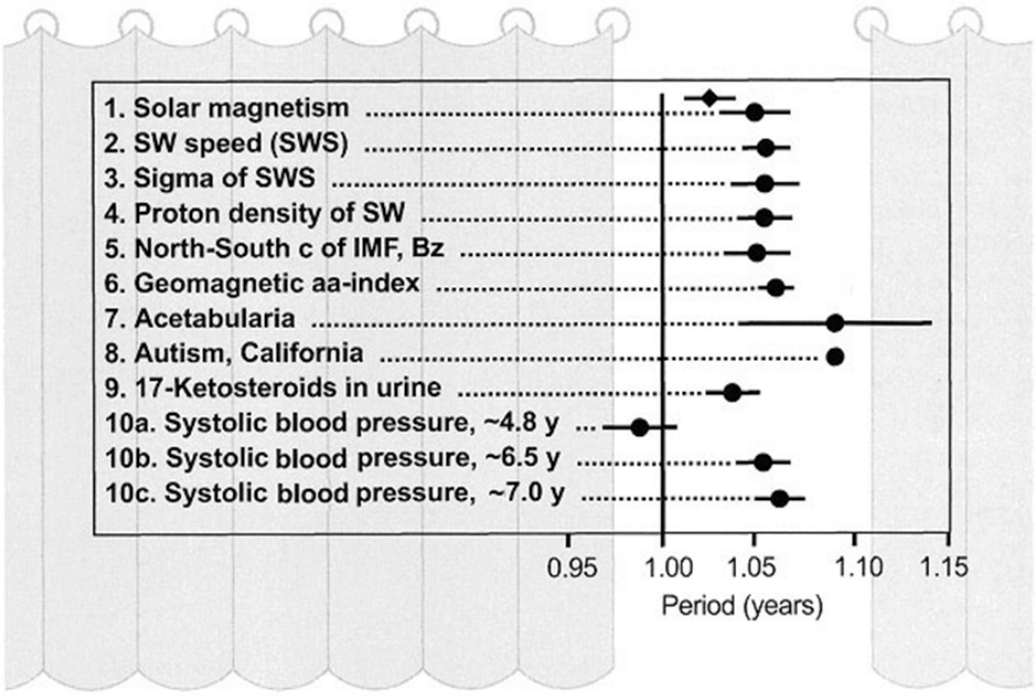
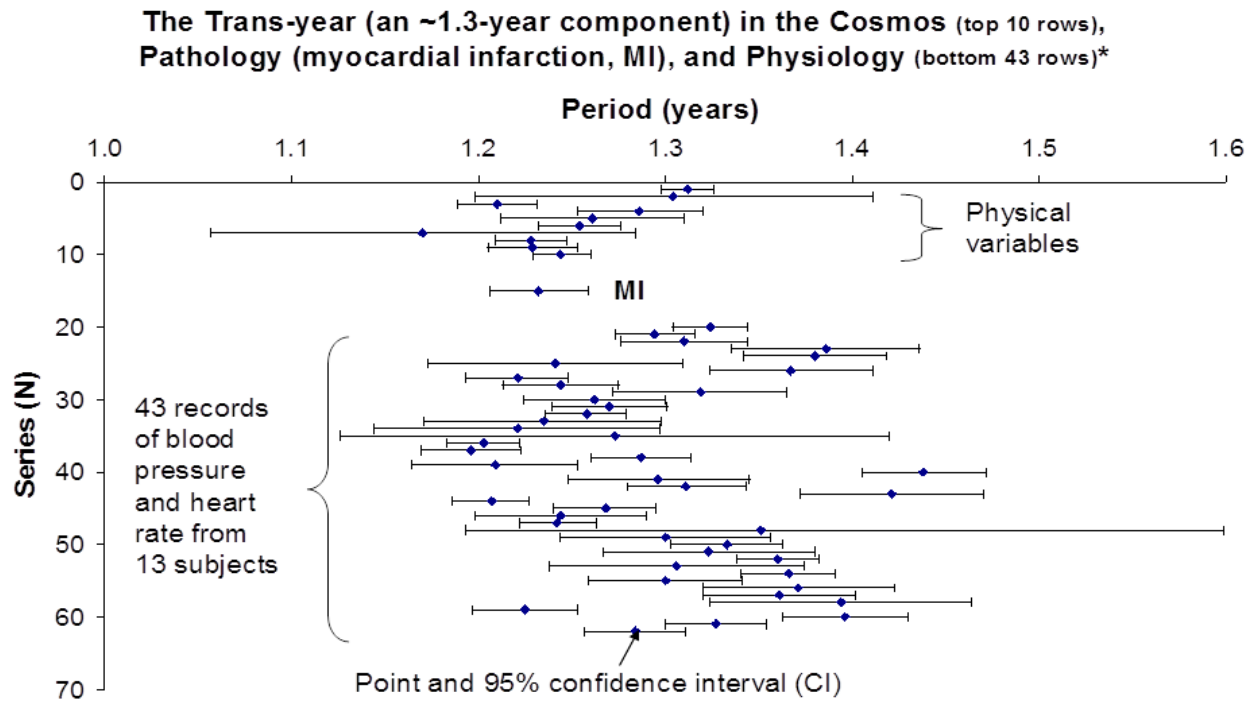


Figure 30B. Near-transyears around us (rows 1–6) and in living matter (rows 7–10). © Halberg.



* **All differing by non-overlapping 95% CIs from the precise calendar year and many differing among each other, a putative hint of endogenicity.** Similar results found for another man providing 3 additional series.

Figure 30C. Far-transyears around us (top 10), incidence of myocardial infarctions in Minnesota (MI), and in 43 blood pressure and heart rate records from 13 subjects who provided longitudinal records covering several years. © Halberg.

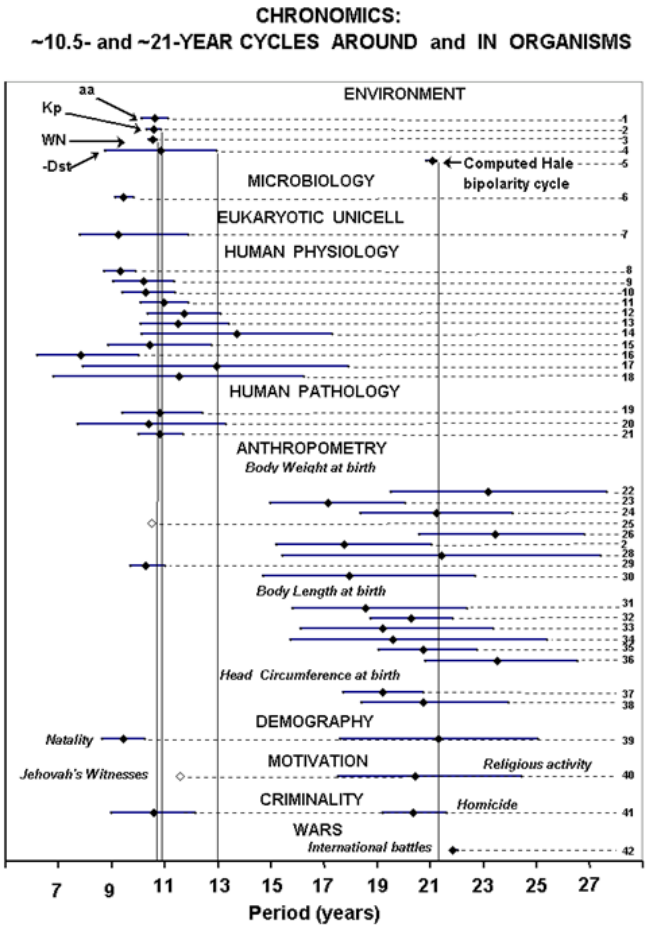


Figure 31A. Paradecadals and paradidecadals, ~10.5- and ~21-year cycles similar in length to the Schwabe and Hale solar activity cycles characterize a host of biological variables, from micro-organisms to human physiology, pathology, anthropometry and sociology, assessed from population statistics, yet critically dependent upon also-available individual "pilot studies". Such self-experimentation is indispensable for a scrutiny of mechanisms underlying population cycles. © Halberg.

Chronomics: ~10.5- and ~21-year cycles in and around us

	Line		Period (years) Lower limit*	Best Fit	Upper limit*	Series duration Dates	Years	Number of data	Geographic site
Environment	1	aa = Antipodal Geomagnetic Index	10.12	**10.63**	11.13	1890-1999	110	1 / year	
	2	Kp = Planetary Geomagnetic disturbance	10.32	**10.58**	10.85	1932-1999	68	1 / month	
	3	WN = Wolf relative sunspot number	10.37	**10.54**	10.70	1890-1999	110	1 / year	
	4	-Dst = Equatorial geomagnetic disturbance	8.75	**10.85**	12.96	1973-1999	27	"	
			10.48	**10.51**	10.55	1700-1999	300	"	
	5	Bipolarity "Hale Cycle" **	20.86	**21.10**	21.26	1890-1999	110	"	
			21.42	**21.428**	21.43	1700-1999	300	"	
Biology	6	Prokaryotes: Air Bacterial Sectoring	9.12	**9.46**	9.81	1970-1982	13	3,744	Italy
	7	Eukaryotes: Unicellular Algal O_2 Production	7.79	**9.24**	11.87	1980-1991	11	324	Germany
Physiology* **	8	Mood (RBS)	10.11	**11.50**	13.41	1966-1998	33	~5 / day	USA
	9	Time (1-Minute) Estimation (RBS)	9.38	**10.29**	11.37	1966-1998	33	"	"
	10	Urinary 17-ketosteroid excretion (CH)	8.70	**9.30**	9.90	1948-1963	15	1 / day	Denmark
	11	Peak Expiratory Flow (RBS)	10.36	**11.74**	13.11	1966-1998	33	~5 / day	USA
	12	Respiratory Rate (RBS)	10.13	**12.50**	17.32	1966-1998	33	"	"
	13	Systolic Blood Pressure - SBP (RBS)	9.05	**10.21**	11.36	1966-1998	33	"	"
	14	Standard Deviation of SBP (YW)	8.85	**10.43**	12.76	1987-1998	11	~48 / day	Japan
	15	Diastolic Blood Pressure - DBP (RBS)	10.09	**10.98**	11.87	1966-1998	33	~5 / day	USA
	16	Standard Deviation of DBP (YW)	6.18	**7.82**	10.02	1987-1998	11	~48 / day	Japan
	17	Heart Rate - HR (YW)	9.54	**12.93**	17.91	1987-1998	11	"	"
	18	Standard Deviation of HR (YW)	8.27	**11.52**	16.22	1987-1998	11	"	"
Pathology	19	Myocardial Infarction	10.00	**10.80**	11.70	1960-1996	37	129,205	USA
	20	Leptospirosis	9.40	**10.80**	12.40	1949-1995	47	2,907	Slovakia
	21	Diabetes	7.70	**10.40**	13.30	1985-1995	11	1,369	"
Anthropo-		***Body Weight*** ***Boys***							
metry	22	Minnesota	19.53	**23.19**	27.67	1963-1998	36	2,136,745	USA
at birth	23	Alma-Ata Russians	14.99	**17.17**	20.07	1946-1998	53	9,056	Kazakhstan
	24	" Kazakhs	18.39	**21.24**	24.05	1946-1998	53	3,459	"
	25	Moscow		**10.49**		1874-1985	112	5,987	Russia
		Girls							
	26	Minnesota	20.58	**23.46**	26.83	1963-1998	36	1,039,464	USA
	27	Alma-Ata Russians	15.21	**17.75**	21.06	1946-1998	53	9,105	Kazakhstan
	28	" Kazakhs	15.44	**21.45**	27.45	1946-1998	53	3,448	"
	29	Moscow	9.70	**10.29**	11.01	1874-1985	112	5,840	Russia
		Both genders							
	30	Denmark	14.71	**17.94**	22.68	1973-1994	22	1,166,206	Denmark
		Body Length ***Boys***							
	31	Alma-Ata Russians	15.82	**18.58**	22.38	1946-1998	53	9,026	Kazakhstan
	32	Moscow	18.76	**20.28**	21.86	1874-1985	112	5,976	Russia
		Girls							
	33	Alma-Ata Russians	16.13	**19.20**	23.39	1946-1998	53	9,105	Kazakhstan
	34	" Kazakhs	15.72	**19.60**	25.40	1946-1998	53	3,485	"
	35	Moscow	19.05	**20.76**	22.78	1874-1985	112	5,976	Russia
		Both genders							
	36	Denmark	20.81	**23.55**	26.55	1973-1994	22	1,166,206	Denmark
		Head Circumference							
	37	***Boys*** Moscow	17.71	**19.23**	20.75	1874-1985	112	5,976	Russia
	38	***Girls*** "	18.42	**20.73**	23.95	1874-1985	112	5,820	"
Demography	39	Birth rate	8.63	**9.43**	10.23	1940-1996	57	57	USA
			17.61	**21.33**	25.05	1940-1996			
Motivation	41	Religious activity of Jehovah's Witnesses	17.52	**20.44**	24.45	1950-1999	50	328,572[#]	Worldwide
								5,653,987[##]	
Criminality	40	Homicide	8.99	**10.58**	12.16	1900-1998	99	99	USA
			19.23	**20.35**	21.62				
Wars	42	International battles	21.87	**21.96**	22.06	599BC-1957	2556	2556	Worldwide

* 95% confidence limit; not shown if cycle is not statistically significant.
** Computed by changing the sign of WN at each WN minimum.
***RBS - Dr. Robert B. Sothern, CH - Dr. Christian Hamburger, YW - Dr. Yoshihiko Watanabe.
[#] in 1950, [##] in 1999, pool of 103 plus other unspecified number of sites.

Figure 31B. Key to Figure 31A. © Halberg.

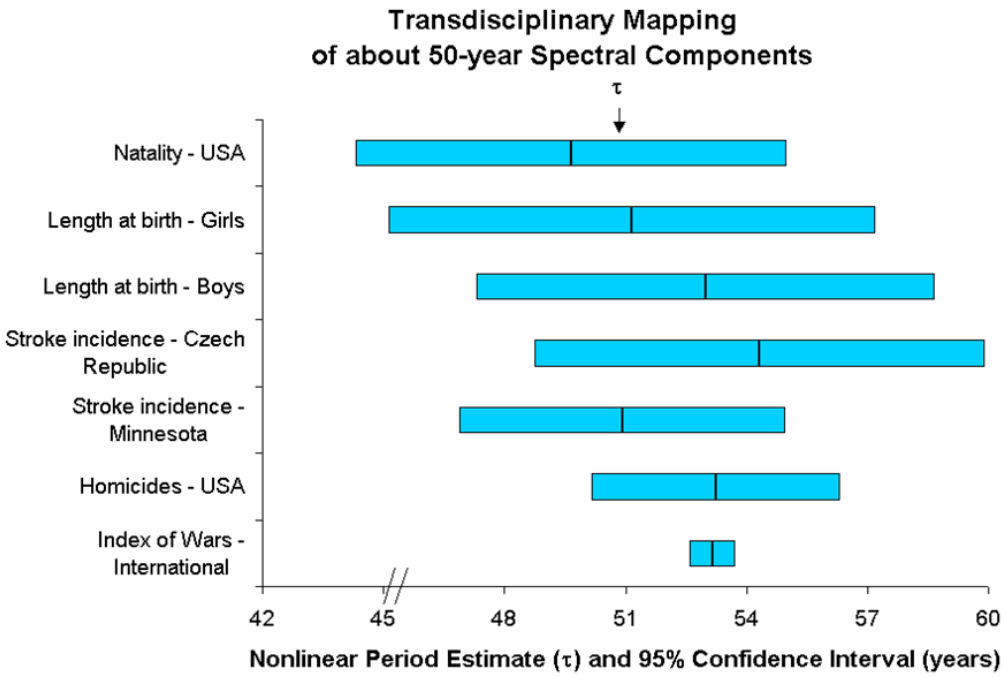


Figure 31C. Kondratiev cycle affecting the biosphere. © Halberg.

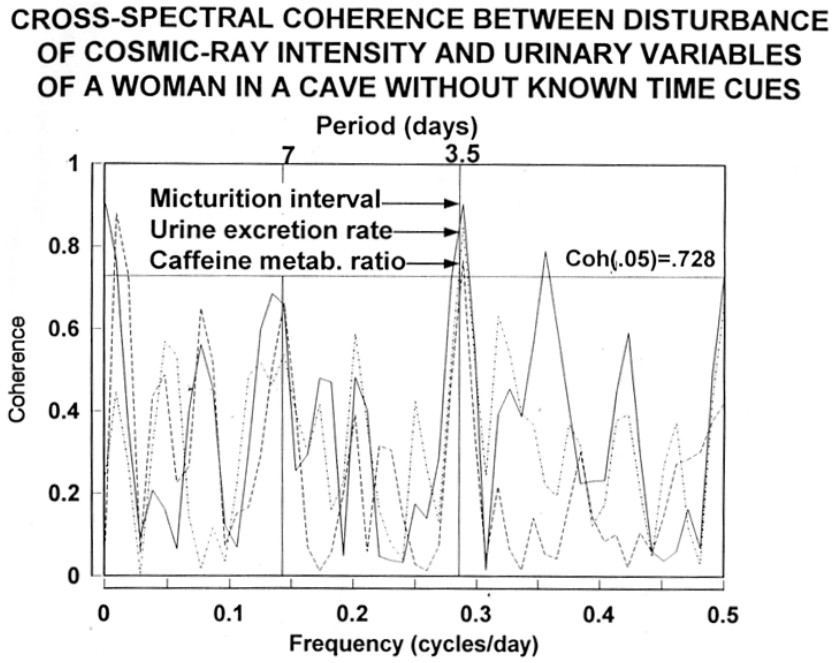


Figure 32A. Coherence at a period of about 3.5 days is found between the daily standard deviation of hourly neutron monitor courses from Dourbes, Belgium, and daily values for the inter-micturition interval, urine excretion rate and caffeine metabolite ratio of a woman (VLG) during social isolation in a cave. The coherence values are 0.90 (P = 0.001), 0.85 (P = 0.006) and 0.77 (P = 0.029) for each variable, respectively, calculated by standard approximate χ^2. At a period of about 7 days, similar agreement is found among the three variables, albeit coherence with the environmental variable is not statistically significant. © Halberg.

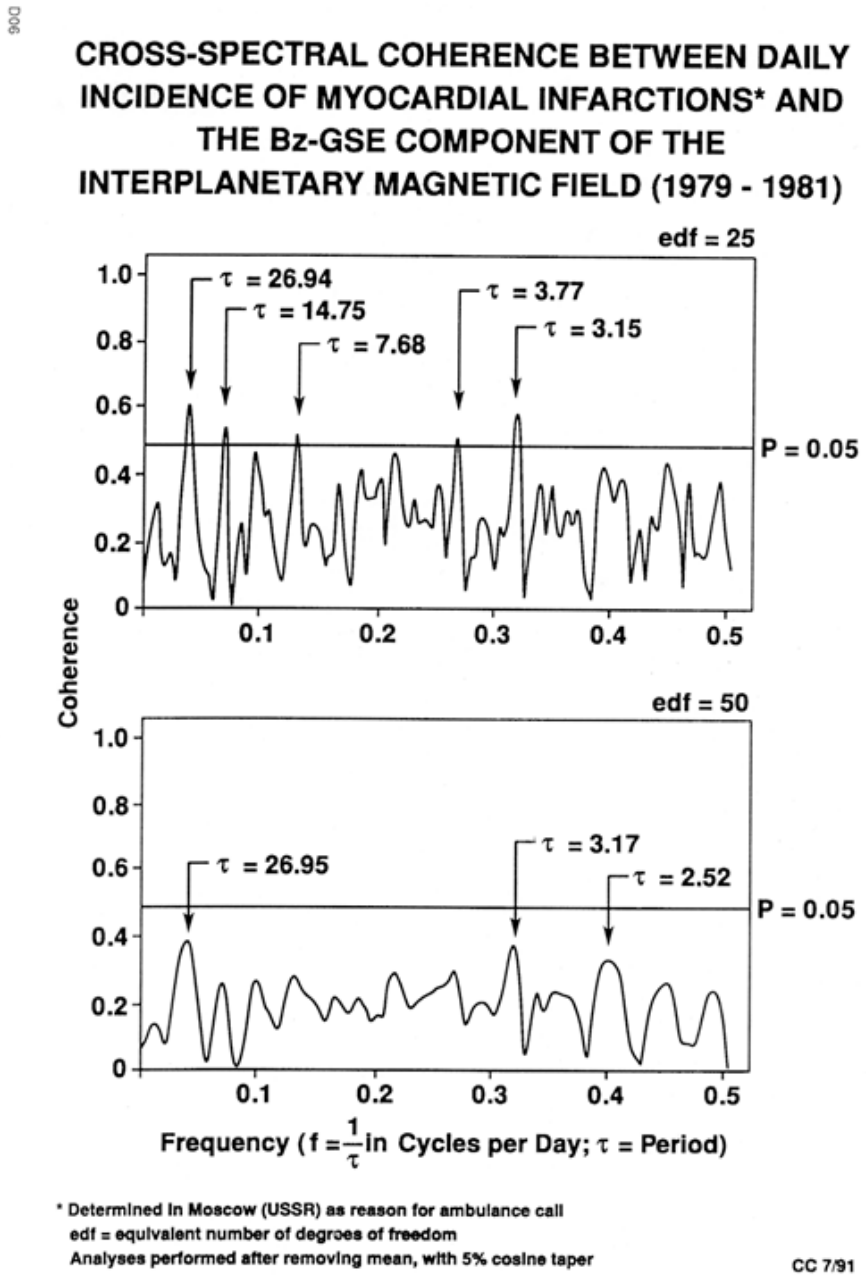


Figure 32B. Multiple coherence findings depend, of course, upon resolution used (54). © Halberg.

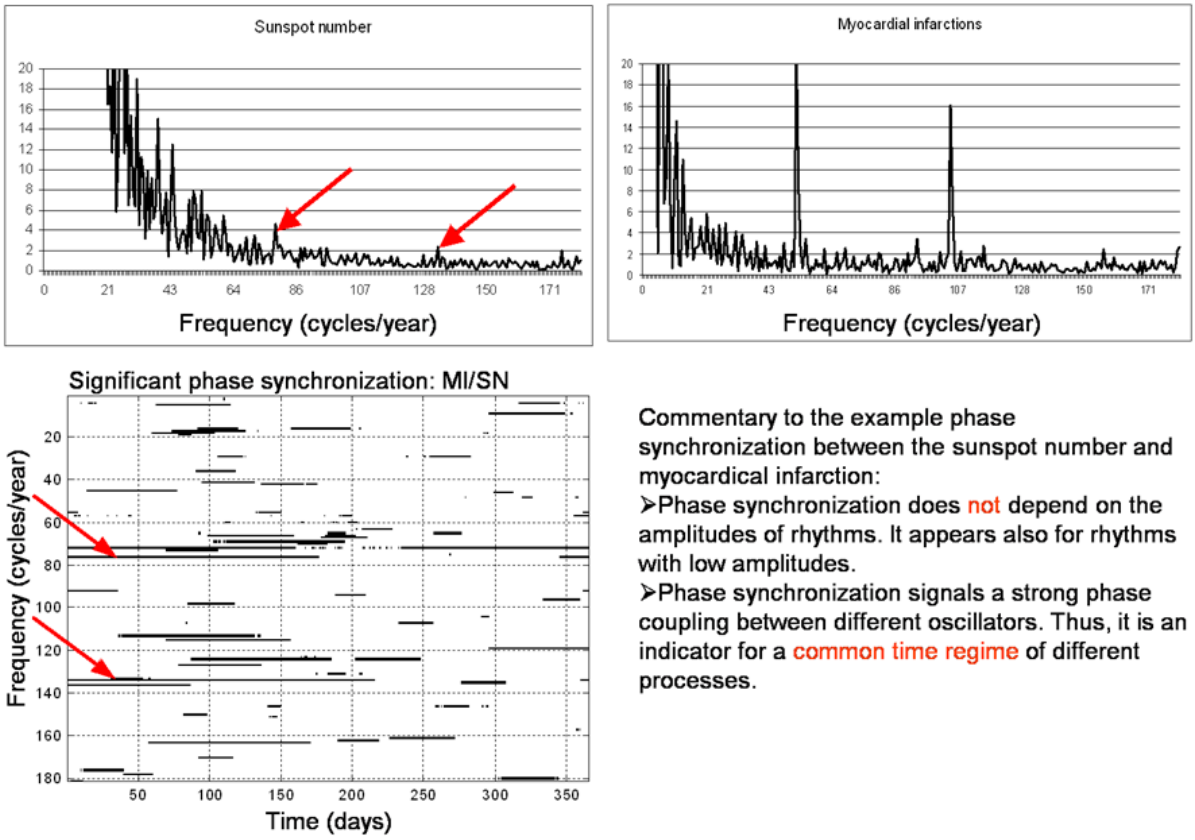


Figure 32C. Cross-spectral coherences are time-varying. © Halberg.

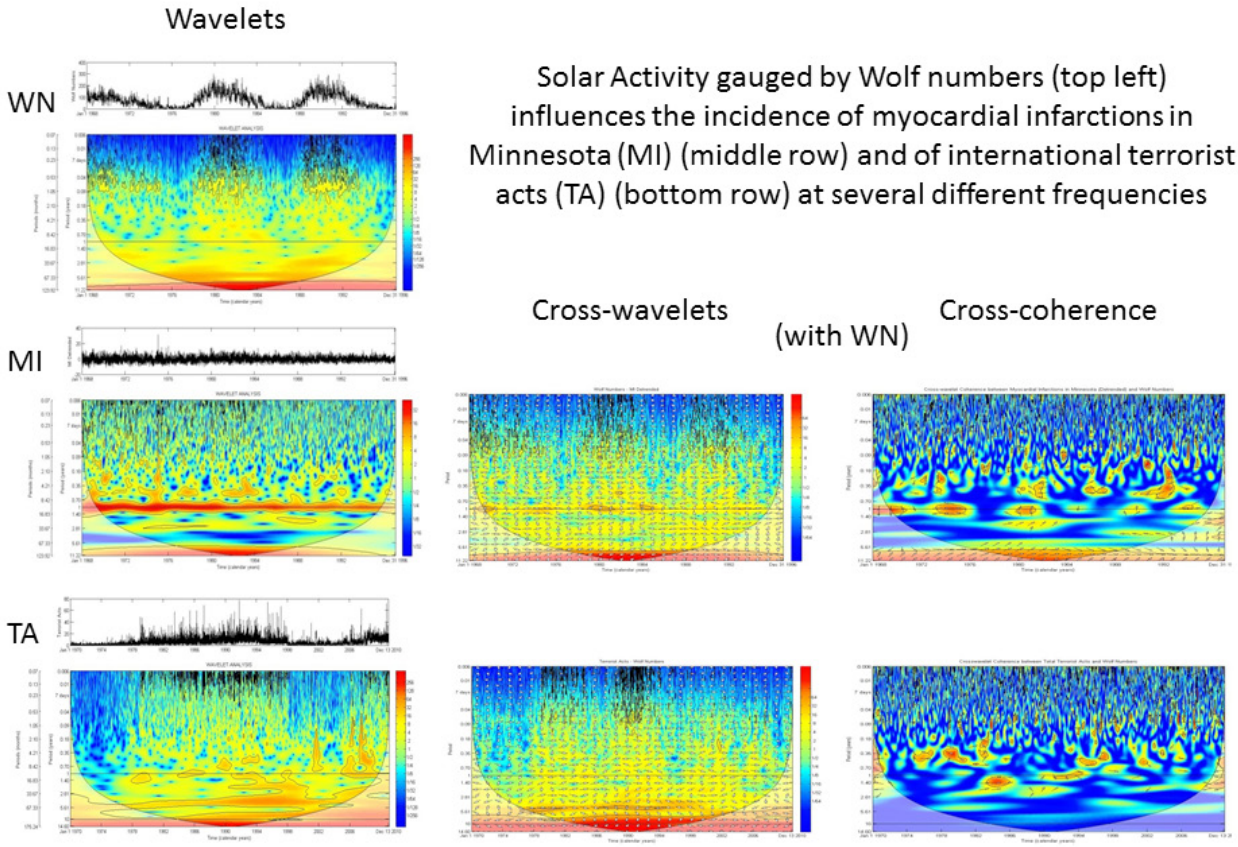


Figure 32D. Cross-wavelet coherence with Wolf numbers (WN, gauging solar activity, top row) differs between the incidence of myocardial infarctions in Minnesota (MI, middle row) and the incidence of international terrorist acts (TA, from the total Global Terrorism Database, bottom row). Whereas a low-frequency component is visible in the wavelet spectra of all three variables (left) and in the cross-wavelets of MI and TA with WN (middle), only MI (but not TA) shows coherence in this region. © Halberg.

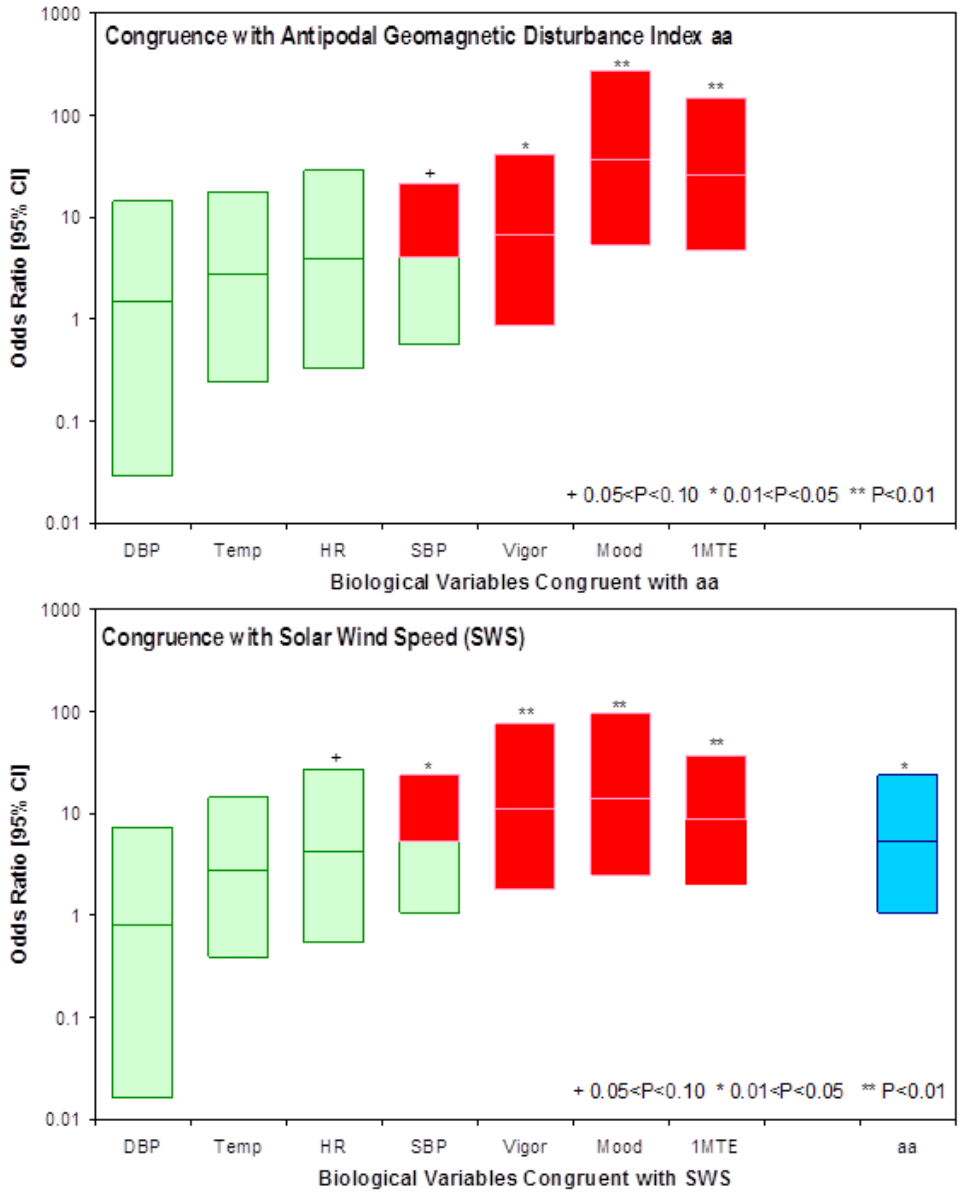


Figure 33. Anticipated influence of the antipodal index of geomagnetic disturbance aa (top) and of the non-photic environment (gauged by solar wind speed, an approximation of interplanetary magnetism) on human psychophysiology was assessed by means of the congruence of periods of their spectral components (defined by overlap of the 95% confidence intervals of the periods, τs, in the frequency range of one cycle in 2.5 years to 3 cycles per year). The biological data stem from 40 years of self-measurements of oral temperature (Temp), systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) and of ratings of mood and vigor and the estimation of 1-minute by counting (1MTE), performed about 5 times a day by a clinically healthy man, Dr. Robert B. Sothern. Congruences (assessed by means of odds ratios based on the noncentral hypergeometric distribution) found for 1MTE and for several other variables more than equal that of the known association of helio- and geo-magnetism (bottom, last column on right of dashed vertical line in blue). Mental functions (full red) show higher congruence than somatic functions (green). Among the latter, SBP is responsive, perhaps constituting a seemingly acceptable proxy for the mental functions. P-values are based on the non-central Fisher hypergeometric distribution, with 95% confidence intervals computed using Fisher's exact test, used since the null hypothesis was rejected in some, yet not all cases. © Halberg.

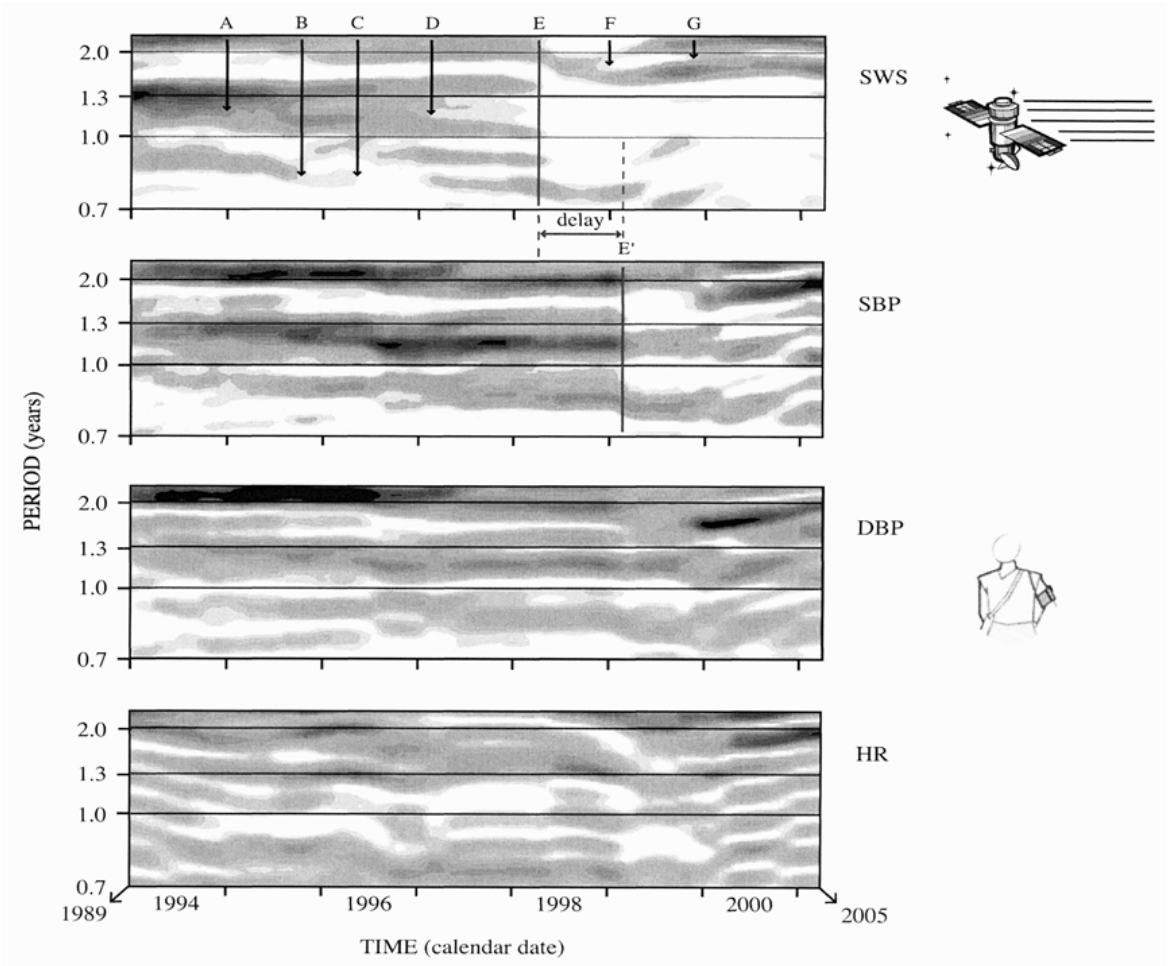
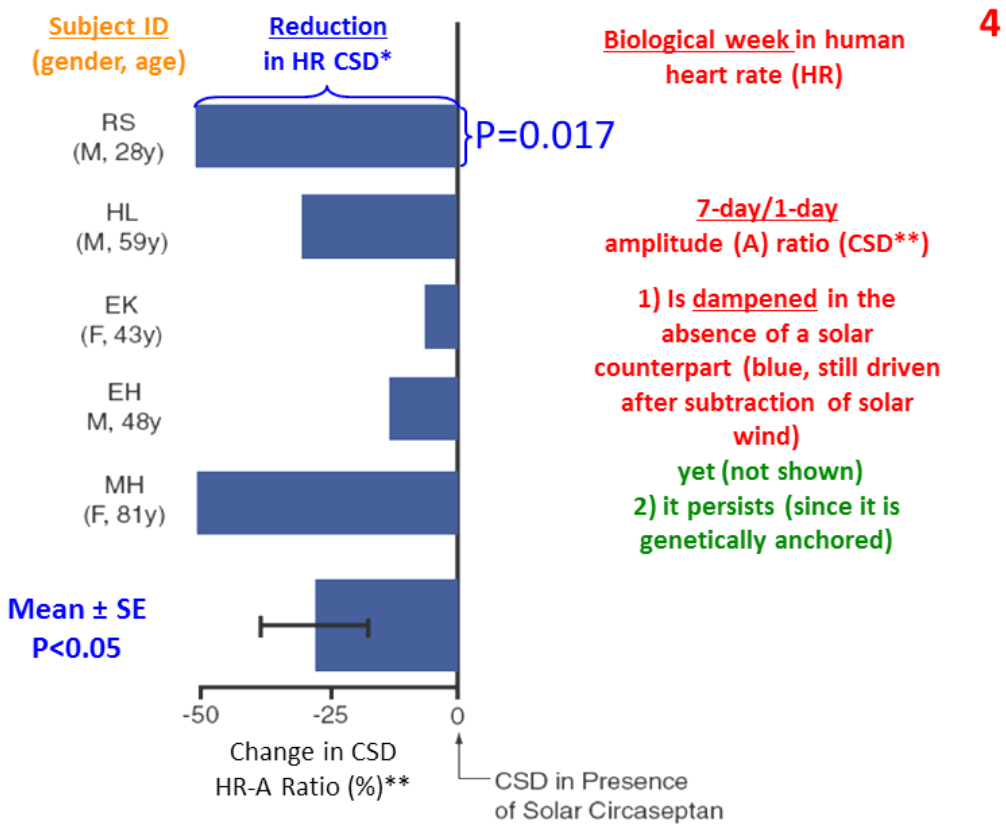


Figure 34. The transyear can prominently characterize solar wind speed, as shown in the top gliding spectral window by the wide dark band around 1.3 years (vertical scale are frequencies in the range of 1 cycle in 2 to 0.7 year(s)). This component, however, is Aeolian in nature, its characteristics (frequency and amplitude) changing as a function of time. This is exemplified around 1998 (E) when its amplitude is considerably decreased (the darker the band, the larger the amplitude is). After E, the transyear is no longer detected in solar wind speed. A transyear is also found to characterize systolic blood pressure (SBP) of a man (FH) who monitored himself around the clock for over 23 years (with interruptions), as seen in the gliding spectral window (row 2). With a lag (at E'), the transyear in FH's SBP is dampened but remains detectable, suggesting that the frequencies characterizing the solar wind may still drive us and may be built into us since they persist in the absence of a counterpart in the Sun. Somewhat similar results are also seen for diastolic blood pressure (DBP, row 3) and heart rate (HR, row 4), but they are most apparent for SBP. © *Halberg*



*CSD: circaseptan (7-day)-to-circadian (1-day) A ratio
**When 7-day component in sunspot area has no 7-day component (as analyzed by Y.S. Vernova et al., Geomagnetism and Aeronomy 1983; 23: 425-427).

Figure 35. An ~7-day spectral component in the heart rate of five men is less prominent when the solar wind loses its counterpart of corresponding length. Implied, but not shown, is the persistence in the biosphere of an ~7-day component that can be amplified (driven) by a reciprocal component in solar activity. © Halberg.

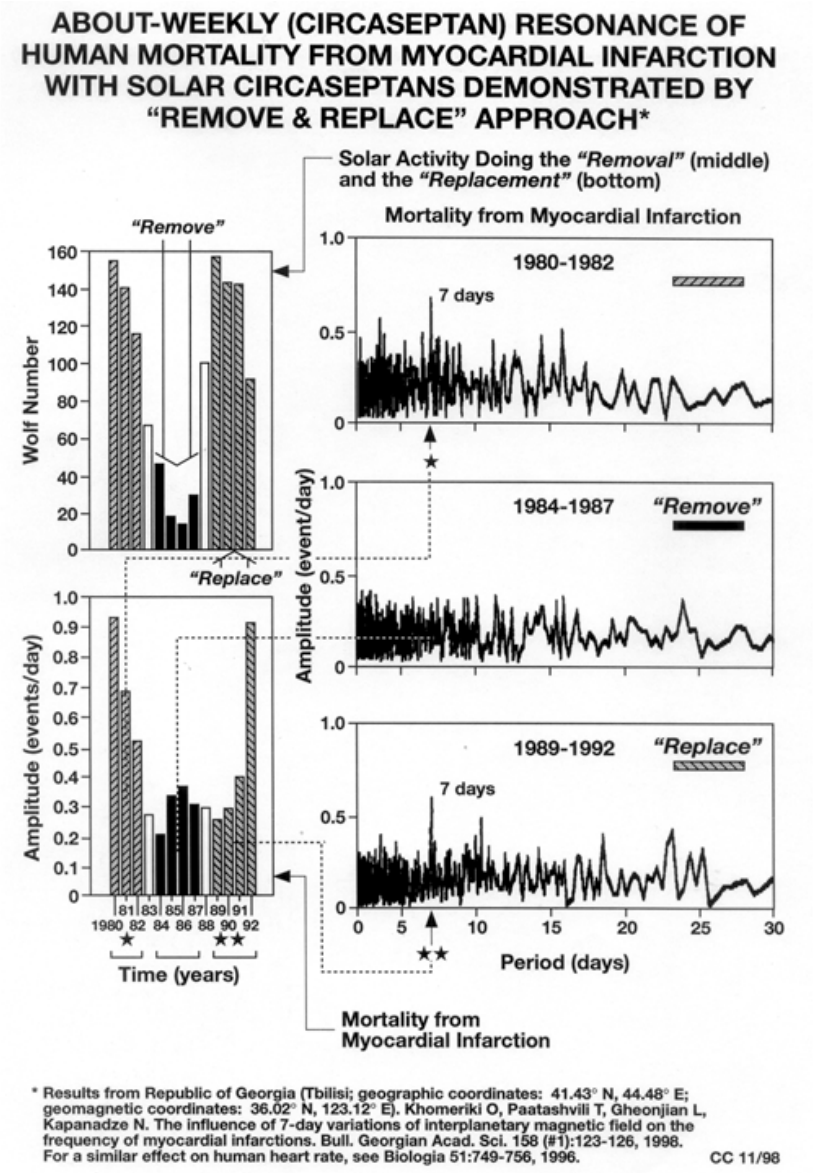


Figure 36. Another remove-and-replace approach focuses on a weekly component by investigators from the Republic of Georgia who built a clinical facility to study effects of geomagnetism. © Halberg.

PHYSICAL THERAPY (PT) CONCERNS IN THE USA COULD LEAD TO PREHABILITATION COMPLEMENTING REHABILITATION

OTHILD SCHWARTZKOPFF, GERMAINE CORNELISSEN AND FRANZ HALBERG
Halberg Chronobiology Center, University of Minnesota, Minneapolis, MN, USA

The main point from a publication in Physical Therapy 2011 (Nov 11); 91 (11) by Sullivan KJ et al. is described in its title: "A vision for society by the American Physical Therapy Association [APTA]: physical therapy as partners [sic] in the national health agenda". Once PT is recognized as an equal partner in the execution of health care, there is the urge, and also a necessity, to give PT professionals a broader field of responsibility, a stronger self-awareness and a better public perception of physical therapy as a doctoring profession. A more affordable health care could also have an impact on the demand for PT services.

The physical therapist is described as "part of the health care professional workforce, qualified to practice as one of the 'health diagnosing and treating practitioners' " in the 2010–2011 edition of the US Department of Labor's Occupational Outlook Handbook. The aim and desire for the future would be to be part of the health care professional workforce, qualified to practice, as diagnosing and treating practitioners and to be active also in health promotion.

It will be necessary to advance the professional preparation of the physical therapist to achieve a clinical doctorate for access and autonomy of care. With it comes professional responsibility, including ethical and moral duty of the profession, meeting the needs of the society and new responsibilities should be seen as a social contract.

Let us add that, as a first step toward these goals, PT can enter and map the otherwise neglected normal range, in order to detect variability disorders with modern technology, in particular vascular variability anomalies, VVAs, disorders, VVDs, and, while VVDs accumulate, vascular variability syndromes, VVSs, mostly new diagnoses to be acted upon to maintain wellness. As an important first step toward this goal, C-ABPM could detect VVAs and could be a marker for other variability disorders more generally with respect to the dynamics of the normal range of variation, which can be explored in time series but not in spotchecks, a challenge already met by the initiation of C-ABPM in Brno (2–5). Part of the senior author's (OS) personal monitoring will be demonstrated in a companion presentation from our institute, documenting technical details. The merits of a glocal (**glo**bal + lo**cal**) analysis of time series (e.g., of paired consecutive daily and weekly summaries of the same data emerge. Artifacts from gaps in the data are shortcomings. Nonetheless, the possibility of learning about differing solar effects upon different variables of the same person is noted, as is the plan for pooling results on individuals to also examine the dynamics of populations.

Support: GM-13981 (FH), University of Minnesota Supercomputing Institute (GC, FH)

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INTERNATIONAL PROJECTS "WOMB TO TOMB" AND "BIOCOS (BIOSPHERE AND THE COSMOS)" IN HALBERG CHRONOBIOLOGY CENTER, MINNESOTA: GERMAINE CORNELISSEN

JARMILA SIEGELOVA
Dept. of Physiotherapy and Rehabilitation, Dept. of Sports Medicine and Rehabilitation, Faculty of Medicine, Masaryk University, St. Ann's University Hospital in Brno

Prof. Dr. Germaine Cornelissen, Ph.D.

I am honored to be asked to mention the contribution of my friend Prof. Germaine Cornelissen to the chronobiology in the last thirty years. Prof. Germaine Cornelissen is a long-time coworker of Prof. Franz Halberg in Halberg Chronobiology Center, University of Minnesota, USA.

Prof. Germaine Cornelissen is professor in the Department of Integrative Biology and Physiology and co-Director of Halberg University Center, University of Minnesota, Minneapolis, USA from 2008 until now.

Prof. Germaine Cornelissen was born on November 22, 1949 in Brussels. She studied Physics in University of Brussels, where she graduated in 1971 (M.S. in Physics and M.Ed., University of Brussels). She continued her studies and in 1976 she obtained the degree Ph.D. in Physics in University of Brussels.

Prof. Cornelissen started studies in her main scientific task - chronobiology in 1976 in the Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis headed by Prof. Franz Halberg, founder of modern chronobiology. As a fellow (1976–1982) she admired all new scientific approaches and findings in chronobiology, she used her knowledge in physics and mathematics and applied it to chronobiology. At that time Dr. Germaine Cornelissen was a very hard working scientist who in the team of Prof. Franz Halberg cooperated with scientists in many countries and summarized a lot of chronobiological data, covering practice and theory of chronobiology. She was awarded for her intensive scientific work in chronobiology in 1983 with Hoest Foundation Chronobiologia Award. From 1982 to 1991 she held the position of Associate and later Assistant Professor (1987–1992) in the Department of

Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, USA. At that time she was also Member of the board in International Society for Chronobiology (1985–1995).

In 1990 Prof. Franz Halberg and Prof. Germaine Cornelissen 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 Cornelissen 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 subject 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 Cornelissen 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 in the following day analyzed by Prof. G. Cornelissen. 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. Cornelissen, 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 Cornelissen prepared a lot of publications for congresses and symposia in Brno.

The Brno team visited Minnesota in 1995 and at that time Prof. Germaine Cornelissen together with the Brno team evaluated two ambulatory monitors when the scientists measured themselves. The scientific team placed blood pressure cuffs on both arms and carried it fourteen days. The results were evaluated and published also by Prof. Cornelissen.

In 1987 Prof. Cornelissen was appointed the secretary in North American branch of the International Society for Research on Civilization Diseases and the Environment (SRMCE). She summarized and published a lot of papers about risks of civilization in morbidity and mortality of cardiovascular diseases. In 1994 Prof. Cornelissen became coordinator of international chronobiology project Womb-to-Tomb Study, now BIOCOS (BIOsphere and the COSmos). The Brno team is a member of both international projects.

On November 22, 1994 BIOCOS was described for the first time. The Biosphere and the Cosmos, BIOCOS, as the task of building a novel transdisciplinary spectrum was pursued, and further periods of decades, centuries, and thousands and millions of years were documented. Much of the evidence was provided very successfully by Germaine Cornelissen, Ph.D., Professor of Integrative Biology and Physiology at the University of Minnesota.

Scientific capabilities of Prof. Cornelissen were appreciated by a number of awards, citations and membership in scientific organizations. Prof. Cornelissen is Member of Sigma Xi Society since 1988, Member of Editorial Board of Chronobiologia from 1989 to1991, of Editorial Board of Il Policlinico from 1991 to 1996, contributes to Neuroendocrinology Letters since 1999, Geronto-Geriatrics since 1999, Journal of Applied Biomedicine since 2006, World

Heart Journal since 2007, Journal of Experimental Therapeutics and Oncology since 2010, was Co-Editor of Chronobiologia from 1991 to 1994, Guest Editor of Psychophysiology (1992), Neuroendocrinology Letters (2003), The Open Nutriceuticals Journal (2012), was on Board of Directors, Underlab Project (Ancona, Italy) (1993–1996), has been Member Book Committee, National Chapters of Phi Beta Kappa since 2000. She became Honorary Member of Cardiff Scientific Society (2002), Advisory Board in International College of Nutrition and International College of Cardiology, MEODEA, Moradabad, India (2005), Foreign Member of Problem Commission on Chronobiology and Chronomedicine in Russian Academy of Medical Sciences (2006), Member of Leibniz Society, former Academy of Science of the German Democratic Republic (2009), Member of International Academy of Science (2010).

Prof. Cornelissen participated in many international Congresses and Symposia and workshops. In 2008 Dr. Germaine Cornelissen was appointed Professor in Department of Integrative Biology and Physiology, and co-Director of Halberg Chronobiology Center, University of Minnesota, Minneapolis, USA. Prof. Cornelissen crossed from physics to biomedicine and added a lot of transdisciplinary information. In chronobiology one of her most important challenges remains, in all zones on earth and beyond, to be the exploitation of vascular variability disorders in man for a universal preventive health care based on cyber-implemented self-help in collecting time series of chronobiological measurement for the multiple Chronobiologic purposes the time series of biological data may serve in health care to minimize the cardiovascular evence like stroke, infarctus of myocardium and other serious diseases in prevention for individuals first and foremost.

Profits of her many chronobiological analyses of data from all over the world relate both to medical and transdisciplinary research. Medically, by her analyses of data, she compares the relative merits of harbingers of risk. In addition, she seeks an understanding of the effects of the sun in dealing with aggression and other diseases of society. The effects of the sun on living organism and man are now shown by Prof. Cornelissen and are documented in many chronobiological papers.

I thank prof. Germanine Cornelissen for a long lasting cooperation with Masaryk University and I hope for the continuation for the future.

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CLINICAL APPLICATION OF CARDIO-ANKLE VASCULAR INDEX (CAVI) AS A MARKER OF ARTERIAL WALL STIFFNESS

KOHJI SHIRAI, [1] NORIO SATO
Division of Vascular Function, Internal Medicine, Sakura Hospital, Tōho University Chiba, Japan, [1] Fukuda Denshi Co., Tokyo, Japan

PRINCIPLE OF CAVI

The Cardio-Ankle Vascular Index (CAVI) is a new indicator of the stiffness of arteries from the origin of the aorta to the ankle of the lower leg. The method to measure CAVI is illustrated in Fig.1.

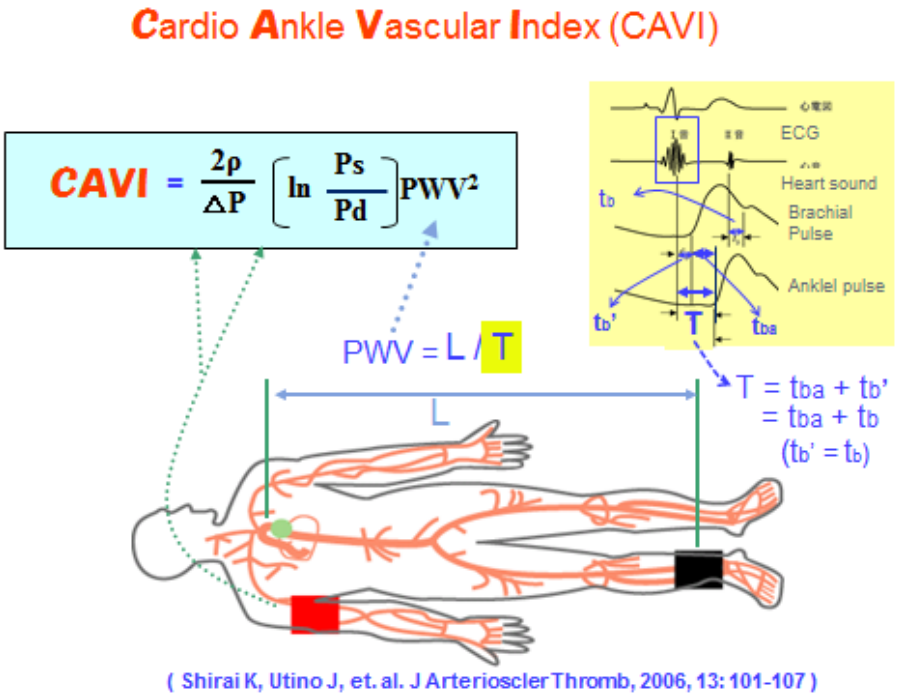

Figure 1.

A subject is placed in supine position and electrocardiogram and heart sound are monitored. PWV between heart and ankle is obtained by L/T where L is the distance from the aortic valve to the ankle, and T is the time during which PWV propagates from the aortic valve to the ankle (or the sum of tb and tba in place of t'b and tba, because t'b and tb are theoretically equal: tba is the time between the rise of the brachial pulse wave and the rise of the ankle pulse wave, tb is the time between the aortic valve's closing sound and the notch of the brachial pulse wave, and t'b is the time between the aortic valve's opening sound and the rise of the brachial pulse wave). The scale conversion from PWV to CAVI is performed by the following formula:

$$\mathbf{CAVI = a\,[\{2}\rho \times 1/(SBP - DBP)\} \times \{\ln (SBP/DBP) \times PWV^2\}\mathbf{] + b}$$

where SBP and DBP are systolic and diastolic blood pressure values, respectively, PWV is the pulse wave velocity between heart and ankle, ρ is blood density, and a and b are constants. This equation was derived from Bramwell-Hill's equation and stiffness parameter ß (1). Scale conversion constants are determined so as to match CAVI with PWV by Hasegawa's method (2). CAVI, a stiffness and arteriosclerosis indicator of thorax, abdomen, common iliac, femoral and tibial arteries, was measured by VaSera VS-1500 manufactured by Fukuda-Denshi Company, LTD (Tokyo, Japan). CAVI is essentially independent of blood pressure at a measuring time (Fig. 2).

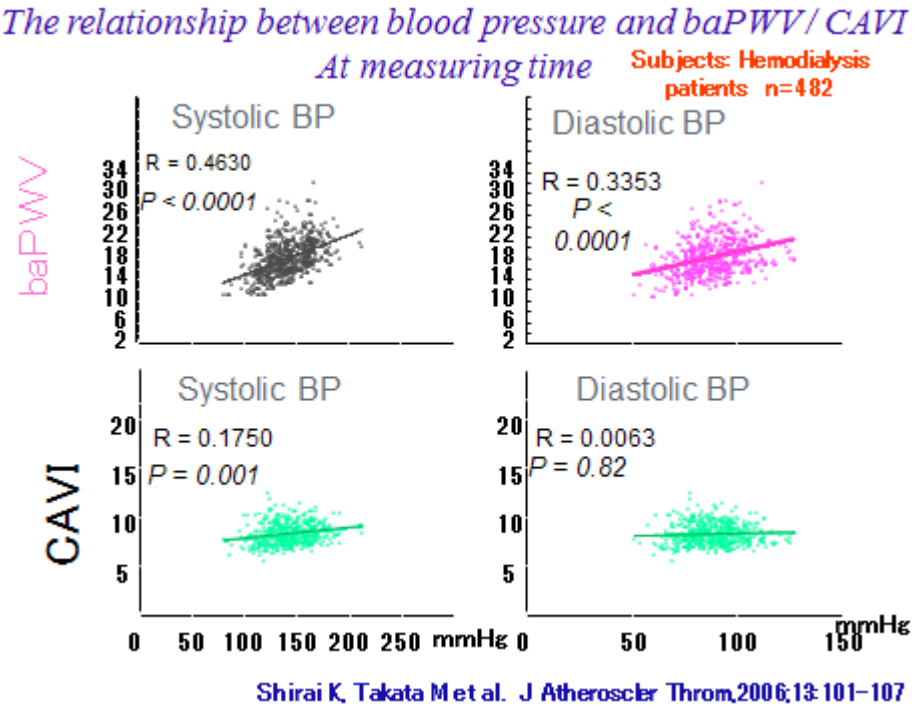

Figure 2.

This was first confirmed in the study by Shirai K. et al (2011) using adrenergic β1 receptor-blocking agent in humans (3). When metoprolol a selective β1-blocking agent was administered, blood pressure decreased (probably due to the decrease in cardiac contraction) and also the pulse wave velocity (PWV). At this time CAVI remained constant (Fig. 3, left). When α-blocker doxazosin was administered (Fig. 3, right), CAVI decreased as well as PWV. These results indicated that CAVI reflects the smooth muscle cell contracture. Then, it is suggested that CAVI is composed of both organic functional stiffness.

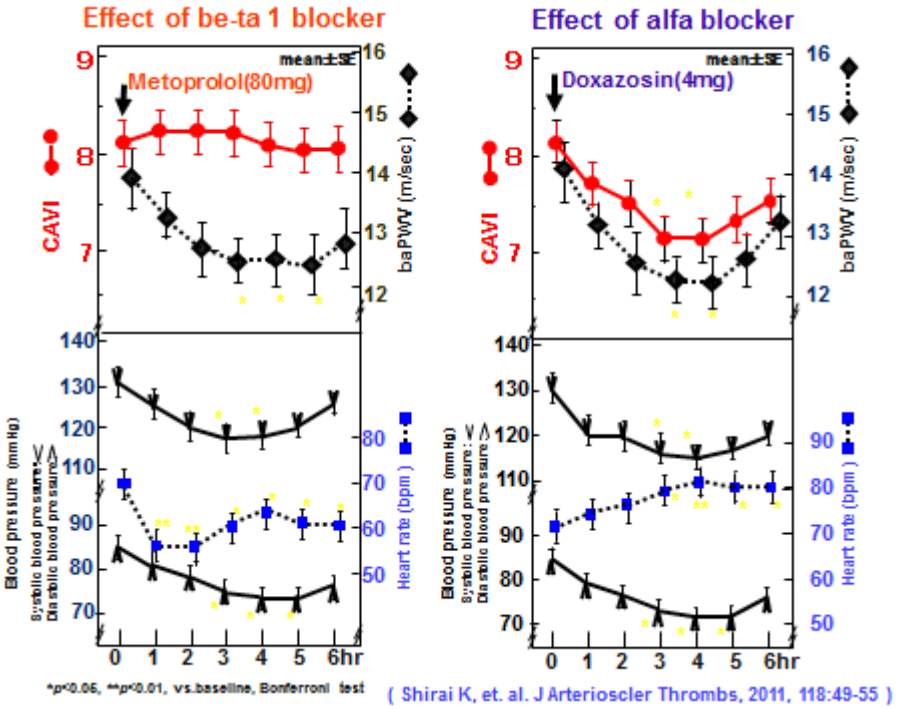

Fig. 3

CAVI IN VARIOUS ARTERIOSCLEROTIC DISEASES

The association between serum lipid levels and atherosclerotic disease, namely coronary heart disease, has been established through the findings from several epidemiological studies such as the Seven Countries Study (4) or Multiple Risk Factor Intervention Trial Study (5). Nakamura et al. (2008) reported that the number of stenotic coronary vessels correlates with CAVI in patients with suspected ischemic coronary disease who took a coronary angiography (6). Namekata et al. reported that abnormally high PWV was significantly associated with 4.5 or greater value of the ratio of total cholesterol to high density lipoprotein (HDL) cholesterol implying that abnormal lipid imbalance is a risk factor of arterial stiffness and arteriosclerosis (7). Aging is the strongest risk factor of arteriosclerosis. With increasing age the CAVI value of both men and women becomes higher (Fig.4).

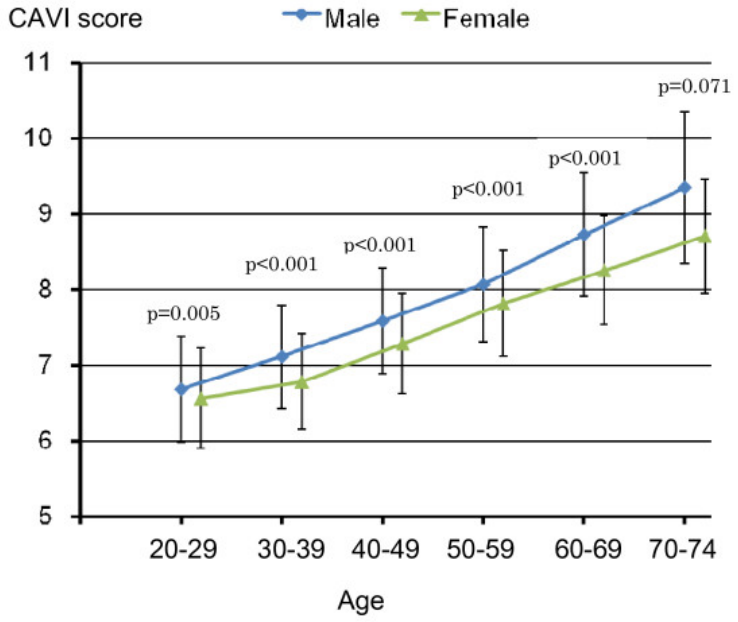

Figure 4. Differences in average CAVI scores by age between males (blue line) and females (green line) among CVD risk-free individuals based on results shown in Table 2 (Vertical bars indicate standard deviation).

CAVI value is approximately 0.5 higher in men than women (equivalent to 10 years of age). A recent report supports such an association by showing that age-specific average CAVI scores among persons with hypercholesterolemia and hypertriglyceridemia of ages 40 and over were significantly greater than those among CVD risk-free persons for the same age-specific groups (8). This same study have shown that age-specific average CAVI scores of all CVD high-risk persons combined were significantly higher than those of the CVD risk-free group after 40 years of age indicating that the overall arteriosclerosis status of the CVD high-risk group was significantly worse than that of the CVD risk-free group. Because no difference in average CAVI scores between the two groups was detected before 40 years of age, effective CAVI screening might be recommended for people age 40 and over. CAVI can demonstrate the true effects of blood pressure on the properties of arterial wall. CAVI declines with valsartan, olmesartan, and candesartan among the angiotensin II receptor blockers (ARBs). Comparison between ARB and calcium channel blockers showed, that olmesartan improves CAVI much more than amlodipine despite equivalent decrease in blood pressure (9). This was the first time to demonstrate the effects of blood pressure decreasing drugs on arterial stiffness using by CAVI only. CAVI shows a higher value during acute phase of increased glucose level and also in chronic hyperglycemia. CAVI decreases by controlling HbA1c using drugs such as insulin, glicranide, and DPP-4 inhibitor. It seems that CAVI might be a good marker of blood glucose control in routine clinical practice. Diabetes mellitus is proven to be a risk factor for cardiovascular disease (10). It was reported that cardiovascular risk among diabetic subjects was 5 times higher than among non-diabetics and PWV values were associated with fasting glucose levels among diabetics (11). An odds ratio for having abnormally high PWV among diabetics is also reported to be 3.66

($p < 0.001$) as compared to non-diabetics (7). These results also confirm significantly higher average age-specific CAVI scores among persons with hyperglycemia after 40 years of age than those among CVD risk-free persons. Higher values of CAVI were found in subjects with dyslipidemia (12). However, CAVI is not necessarily high in familial hypercholesterolemia (LDL-receptor deficiency). In the initial stages of arteriosclerosis in hypercholesterolemia, fatty streak are present but the arteries do not stiffen and CAVI might not be elevated. Stiffness of the arterial wall increases only when chronic inflammatory reaction occurs. Administration of pitavastatin reduces CAVI (13). CAVI value is high in smokers and smoking cessation reduces CAVI in few months (14). Kato et al. (2011) showed that high CAVI values in patients with sleep apnea syndrome (15) could be decreased after administration of continuous positive pressure assisting therapy (CPAP). It is possible to conclude that all of the cardiovascular risk factors are integrated into the smooth muscle cells layer in the artery wall, resulting in an elevation of CAVI (Fig.5).

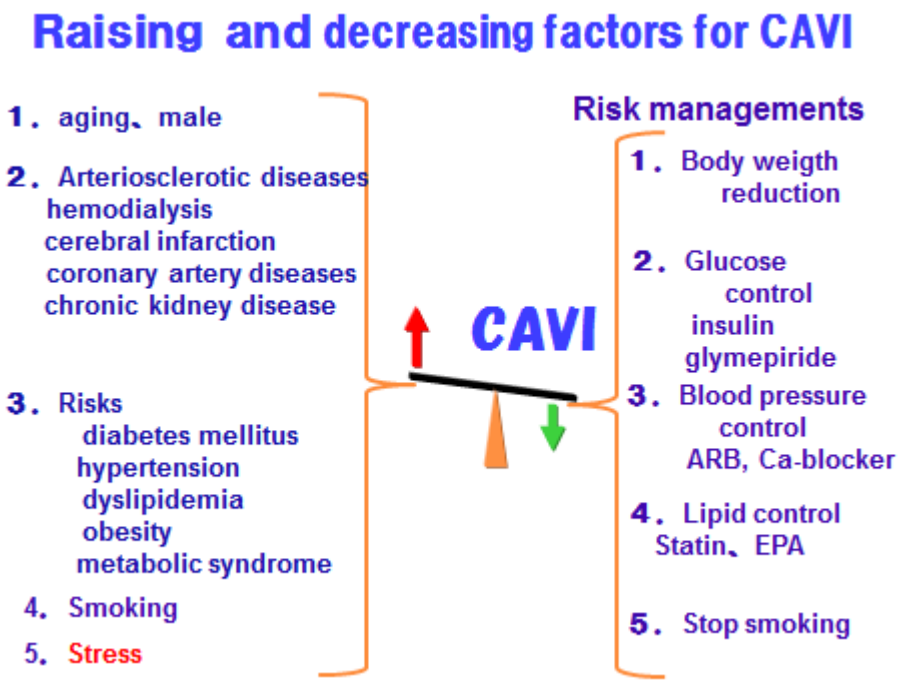

Figure 5.

Our preliminary and unpublished data also showed that the incidence of death (in 5 years) in subjects with CAVI value under 9 was significantly lower compared to 506 high risk patients with CAVI over 9.

CONCLUSION AND FUTURE OF CAVI

VaSera VS-1500, which was used in above mentioned studies, was designed to measure CAVI scores independent of blood pressure and CAVI scores represent the extent of arteriosclerosis between the aortic valve and the ankle. CAVI scores allows to evaluate the extent of arteriosclerosis in the major arteries between the aortic valve and the ankle, to screen persons with subclinical stage of CVD, and provide an opportunity to modify diet and lifestyle to improve CAVI scores as reported by Satoh et al (2008). Thus, the use of CAVI scores potentially leads to savings on high treatment costs and to prolonging many productive lives (16). CAVI is not only a good surrogate marker of arteriosclerosis but also reflects actual compliance of the artery. Analysis of vascular functions using CAVI will develop a new field in clinical medicine.

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CIGARETTE SMOKING AND THE CARDIO-ANKLE VASCULAR INDEX (CAVI) OF ARTERIAL STIFFNESS: A REPORT FROM CZECH POPULATION DATASET

PETR DOBSAK, [A] VLADIMIR SOSKA, [B] ONDREJ SOCHOR, MICHAELA FRANTISOVA, [B] VLASTIMIL RACEK, PAVEL HOMOLKA, PAVEL VANK, MICHAELA SOSIKOVA, [C] LADISLAV DUSEK L., [C] JIRI JARKOVSKY, [D] MARIE NOVAKOVA, JARMILA SIEGELOVA

Department of Physiotherapy and Department of Sports Medicine and Rehabilitation, Faculty of Medicine, Masaryk University, St. Ann's University Hospital in Brno, Czech Republic

[a] Department of Biochemistry, Faculty of Medicine, Masaryk University, Brno, Czech Republic, [b] 2nd Department of Internal Medicine, St. Ann's University Hospital in Brno and Masaryk University, Brno, Czech Republic, [c] Institute of Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Brno, Czech Republic, [d] Institute of Physiology, Faculty of Medicine, Masaryk University, Brno, Czech Republic

ABSTRACT

This study focused on the effects of chronic smoking on the elasticity of large arteries in healthy smokers (349 males, 291 females) and nonsmokers (1.089 males, 400 females). Mean age range was 20–40 years. Arterial stiffness was measured by the device VaSera® 1500 (Fukuda Denshi Co., Tokyo, J) and expressed as cardio-ankle vascular index (CAVI). Statistical analysis showed a significantly higher CAVI in chronic smokers of both sexes than in healthy controls ($P < 0.01$). It is possible to conclude that long-term cigarette smoking increases significantly global arterial stiffness and thus represents also a higher risk of future cardiovascular event.

KEY WORDS

arterial stiffness; cardio-ankle vascular index (CAVI); smoking

INTRODUCTION

Tobacco smoking has been proven to be a major risk factor in the development and progression of cardiovascular diseases. (1). Chronic smoking increases arterial stiffness (AS) and this may play a crucial role in the development of hypertension and arteriosclerosis (2). High AS (recognized as an independent predictor of cardiovascular death) is characterized by reduced capacity of arterial vascular tree and strong increase of pulse pressure and shear stress (3, 4). Therefore, quick and simple non-invasive monitoring of AS is considered as very valuable approach in the early prevention of the onset of cardiovascular diseases. The traditional, still widely used method for early detection of the arteriosclerotic process is the measurement of brachio-ankle pulse wave velocity (baPWV – 5, 6). Parameter baPWV provides precise data but is strongly influenced by actual changes of blood pressure (BP). This means that its assessment and interpretation is sometimes difficult and inaccurate. Only few years ago Japanese scientists developed and introduced into clinical praxis a new method for non-invasive measurement of AS. This method is based on the parameter which defines arterial wall stiffness called cardio-ankle vascular index (CAVI). CAVI measures the pulse-wave velocity (PWV) from heart to ankles and blood pressure and reflects the elastic features of the arterial wall between aorta and great peripheral arteries (7). Several reports clearly demonstrated that CAVI is associated with the development of atherosclerosis in large arteries (8, 9). CAVI has one unique advantage – contrary to baPWV, its value is not influenced by BP at the time of measurement (10). However, the vast majority of available data regarding the use of CAVI was done by the Japanese authors and currently there is only minimal experience with CAVI

measurement in European populations. The aim of this study was to assess the values of parameter CAVI in healthy non-smokers and their comparison with chronic smokers in Czech population sample.

PATIENTS AND METHODS

Recruitment of healthy volunteers was carried out in St.Anna Faculty Hospital in Brno by a campaign in radio and newspapers. In total, 1434 (743 men; 691 women) volunteers (age range 20 to 40 years) accepted to participate in the study. The smoking habits and the health status were assessed by a simple questionnaire. Then, the subjects were divided into 2 groups: a) group smokers, and b) controls. Smoking male subjects (n = 349) smoked on average 10 cigarettes/day for 8.5 ± 4.2 years; the smoking females (n = 291) smoked on average 6 cigarettes/day for 6.1 ± 2.4 years. None of the subjects from both groups had hypertension, diabetes mellitus or cardiovascular disease. CAVI in both groups was measured by VaSera® 1500 device (Fukuda Denshi Co, Tokyo, Japan) using standard protocol published previously (11). Examination was performed in supine position. Four pressure cuffs were placed on limbs, 1 microphone (phonocardiogram) above upper margin of sternum and 2 ECG leads on both upper limbs. CAVI was automatically calculated according to following formula:

$$\mathbf{CAVI = a\,[\{2\rho\ x\ 1/(SBP - DBP)\}\ x\ ln\ \{(SBP/DBP)\ x\ PWV^2]\} + b}$$

(ρ = blood density; a and b = constants)

In order to minimize adverse effects of cuff inflation on blood flow dynamics, the pulse waves were recorded only when the cuffs were inflated to the pressure lower than the diastolic one (50mmHg). Blood pressure (BP) on limbs was measured by oscillometric method; values of systolic BP (SBP), diastolic BP (DBP) and pulse pressure (PP) were obtained from record of BP on right brachial artery. Subjects with ankle-brachial index (ABI) lower than 0.9 were excluded from this study.

Statistical analysis was performed by the Institute of Biostatistics and Analyses (Faculty of Medicine, Masaryk University Brno, Czech Republic) using SPSS 19.0.1 (IBM Corporation, 2010). The differences between smokers and nonsmokers were analyzed using one-way ANOVA followed by Tukey post-hoc test and expressed as mean ± SD. The value of $P < 0.05$ was considered as significant.

All patients signed informed consent to participate in the study. The study was approved by the local Ethics Committee and conforms to the principles outlined in the Declaration of Helsinki (revised 2000) and to the GCP guidelines of the European Community.

RESULTS

The mean CAVI value in chronic male smokers was significantly higher (**Fig. 1**) than in male controls (8.1 ± 2.6 vs. 7.2 ± 2.9; $P < 0.01$).

Similar results were found also when compared smoking and nonsmoking females (**Fig. 2**): the mean value of CAVI in female smokers was significantly higher than in female controls (7.3 ± 3.8 vs. 6.4 ± 2.5; $P < 0.05$).

There were no significant differences in systolic (SBP) and diastolic (DBP) blood pressure at the time of measurement between groups of male smokers (SBP was 128.3 ± 7 and DBP 82.7 ± 6 mmHg; NS) and male controls (SBP was 130.2 ± 5 and DBP 85.2 ± 7 mmHg; NS). Similar finding was also observed in the female smokers (SBP was 125.6 ± 8 and DBP 77.1 ± 5 mmHg; NS) and female controls (SBP was 126.9 ± 7 and DBP 75.5 ± 7 mmHg; NS).

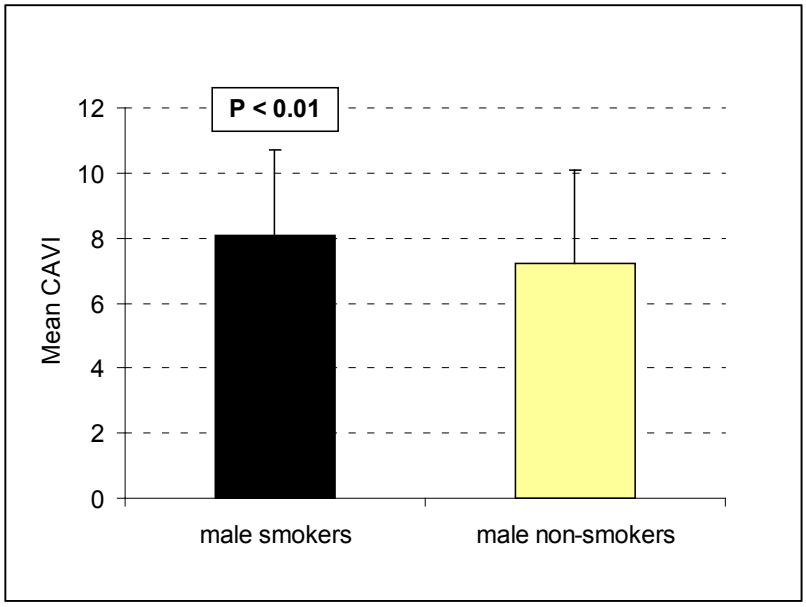

Figure 1. Comparison of CAVI value in male smokers and non-smokers (mean ± SD).

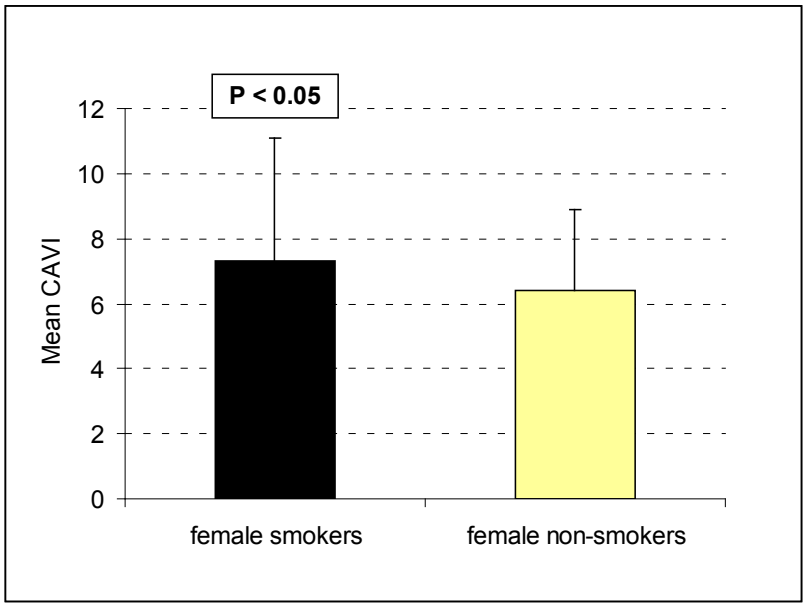

Figure 2. Comparison of CAVI value in female smokers and non-smokers (mean ± SD).

DISCUSSION

There is no doubt that cigarette smoking compromises the stability of the vessel wall, resulting in arterial stiffening. A number of pathophysiological mechanisms responsible for the increased arterial stiffness by chronic inhalation of tobacco smoke were identified. Fundamental is the effect of nicotine which stimulates central nervous system and enhances the release of catecholamines from sympathetic ganglia. The permanent presence of high plasmatic level of these vasoconstrictory substances can lead to impaired nitric oxide production and underlies the progression of endothelial dysfunction (12, 13).

The present brief report has shown a significant effect of chronic cigarette smoking on the increase of arterial stiffness of large arteries assessed by parameter CAVI. Furthermore, we have demonstrated that the deleterious effect of chronic smoking is present in relatively young people (20–40 years) regardless of their gender. Our results per-

formed in Czech population sample suggest also that the hemodynamic consequences of chronic smoking may have been underestimated. Arterial stiffness is now widely recognized as a more sensitive prognostic factor of vascular events than either systolic or diastolic BP alone in adult populations. Smoking in the younger population, particularly in women, is still very frequent in many member countries of the European Union. An additional comparison of the CAVI values in smokers with preliminary interim standards for the Czech healthy population showed that elasticity of arteries in smokers (both male and female) corresponds to healthy subjects about 10 years older. From this point of view it is likely, that female gender do not play any protective role on vascular system in long-term smoking. On the other hand, early and accurate detection of arterial elasticity changes provides also an opportunity for adequate intervention, such as lifestyle modification.

Results of this study confirm the previous observations comparing smokers and non-smoking controls. Kool et al. (1993) showed that smoking decreases arterial elasticity of large elastic and medium-sized peripheral arteries (14). Another study reported an acute decrease of the compliance of radial artery after smoking of only 1 cigarette (15). Inhalation of cigarette smoke provokes deep disturbances in vascular function of central and peripheral vessels (16, 17). McVeigh et al. (1997) demonstrated strong abnormalities in the brachial artery pressure waveforms in chronic smokers (18). Moreover, cigarette smoking in older subjects without atherosclerosis is associated with rise of stiffness in carotid arteries (19). Similarly to the present study, also Kubozono et al. (2011) reported that chronic cigarette smokers have abnormal values of the CAVI and baPWV parameters (20). One most recent trial demonstrated that there is a significant association between the number of cigarettes smoked per day and arterial stiffness measured by CAVI (21). However, these harmful effects are not definite and could be reversed by smoking cessation (22).

CONCLUSION

According to the presented results chronic smokers have significantly worse arterial stiffness than non-smokers. This finding means also that long-term smoking increases the arterial wall stiffness and global cardiovascular risk. One of the main outcomes for clinical praxis is that CAVI was proven to be a valuable parameter for assessment of arterial stiffness caused by smoking. Therefore, regular CAVI monitoring in active smokers may help to popularize and enhance smoking cessation.

ACKNOWLEDGEMENT

This study was supported by **Fukuda Denshi Co., Tokyo, Japan**.

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DAY-TO-DAY VARIABILITY OF 24-HOUR MEAN BLOOD PRESSURE IN MAN: SEVEN-DAY AMBULATORY BLOOD PRESSURE MONITORING

JARMILA SIEGELOVA, ALENA HAVELKOVA, MICHAL POHANKA, JIRI DUSEK, LEONA DUNKLEROVA, PETR DOBSAK, *GERMAINE CORNELISSEN, *FRANZ HALBERG
Department of Physiotherapy, Dept. of Sport Medicine and Rehabilitation, Faculty of Medicine, Masaryk University, Brno, St. Ann's University Hospital in Brno, Czech Republic
**University of Minnesota, USA*

Dedicated to the 93rd anniversary of Prof. Franz Halberg

INTRODUCTION

Ambulatory blood pressure monitoring has an important place in defining abnormal pattern of blood pressure. Clinical measurement of blood pressure will continue to be useful for screening and management of suspected and true hypertension, ambulatory blood pressure monitoring provides considerable added value towards accurate diagnosis and provision of the optimal care in uncompleted hypertension as well as for patients with moderate or severe cardiovascular risk. The cardiovascular risk is based on assessment of all major risk factors, age, sex, waist circumferences, BMI, family history, blood lipids, glucose metabolism, style of life (Guidelines 2007).

In previous studies Halberg et al. (2009, 2010, 2011, 2012) and Siegelova et al. (2006, 2011) have shown the differences in repeated ambulatory blood pressure monitoring, therefore we started with the ambulatory blood pressure monitoring lasting seven consecutive days.

Johansson et al. in Finn-home study (2010) used the 7-day home blood pressure monitoring to demonstrate the prognostic significance of home BP and heart rate variability. Several studies indicate that home BP measurement offers better prognostic value than office BP. Results of our laboratory suggest the drawback of 24-hours ambulatory blood pressure monitoring.

METHODS

Thirty subjects (18 males, 12 females), twenty one years to seventy three years old, were recruited for seven-day blood pressure monitoring. Medical Instruments A and D (Japan) were used for ambulatory blood pressure monitoring (oscillation method). One-hour means of systolic (SBP) and diastolic blood pressure (DBP) were evaluated, where night-time was considered from midnight to 06.00 h and day-time from 10.00 to 22.00 h, avoiding the transitional periods. Mean day-time and mean night-time SBP and DBP were evaluated every day.

RESULTS

To compare 24-hour mean and 7-day means the Bland-Altman plots were constructed (Fig. 1, Fig. 2, Fig. 3, Fig. 4). The ± 1.96 standard deviation of the difference (mmHg) among the seven-day mean and every day means was 12.43 for SBP-day, 13.86 for SBP-night, 8.57 for DBP-day and 10.82 for DBP-night. Taking into account the Guidelines for Management of Hypertension (2007) all values are too large to make possible a reliable guidance of indication

for treatment based on 24-hour mean values of blood pressure. According to this the threshold for definition of hypertension for systolic blood pressure is 140 mmHg in the office or clinic. Ambulatory blood pressure monitoring values are lower, 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 blood pressure monitoring during day.

Taking 135 mmHg of day-time systolic pressure as a threshold for indication to treatment, then 13 patients (43 %) were under this value every day and nobody was over this value every day. 17 patients (57 %) were one day indicated for treatment and the other day not.

Similarly, if 120 mmHg of night-time systolic pressure is the threshold, then 10 subjects (33 %) were indicated one day for treatment and the other day not.

Corresponding value of threshold for diastolic day-time pressure is 85 mmHg, thus 22 patients (73 %) were one day indicated for treatment and the other day not and for night diastolic pressure of 70 mmHg 24 patients (80 %) were indicated one day for treatment and the other day not. Only one patient (3 %) was indicated for treatment every day on the DBP night basis.

CONCLUSION

Those data demonstrate large day-to-day SBP and DBP mean day-time and mean night-time variability and suggest that long time home BP monitoring is preferable method for diagnosis and treatment of hypertension.

Support: GM-13981 (FH), University of Minnesota Supercomputing Institute (GC, FH)

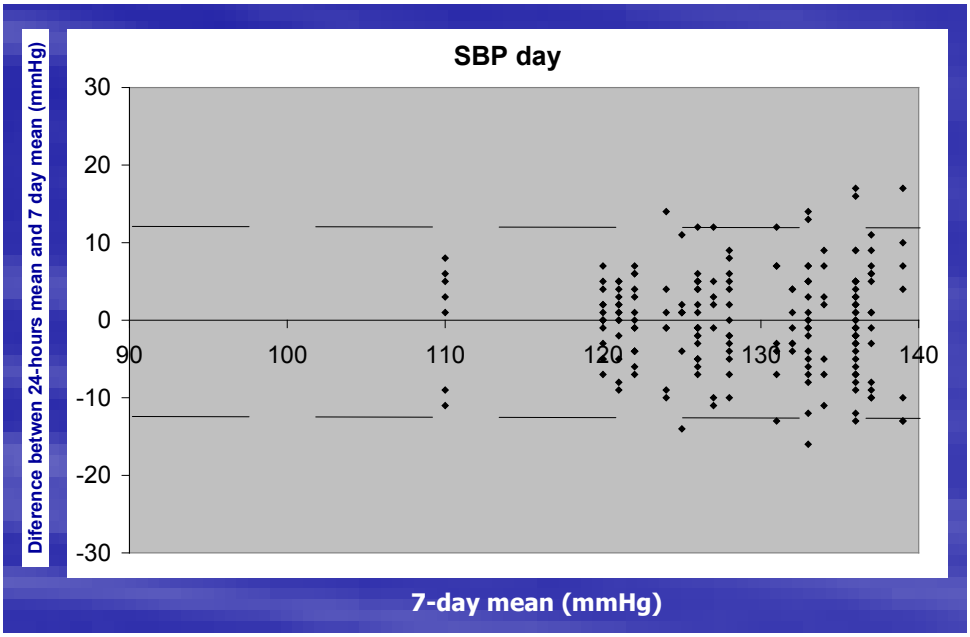

Figure 1. Bland-Altman plots. Comparisons between 7-days means and 24-hours means of SBP during day. The ± 1.96 standard deviations of the difference are indicated (dashed line).

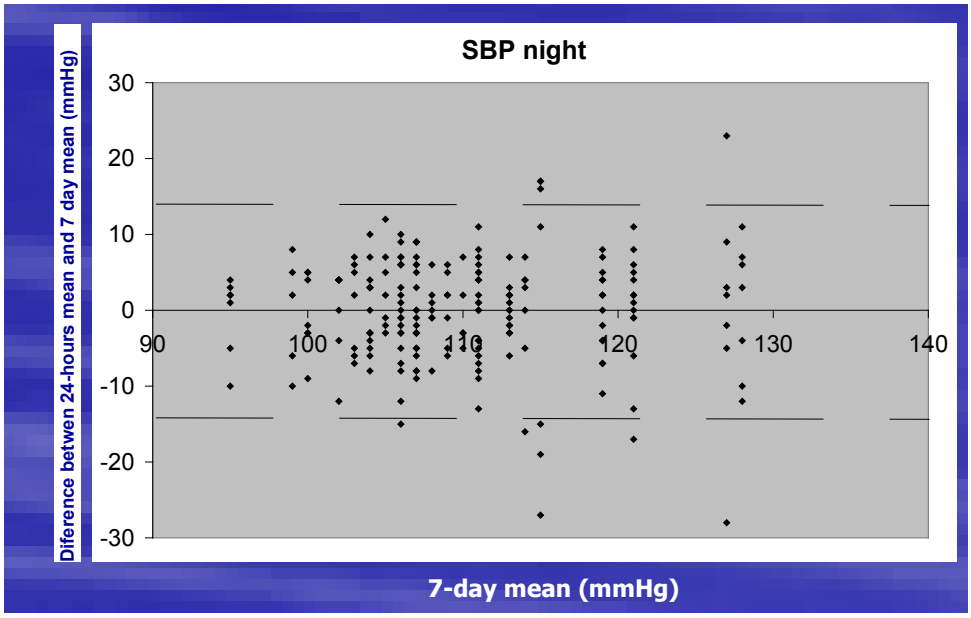

Figure 2. Bland-Altman plots. Comparisons between 7-days means and 24-hours means of SBP at night. The ± 1.96 standard deviations of the difference are indicated (dashed line).

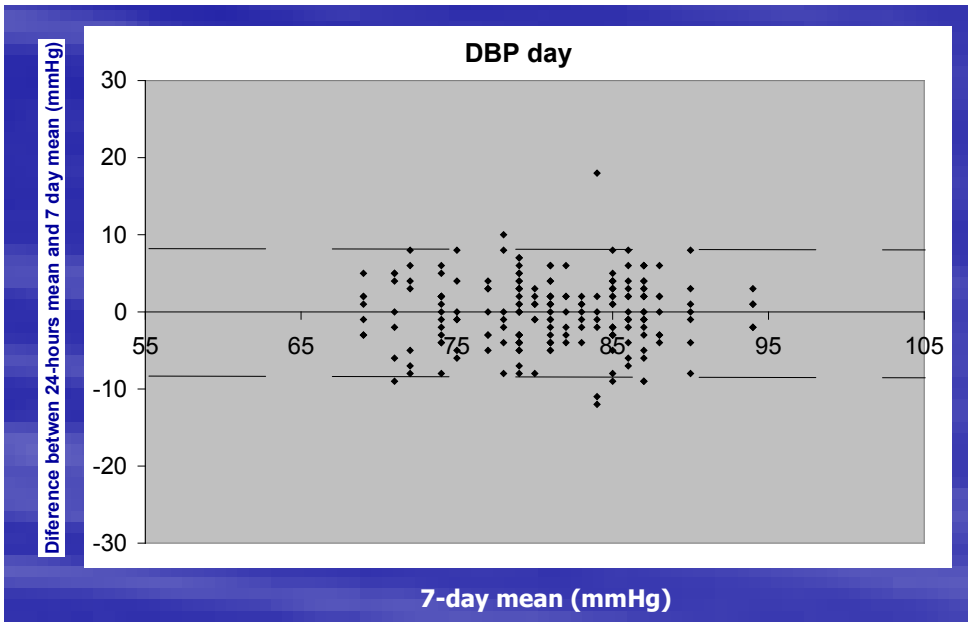

Figure 3. Bland-Altman plots. Comparisons between 7-days means and 24-hours means of DBP during day. The ± 1.96 standard deviations of the difference are indicated (dashed line).

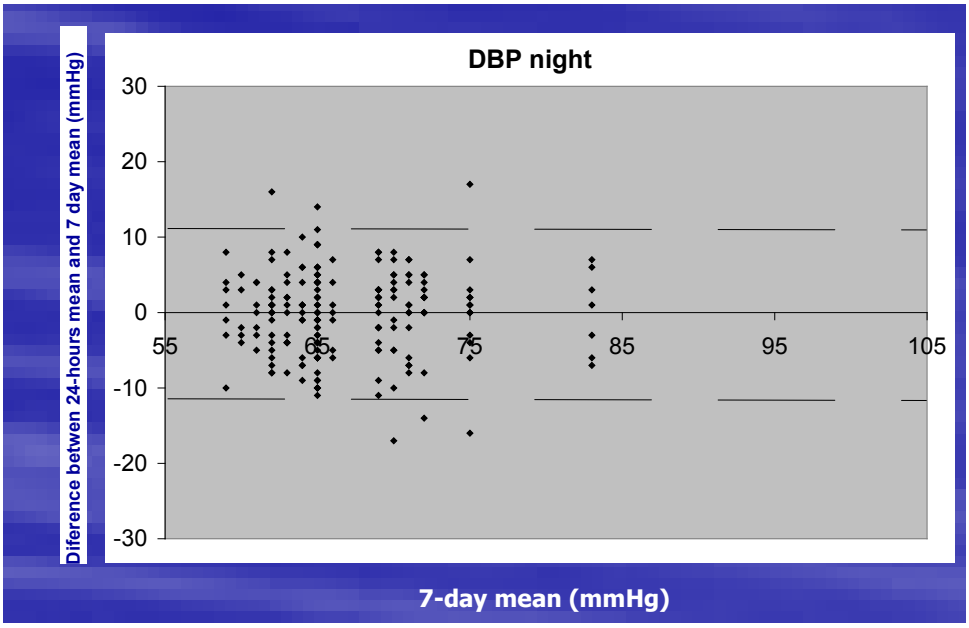

Figure 4. Bland-Altman plots. Comparisons between 7-days means and 24-hours means of DBP during night. The ± 1.96 standard deviations of the difference are indicated (dashed line).

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

JARMILA SIEGELOVA, ALENA HAVELKOVA, JIRI DUSEK, MICHAL POHANKA, LEONA DUNKLEROVA, PAVEL VANK, PETR DOBSAK, GERMAINE CORNELISSEN*, FRANZ HALBERG*
Department of Physiotherapy, Department of Sport Medicine and Rehabilitation, Faculty of Medicine, Masaryk University, St. Ann's University Hospital in Brno, CZ
**University of Minnesota, USA*

Dedicated to the 80th anniversary of Prof. Thomas Kenner

INTRODUCTION

Because 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 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).

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.

Table 1.

Table 5 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

In the presentation in 2010 we have shown that variations of night-time and day-time blood pressure during 7-day continuous ambulatory monitoring are large. In 31 healthy subjects at rest we have shown at daytime and at night big differences given in Fig. 1, 2, 3, 4.

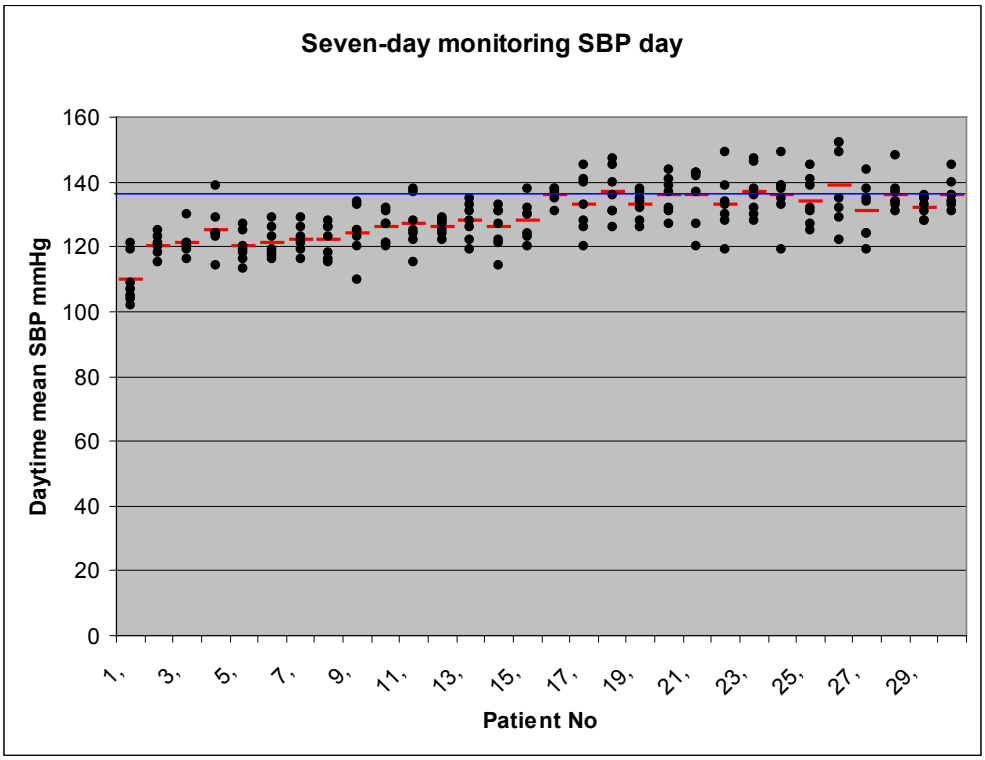

Figure 1. The variability of one-daytime SBP values during 7-day monitoring. The patients were ordered according mean 7-day SBP (patient No 1: 107 mmHg, patient No 30: 131 mmHg; median value: 123 mmHg). One-day mean values (point) and 7-day mean values (dash) are indicated.

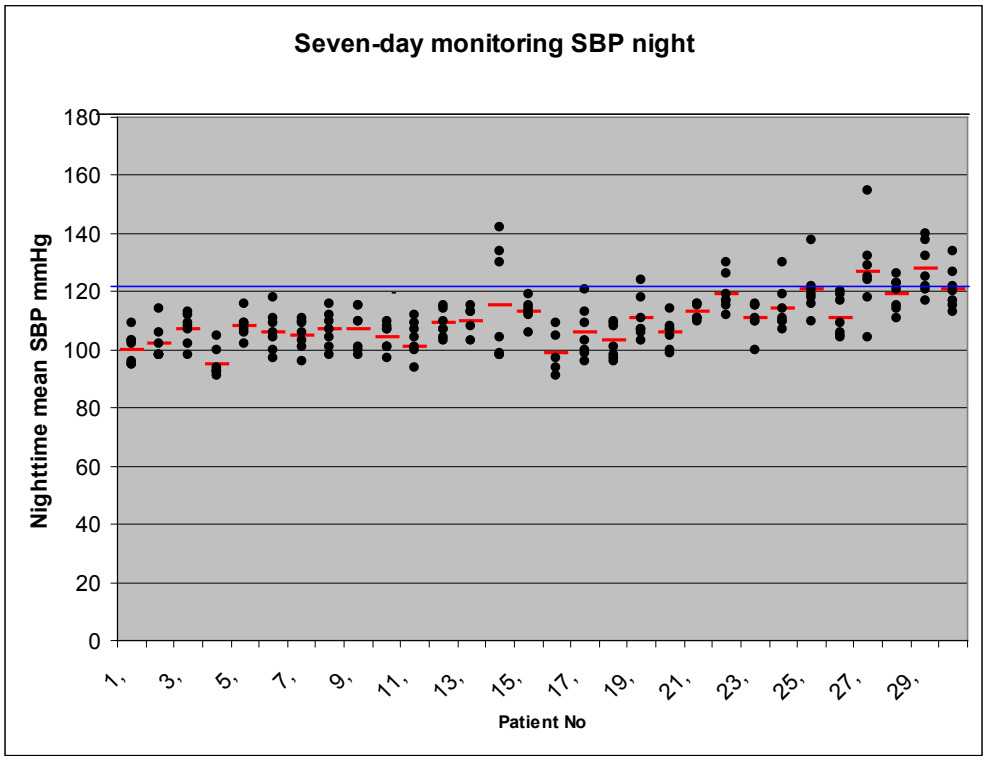

Figure 2. The variability of one-nighttime SBP values during 7-day monitoring. The patients were ordered according mean 7-day SBP (patient No 1: 107 mmHg, patient No 30: 131 mmHg; median value: 123 mmHg). One-day mean values (point) and 7-day mean values (dash) are indicated.

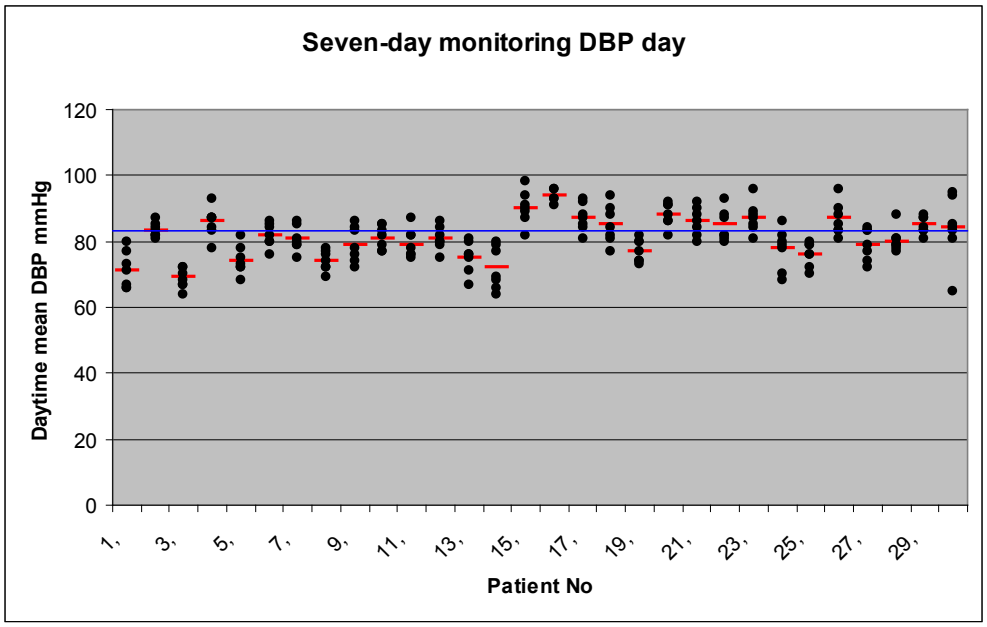

Figure 3. The variability of one-daytime DBP values during 7-day monitoring. The patients were ordered according mean 7-day SBP (patient No 1: 107 mmHg, patient No 30: 131 mmHg; median value: 123 mmHg). One-day mean values (point) and 7-day mean values (dash) are indicated.

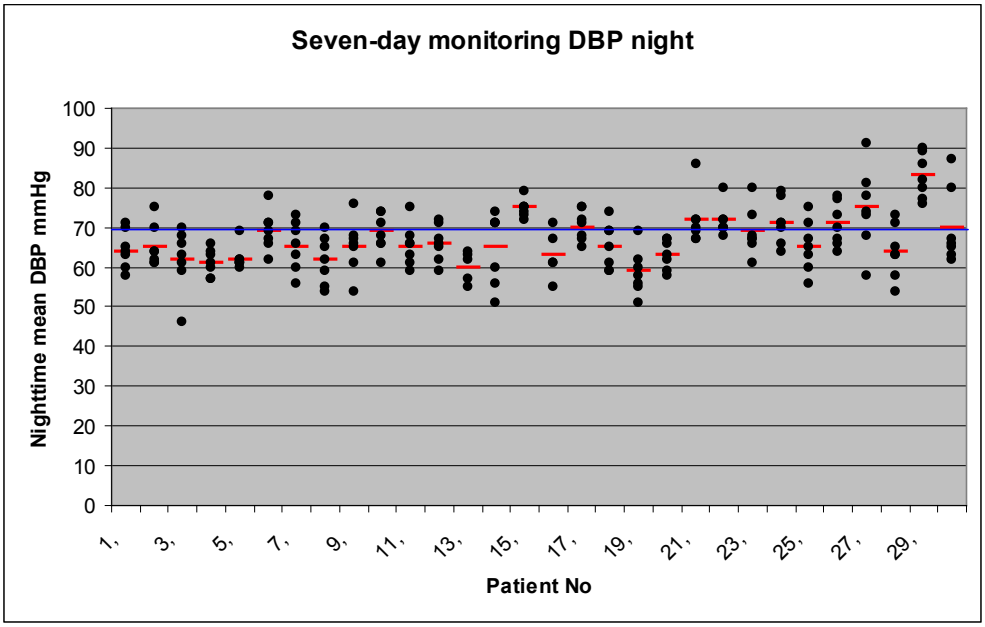

Figure 4. The variability of one-nighttime DBP values during 7-day monitoring. The patients were ordered according mean 7-day SBP (patient No 1: 107 mmHg, patient No 30: 131 mmHg; median value: 123 mmHg). One-day mean values (point) and 7-day mean values (dash) are indicated.

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.

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, 2× during week, constant load 120 W, lasting 60 min. Every exercise unit was composed from warm-up period 3 min, load 54 min and cool-down period 3 min.

METHODS

The subjects were recruited for seven-day blood pressure monitoring. Medical Instruments (A&D, Japan) were used for ambulatory blood pressure monitoring (oscillation method). One-hour means of systolic and diastolic blood pressure were evaluated.

Mean day-time and mean night-time systolic and diastolic pressures were evaluated every day and we calculated mean systolic and diastolic blood pressure for seven days.

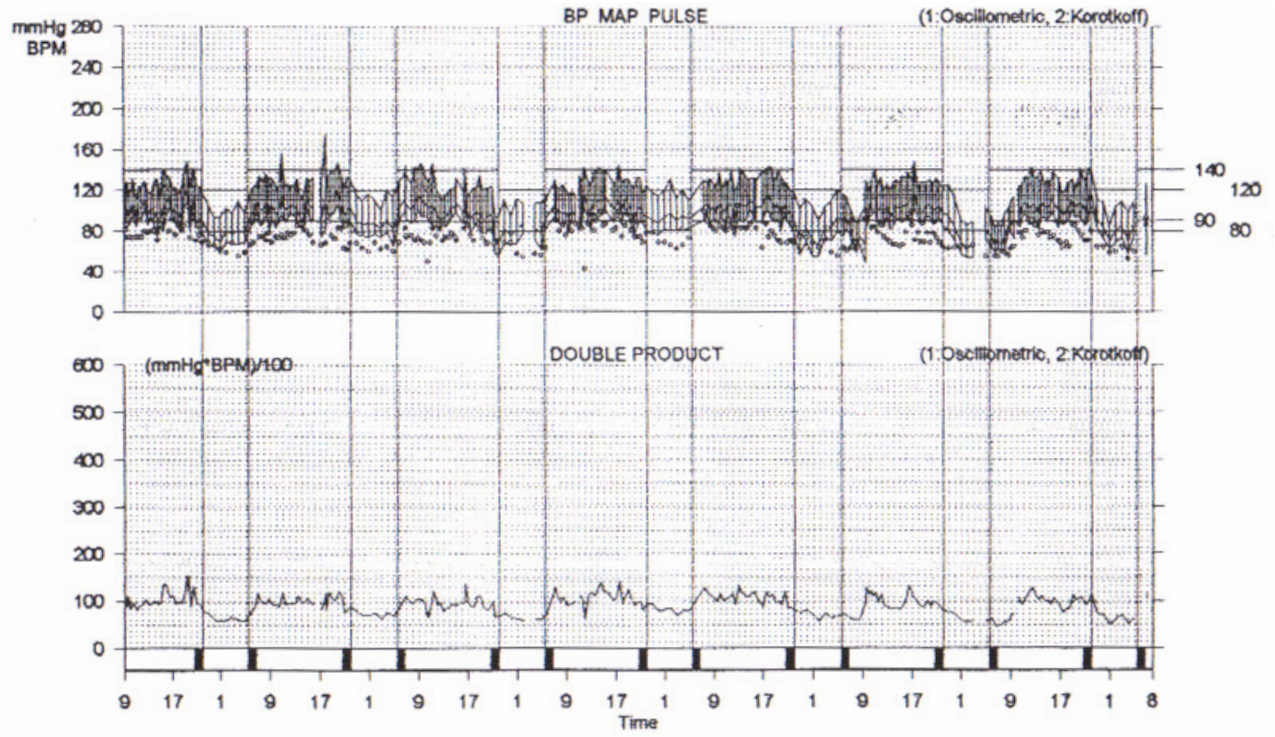

Figure 5. Seven-day ambulatory blood pressure monitoring in one man

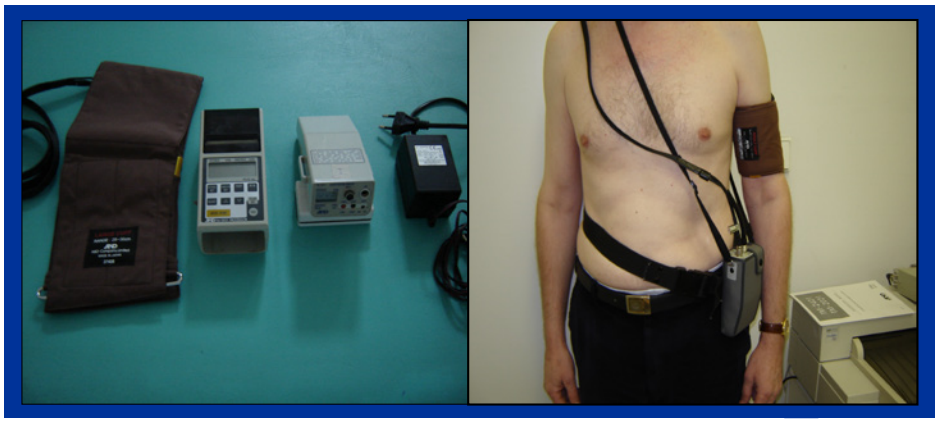

Figure 6. Medical Instruments (A&D, Japan) – ambulatory blood pressure monitoring

RESULTS

The healthy subjects (men) were ordered according 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. 7 at rest and in Fig. 8 during exercise.

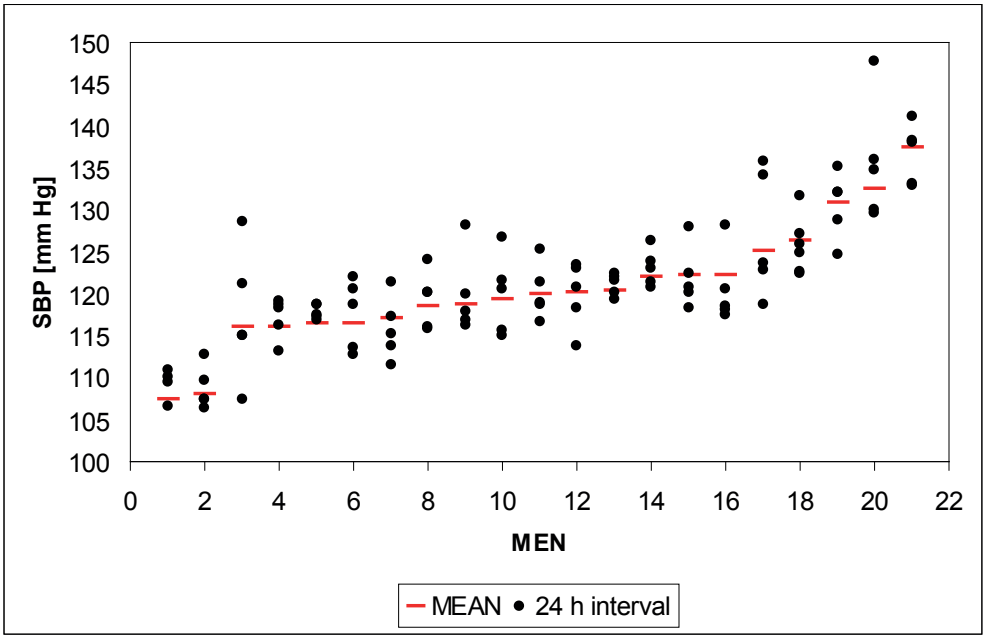

Figure 7. The variability of 24-hour mean systolic blood pressure (black points) and 7-day mean systolic blood pressure (red line) at rest in 21 healthy subjects.

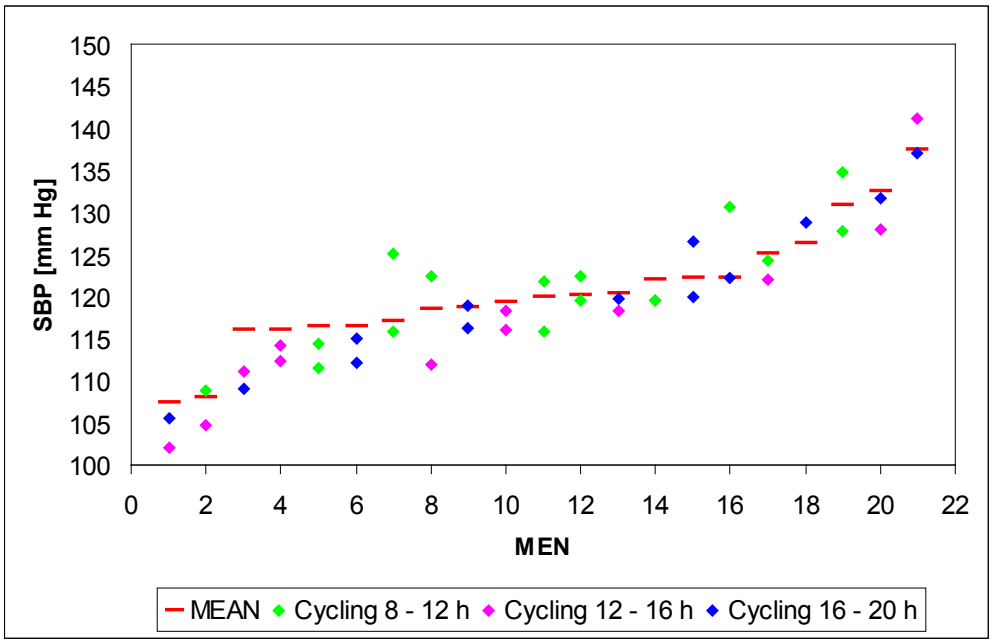

Figure 8. The variability of 24-hour mean systolic blood pressure (points in color) and 7-day mean systolic blood pressure (red line) during exercise in 21 healthy subjects.

The variability of one-daytime DBP values during 7-day monitoring is seen in Fig. 9 at rest and in Fig. 10 during exercise.

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

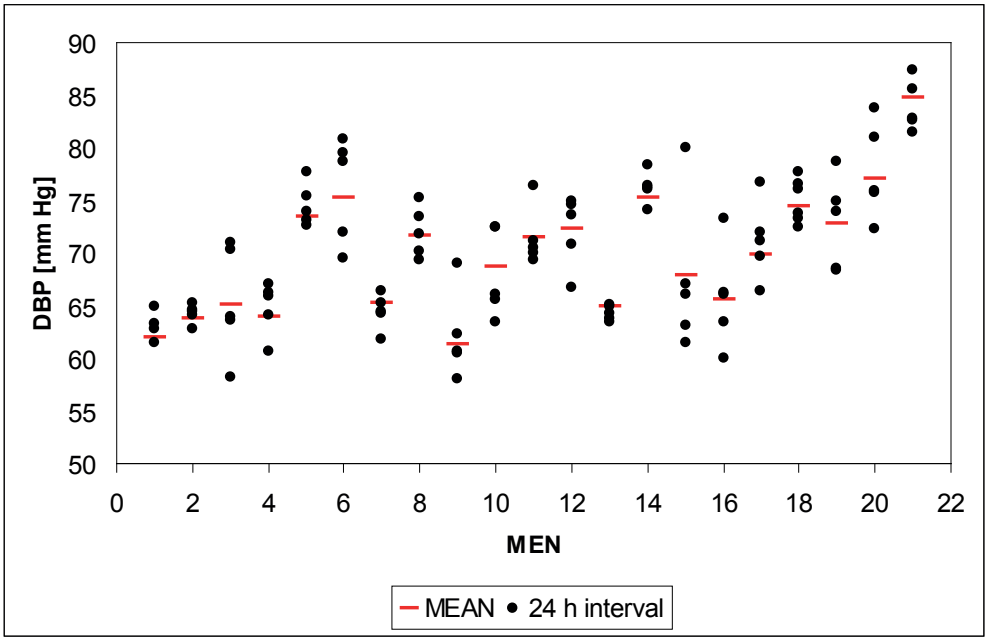

Figure 9. The variability of 24-hour mean diastolic blood pressure (black points) and 7-day mean diastolic blood pressure (red line) at rest in 21 healthy subjects.

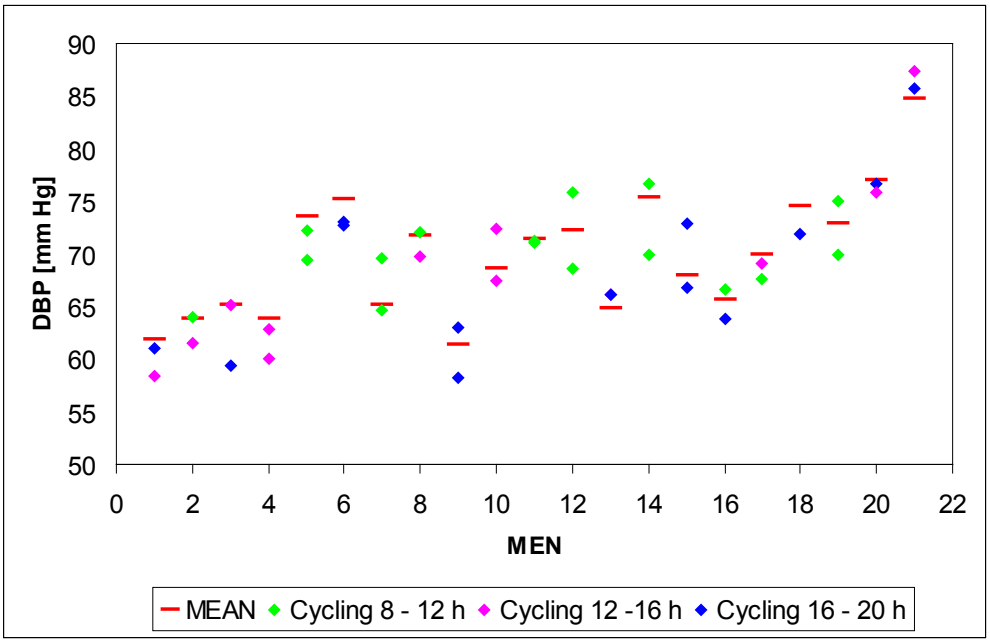

Figure 10. The variability of 24-hour mean diastolic blood pressure (points in color) and 7-day mean diastolic blood pressure (red line) during exercise in 21 healthy subjects.

DISCUSSION

Seven-day ambulatory blood pressure monitoring demonstrates large day-to-day variability of blood pressure at rest. Our studies indicate with blood pressure monitoring that longer monitoring, preferably for 7 days, is recommended.

In our presentation we show a large variability of 24-hour profile at rest in 5 days and in 2 days with exercise. The variability day-to-day in 24-hour profile was presented at rest and during exercise in 21 healthy subjects. During exercise, even that these data were measured only 2 days we observed similar variability as it was described at rest before.

Hypertension is currently diagnosed mostly by means of a single measurement or a few measurements during few consecutive examinations. This practice can be associated with over 40 % false diagnoses due in part to 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 measurement or a few measurements, but for avoiding misdiagnosis is not sufficient. 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, under the guidance of professor Halberg and professor Cornélissen.

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 treatment.

CONCLUSION

From the results we can conclude that 24-hour blood pressure profile at rest and during exercise varies day-to-day and we recommend the 7-day blood pressure monitoring. The education for long-lasting self-monitoring is the best approach for management of hypertension.

Support: GM-13981 (FH), University of Minnesota Supercomputing Institute (GC, FH)

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FATHER OF CHRONOBIOLOGY: PROF. DR. FRANZ HALBERG, 93 YEARS OF AGE

JARMILA SIEGELOVA
Dept. of Physiotherapy and Rehabilitation, Dept. of Sportsmedicine and Rehabilitation, Faculty of Medicine, Masaryk University, St. Ann's University Hospital in Brno, Brno

Franz Halberg, M.D., Dr. h.c. (Montpellier), Dr. h.c. (Ferrara), Dr. h.c. (Tyumen), Dr. h.c. (Brno), Dr. h.c. (L'Aquila), Dr. h.c. (People's Friendship University of Russia, Moscow), Professor of Laboratory Medicine and Pathology, Physiology, Biology, Bioengineering and Oral medicine, Director, Halberg Chronobiology Center, University of Minnesota, Mayo Mail Code 8609, Dept of Laboratory Medicine, Minneapolis Campus 420 Delaware Street SE, Minneapolis, MN 55455, USA

Franz Halberg is a founder of modern chronobiology. Unlike other famous scientists devoting there activities mostly to presentation of honorary lectures at international scientific conferences Prof Halberg continues in scientific work. This fact demonstrates the list of his scientific papers on WEB of Science which contains 1172 scientific papers, Science Citation Report of Franz Halberg contains 13874 citations, and his H-index is 53.

Prof Halberg suffers by the fact, that his ideas overrun the development of science for tens of years. He suggested the ambulatory 24 hours blood monitoring in 1948. We feel honored to have had the possibility of cooperation with Professor Halberg since 1980s. In the year 2000, Prof. Franz Halberg from University of Minnesota, USA, received the degree of honorary doctor of Masaryk University Brno. The first scientific study using the Halberg's method in Czech Republic was published in 1993. Also the treatment of oncology diseases on the chronobiological basis started many years after Halberg suggestion. The last Halberg proposal for diagnosis of vascular variability disorders on the basis of several day ambulatory blood pressure and heart rate monitoring or on the basis of several days lasted self-monitoring is nowadays not broadly accepted; despite it enables the risk stratification of hypertensive patients. The risk-stratification guided treatment is more effective than the treatment based on diagnosis only.

I and my colleges from Masaryk University Brno wish professor Halberg good health necessary to continue his scientific work for many years. I also wish scientific community to accept all Franz Halberg ideas as quickly as possible, because it is an interest of patients all over the world. Ad multos annos!

SELECTED PUBLICATIONS

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DYSPHAGIA AFTER STROKE

PETR KONECNY (1,2,3), MILAN ELFMARK (3,5), STANISLAV HORAK (3), JARMILA SIEGELOVA (2), PETR DOBSAK (2), TOMAS KADLCIK (4), MARCELA CHARVATOVA (4), JARMILA SKOTAKOVA (4)
Department of Rehabilitation, The Mercifil Brothers' Hospital in Brno, Department of Physioterapy and Rehabilitation, Masaryk University, Brno, Department of Rehabilitation, Palacky University Olomouc, Department of Radiology, The University Hospital Brno, Department of Natural Sciences in Kinanthropology, Palacky University Olomouc

ANNOTATION

Swallowing disorders are often found in patients after stroke.

These problems can be cured using targeted orofacial rehabilitation. This cure can be documented by instruments measuring changes in swallowing during the following prospective clinical study.

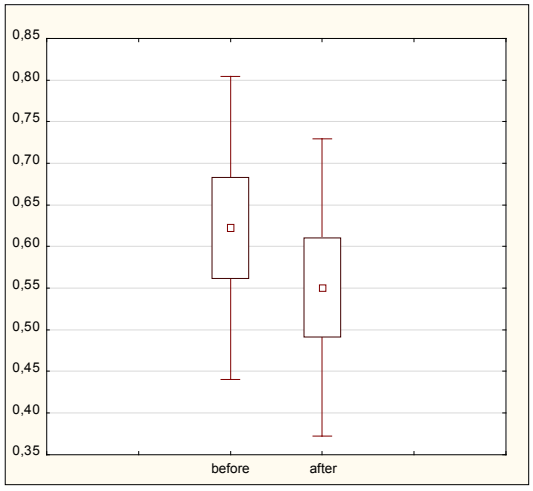
Introduction
Dysphagia, a disorder in swallowing solid or liquid food, occurs very often in bulbar or pseudobulbar syndrome in patients after stroke in about 40–60 percent of cases (1). Orofacial rehabilitation is very significant in this context, with an impact not only on the treatment of eating disorders, but also on other orofacial functions (facial expressions, speech), general health and overall quality of life (2, 3).

Methods
A prospective pilot study evaluating the effect of orofacial rehabilitation (focusing mainly on treatment of hyoid muscles) in 9 patients after stroke with dysphagia. Evaluation was performed using videofluoroscopy (VFSS) by measuring the duration of each phase of swallowing (Fig. 1). Measurements were performed at the beginning (before orofacial rehabilitation) and 8 weeks (after orofacial rehabilitation). The measured values were statistically processed and evaluated using the Wilcoxon test, with the level of statistical significance of $p < 0.050$.

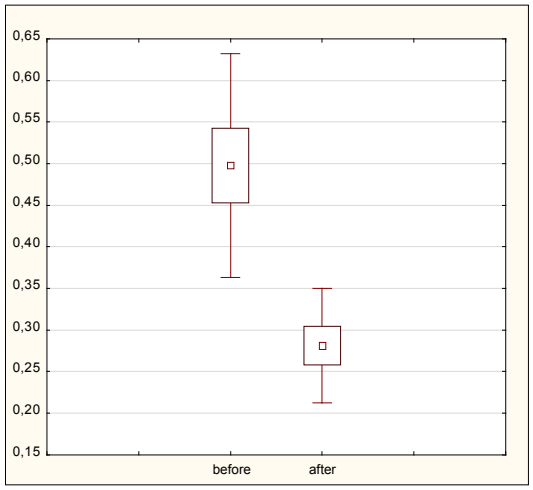
Results
Based on the comparison of the time differences (R) in swallowing phases before and after orofacial rehabilitation, there were found significant differences in the parameters OTT (Oral transport time) $R = 0.071 \pm 0.027$, $p = 0.008$ (Graph 1.), PTT (Pharyngeal transit time) $R = 0.217 \pm 0.087$, $p = 0.008$ (Graph 2.), VPL (Velopharyngeal lock) $R = 0.0260 \pm 0.0028$, $p = 0.043$ (Graph 3.), RBS (Rastatter Biodynamik Score – time of the maximum elevation of the hyoid bone) $R = 0.089 \pm 0.074$, $p = 0.012$ (Graph 4.).

Conclusion
After the 8-week rehabilitation of the hyoid bone muscles during orofacial rehabilitation there ocured improvment in food swallowing in dysphagic patients after stroke as well as in transport times of individual stages of swallowing measured using VFSS.

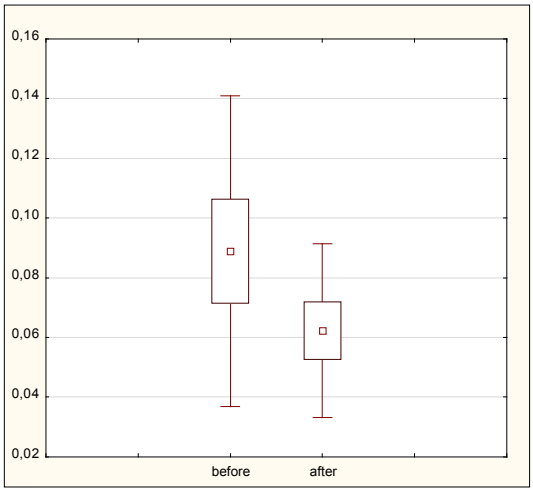
Based on the obtained results it can be stated that the orofacial rehabilitation is of great importance in the treatment of swallowing disorders in patients after stroke.



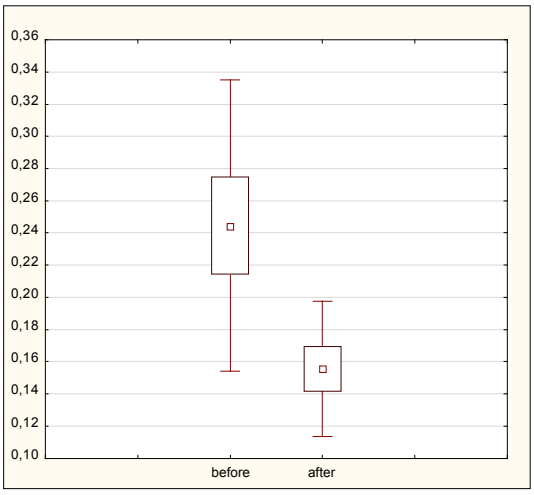
Graph 1. Oral transit time(OTT) before and after orofacial rehabilitation.



Graph 2. Pharyngeal transit time (PTT) before and after orofacial rehabilitation.



Graph 3. Velopharyngeal lock (VPL) before and after orofacial rehabilitation.



Graph 4. RBS – rastatter biodynamik score before and after orofacial rehabilitation.

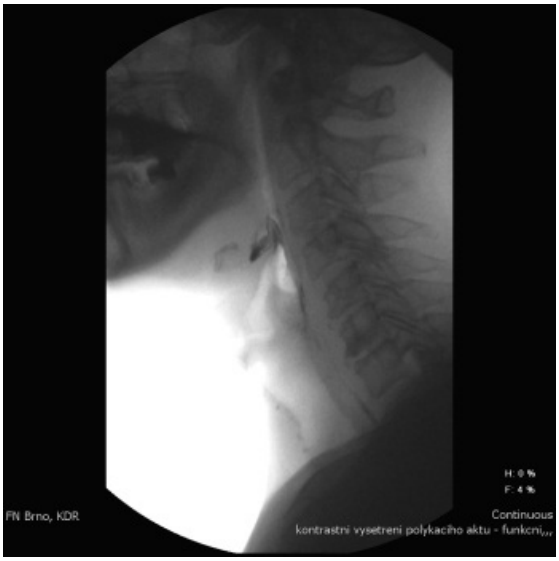


Figure 1. Videofluoroscopy (VFSS)

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AD MULTOS ANNOS SANOS PROF. MUDR. JARMILA SIEGELOVA, DRSC.

FRANZ HALBERG, GERMAINE CORNELISSEN AND OTHILD SCHWARTZKOPFF
Halberg Chronobiology Laboratory, University of Minnesota, Minneapolis, USA for the international project on the Biosphere and the Cosmos, BIOCOS

For a young woman celebrating her 70th birthday,
with the good wishes of the international community to continue contributing for much longer.

Ten years ago (1), the late prof. MUDr. Bohumil Fiser, CSc., then Czech minister of health and board member of WHO, and your colleague and friend, not only remembered Jarmilka, but as one who grew up with her scientifically and shared many aspects of her professional life, he commented on her achievements in great detail. He emphasized the basic fact that "a week rhythm in circulatory quantities which results from natural regularities and not from evolution of the society, was documented by her as a 7-day fluctuation of blood pressure and pulse rate in new-borns at the Teaching Hospital Brno" and that this circaseptan, with an amplitude greater than the circadian "is synchronized by the moment of birth and is independent of week days." In addition to being an independent investigator second to none, as Bohumil recognized, I can attest to his emphasis that she has been a productive member of an international team, and the first physician-scientist to introduce chronobiologically interpreted blood pressure monitoring to Europe and thus again, like a fellow Brunensian, Johann Gregor Mendel, opened a normal range, a diversity in time. While Mendel's pea patch led to the science of diversity in space, Jarmilka again placed her city and country at the forefront of breakthroughs so that no longer is "physiological" equated to "random" in the normal range at least for blood pressure, as is still the case with each laboratory result remaining time-unqualified. Her chronobiologically interpreted blood pressure monitoring serves to discover new variability disorders, to start with circadian vascular anomalies. Infradian alterations of variability and diagnoses in other areas than the blood circulation will indubitably follow if, as we hope, her university grants her the opportunity to continue what she not only started, but developed in a tradition of Brunensian contributions to the circulation of blood, and in the tradition of doing on herself what she intended for others. When she arrived in Minnesota with Bohumil and her dear colleague Jiri Dusek, no sooner then were they in town from the airport that they all donned two instruments and showed on themselves the extent to which results agreed. This attitude was introduced by Jan Evangelista Purkyne, who studied digitalis on himself. To complete the list that Bohumil started, based on a tete-a-tete with Prof. Cornélissen, the two were instrumental in a design that allowed Jarmilka the demonstration that aspirin has different effects at different circadian stages, a featin chronotherapy second to none, promptly published by the American Medical Association. We hope the list continues.

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Professor Franz Halberg and Professor Germaine Cornélissen – Videoconference, January 12, 2012

Dr. Othild Schwartzkopff, Prof. Franz Halberg, Dr. Jiří Dušek, Prof. Thomas Kenner,
Brigitte Kenner, Prof. Jarmila Siegelová – Videoconference, January 12, 2012

SUN'S AND EARTH'S MAGNETISM: FEATURES OF COMMUNICABLE DISEASE ETIOLOGY

FRANZ HALBERG*, SHIYU HONG, LYAZZAT GUMAROVA, GERMAINE CORNÉLISSEN
Halberg Chronobiology Center, University of Minnesota, Minneapolis, MN, USA

KEYWORDS:

diphtheria, helio- and geomagnetism, infectious diseases, space weather, wavelet analysis

Running head: Cycles in communicable disease incidence

INTRODUCTION

The association of human health and disease with space weather was the topic of a long series of presentations at a recent meeting in Moscow and was also dealt with at earlier conferences (1, 2), with focus on non-communicable diseases.

METHODS

By meta-analyses of data published by Alexander Leonidovich Chizhevsky in the 20th century dating back to the span from 1860 to 1910 (3), we here add evidence (from cross-wavelet coherence) (4) for an association of terrestrial and solar magnetism with several infectious diseases that were common in the past.

RESULTS

Figure 1 (top) shows a wavelet of the incidence pattern of diphtheria and croup (pooled) in Denmark from 1860–1910. An about 12.4-year component is seen to characterize the incidence pattern; it is within the cone of influence. Another component with a period (τ) of about 29.5 years is outside this cone. Both components are validated and are within the CIs (95% confidence intervals) of the nonlinearly extended cosinor, applied to the same time series on diphtheria and croup (not shown) and, earlier to many other records on human affairs in health and disease (5).

Wavelets of Wolf numbers, WN (Figure 1, middle), and of the antipodal geomagnetic index aa (Figure 1, bottom) show maxima corresponding to the anticipated ~11.7-year cycle, also seen from the spectra plotted vertically next to the color key. The numbers indicate the period length (in years) corresponding to local maxima in amplitudes; but the color code matters most. The wavelet of aa also reveals the presence of an about 22.1-year component differing from the smaller about 19.7-year peaklet observed for WN. Both these peaks are less prominent than the about 29.5-year peak found for diphtheria and croup.

Figure 2 shows cross-wavelet transforms (left) and coherence displays (right) of WN (top) and aa (bottom) with diphtheria and croup. The 11.7-year τ within the cone of influence stands out in association with both WN and aa in the cross-wavelets. An added large peak at 24.2 years is seen in association with aa. Peaklets are seen at ~23 and ~44 years in association with WN. Strong coherences around 10.4 (WN) or 11.0 (aa) years inside the cone of influence and additional strong coherences outside this cone around 23.4 (aa) or less intensely around 22.1 (WN) years are interesting. Added coherences around 5.5 years and at still shorter τs in association with WN are intermittently

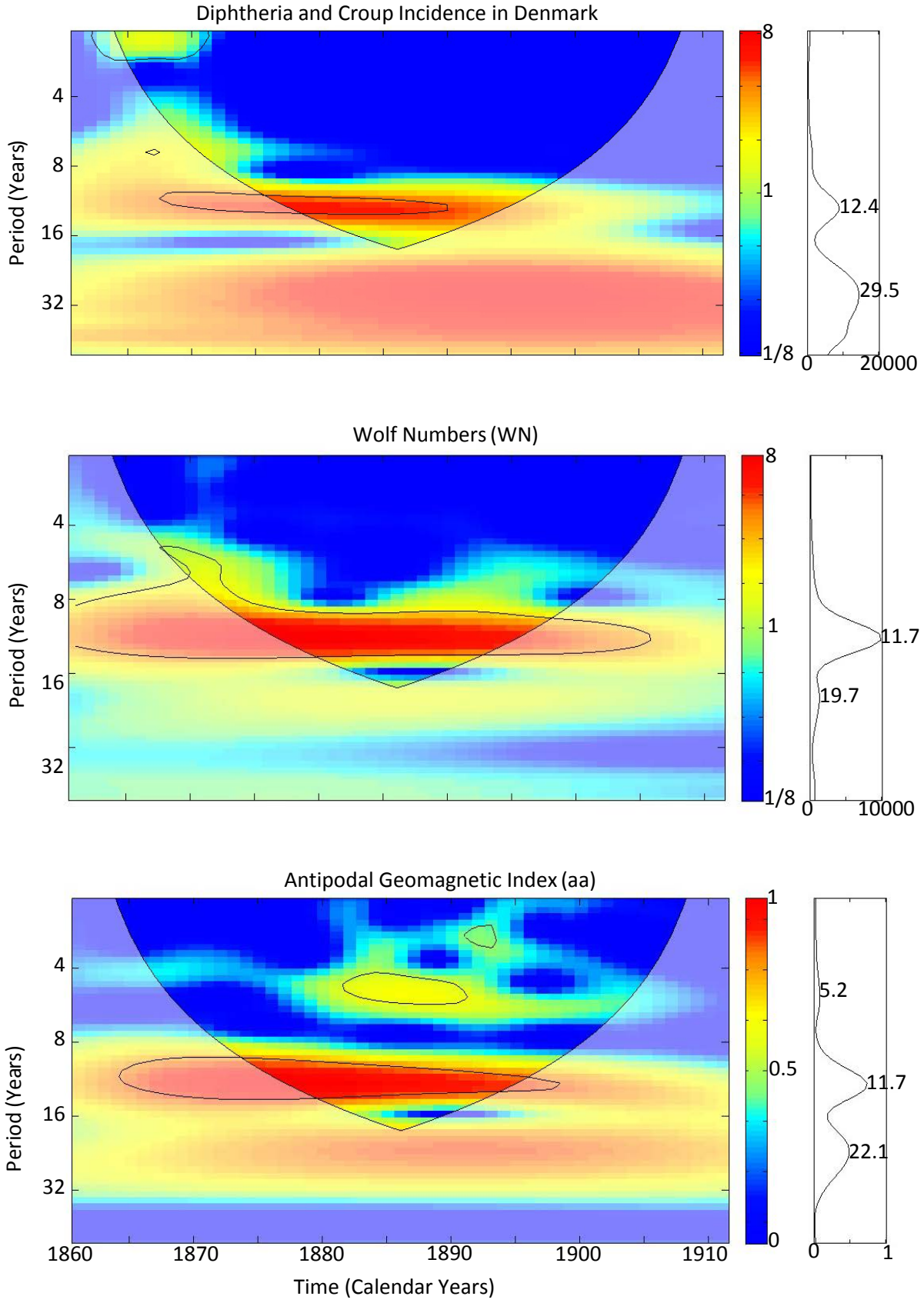

Figure 1. Wavelet analyses of incidence pattern of two infectious diseases (pooled) centuries ago (top row), of Wolf sunspot numbers (middle), and of the antipodal geomagnetic index aa (bottom), with peaks indicated by color (key), and by numbers at the maxima in the spectrum (right, next to the color key) show a putative reflection of past and/or present solar variability. © Halberg.

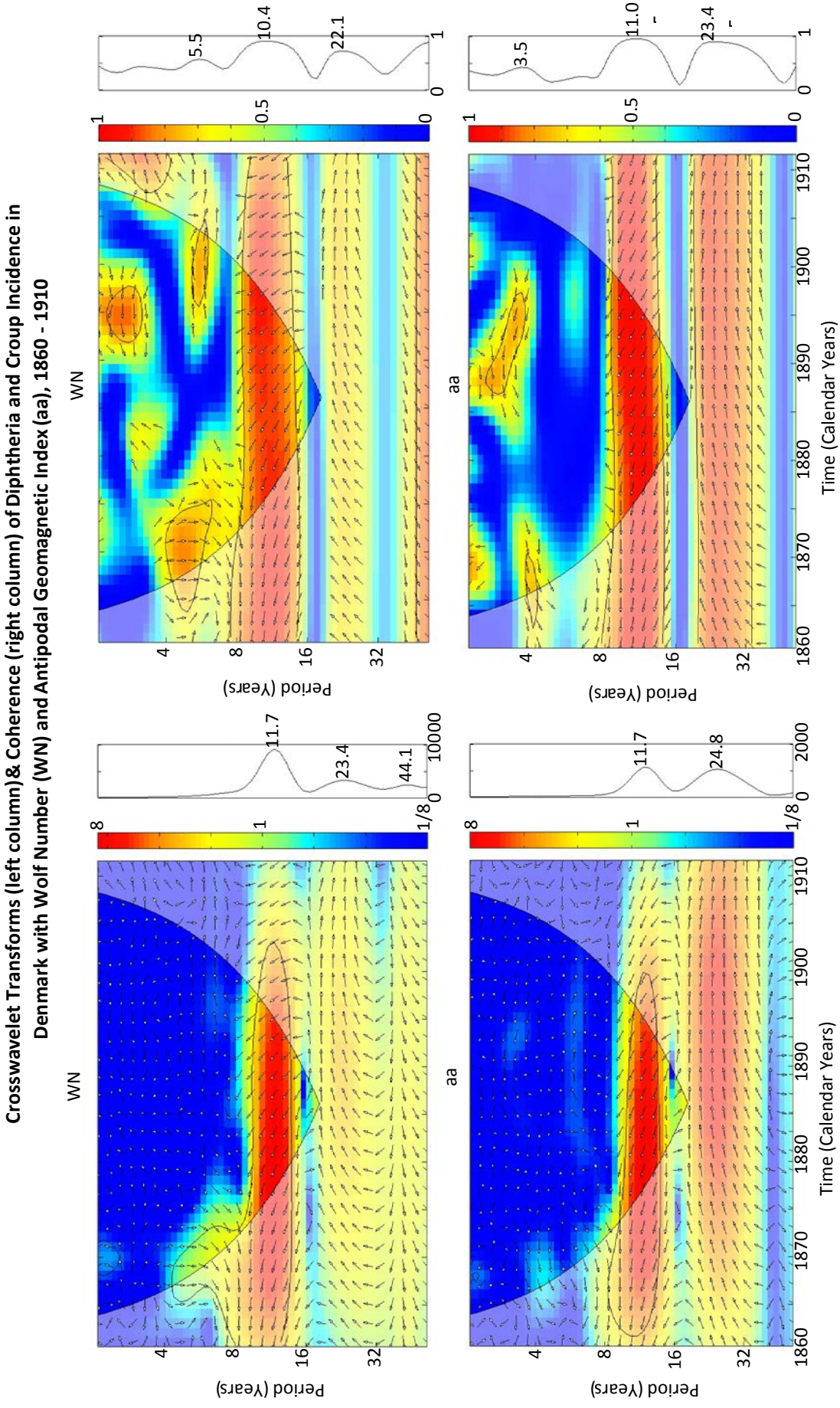

Figure 2. Cross-wavelet transforms show a strong association of the incidence of two infectious diseases (pooled) with WN and aa at a period, τ, of 11.7 years within the cone of influence. Coherence (right) is also found within the cone of influence at 10.4 and 11.0 years. These τs are also near those validated for the incidence of diphtheria and croup by the extended nonlinear cosinor (not shown) that suggests the statistical significance of differences among the two aspects of solar and earth magnetism's association with rampant pandemics, some within the cone of influence. © Halberg.

statistically significant (as seen from black contours). Again, there is a difference in spectral location between WN and aa, the overall peak occurring around 3.5 years for aa.

COMMENT

Among para-annual components, solar wind speed, a measure of interplanetary magnetism, and aa share some frequencies but differ at others (6). Here we find that, in the decadal range, both WN and aa, gauging solar and terrestrial magnetism, respectively, shared coherence (within the cone of influence) with the main cycle characterizing communicable diseases, such as diphtheria and croup, in the past when they were pandemic. Just as helio-, interplanetary or geomagnetism can influence sudden cardiac death (6), they also influenced communicable diseases, probably via the host, whose steroidal defense shows a proven decadal cycle (6) and by the invading microorganism, whose mutations can also undergo a similar cycle mirroring that of sunspots (6). Cycles in the sun's and the earth's magnetism are features of both communicable and noncommunicable disease etiology and, in both cases, are geographically, selectively assorted, shown elsewhere (6).

Support: GM-13981 (FH), University of Minnesota Supercomputing Institute (GC, FH).

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CELEBRATION OF A LIFETIME'S ACHIEVEMENTS IN CARDIOVASCULAR CHRONOMICS. A TRIBUTE TO FRANZ HALBERG ON THE OCCASION OF HIS 93RD BIRTHDAY

GERMAINE CORNELISSEN
Halberg Chronobiology Center University of Minnesota, USA

DEDICATION

By adding TIME to the existing body of knowledge in all of biology and medicine, and by recognizing the crucial role this new element was to play in all matters of life, Franz Halberg developed the new science of chronobiology. By insisting on an inferential statistical foundation, a microscopy in time was born. By adding a telescopy in time with a methodical scrutiny of non-photic as well as photic environmental influences on biota, chronomics flourished.

Born on July 5, 1919 in Romania, Franz studied the adrenal as a university assistant in post-World War II Innsbruck, Austria. He did so at Harvard Medical School, where he held a World Health Organization fellowship in clinical endocrinology in 1948. In 1949, he moved to the University of Minnesota, which saw his breakthrough experiments that led to the important discovery that circadian rhythms are partly endogenous and can be manipulated by environmental synchronizers, notably the lighting and feeding schedules. His results were published in 1969 in a citation classic (1). By 1958, Franz had recognized the important role played by the cell's RNA and DNA cycles, which he was first to demonstrate as complementing the hypothalamic-pituitary-adrenal system as mediator of photic inputs.

His work 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 received honorary doctorates from the University of Montpellier (France), Ferrara (Italy), Tyumen (Siberia), Brno (Czech Republic), L'Aquila (Italy), and most recently People's Friendship University of Russia (Moscow, Russia). At over 93 years of age and still active 7 days a week in the Center named after him at the University of Minnesota, he is one of the last recipients of a lifetime career award from the National Institutes of Health. His achievements in the new field of chronomics also 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.

In over 3,400 published titles in cooperation with colleagues from all five continents, major accomplishemts of Franz include the following highlights. First, rhythms are not trivial as they can tip the scale between health and disease and even between life and death. Second, after suggesting the hypothalamus mediated light information, Franz fought from the start the idea that the suprachiasmatic nuclei were "the" master clock. After a debate that lasted more than a decade, Franz's view has been vindicated now that modern molecular biological techniques have shown the presence of oscillators in practically every cell, in the brain as well as in the periphery. Third, as the crowning of a distinguished career, Franz's early vision that rhythms were not trivial but rather constituted the founding block of life itself is being unveiled by findings that alterations in clock genes are not only responsible for alterations in circadian rhythms but are fundamentally involved in a host of diseased conditions from addiction and cancer to cardiovascular disease. Last but not least, his mapping of a much broader time structure includes cycles with frequencies covering 10 orders of magnitude, aligned between biology and physics by means of an armamentarium of analytical procedures, including a remove-and-replace approach extended from endocrinology to a true transdisciplinary endeavor.

Franz's most recent work addresses wide-ranging applications from the optimization of individualized health care to concerns for the health of societies. Toward this goal, the automatic monitoring of vital signs, as a start of blood pressure and heart rate, serves the multiple purposes of enlarging the scope of Humboldt's purely physical monitoring into an endeavor advancing both the biomedical field and physics in a truly unified science and leading to a noo-

sphere that is organized by a novel spectrum of congruent cycles in us and around us, photic cycles and non-photic (unseen) ones, some of the latter already mapped transdisciplinarily.

ABSTRACT

Cardiovascular disease is one of the leading causes of death. An elevated blood pressure is widely recognized as a factor associated with an increased cardiovascular disease risk. Several outcome studies based on automatic around-the-clock monitoring of blood pressure and heart rate have shown that alterations of the variability in these variables, notably those related to their circadian pattern also increase risk, even more so than a high blood pressure itself. Vascular Variability Anomalies (VVAs), and when they persist, Vascular Variability Disorders (VVDs) are introduced, as are methods to detect them and to determine optimal treatment times.

INTRODUCTION

In 1733, blood pressure was first directly measured in an artery by the English naturalist, the Reverend Stephen Hales (2). An Austrian physician, von Basch (1876), then developed a convenient and simple way of measuring blood pressure by connecting a small balloon to either a mercury column or sometimes an aneroid manometer. The balloon was placed over the artery in the wrist and compressed until the pulsation of the artery in the wrist below the balloon was obliterated. The pressure at which the pulsation disappeared gave a reasonably accurate measurement of systolic pressure. He soon realized that the higher the systolic blood pressure, the greater the risk of stroke and kidney disease (2). The term "sphygmomanometer" comes from the Greek "sphygmós" (pulse) and the scientific word "manometer" (pressure meter). The device was invented by Samuel Siegfried Karl Ritter von Basch in 1881 (3), extensively tested by Ignaz Zadek (4, 5). By 1881, data from Zadek were available to assess periodicities of about 24, 84 and 168 hours (6), Figure 1.

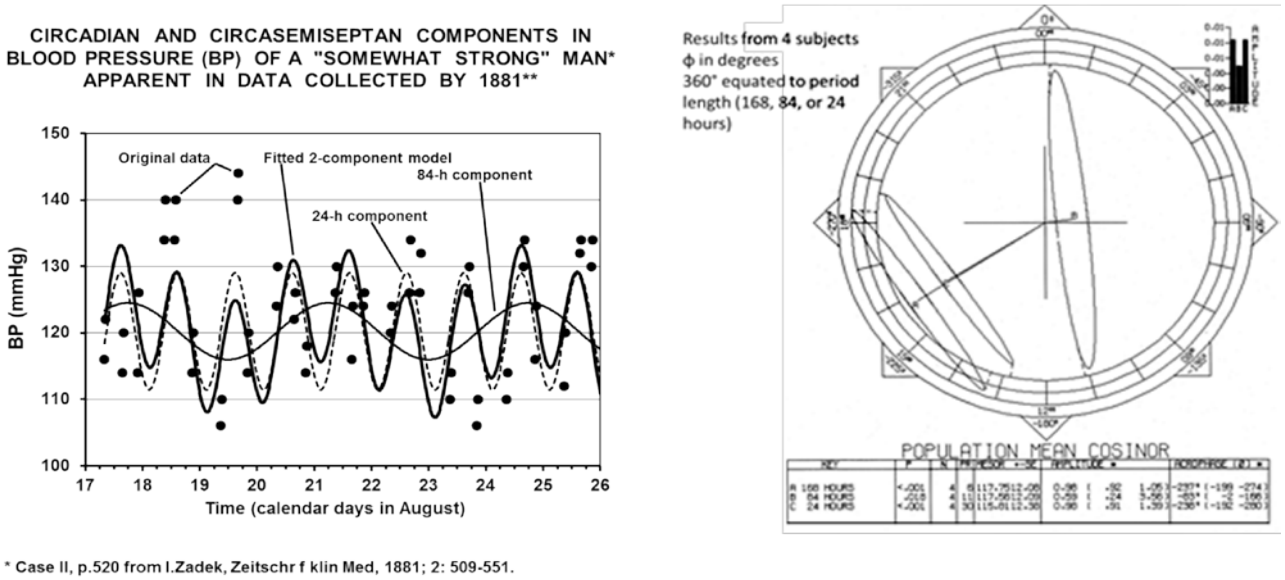

Figure 1. Original data collected by Ignaz Zadek on one of his patients. A composite model consisting of cosine curves with periods of 24 and 84 hours fitted to the data is also shown (left). All three components with periods of 24, 84, and 168 hours are statistically significant by population-mean cosinor, the small number of subjects (4) notwithstanding (right). © Halberg (with permission).

In 1904, Theodore C Janeway of Johns Hopkins University (Baltimore), the opinion leader of his time, wrote "... it is essential that a record of the pressure be made at frequent intervals at some time previous [presumably to an examination], to establish the normal level and the extent of the periodic variations. When this is done, it may be possible to

demonstrate changes of small extent, which, lacking this standard, for comparison, would be considered within the limits of normal variation." (7). By 1974, Frederic C Bartter wrote "By conventional standards, this patient is clearly normotensive every morning. Yet the blood pressure determined each day at 6 in the afternoon provides especially convincing evidence that this patient is a hypertensive. ... My plea today is that information contained in such curves [cosinor fits] become a routine minimal amount of information accepted for the description of a patient's blood pressure. The analysis of this information by cosinor should become a routine. It is essential that enough information be collected to allow objective characterization of a periodic phenomenon, to wit, an estimate of M [the time structure or chronome-adjusted mean, or MESOR] ... an estimate of [the amplitude] A itself, and finally an estimate of acrophase, ϕ [a measure of timing]. In this way, a patient can be compared with himself at another time, or under another treatment, and the patient can be compared with a normal or with another patient." (8). As seen from Figure 2, the large-amplitude circadian variation in blood pressure readily accounts for the diverging diagnoses made by the two physicians who saw the same patient at different times of the day, as also illustrated in the abstract (Figure 2, bottom).

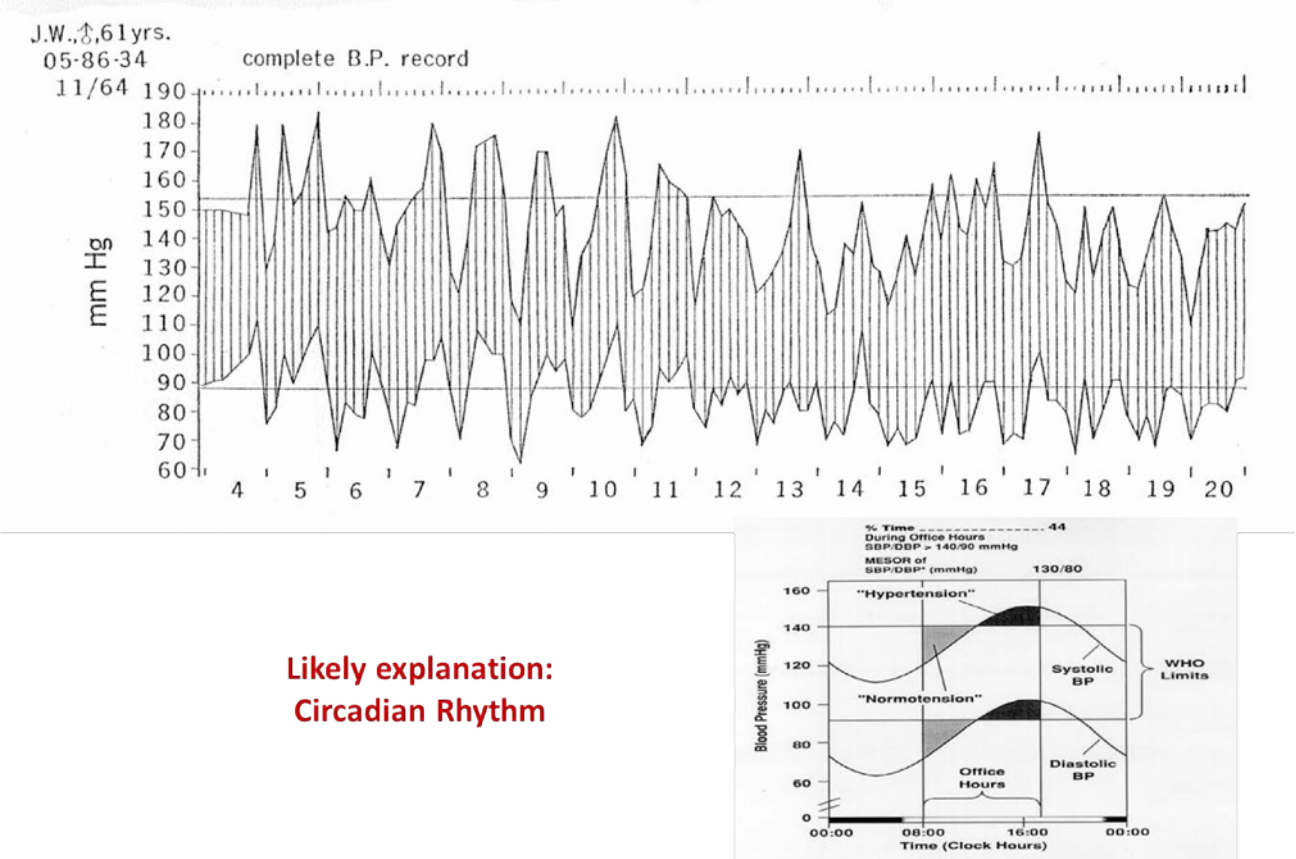

Figure 2. Original data from FC Bartter on his patient who was diagnosed as normotensive by the physician who examined him in the morning and as hypertensive by the physician who saw him in the afternoon. Data collected around the clock when he was hospitalized at the US National Institutes of Health readily account for the discrepant diagnoses in view of the large-amplitude circadian variation in his blood pressure. The circadian-stage dependence of the diagnosis of high blood pressure is illustrated in the abstract (bottom right) when it is based on single casual measurements during office hours interpreted by fixed limits. Indeed, the circadian rhythm in blood pressure can, in itself, even in the absence of measurement error, result in contradictory diagnoses. Computations are based on a 24-hour cosine curve with an amplitude of 20 mmHg (slightly above the upper 95% prediction limit in clinically healthy adults) and an acrophase of −240 ° (4 PM). © Halberg (with permission).

Blood pressure first became easy to measure in 1896 when an Italian physician, Riva Rocci, developed what we would now recognize as a conventional mercury sphygmomanometer with a cuff around the arm, which was inflated until the pulsation of the artery could no longer be felt. A few years later, Nicolai Korotkoff, a Russian army surgeon (1904), realized that by listening with a stethoscope below the cuff over the artery at the elbow, characteristic sounds were heard at the systolic pressure, but also at the lower pressure (diastolic) when the heart relaxes. It became very easy to measure both systolic and diastolic pressure accurately with a stethoscope (2).

CONTRIBUTIONS BY FRANZ HALBERG VIEWED FROM A HISTORICAL PERSPECTIVE

Using a mercury sphygmomanometer, Franz directed several studies on school children in Minnesota (9, 10), Connecticut (11) and Arkansas (12), complemented later by investigations elsewhere in the USA (13, 14). He convinced colleagues abroad to conduct similar studies, notably in Italy (15) and Portugal (16). These investigations provided the first hint of the importance to assess the circadian amplitude of blood pressure to gauge cardiovascular disease risk. They all corroborate results observed in the experimental laboratory on the stroke-prone Okamoto rat, where the 24-hour amplitude increased before the average did (17).

Under the leadership of Franz Halberg, a large Minnesota-Kyushu study (18) took place in which blood pressure was measured automatically around-the-clock with an analog device, the arteriosonde. Dots on a moving paper had to be converted from position to mmHg and date/time. Frequent calibrations were required to assure the accuracy of both time and blood pressure readings. Nevertheless, important information could be collected non-invasively on human subjects during both sleep and wakefulness, and circadian rhythm parameters could be associated with cardiovascular disease risk and hormonal determinations obtained around-the-clock concomitantly. The MESOR of diastolic blood pressure and cardiovascular disease risk assessed by questionnaire were both found to correlate negatively with the circannual amplitude of aldosterone, Figure 3 (18). The data also served to build the first individualized time-specified reference values (chronodesms), Figure 4.

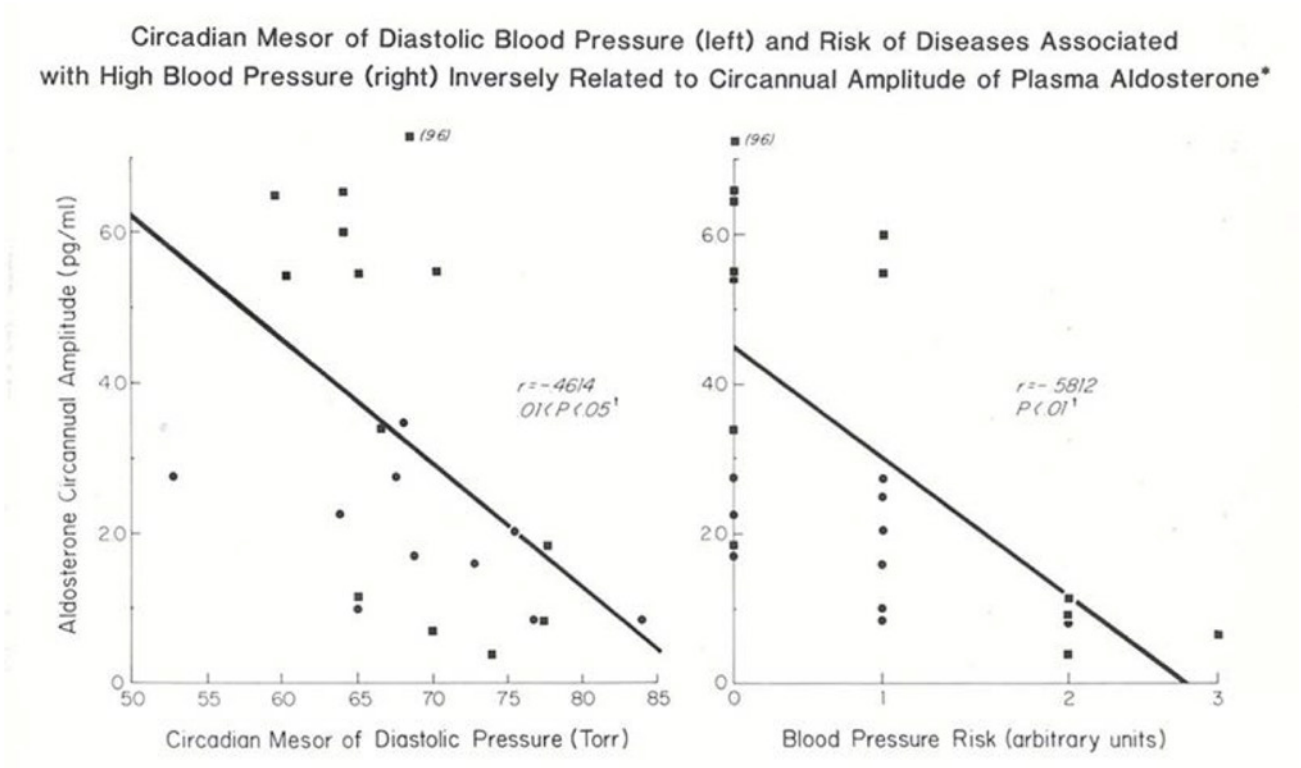

Figure 3. Negative correlation of the circannual amplitude of circulating aldosterone versus the circadian MESOR of diastolic blood pressure of clinically healthy women at different risks of developing breast cancer (left) and versus their cardiovascular disease risk assessed by questionnaire (right) (18).© Halberg (with permission).

A fully automatic portable if not quite yet ambulatory blood pressure became available in the 1980s, developed by Masayuki Shinoda in Komaki, Japan. Franz and his wife Erna used it extensively and were first to obtain longitudinal records of around-the-clock measurements over several weeks. The data thus collected led to important new findings. First, an increase in blood pressure around mid-sleep was documented and validated in inferential statistical terms (19), followed by a steeper increase after awakening, Figure 5. Second, the circadian rhythm in blood pressure was shown to persist during bedrest (20), in keeping with an earlier study by Reinberg et al. (21). Third, the data

served to outline some important sampling requirements. The need to monitor for more than a single 24-hour span became obvious from the large gain in accuracy of the estimation of circadian characteristics when prolonging the record length from 24 to 48 hours (22).

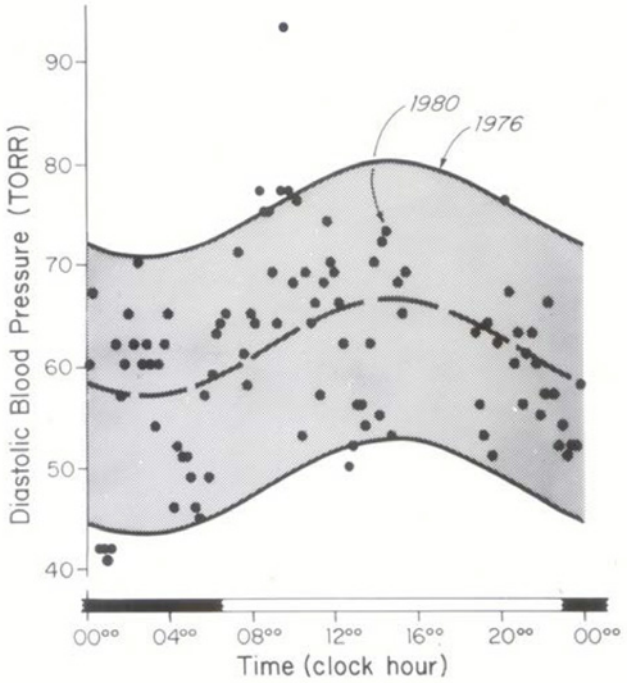

Figure 4. Individualized chronodesm (time-specified reference values) for diastolic blood pressure. Reference standars were established on the basis of data collected in 1976. Only few values obtained in 1980 are outside the limits, indicating that the diastolic blood pressure of this subject did not change markedly within these 4 years. © Halberg (with permission).

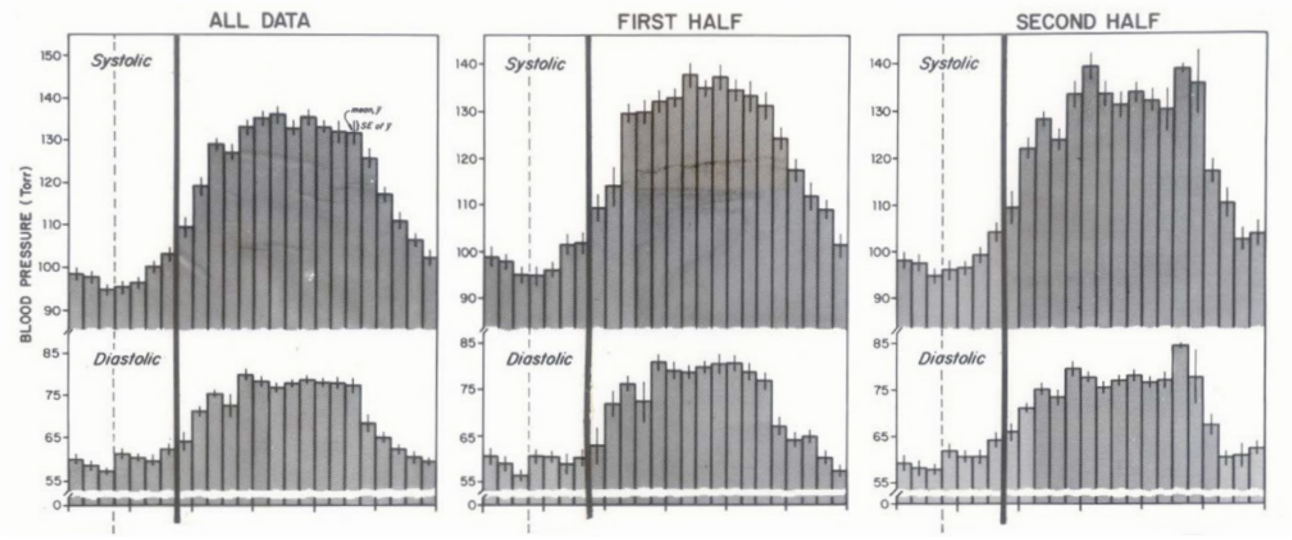

Figure 5. Small but statistically significant increase in blood pressure around mid-sleep (dashed vertical line) before the larger per-awakening increase (solid vertical line) in a clinically healthy woman. Result on all data (left) is validated when data set is split into two halves (middle and right) (19). © Halberg (with permission).

A similar model of an automatic portable device also became available for neonatal monitoring. A larger circadian amplitude of blood pressure in babies with a positive than in those with a negative family history of high blood pressure and/or related cardiovascular disease was in keeping with results from self-measurements in school children (23). As further neonatal data accumulated, the result had to be qualified, the failure to detect a difference in data collected a few years later (24) eventually accounted for by the modulation of circadian neonatal blood pressure characteristics by an about 11-year cycle similar to variations seen in solar activity (25). Neonatal blood pressure

monitoring in Italy, where the late Brunetto Tarquini cooperated with Franz, led to the discovery of a prominent about-weekly variation overshadowing the circadian variation at birth. The finding, originally made on the basis of transverse data, Figure 6 (26) was later confirmed on longer individual records (27). Circaseptans in neonatal blood pressure were found to be influenced by geomagnetics in cooperation with Elena V Syutkina (28), whereas in Brno, Jarmila Siegelova provided evidence for a partly built-in week (29), supported by data collected in the intensive care unit both in the Czech Republic (30) and in Minnesota (31), Figure 7.

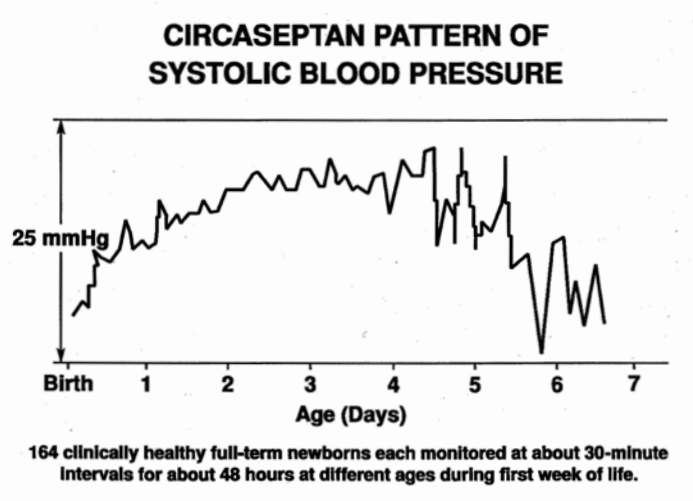

Figure 6. About-weekly variation in neonatal systolic blood pressure, first assessed on the basis of hybrid data, each baby being monitored for about 2 days but starting at different times after birth (26). © Halberg (with permission).

As different kinds of ambulatory devices became available, records could be obtained from clinically healthy people of all ages. Franz was instrumental in furthering the methodology needed to determine reference values in health that are time-specified to account for the circadian variation, while also recognizing the desirability to qualify the reference standards by gender, age and ethnicity. New, more relevant questions could be addressed, such as whether circadian rhythm characteristics were within or outside acceptable limits, and whether a profile over time was deviating from time-specified norms. If so, the extent and timing of excess were found to constitute valuable information for guiding the timing of anti-hypertensive medication, information obtained by chronobiologically-interpreted ABPM and summarized in a computer-generated form, the sphygmochron (32–35).

VASCULAR VARIABILITY ANOMALIES (VVAS), DISORDERS (VVDS) AND SYNDROMES (VVSS)

One important lesson learned from longitudinal records of around-the-clock measurements of blood pressure and heart rate is the large day-to-day variability in circadian characteristics found for a large majority of people. The presence of about-weekly changes in blood pressure and their relevance to mental health (36) led to the requirement of monitoring for at least one week and to repeat the monitoring when abnormality is detected (35). This precaution is taken to reduce the number of false positives and false negatives, so that only those patients in need of medication receive it at the most opportune time. Indeed, transient abnormality during a day or two may often occur and has been related to strain (37, 38).

As noted above, abnormality of circadian characteristics can occur within the physiological range. Hence, an elevated blood pressure (MESOR-hypertension) is only one of several different kinds of VVAs. It is detected when the patient's blood pressure MESOR is above the upper 95% prediction limit for clinically healthy peers matched by gender and age. Today's treatment is focused primarily on lowering an excessive blood pressure MESOR, without any consideration of the circadian amplitude or acrophase. Outcome studies (39–43) have shown, however, that

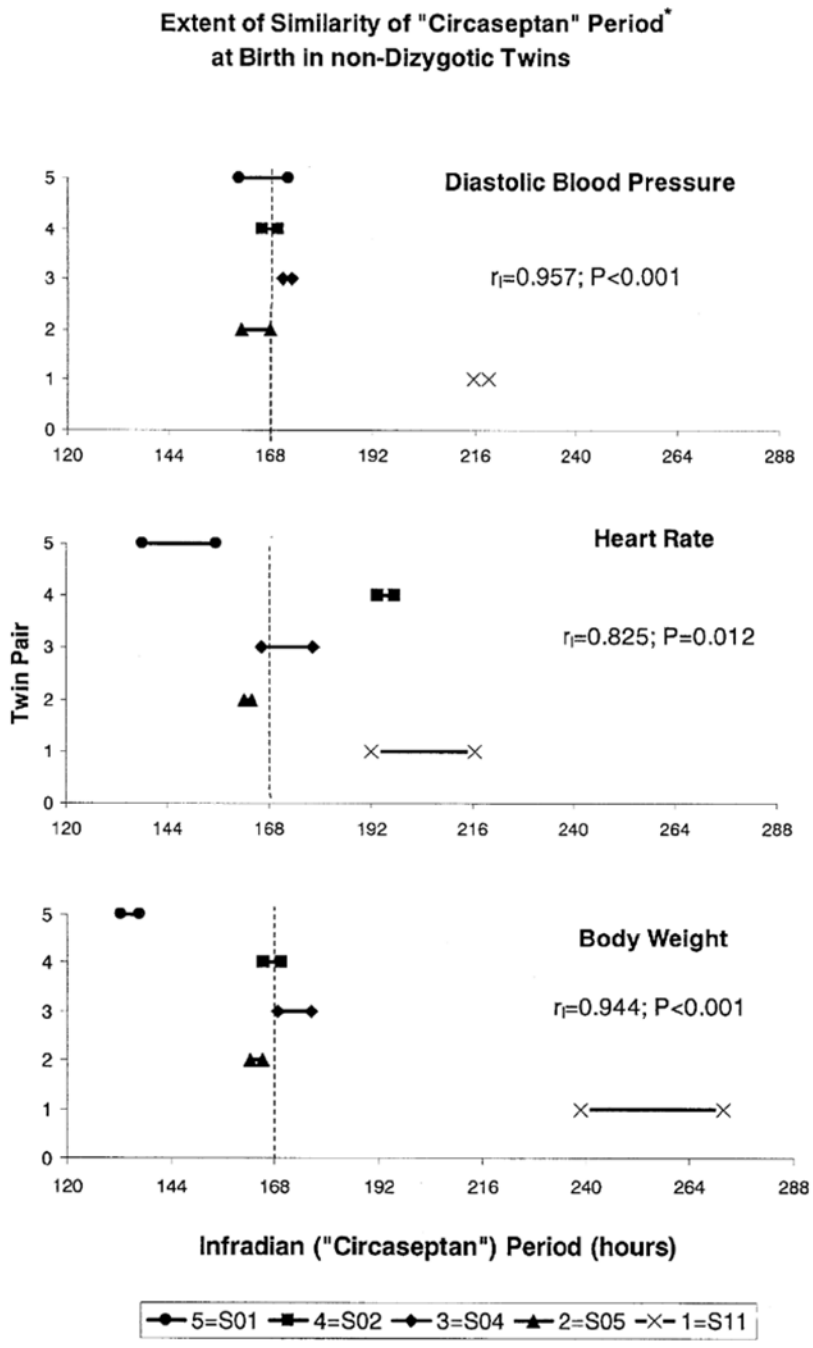

Figure 7. Documentation of the heritability of the circaseptan component by intra-class correlation coefficient, comparing the intra- versus the inter-twin pair variability in the nonlinearly assessed circaseptan period, for data on diastolic blood pressure (top), heart rate (middle), and body weight (bottom), recorded in the neonatal intensive care unit of the University of Minnesota. For these three variables, the circaseptan period was more similar between the twins in a pair than among twin pairs (31). © Halberg (with permission).

an excessive circadian amplitude of blood pressure (CHAT, brief for Circadian Hyper-Amplitude-Tension) is also associated with an increased cardiovascular disease risk, even in MESOR-normotension. It is thus important to make sure that medication taken to lower the blood pressure MESOR does not do so by bringing about CHAT, since this would amount to trade one risk factor for another, perhaps an even worse one. In a clinical trial on the chronotherapy of Hyzaar (44), the same dose of the same medication given to the same patient was shown to either exacerbate CHAT or to eliminate it, depending solely on the circadian stage of its administration (45), Figure 8. Decreasing an

excessive circadian amplitude of blood pressure has been shown indirectly to reduce adverse outcomes (46). An odd acrophase of blood pressure but not of heart rate has also been associated with an increased cardiovascular disease risk, using the left ventricular mass index as a proxy outcome measure (43), Figure 9. This VVA is known as blood pressure ecphasia.

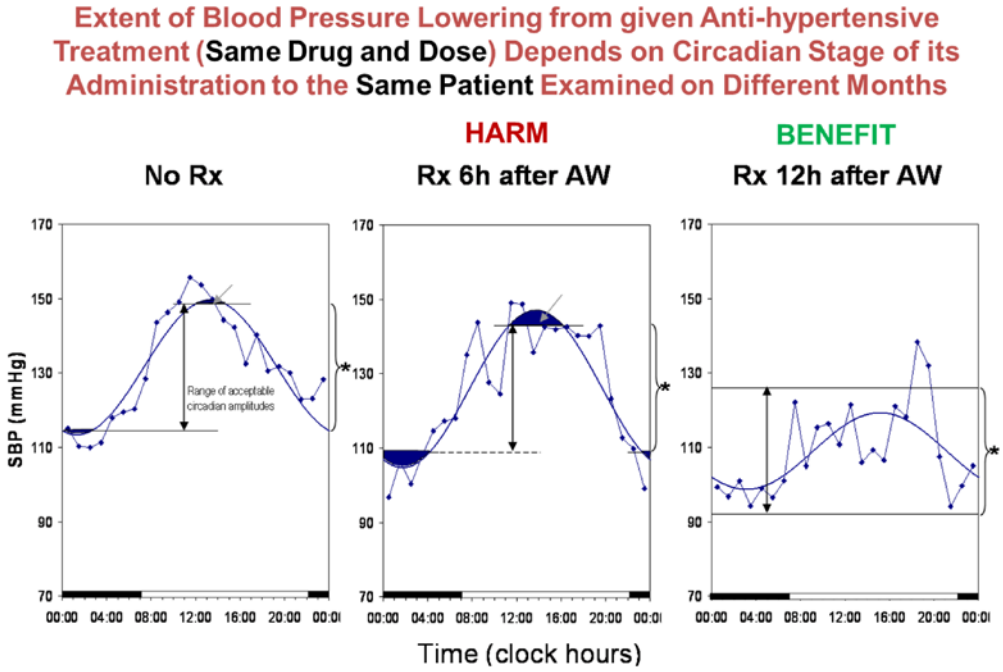

Figure 8. In this chronotherapy trial, patients automatically measured their systolic and diastolic blood pressure and heart rate around-the-clock at 30-minute intervals for 7 days, first without Hyzaar and thereafter after at least one month on Hyzaar administered at a given circadian stage, at awakening and 3, 6, 9, 12 and 15 hours after awakening, with monitoring during the last week on a given timed treatment. In the case of this patient (Su, M, 67y), the presence of CHAT in the absence of treatment is exacerbated when Hyzaar is taken 6 hours after awakening, but it is alleviated when the same dose of Hyzaar is taken in the evening, 12 hours after awakening (45). Data from Y Watanabe. © Halberg (with permission).

Whereas the relation to cardiovascular disease risk is mostly linear for the MESOR, it is strongly nonlinear in the case of the circadian amplitude of blood pressure, as it is for pulse pressure and the standard deviation of heart rate (47). Values above 60 mmHg for pulse pressure and below 7.5 beats/min for the standard deviation of heart rate have been associated with an increased cardiovascular disease risk. An excessive pulse pressure and a deficient heart rate variability are two other VVAs. Ecfrequentia is another VVA, seldom diagnosed but consistently found in an extensively studied case of recurring adynamia (48).

The urgent need to diagnose VVDs, ascertaining that they are not transient VVAs, stems from results of outcome studies showing the drastic increase in cardiovascular risk when one or several VVDs are present and complicate MESOR-hypertension, Figure 10 (35, 45). Uncomplicated MESOR-hypertension was associated with less a morbid event within 6 years in less than 10 % of the patients. With each additional VVD complicating MESOR-hypertension, the percentage of patients suffering an adverse event increased dramatically, reaching 100 % when all VVDs tested in the study were present concomitantly.

CONCLUDING REMARKS

Just like splitting the atom released much energy, entering the normal range to resolve lawful variability yields valuable new information. This can be achieved by physiologic monitoring, collecting data around the clock for a week or longer and by analyzing the data chronobiologically, interpreting the results in the light of time-specified reference values qualified by gender and age.

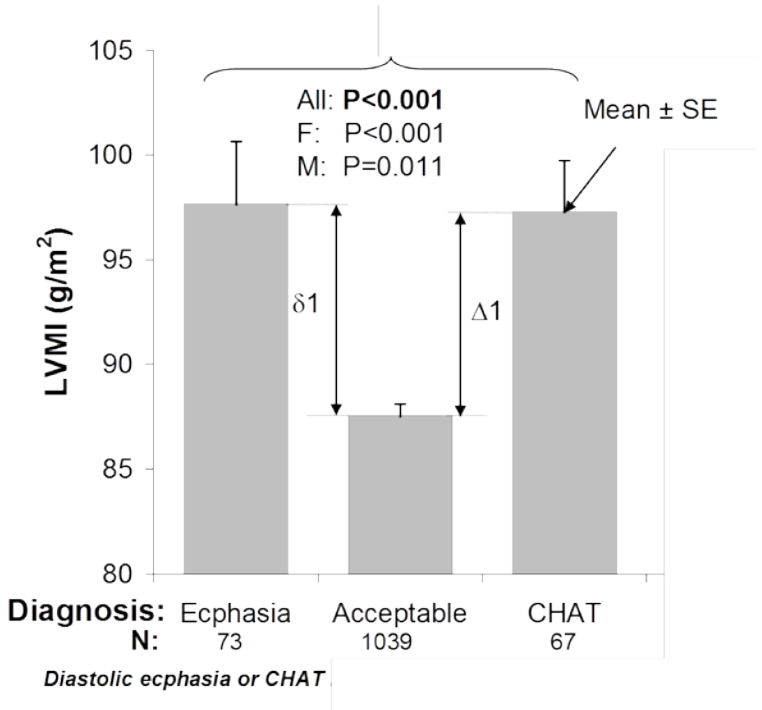

Figure 9. Left Ventricular Mass Index (LVMI), used as a surrogate outcome measure, available from all 1179 untreated participants in this study, is compared among patients classified in terms of circadian characteristics assessed by cosinor. Results are comparison by 1-way ANOVA overall (All) and separately for women (F) and men (M). LVMI values are greatly elevated when diastolic ecphasia or CHAT is diagnosed (corresponding to abnormal circadian patterns of diastolic blood pressure). Data from CH Chen. © Halberg (with permission).

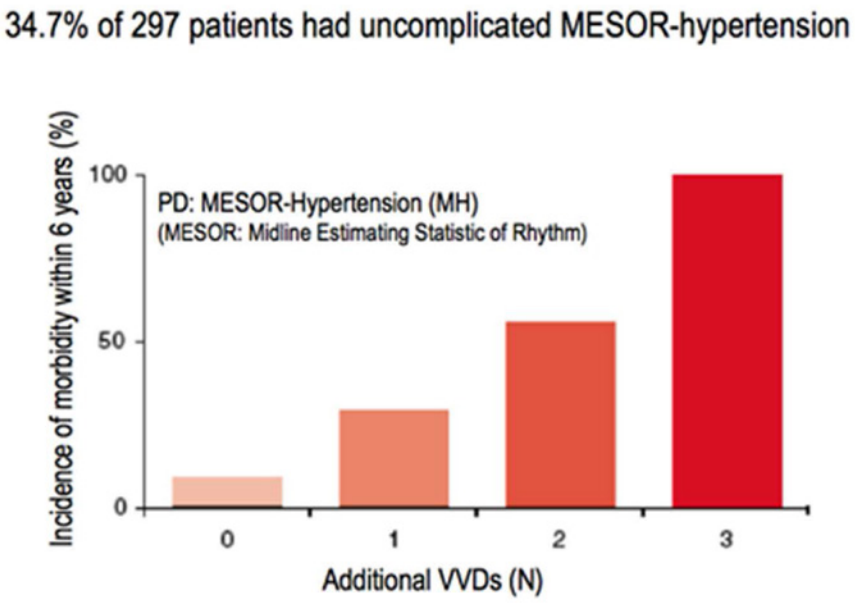

Figure 10. Results from an outcome study in a clinic population of 297 patients (39, 40). Blood pressure and heart rate of each subject were monitored around the clock for 2 days at 15-minute intervals at the start of study. Each record was analyzed chronobiologically and results interpreted in the light of time-specified reference limits qualified by gender and age. On this basis, the following VVAs were diagnosed: MESOR-hypertension, excessive pulse pressure (EPP), CHAT, and deficient heart rate variability (DHRV) and their incidence related to outcomes (cerebral ischemic attack, coronary artery disease, nephropathy, and/or retinopathy). Outcomes, absent at the start of study in these non-diabetic patients, were checked every 6 months for 6 years, to estimate the relative risk associated with each VVA alone or in combination with 1, 2, or 3 additional VVAs. Among the 176 patients with MESOR-hypertension, 103 (34.7 % of the whole study population of 297 patients) had no other VVA, 55 (18.5 %) had one additional VVA (EPP, CHAT, or DHRV), 15 (5.1%) and 3 (1.0%) had two or three additional VVAs. In the latter group, all 3 patients had a morbid outcome within 6 years of the monitoring. Data from K Otsuka. © Halberg *(with permission)*.

The fact that not all drugs have a similar effect on the circadian characteristics of blood pressure, and that the same dose of the same drug can have different effects on the same patient as a function of when (at what circadian stage in relation to awakening) it is administered, the optimal time differing from patient to patient, it is important to individualize chronotherapy. To that effect, N-of-1 studies (49) are essential, as are statistical procedures applicable to the individual patient, such as parameter tests (50) and cumulative control charts (CUSUM) (51). Part of the individualization of treatment and treatment timing is directly linked to the chronodiagnosis, that is the kind of VVD detected for a given patient. Intuitively, a patient with most blood pressure excess by night should not be treated the same way as a patient with most blood pressure excess by day, even when their 24-hour average value is similar. This combination of chronotherapy and chronodiagnosis has been referred to as chronotheranostics (52).

A major argument often put forward against this vision of Franz Halberg relates to cost. The status quo indeed has the monitoring performed under the physician's care. This needs not be the case, however. The patient with diabetes is taught how to measure blood glucose and to adjust the dose of insulin accordingly. Blood pressure monitoring is much easier and it is not invasive. As discussed in an extensive consensus document under Franz's direction (35), monitoring could become part of self-help in healthcare. Physicians can be spared much of the routine monitoring that can be relegated to the patients themselves until a VVD is detected and confirmed. He has visualized the development of a website to render this possible.

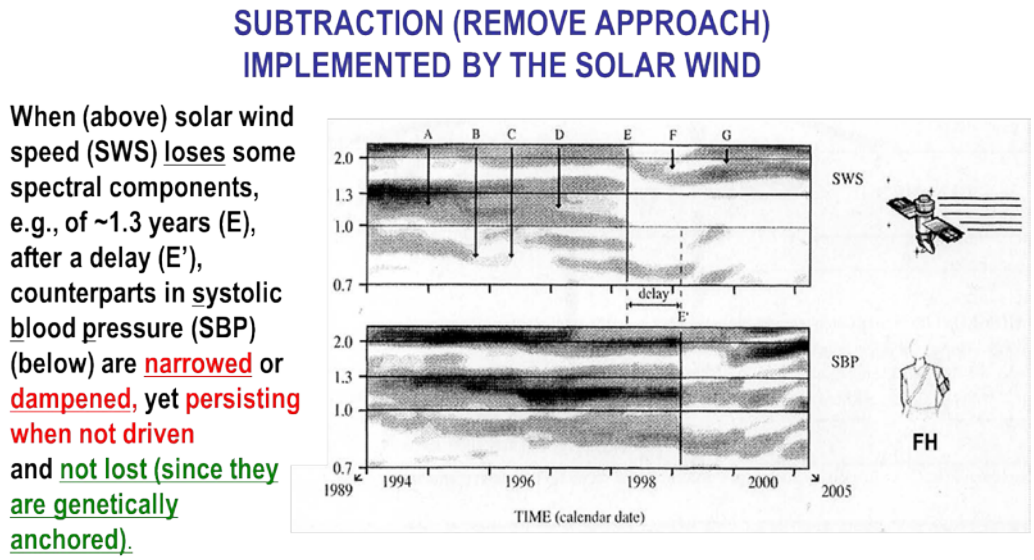

Figure 11. Wobbliness of the transyear component (with a period of about 1.3 years) is observed for both solar wind speed (top) and the systolic blood pressure of an elderly man (bottom) in gliding spectra computed with an interval of 8 years displaced by 1-month increments in the frequency range of one cycle in 2.5 years to 2.5 cycles per year with a 0.05 harmonic increment. Results suggest that the transyear may be partly built-in while also being influenced by space weather (53). © Halberg *(with permission)*.

An enormous dividend can also be reaped from the physiological monitoring, also included in the website visualized by Franz. It consists of the rigorous study of environmental influences from near and far. Coperiodisms, that is shared frequencies, have already been documented and are part of an emerging atlas. Examples include the partly resonant, partly inherited transyear (about 1.3-year cycle) of his own systolic blood pressure in relation to the solar wind (Figure 11) and the possible use of systolic blood pressure to assess congruence between space weather and human physiology (Figure 12), mental functions showing an even greater association than two physical variables,

solar wind speed and the antipodal index of geomagnetic disturbance aa, known to have similar time structures in the frequency window investigated (53, 54).

Support: GM-13981 (FH), University of Minnesota Supercomputing Institute (GC, FH).

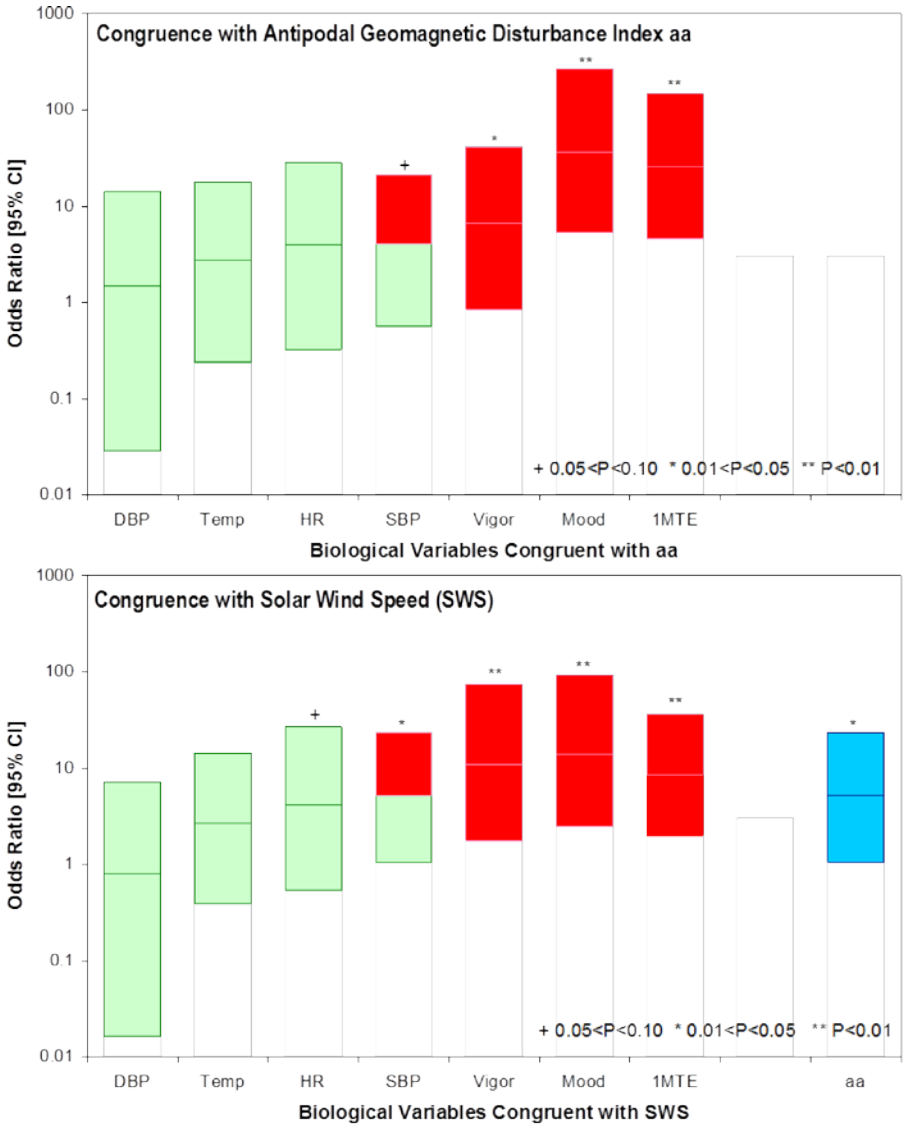

Figure 12. Human mental functions (vigor, mood and 1-minute time estimation) are as closely associated with our cosmos as is the well-known association of the sun's and the earth's magnetism (extreme lower right). Systolic blood pressure monitoring for preventive health maintenance provides data that, as a dividend, may serve to monitor the cosmos and its influence on societal diseases by testing the likelihood that congruence (correspondence of common cycles in and around us) is due to chance. Anticipated influence of the antipodal index of geomagnetic disturbance aa (top) and of the non-photic environment (gauged by solar wind speed, an approximation of interplanetary magnetism) on human psychophysiology was assessed by means of the congruence of periods of their spectral components (defined by overlap of the 95% confidence intervals of the periods, in the frequency range of one cycle in 2.5 years to 3 cycles per year). The biological data stem from 40 years of self-measurements of oral temperature (Temp), systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) and of ratings of mood and vigor and the estimation of 1-minute by counting (1MTE), performed about 5 times a day by a clinically healthy man (RBS). Congruences (assessed by means of odds ratios based on the noncentral hypergeometric distribution) found for 1MTE and for several other variables more than equal that of the known association of helio- and geo-magnetism (bottom, last column on right of dashed vertical line). Mental functions show higher congruence than somatic functions. Among the latter, systolic blood pressure is responsive, perhaps constituting a seemingly acceptable proxy for the mental functions. P-values are based on the non-central Fisher hypergeometric distribution, with 95% confidence intervals computed using Fisher's exact test, used since the null hypothesis was rejected in some, yet not all cases (53, 54).

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WHAT IS THE BEST TIME TO EXERCISE?

R. B. SINGH[1], FRANZ HALBERG[2], JARMILA SIEGELOVA[3], GERMAINE CORNELISSEN[2]
[1] *Halberg Hospital and Research Institute, Moradabad, India*
[2] *Halberg Chronobiology Center, University of Minnesota, Minneapolis, MN, USA*
[3] *Masaryk University, Brno, Czech Republic*

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

The same daily dose of the same medication administered to the same patient has different effects on the circadian pattern of blood pressure depending on when it is administered (1, 2). This circadian stage-dependent effect of a given treatment has been observed with both pharmacologic and non-pharmacologic interventions. Whereas an elevated blood pressure is a known cardiovascular disease risk factor, other alterations of the circadian patterns of blood pressure and heart rate have also been related to an increased cardiovascular disease risk, including too large a circadian amplitude of blood pressure (3).

As part of a healthy lifestyle or for rehabilitation purposes, exercise is currently practiced at times of convenience rather than pertinence. To examine whether the timing of exercise can be optimized on an individual basis, a 68-year old man measured his blood pressure and heart rate around the clock at 30-min intervals with an ambulatory monitor (TM-2421, A&D, Tokyo, Japan) for spans of 4–7 days during which he exercised at different times (around 06.00, 09.00, 12.00, 15.30, and 18.00). Each day's data as well as each record as a whole was analyzed by cosinor to obtain estimates of the MESOR (M, rhythm-adjusted mean), and 24-hour amplitude and acrophase (phase of fitted model's maximum) (4). Results were assigned to the clock hour of exercise during the given span to yield new time series amenable to cosinor analysis (4), complementing the one-way analysis of variance, the main effect being timing of exercise.

Systolic and diastolic blood pressures were predictably higher during the span when exercise was performed daily around noon as compared to spans when it was done earlier or later in the day, Figure 1. On the average, their daily MESORs were 9.5 or 7.1 mmHg higher when exercise was done around 15.30 (SBP) or noon (DBP) by comparison to 06.00 in the morning. The circadian amplitude of heart rate was also predictably larger (by a factor of about 2) when exercise was performed around noon ($P = 0.042$ by cosinor).

The immediate response of blood pressure and heart rate to graded exercise was also circadian stage-dependent in an earlier study on four marathon runners. The smallest blood pressure response occurred around mid-day, larger decreases observed when exercise was done earlier or later in the day (5). Exercise by a 46-year old man 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 potentially carrying an increased cardiovascular disease risk, as recorded by one of us (JS).

Depending on whether the circadian pattern of blood pressure at the outset tends to have too large an amplitude or not, exercise should be timed to reduce both long-term and short-term blood pressure without bringing about an abnormal variability in blood pressure that may be harmful. Ambulatory monitoring interpreted chronobiologically can serve for the optimization of the timing of exercise on an individual basis.

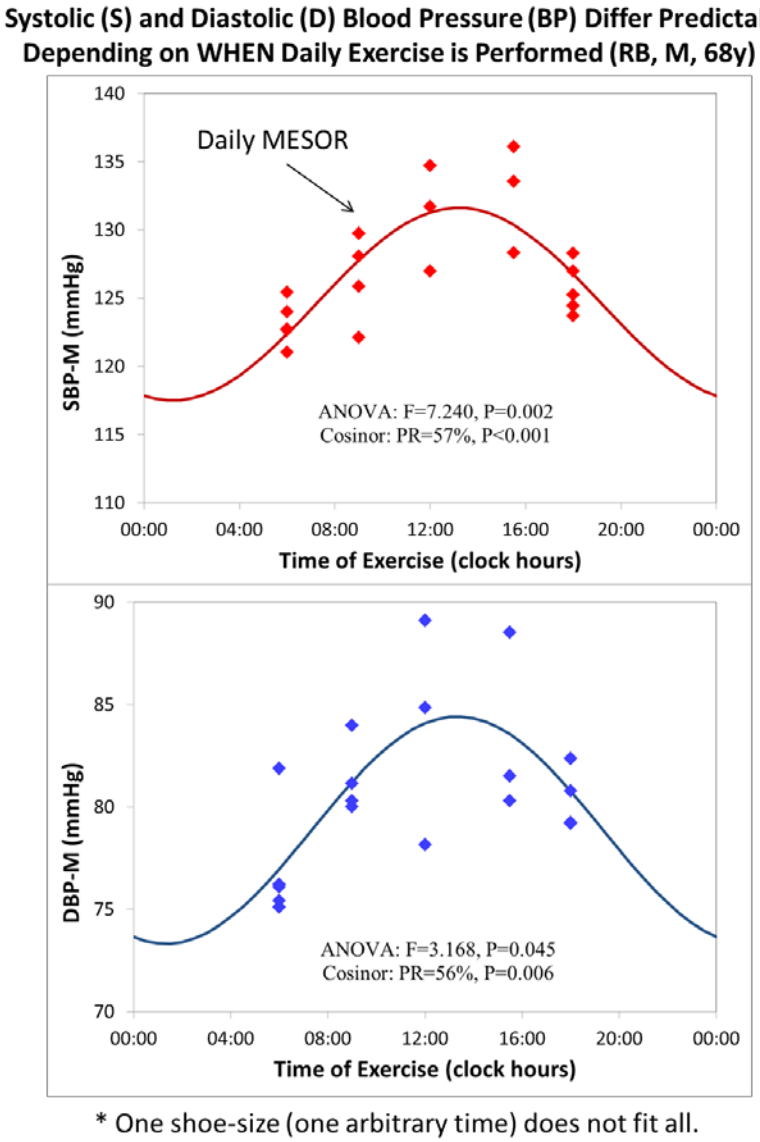

Figure 1.

Support: GM-13981 (FH), University of Minnesota Supercomputing Institute (GC, FH)

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CHRONOMIC CLOUD SYSTEM FOR CHRONORISK-INTERPRETED AMBULATORY BLOOD PRESSURE MONITORING (C-ABPM)?

YINJING GUO[1], GERMAINE CORNELISSEN[2], BING WU[2], LARRY A. BEATY[3], CHRIS ADAMS[3], EL NOLLEY[3], JINYI WU[2], FRANZ HALBERG[2]

[1] *Shandong University of Science and Technology, Shandong, China*

[2] *Halberg Chronobiology Center, University of Minnesota, Minneapolis, MN, USA*

[3] *Phoenix Group of IEEE Engineers, Minneapolis, MN, USA*

1. DEFINITIONS

Chronobiology is the study of chronomes (biological time structures), including rhythms documented, among others, in Minnesota, Table 1 (1–3). Chronomics is the study of ongoing interactions among biological and environmental chronomes, the latter from near and far, Table 2 (2, 3).

2. CLOUD COMPUTING: STATUS QUO (4–30)

Cloud computing involves a high-efficiency computing model utilizing resources on the Internet in a (cloud) center providing services for, e.g., an application layer, a platform layer and an infrastructure layer, which should overcome problems encountered in the conventional fragmented status quo of information technology (IT) systems. Clouds should emphasize IT aggregation, optimization, dynamic allocation and streamlining and easy automatic recovery of information at preset intervals for repeated passes over the same data resources, aiming at cost savings in information technology, reducing energy consumption and improving the efficiency of a national and eventually of an international multilingual data center yet to be created.

3. HISTORY

Cloud computing steps follow major prior developments from mainframe computers before and after 1965, to the personal computer which first became popular around 1980, and the Internet revolution which began around 1995. Cloud computing began around 2010. Every such technological change led to significant turmoil and change in the competitive landscape between enterprise, industry or even countries, with the Internet revolution to some extent taking advantage of the American/information superhighway/ strategy. Whether or not there is an about (~) 15-year periodicity in the foregoing computational developments constitutes a possibility attributed to Lou Gerstner, former chief executive officer of IBM.

An ~15-year cycle has been reported in the blood circulation of some individuals (2, 3), further as a physical global solar cycle (31) and one in interplanetary magnetism [in data linearly showing a 17-year cycle (32) that upon nonlinear analysis became an ~15-year cycle (3)]. Thus far in health care, cloud computing aims at increasing efficiency in what is already being done today in terms of diagnosing deviations from an assumed static "physiologic range" that is ignored by target values, e.g., for acceptable blood pressures.

4. OUTLOOK

The chronomic cloud's aim is to resolve the dynamics of the currently neglected range as a new diagnostic realm in which strain from all sources, including the heretofore-unassessed load of space weather (2, 3), is resolved, Table 3. Lawful changes within the physiological range include cycles of different frequencies, many of them shared with the environment. They serve for an assessment of health vs. an elevated risk of illness (Figure 1). Diagnosis of circadian risk elevation (Figure 2) already allows the institution of timely non-pharmacological and/or pharmacological timed treatment for a true primary prevention during apparent wellness. Resolving variability within the physiological range can be compared with the splitting of the atom (Figure 3). Just as the latter released much new energy, valuable information becomes available in medicine and biology more broadly. Intervention before the fait accompli of disease leads to the paradox of an improved health care system at a reduced cost (Figure 4) (33, 34).

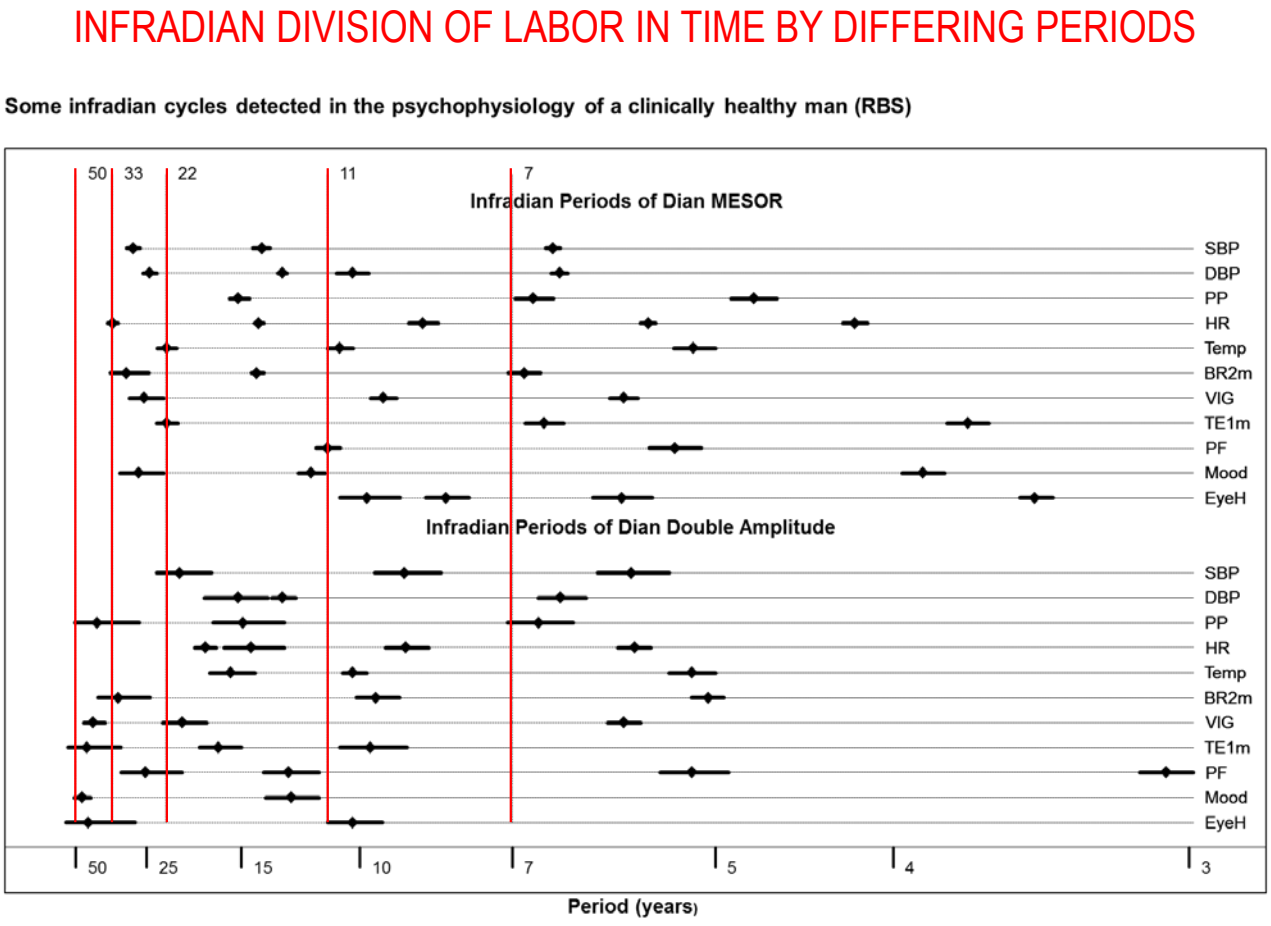


Figure 1. Infradian cycles mapped in a clinically healthy man open a new infradian region of a transdisciplinary spectrum of cycles, of basic interest in themselves and invaluable for new diagnoses, since they characterize sudden cardiac death and suicide among other conditions. Original data of Dr. Robert Sothern. © Halberg.

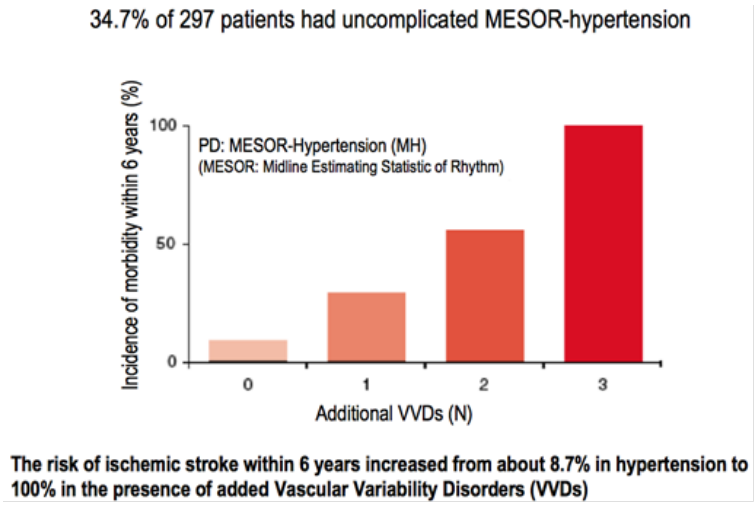


Figure 2. It is not enough to diagnose a high blood pressure, that is more reliably measured as an elevation of the mean (or MESOR), as MESOR-hypertension. When other anomalies (see Figure 5) coexist, there is a great undiagnosed risk of a morbid event. © Halberg.

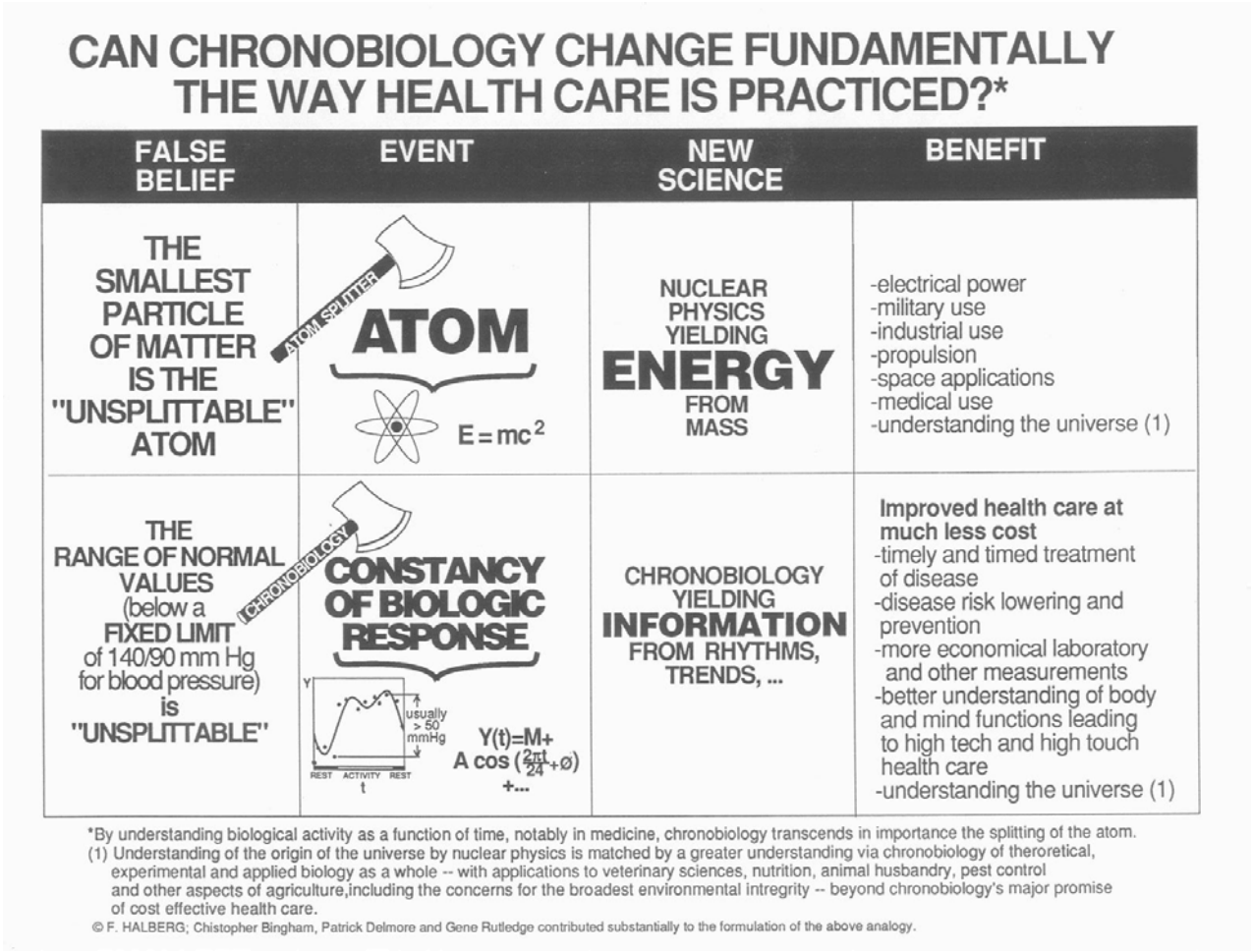


Figure 3. Splitting, i.e., resolving normality into measurable characteristics has a precedent in physics. Just as atomic fission and fusion changed physics, chronobiology and chronomics change a unified science. © Halberg.

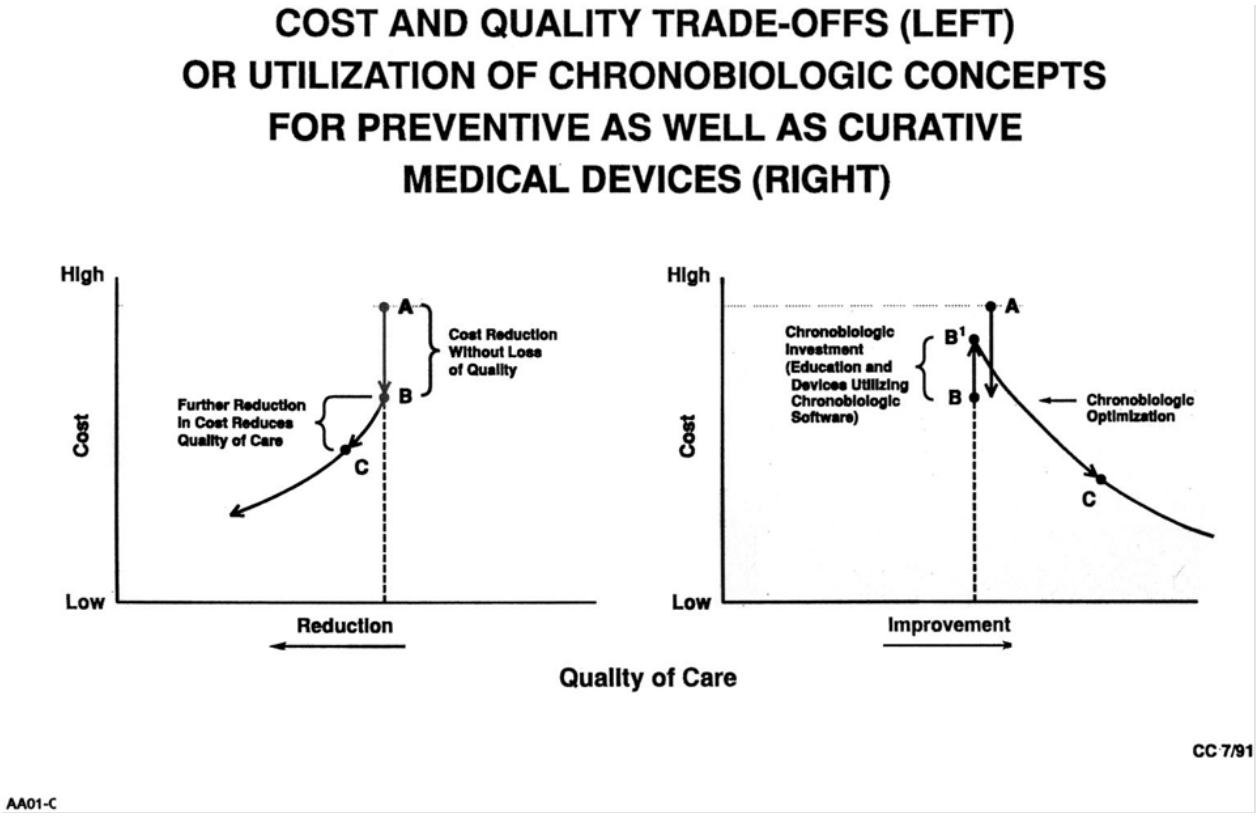
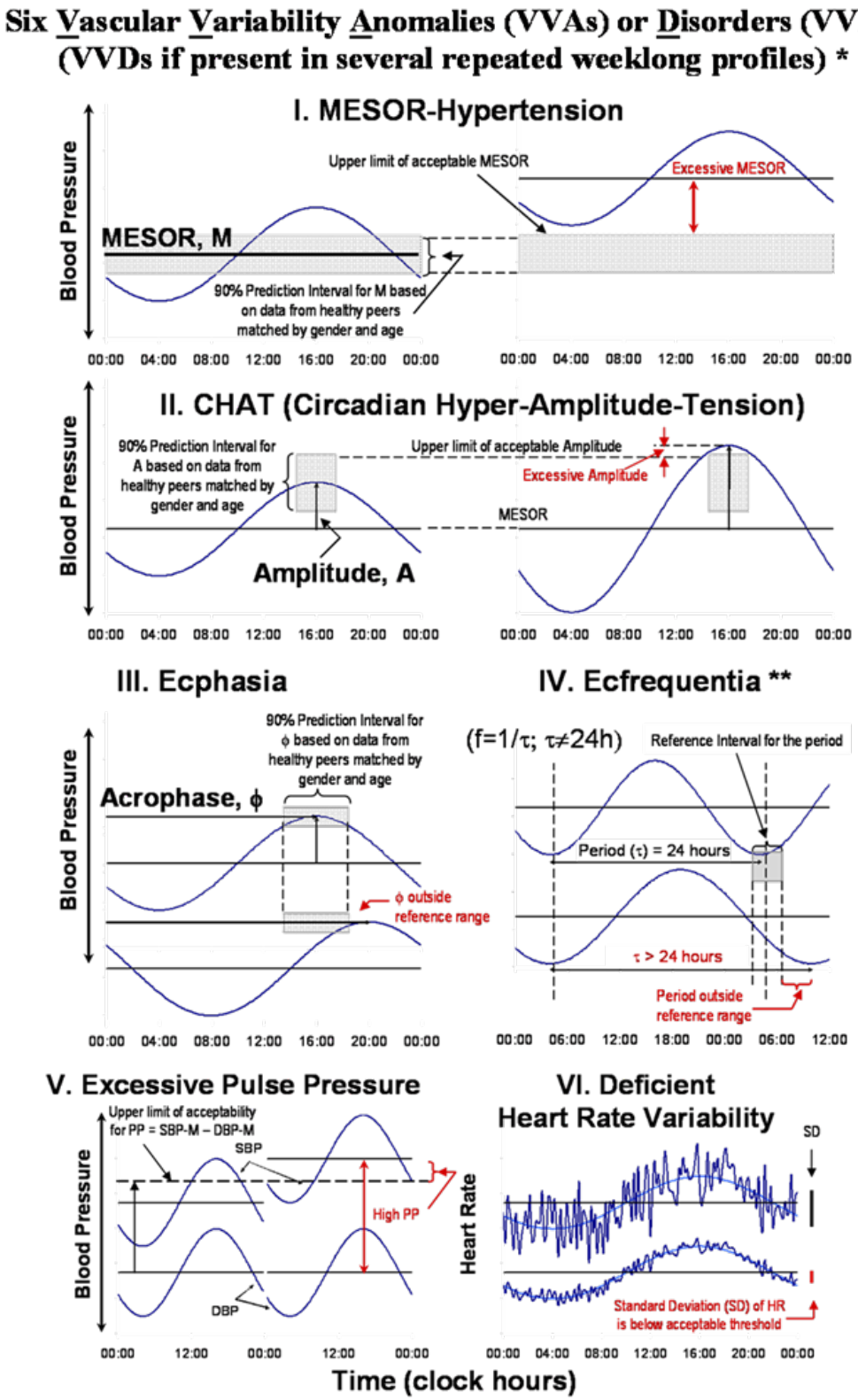


Figure 4. More for less (right) from chronobiology and chronomics, i.e., more by cyber-aided cheaper self-surveillance (right) than from visits to care providers and hospitals (left). © Halberg.

5. SYSTEM FUNCTIONS

- For patients with chronobiologically analyzed ambulatory blood pressure and heart rate records (C-ABPM) to detect anomalies in an "as-one-goes" strain test. This is a first, most cost-effective step with diverse important dividends (35, 36), eventually to be followed by ambulatory blood oxygen saturation recording, running electrocardiograms, electroencephalograms, and other physiological functions to be added step-by-step.
- Expert systems through chronobiology and chronomics may automatically realize diagnoses of an elevated disease risk, such as circadian vascular variability anomalies, cVVAs (Figure 5), eventually to be followed by the detection of extracircadian anomalies complementing cVVAs (35, 36; cf. 3, 4).
- Global positioning would automatically indicate an individual's position on an electronic map of the service center, automatically navigate and deploy medical services personnel when needed.
- Establish a massive electronic patient database and use data mining technologies for psychophysiology, anthropometry, epidemiology and sociology, to obtain earliest signs of emerging epidemics and track the source of the outbreak, in addition to providing information for further improved diagnoses and basic data for medical services and all other human affairs dealt with by a centralized website (Figure 6) in an international data center.



* Validated by chronobiologic analysis of around-the-clock 7-day/24-hour records of measurements at 1-hour or shorter intervals, interpreted in the light of time-specified reference standards qualified by gender and age. ** Ecfrequentia: short for frequency (f) alteration (e.g., desynchronization) that can be Dysfrequentia when associated with symptoms and/or persisting in repeated consecutive 7-day records.

Figure 5. Abstract description of Vascular Variability Anomalies, VVAs. A double product (systolic blood pressure x heart rate/100) above 100 is another VVA not here shown. Consequences of coexisting VVAs are summarized in Figure 2. © Halberg.

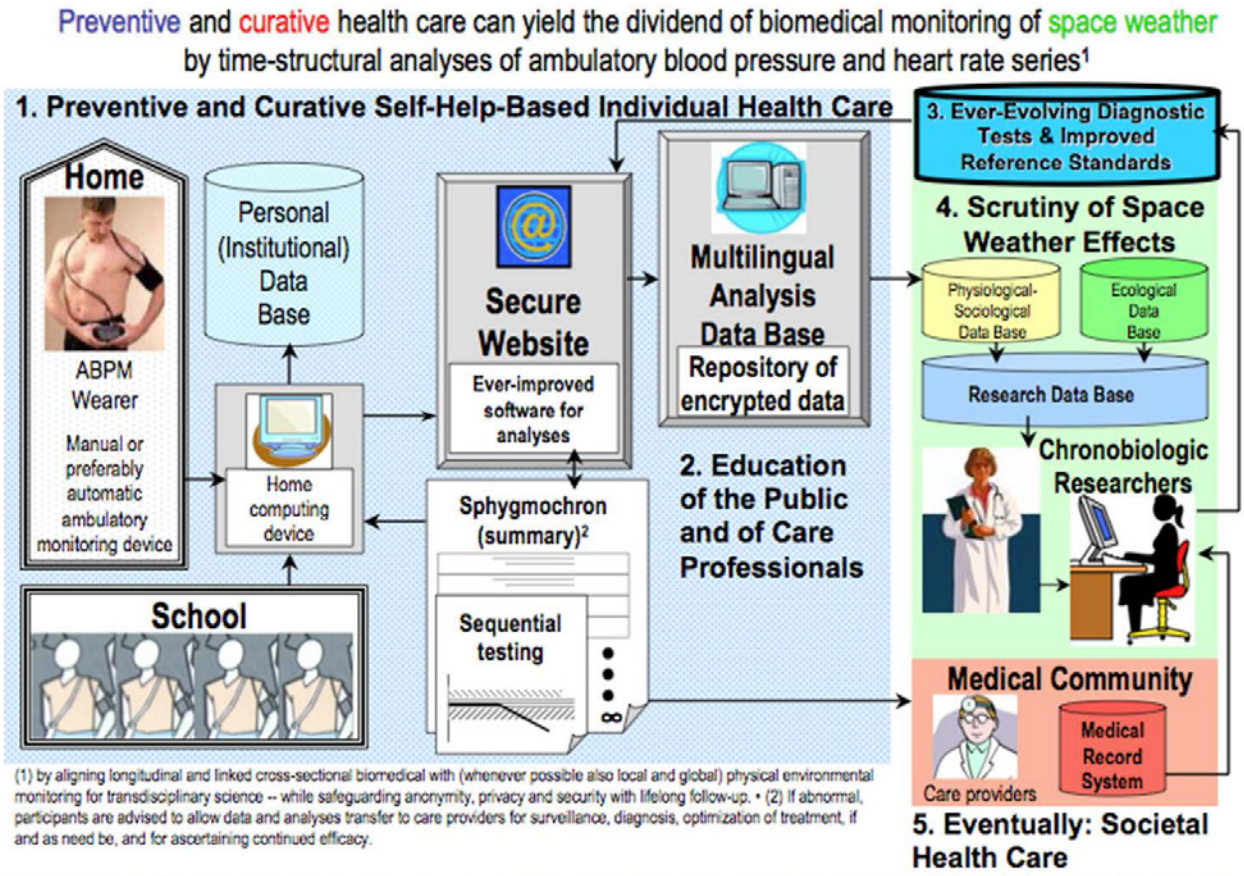


Figure 6. The many dividends from a chronomic cloud system with a website in a data center for service in self-surveillance to individuals, as background for care givers and for research on natural and human-made cataclysm prevention and/or evasion, all by one as-one-goes lifetime's strain test, aligned with results, among others, from space weather stations, health departments' epidemiology, police departments' information on crime rates and economics for research in a unified science. © Halberg.

6. BEYOND A CHINESE CHRONOBIOLOGIC-CHRONOMIC CLOUD

Every crisis, financial or other, gave birth to some new technology, which in turn was a tremendous impetus to help the economy, especially industry, get out of the crisis.

Premier Wen

In Wuxi in August 2009, Premier Wen of China reportedly (by YG) said that there were at least three things to do as soon as possible:

a. Combine applications of medical, social and environmental monitoring systems with third- and fourth-generation cellphone systems;
b. Accelerate the development of cloud computing in major national science and technology centers;
c. Establish a central national information center ("Sensoring China").

At this point, cloud computing officially entered the public eye in the People's Republic. Subsequently, Premier Wen also mentioned on many occasions that China has put the Internet and cloud computing into its future development plans. The time may come when this may be a principal export market from China.

7. DISCUSSION

A project on The BIOsphere and the COSmos, BIOCOS, currently ongoing worldwide on a minuscule scale (2, 3), nonetheless:

a. Provides information revealing that C-ABPM detects an individual's circadian VVAs and thus can gauge emotional and other loads as a strain test;
b. Predicts, by population monitoring, risks greater than a high blood pressure in the form of VVAs (Figure 5);
c. Shows that a high blood pressure average, a circadian VVA in itself, changes the risk of a morbid event from ~8 to 100% in this study when coexisting with other cVVAs, detected only by C-ABPM, (Figure 5);
d. Detects prediabetes; and thus, by a and c above
e. Predicts a premetabolic syndrome;
f. Documents that systolic blood pressure can be a proxy gauging the effect of interplanetary and terrestrial magnetism; and
g. Indicates that systolic blood pressure can also monitor the pre-earthquake environment (2, 3).

8. CONCLUSION

Koop et al. (37) visualize a cyber-health care for 2026 to achieve cost-effectively what is being done today. Preparations for their system could be implemented by C-ABPM earlier, perhaps by a cloud system communicating with a website. As a first step, C-ABPM for severe disease, such as stroke prevention, notably for the elderly, could serve as an initial application since BIOCOS has provided concept validation, except for the cellphone link.

Support: GM-13981 (FH), University of Minnesota Supercomputing Institute (GC, FH)

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TABLES

Table 1. **Minnesota contributions leading to chronobiology** (Annu Rev Physiol 1969; 31: 675–725) **resolving biological time structures, including circadian** (Z Vitamin-, Hormon-u Fermentforsch 1959; 10: 225–296) **and other rhythms**

1.	The partly **genetic basis of circadian rhythm** characteristics and their uncertainties initially documented by differences in extent of within-day change of circulating eosinophil cell counts, among inbred strains of mice (1950) (Proc Soc exp Biol 1950; 75: 846–847) and by **periods in core temperature, differing from their environmental 24-hour counterparts** after blindness, "free-running" (Am J Physiol 1954; 179: 229–255). Human hereditary aspects of about (~) 24-hour and ~7-day cycles documented on twins (Biomed & Pharmacother 2001; 55 [Suppl 1]: 32s–50s).
2.	The importance of the **adrenal cortical cycle**: documented by a **"remove"** (and replace) **approach** (1951: Journal-Lancet [Minneapolis] 1951; 71: 312–319; Journal-Lancet [Minneapolis] 1953; 73: 20–3; Postgrad Med 1958; 24, 349–3582).
3.	**Light and feeding schedules**, competing environmental **synchronizers** of circadian rhythms, mealtime dominating on a restricted diet (1953: Am J Physiol 1953; 174: 109–122).
4.	Timing in the cell: RNA and DNA are strongly circadian periodic; **RNA synthesis precedes DNA formation** in the cell cycle, describing what really happens in time in cellular transcription. Also, that a rhythm in cell membrane phospholipid peaks before RNA formation (1958; Proc Soc exp Biol (NY) 1958; 97, 897–900). First hint that RNA may also precede DNA in evolution.
5.	Importance of **hypothalamus** traced from the eyes as transducers of lighting regimen effects on circadian period of adrenal cortex over the pituitary to the CNS (1954: In: Withrow RB, Ed. Photoperiodism and Related Phenomena in Plants and Animals. Ed. Publ. No. 55. Washington DC: AAAS; 1959. p. 803–878; many subsequent articles) and to the **cell**. (The suprachiasmatic nucleus, part of the hypothalamus, was identified later, and its then-claimed importance as sole timer was debunked by 1958 and subsequently (Chronobiologia 1979; 6: 405–424; Anat Rec 1974; 180: 47–52). The long-denied timing mechanisms in the periphery, denied for decades, are also now accepted.
6.	**Timing for the body as a whole:** different, including opposite effects of the same hormones (growth hormone, ACTH, TSH) or (e.g., anti-cancer) drugs, or of the same number of calories, depending only on the circadian timing of administration (1973; Experientia [Basel] 1973; 29: 909–934; Peptide chronomics. In: Kastin A, Ed. Handbook of Biologically Active Peptides. Amsterdam: Elsevier; 2006. p. 1529–1564).
7.	**Circadian rhythms tip the scale between life and death** in response to many stimuli: physical stimulus (noise) (1955: Proc Soc exp Biol (NY) 1955; 88: 169–173); whole-body irradiation (Haus E, Halberg F, Loken MK, in Scheving LE, Halberg F, Pauly JE, Eds. Chronobiology, Proc. Int. Soc. for the Study of Biological Rhythms, Little Rock, Ark. Stuttgart: Georg Thieme Publishers/Tokyo: Igaku Shoin Ltd.; 1974. p. 115–122); chemical (alcohol) (J appl Physiol 1959; 14, 878–880); biochemical (endotoxin) (J clin Endocrinol 1955; 15: 887); drug (ouabain) (Fed Proc 1959; 18: 63), culminating in the doubling of the 2-year survival rate in patients with advanced perioral cancers (Guest Lecture, Proc. 30th Ann. Cong. Rad., January 1977, Post-Graduate Institute of Medical Education and Research, Chandigarh, India, 8 pp; J Exp Therapeutics Oncol 2003; 3: 223–260).

Table 1: continue

8.	**Circadian rhythmicity in a prokaryote** (without a nucleus), originally strongly contradicted by a committee on the molecular basis of circadian rhythms (Report of the Dahlem Workshop on the Molecular Basis of *Circadian Rhythms, Berlin, November 3–7, 1975. Berlin: Dahlem Konferenzen, 1976: 462 pp); that partly endogenous rhythms are found in all life (Proc MN Acad Sci 1961; 29: 227–239) is now universally accepted.
9.	**A broad set of statistical methods and programs** for detecting, validating, quantifying and comparing (always with uncertainties estimated) rhythms, trends and chaos starting with the linear and nonlinear cosinor (in von Mayersbach H, Ed. The Cellular Aspects of Biorhythms, Springer Verlag, NY, 1967, pp. 20–48; cf. Acta med rom 1980; 18: 399–440).
10.	Discovery of an (eventually long) list of periods in addition to about-daily (circadian) periods, starting with the **biological near-week**, followed by discovery of the corresponding **geomagnetic near-week** followed by numerous other infradian periods (1965: Acta endocrinol 1965; 50 [Suppl 103]: 5–54; University of Minnesota/Medtronic Chronobiology Seminar Series, #1, December 1991), leading from chronobiology, a figurative microscopy in time, to chronomics, a figurative telescopy in time.

Table 2*. Minnesotan contributions to chronomics, resolving transdisciplinary geo-bio-noospheric coperiodisms leading to a unified science and art (Biomed & Pharmacother 2004; 58 [Suppl 1]: S150–S187)

1.	A set of methods and programs resolving, with **uncertainties**, **coexisting multiple**, **sometimes spectrally neighboring periods**, **τ**, **with non-overlapping CIs (95% confidence intervals) of □**, **revealing and mapping non-stationarity in time and space** (including the transient disappearance of an aeolian nonphotic component in certain spectral or geographic locations).
2.	**Congruences** defined by overlapping CIs of period, τ, and/or phase, □, e.g., within the organism (division of labor in time), within the environment (e.g., Kp vs. Wolf numbers, geo- vs. heliomagnetism) or external-internal congruences (e.g., blood pressure and geomagnetism) at a given □
3.	**New internal-external congruent CIs of □s define coperiodisms**, some found first in living matter and next in the abiotic environment, others vice versa, constituting a transdisciplinary spectrum with component τs of **a near-week**, **an about (~) 2-week**, **~1-month**, **~5-month (quinmensal)**, **semiannual**, **circannual**, **near- and far-transannual**, **diennian**, **septennian**, **decadal**, **~15–17-year**, **paradecadal**, **paradidecadal**, **paratridecadal (BEL, Bruckner-Egeson-Lockyer, near 30–40-years)**, **~50-year (semicentennian)**, **transsemicentennian**, **semimillennian and myriadennian components**.
4.	Partial endogenicity, **genetic coding** supported by τs with nonoverlapping CIs in and around us (free-run), and by "after single stimulus" manifestation ("induction")
5.	Brain (pineal and suprachiasmatic nucleus, SCN) (mediating) or heart, circulation and cell (reflecting) non-photic environmental effects (shown by SCN ablation or magnetic storm effects).
6.	Nonphotic spectral components in populations of **eukaryotes and prokaryotes** (decadals in bacterial mutations).
7.	**Selective assortment (SA)** of τs (or □s) among and within individuals, in organ systems, variables, cycle characteristics (MESOR vs. amplitude), and in their lock-ins (of □, e.g., of 17-ketosteroids with Kp and urine volume not with Kp but possibly with Wolf numbers)
8.	**SA** of τs in different variables of the same population or of phases at a fixed □ in different populations.
9.	Nonphotics can tip the scale between little or none versus many **infections**, **sudden cardiac death**, **suicide** and **terrorism**.
10.	Odds ratios for the number of shared frequencies between human mental functions and either helio- or geo- magnetism more than match the association of helio- and geo-magnetism to each other.

*Rules learned from decades-long longitudinal studies of populations and of individuals analyzed globally and locally, **glocally in space and time**, as a method as well as a map, updated **progressively** at intervals determined by the cycles detected **and pergressively** surveilled in serial sections and their sequential analysis in repeated passes over the accumulating data for resolution of changes in characteristics of each cycle in individuals, eventually from womb to tomb and in populations beyond the human lifespan

CHOICES IN DEALING WITH RESPECT TO PERSONAL, SOCIETAL (HUMAN-MADE) AND NATURAL DISASTERS

1. We currently try, but may not be able, to respond to each cataclysm after it occurs, whether it is a massive stroke, a crime, a terrorist attack or an earthquake;

2. we can assess currently conventional risk factors and try to reduce their impact according to visits with a care provider, but fly blind with respect to vascular and other variability disorders that cannot be detected by a single or 24-hour spotcheck, or **alternatively**;

3. the individual and society can survey the time structure of personal health by, first, vascular monitoring and society can implement a system using the physiological data aligned with those from epidemiological and

social monitoring, with the tools of a temporal microscope (chronobiology) and telescope (chronomics), to assess one's position by comparing a personalized with a corresponding gender-age-ethnicity-matched chronousphere providing reference standards as glocal maps via an international website.

Of particular interest are far-transyears, mostly between 1.2 and 1.9 years, which drift in frequency or phase and wax and wane in amplitude to the point of disappearance and reappearance. So do near-transyears, longer than 1 year but shorter than 1.2 years, found after their detection in biology in solar and terrestrial magnetism and other counterparts, just as we found the geomagnetic near-week in Kp, validated by Roederer and extended to aa by Vladimirsky as a counterpart to a set of biological near-weeks, most of which differ from precisely one week and may hence be partly built-in.

***Table 3*. Chronobiological and chronomic concepts, tools and long-term goals**

Time structures (chronomes) around us are aligned with chronomes in us, by chronomics (figurative telescopy in time), complementing chronobiology, the study of the mechanisms and applications of biological chronomes, complementary genomes, a figurative microscopy in time (1)*

** Numbers in ( ) indicate bibliographical references; numbers in [ ] indicate endnotes.*

View of:	I. Current homeostatic response physiology	II. Time-structural (chronome) physiology	Utility of II
1. Definition of normalcy, e.g., health	Negative: absence of abnormality, e.g., of disease [1, 2]. Curtain of ignorance on everyday physiology outside the normal range of reference values	Positive: parametric and nonparametric assessment (cf. 9). Alteration in the normal range will be detected	Time structural (chronomic endpoints): the control in whatever we do [3]
2. Quantification of normalcy, e.g., health	Population-based: percent abnormality, e.g., morbidity and mortality	Individualized: P-values for statistical significance and for scientific (i.e., clinical) signification	Recognizing risk of abnormality before the fait accompli of catastrophe
3. Interpretation of reality	Putative (imaginary) set points, e.g., the fiction of a true time-invariant blood pressure	Chronomes: consisting of a) rhythms; b) trends; c) deterministic and other chaos; d) any residuals and interactions among a, b, c and d	Chronorisk syndromes: 1) circadian overswinging of blood pressure; or 2) chronome alteration with heart rate jitter deficit; or 3) circadian vascular rhythm alteration; or 4) altered about-yearly rhythms in circulating prolactin and TSH signaling breast and prostatic cancer risk elevation
4. Variability	Confounder (foe)	Of interest in its own right (friend)	Tool and invaluable source of much information [4]
5. Biosystems' behavior if perturbed	Settling down to an imaginary steady state (constancy) or limited random 'hunting', e.g., as (mistakenly anticipated) when a single blood pressure is taken after some (≤ 30) minutes of rest	Dynamic chronomes that characterize health within chronobiologic limits set by the intermodulation of the chronomes' α-, β-, γ- and δ- (spontaneous, reactive and modulating) rhythms (2), e.g., a large circadian change in blood pressure during bed rest	Positive individualized quantification of health
6. Analogy	Thermostats with "hunting" noise (information lost)	Pendulums in resolvable chronomes	Prediction from parameters
7. Physiologic or normal ranges of variation	Broad, random, indivisible; equated to noise, neglecting current standard for diagnosis and treatment	Structured, predictable [5]; resolved into reference ranges (chronodesms) for chronomes	Circadian blood pressure amplitude (bp-a) or circadian standard deviation (SD) for detecting effect of in utero exposure to betamimetics

***Table 3*. continue**

View of:	I. Current homeostatic response physiology	II. Time-structural (chronome) physiology	Utility of II
8. Action?	Confounder elimination incompatible with detection of circadian blood pressure disorder	Monitoring and as-one-goes analyses, and on this basis, action	Detects treatable overswinging of BP-A, which carries a 720% increase in risk of ischemic stroke; improves cancer treatment
9. Endpoints	• Original values: Casual measurements at times of convenience, not necessarily of pertinence (e.g., of 'the' blood pressure with > 40 % uncertainty in diagnosis in cases of border-line hypertension) (4): Time-unspecified: • mean • SE	Time-specified chrones in chronomes: Time-coded: • original values • SD • MESOR(s) • period(s), τ • amplitude(s), A • acrophase(s), ϕ • waveform(s) (A,ϕ) • pairs of harmonics • trends • chaotic dimensions • residuals	Chronobiologic software: • provides information, e.g., on points 3 and 4 above • guides timed treatment that has greatly prolonged the survival of cancer patients
10. Sources of variation	Exogenous responses to stimuli from proximity mostly from the habitat niche	Endogenous and exogenous; responses to stimuli from near and far, including cosmos	Resolution of impact of storms in space on myocardial infarctions on earth: space weather report? [6]
11. Mechanism	Feedbacks along axes: unstructured 'modulation' like the deus ex machina in a physiological tragedy since outcomes may be unpredictable	Feedsidewards in networks with alternating outcomes: predictable (insofar as rhythmic) as a chronomodulation	Predictable since rhythmic neuro-endocrine-vascular intermodulations can account for outcomes that may be as different as stimulation vs. inhibition of immunity
12. Hierarchy	Up/down	Collateral: alternating primacy among intermodulating multifrequency rhythms in chronomes	Focusing on selected tasks at different times
13. Teleonomy	Righting and regulation	Anticipatory, preparatory coordination	Greater flexibility
14. Simplified analogy	Thermostat	Pendulum	Prediction of risk by alteration of parameters
15. Biological evolution	Darwinian, externally adaptive	More and more internal and integrative while externally adaptive to both nature and nurture	Instrumented self-help
16. Health and environmental care	Medical treatment often limited and late, given mostly after the diagnosis of overt disease [7]	Optimization according to marker chronomes (of interventions by drugs and/or devices, e.g., pacemakers, with diagnosis and treatment refined by narrowed reference range and assessment within that range of chronorisk leading to preventive treatment timed by marker rhythms (that also serve to validate effect)	E.g., catastrophic and iatrogenic disease prevention

***Table 3*. continue**

View of:	I. Current homeostatic response physiology	II. Time-structural (chronome) physiology	Utility of II
17. Animal husbandry, apiculture, aquaculture and economic entomology	Timed by convenience	Chronome-based	Optimization: greater efficacy; fewer undesirable effects
18. Value	Often wasteful	Cost-effective	Waste reduced
19. Seeking inanimate and animate origins	Stratigraphy for identifying, in geologically space, sequences in time; radiocarbon dating	Additional tracing of chrono-mo-ontogeny and chronomo-phylogeny [8] in the context of glimpses of cycles in corresponding spans of a figurative cosmo-ontogeny (8)	Adds to knowledge of the past to better optimize the future
20. Life in the scheme of physical and cultural things	Survival of the fittest with humans dominating food chains viewed in the perspective of bioenergetics in a mostly terrestrial ecology	Physically and socially chronomodulating and thus informatively and integratively evolving biota molded by human culture Homo not only faber but cosmoinformans and chronomodulans in a budding broad chrono-cosmoecology (9)	Humans safeguard the integrity of the biosphere as it extends into the cosmos and as we speculatively, by joining the approaches by ablations. superposed epochs and resonance tests concomitantly explore the temporal aspects-of our origins, possibly represented by our chronomes that in turn may reflect a long-past environment (11)
21. Cosmos	Ignored	The broad spectrum of non-photic environmental cycles, reflected in physiology, predates pathology and sociology (including politics and militarism), as in the ~30-year BEL cycle (12, 13), Figure 2	Survival from hard vascular events of individuals and from war and diseases of societies of populations (11)
22. Investigator satisfaction	**Frustrating work** when (without specification of chronobiologic timing, even at the same clock-hours), one gets confusing and/or obscuring, even opposite results from the same intervention. Up or down regulation may miss or misinterpert a change in amplitude or phase	**Sheer fun:** long-standing controversy is resolved by accounting for both the genetic and broadly environmental bases of the feed-sidewards among inanimate and animate cycles that constitute life; disease risk recognition promises to lead to the prevention or timed treatment of catastrophic diseases such as stroke, cancer or sudden death	Increased productivity

[1] Just as contemporary physics, by fission and fusion, gathers more and more energy by splitting the atom, biomedicine gathers more and more information by splitting the normal value range into time structures, thereby resolving, e.g., trends and chaos as well as rhythms (fission) and looking at their feedsideward interrelations (fusion) for a better understanding of an interdigitated, indivisible Janus-faced inseparable soma and psyche.

[2] Health care, required to deal with disease risk gauged within the normal range, such as conditions in Figure 1, will be missed by current health promotion, a step in the right direction, by its recommendations of attention to diet, exercise or relaxation, but should be preceded and followed by a chronobiological assessment of the timing as well as effect of recommended procedures, rather than merely by the current reliance of ruling out the occurrence of values outside the normal range.

[3] Location and dispersion indices include the determination from histogram of values, of means (arithmetic, geometric, harmonic), median, mode, minimum, maximum, 100% and 90% ranges, interquartile range, standard deviation (SD), weighted SD, standard error (SE); these endpoints are computed from time-unspecified values in the context of the homeostatic approach, whereas in

the chronobiologic framework the location and dispersion indices are used as such on systematic time-specified samples, as time series-derived parameters, i.e., on each of the endpoints of time structures, M, A, □, (A_n,□$_n$), etc.

[4] An international project on The Biosphere and the Cosmos, BIOCOS, focuses first upon chronocardiology in general and blood pressure and heart rate dynamics in particular, for stroke and other catastrophic vascular disease prevention (consult chronobiology home page, http://www.msi.umn.edu/~halberg/).

[5] Information from the physiologic range for prevention, diagnosis or treatment is much refined when this range is individualized and interpreted in the light of a personalized background as well as in the context of gender-, age-, ethnicity- and chronome stage-specification.

[6] The need for forecasting storms in space should be explored further on the basis of systematic studies aligning physiological lifetime monitoring and clinical and archival statistical studies with ongoing physical data collection near and far, both for ascertaining effects and in studying countermeasures. Blood pressure, heart rate and other physiological and psychological monitoring would also provide basic information on any cross-spectral and other associations (feedsidewards) (2) within and among biological and environmental chronomes while further providing reference values of medical interest.

[7] Even if some preventive measures have also been long implemented, e.g., by vaccination, and even if recently more and more hygienic measures (such as exercise and caloric, fat and sodium restriction) are also popular, all can be greatly improved by timing designed with chronobiological individualization. Current action based on group results fails to recognize, for instance, that the blood pressure response to salt (5, 6) may differ as a function of circadian stage, and there are indeed individuals in whom the addition of salt lowers rather than raises blood pressure (6, 7).

[8] Development from the egg of rhythms (some may be much older than shards) and of other constituents of chronomes to trace their homeo- or heterochronically roughly 'recapitulatory' development across species, with both ontogeny and phylogeny, perhaps tracing in their turn the concomitant development of the geocosmic environment. This distant basic goal can be pursued with the immediate reward of obtaining indispensable reference values for the diagnosis of two chronobiologic risk syndromes, circadian hyper-amplitude-tension, briefly CHAT, and chronome alterations of heart rate variability, briefly CAHRVs, just as an extreme deficit in heart rate jitter associated with an increase in the risk of ischemic stroke or of a myocardial infarction of 720 and 550%, respectively.

Support: GM-13981 (FH), University of Minnesota Supercomputing Institute (GC, FH).

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NONINVASIVE METHODS IN CARDIOLOGY 2012

Edited by: HALBERG F., KENNER T., SIEGELOVÁ J., DOBŠÁK P.

Published by Masaryk University in 2012
1st edition, 2012
Printed by: Tiskárna KNOPP, Černčice 24, 549 01 Nové Město nad Metují
Typesetting: Institute Biostatistics and Analyses, Masaryk University
ISBN 978-80-210-6026-5

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ISBN 978-80-210-6026-5