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NONINVASIVE METHODS IN CARDIOLOGY 2011

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Prof. MUDr. Bohumil Fišer, CSc.
(22.10.1943 - 21.3.2011)

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

During his studies at the Faculty of Medicine of Masaryk University he had been working in the Institute of Medical Physics and later Physiology where he extended his considerable knowledge of physics and mathematics; that became a basis for his further activities, mainly in the research of cardiovascular system. After his graduation in 1966 he acquired a valuable medical experience in surgery in the course of his military service (1967–1968). Then he continued his scientific and teaching activities in the Department of Physiology as a lecturer and since 1989 as a senior lecturer. He was appointed a professor in 1995; at that time he was already Head of the Department of Physiology at Masaryk University in Brno.

The scientific and publication activities of professor Fišer, started in 1966 in cooperation with professor Jan Peňáz, were concentrated on frequency analysis of blood pressure oscillations in rabbits. The oscillations of cardiovascular variables were studied in man, also using direct recording of blood pressure in a. brachialis. These experiments using exact original methods of frequency analysis brought the evidence of the ten-second rhythm in heart rate in man. Together with professor Semrád he performed the analysis of pulse pressure and pulse interval in patients with atrial fibrillation, using various mathematical methods and method of Monte Carlo including the heart rate rhythm regulation of heart contractility in man. The study of heart contractility in man confirmed the findings of contractility regulation in isolated heart experiments discovered by professor Vladislav Kruta, professor Pavel Bravený and others co-authors from the same physiological department. His scientific work from the studies mentioned above was finished by CSc. thesis in 1978. He also contributed to the first clinical measurement of cardiac output and first electrophysiological examination of the human heart in St. Anna Teaching Hospital together with professor Bořivoj Semrád, professor Karel Zeman and senior lecturer Josef Šumbera. Further studies analysed the interrelationships between heart rate fluctuations and blood pressure fluctuations using autocorrelation functions and power spectral densities. In 1978 the first description of coherence between pulse interval and systolic

blood pressure was published. Heart rate oscillations in frequency domaine 0.1 Hz were analyzed. These findings are fundamental in determination of baroreflex sensitivity in man. His studies aimed at assessing baroreflex sensitivity continued with the development of another non-invasive method of determination baroreflex sensitivity. Sudden decrease of blood pressure of about 10 to 20 mmHg, evoked by out-flow of blood into vasodilated lower extremities after 5 minutes occlusion, brought about baroreflex-mediated blood pressure changes and changes in cardiac interval. Changes of cardiac interval, monitored beat-to-beat, were used for measurement of baroreflex sensitivity. The new developed method allowed further hemodynamic studies in healthy subjects and clinical examinations, done together with professor Jarmila Siegelová, in patients with essential hypertension. The results of his scientific work professor B. Fišer published in numerous monographs, in experimental original papers and in several pedagogical texts both in his country and in India, Hungary,Germany, Italy, France, Great Britan, Austria and USA. Partial results were given at many scientific meetings.

International cooperation of professor B. Fišer in science and research could be fully extended only after the velvet revolution in 1989. The cooperation with professeur Jean-Paul Martineaud, Medical Faculty, Lariboisiére Hospital, University de Paris (France) was very intensively developed and the common hemodynamic studies were provided as a non-invasive measurement of aortic compliance and blood flow regulation in cerebral arteries, both in healthy subjects and patients, and published in international journals. At the same time, the cooperation with professor Franz Halberg and with professor Germaine Cornelissen, Halberg Chronobiology Center of the University of Minnesota (USA) started. Further studies of circadian variability of cardiovascular variables and baroreflex sensitivity were published in many papers as the result of this common work. In 1995 he was invited as a distinguished scientist for a lecture to the Supercomputer Institute of University of Minnesota (USA) and presented there the paper about the use of supercomputers in prevention of stroke and cardiac death. The international cooperation continued with professor Thomas Kenner, from the Department of Physiology in University in Graz (Austria), where the original studies of heart rate variability, baroreflex sensitivity and chronobiology have been realized and included in the common international project of analysis of cardiovascular control in physiology and pathophysiology.

From 1989 professor B. Fišer in cooperation with professor J. Siegelová organized on Medical Faculty Masaryk University international symposia MEFA and from 2002 every year on Medical Faculty Masaryk University Symposia. Every year were published books, edited by professors F. Halberg, T. Kenner, B. Fišer and J. Siegelova (Chronobiology 1996, Noninvasive methods in cardiology 1999, The importance of chronobiology in diagnosing and therapy of internal medicine 2002, Chronobiological analysis in pathophysiology of cardiovascular system 2003, Chronobiology in medicine 2004, Noninvasive methods in cardiology 2006, Noninvasive methods in cardiology 2007, Noninvasive methods in cardiology 2008, Noninvasive methods in cardiology 2009, Noninvasive methods in cardiology 2010).

Scientific, medical, and organization capabilities of professor B. Fišer were appreciated by a number of awards, citations and memberships in scientific and health organizations and institutions. Professor Fišer was a member of a range of international scientific societies such as International Society of Physiology, French Physiological Society (Societé de Physiologie Francaise), as well as Czech Physiological Society. He participated in many international physiological congresses, symposia and workshops, some of them also organized by him. He was invited to many lectures concerning cardiovascular control mechanisms in France, United Kingdom, Austria and USA. In our republic, he was a member of International Grant Agency of Ministry of Health from 1995 to 2000 and of Grant

Agency of the Czech Republic. In 2000, he was nominated in the function of Minister of Health of the Czech Republic. In this position he was very successful and everybody esteemed his activity in the government. In 2002 he returned to Masaryk University and was in the head position until 2008, and as a professor continued until 21.3.2011. In 2003, he became a Member of Executive Board of WHO (World Health Organization) until 2008.

Noble personal qualities of professor Fišer include not only an extraordinary diligence, but also modesty and tolerance, almost permanent good mood and friendly relation to people. He was always ready to give advice and assistance to younger colleagues to whom he imparts his extensive scientific, research and pedagogical experience. In Department of Physiology he educated from his younger coo-workers two professors of physiology, three senior lectures and a lot of Ph.D. graduated students. His productive life was filled mainly with professional work and with work which was of benefit to the public. His untimely death notwithstanding, he will be with us in spirit in our efforts to change a medicine based on a number of diagnoses to an objective assessment of many novel rhythm and other variability alterations in cardiovascular parameters. Thereby, health care can change from one based on sheer intuition and hard-to-define experience listing a number of diagnoses to an objective assessment of many novel biological rhythms.

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

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Professor Jean-Paul Martineaud
(*27.3.1931-†29.11.2010)

Prof. Dr. Jean-Paul Martineaud, Head Emeritus of the Dept. of Physiology and Dept. of Non invasive Clinical Investigation at the Lariboisière Hospital, University Paris Diderot VI, Teaching Hospitals C.H.U. Lariboisière and Saint-Louis, Paris, France.

He studied at the University of Paris, Medical School where he was graduated in 1963.

Professor Martineaud´s research interest included pathophysiology and fundamental research in cardiovascular system, pathophysiology of temperature control, pathophysiology of exercise, sports medicine and cardiology. His second field of interest was history of medicine.

Prof. J.P. Martineaud, was the Head of the Dept. of Physiology and Dept. of Non invasive Clinical Investigation at the Lariboisière Hospital, University Paris Diderot VI, Teaching Hospitals C.H.U. Lariboisière and Saint-Louis from 1968 to 1996. During this period, he developed the medical service in the Dept. of Non invasive clinical investigations including the diagnostic in the fields of cardiology, angiology, pneumology, ergometry, spiroergometry at the highest scientific level. He was an excellent clinician and was highly appraised from other heads of clinics. When teaching physiology, he was a very good lecturer, with a lot of latest findings in the science. During his long working period he published a lot of original scientific papers.

The figure presents the staff of Dept. of Non invasive Clinical Investigation at the Lariboisière Hospital in December 1995. In the 1st row sitting there are Dr. Philippe Bonnin, Dr. Antoni Kedra, Prof. Dr. Jean-Paul Marineaud and Dr. Olivier Baillart, in the 2nd row on the fifth position Prof. J. Siegelova, in the 4th row on the first position Dr. Etienne Savin, on the third position Prof. Dr. B. Fiser.

Prof. Dr. Jean-Paul Martineaud, as a professor emeritus, worked in the Dept. of Non invasive Clinical Investigation at the Lariboisière Hospital under guidance of the successive Head, prof. Dr. Bernard Levy from 1996 to 2011. During this long working period he educated generations of medical doctors in France and abroad.

Prof. Martineaud and his scientific team has cooperated with Dept. of Physiology, Faculty of Medicine, University of Dakar-Fann, Sénégal and National Institute of Sports and Education of Sénégal, Sénegal. The physiological measurements were done under his guidance in hot climate in Senegal and published together with Prof. Dr. Cissé and Prof. Dr. Samb.

Prof. Martineaud and his scientific team collaborated with University of Tirana, Albania where he and Dr. P. Bonnin have supported, for 15 years, the contemporary education and knowledge in physiology for students of medicine with the help of an European project of teaching.

The longest cooperation was with the Dept. of Physiology in Brno, Masaryk University (at that time Purkyne). Prof. Martineaud started to work in Brno in 1976 with prof. Vladislav Kruta (1909–1977), prof. B. Fiser and prof. J. Siegelova. This cooperation continued for many years. He visited a lot of scientific meetings in Prague, Brno, Bratislava before the revolution in 1989. After the revolution he had been visiting Brno every year until 2005. Prof. J.P. Marineaud acted in Brno as an excellent scientist; he discussed the cardiovascular research regularly with prof. Franz Halberg from University of Minnesota, USA, prof. Thomas Kenner from Graz, Austria and with the Brno team, prof. Bohumil Fiser, prof. J. Siegelova and Dr. Jiri Dusek. Prof. B. Fiser and Prof. J. Siegelova also visited many times Dept. Physiology, Paris and they worked in the position of scientific visitors in Paris. Prof. Martineaud sent also from Paris to Brno Dr. E. Savin many times to Masaryk University to pursue common experimental studies resulting in common research projects. In Brno prof. Martineaud presented every year new results in cardiovascular research, sometimes also in cooperation with the University of Senegal.

Prof. Martineaud received several Awards, Medal of Medical Faculty of Masaryk University in 1995 and the “Prix de l´essai” in 1998 from the “Societé d´-Histoire des Hôpitaux”.

Prof. J.P. Marineaud was a physiologist, scientist and teacher par excellence. He was an extremely busy and productive scientist, clinician and excellent organizer of medical clinical service. His list of his publications is attached. We should never forget that the historical progress in science and medicine was achieved also due to the work of Prof. Dr. J.P. Martineaud.

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    Author(s): SENTOU Y, BAILLIART O, MARTINEAUD JP
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    Author(s): MARTINEAUD JP, LEVY B
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    Author(s): LEVY BI, OLIVA Y, MARTINEAUD JP
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A REVIEW OF CONTINUOUS RECORDING OF BLOOD DENSITY AND OF CIRCADIAN VARIATION OF BLOOD DENSITY.

Thomas Kenner

Dedicated to the memory of Bohumil Fiser
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The Mechanical Oscillator Technique was invented by H. Leopold and Stabinger and is manufactured by *Firma Paar in Graz, Austria*. The technique is based on the determination of the the resonant frequency of a mechanical bending type U-shaped oscillator, filled with or perfused with the sample fluid. The U-shaped glass tube oscillator is fixed at its open ends and excited by electronic means to vibrate perpendicularly to the plane of the U- tube. The oscillator, which we used for most biological measurements is a specially constructed micro-oscillator with a sample volume of 0.1 ml and a heat exchange coil. The frequency of the oscillations depends on the mass of he oscillator including the fluid in this coil.
In the year 1977 T. Kenner, H. Hinghofer-Szalkay and H. Leopold (1) published first animal experiments on continuous recording of blood density using the new technique of the mechanical oscillator principle in animal experiments. In the same year we could, together with H. Pogglitsch (2) demonstrate the clinical usefulness of continuous recording of blood density during hemodialysis. A review paper reporting and summarizing our early results was published by T. Kenner (3) in 1982. During the reported first measurement in hemodialysis, the blood was directly led through the oscillator. Due to problems concerning the sterility of the oscillator, systematic clinical measurements in patients were problematic. Since new non-invasively applicable sensors – based on the measurement of sound-wave-velocity in the blood (4) are available recordings in patients are easily possible.
Fluid density is defined as mass per unit volume. Blood density is closely related to hematocrit. The new technique can be applied for the observation of certain effects of volume-shift between blood and tissue and the effect of different injected solutions.

GENERAL REMARKS

It seems quite interesting to note that the availability of certain methods plays a role for the assessment of the importance of a diagnostic measurement and of the therapeutic relevance of a certain variable. From a more pragmatic viewpoint, the diagnostic value of any method is related to its ability to add information into a model of the system (the patient or one of his organ systems) to be examined.
It seems that the scientific interest in a variable like blood density depends on the availability of a suitable and simple technique for its measurement. For quite a long period of time, the measurement of density was either so complicated or so inaccurate that, with the exception of urine density determination and some measurements of plasma density for the estimation of plasma protein concentration, interest shown in the field of medicine was nearly negligible.
Interestingly enough the first detailed study about the density of blood (the specific weight) was performed by Lloyd Jones in 1887 using a falling drop method. Lloyd Jones found a characteristic age-dependent variation of blood density and a circadian rhythm; see (3). It is remarkable that Chronobiology was taken into account at this early time.
Another early observation on blood density was published by a practitioner in Davos, Switzerland (1902). He observed by his measurements the rise of blood density during stay at high altitudes and the lower blood density in anaemic patients. The methods used were slow and complicated.

Subsequent improvements were still unable to permit such methods to be applied for continuous recording of fluid density.
The newly invented oscillator technique brought a very special new way to record fluid density in general and blood density in particular.
Here three examples will be presented. In his Dissertation, which was supervised by H. Hinghofer-Szalkay (6), Franz Vauti (5) observed and analysed two phenomena in 6 joung persons. Results from one person can be seen in Fig. 1. After 90 min of horizontal position, the shift towards upright position led to a marked increase as well of the blood density (BD) as of the plasma density (PD) and hematocrit (Hkt). In Fig. 1 a period of 2 times 24 hours is plotted. The dotted lines represents upright position; the continuous lines represent horizontal position. The reason of the shift is the movement of Fluid from blood into tissue of the lower body.

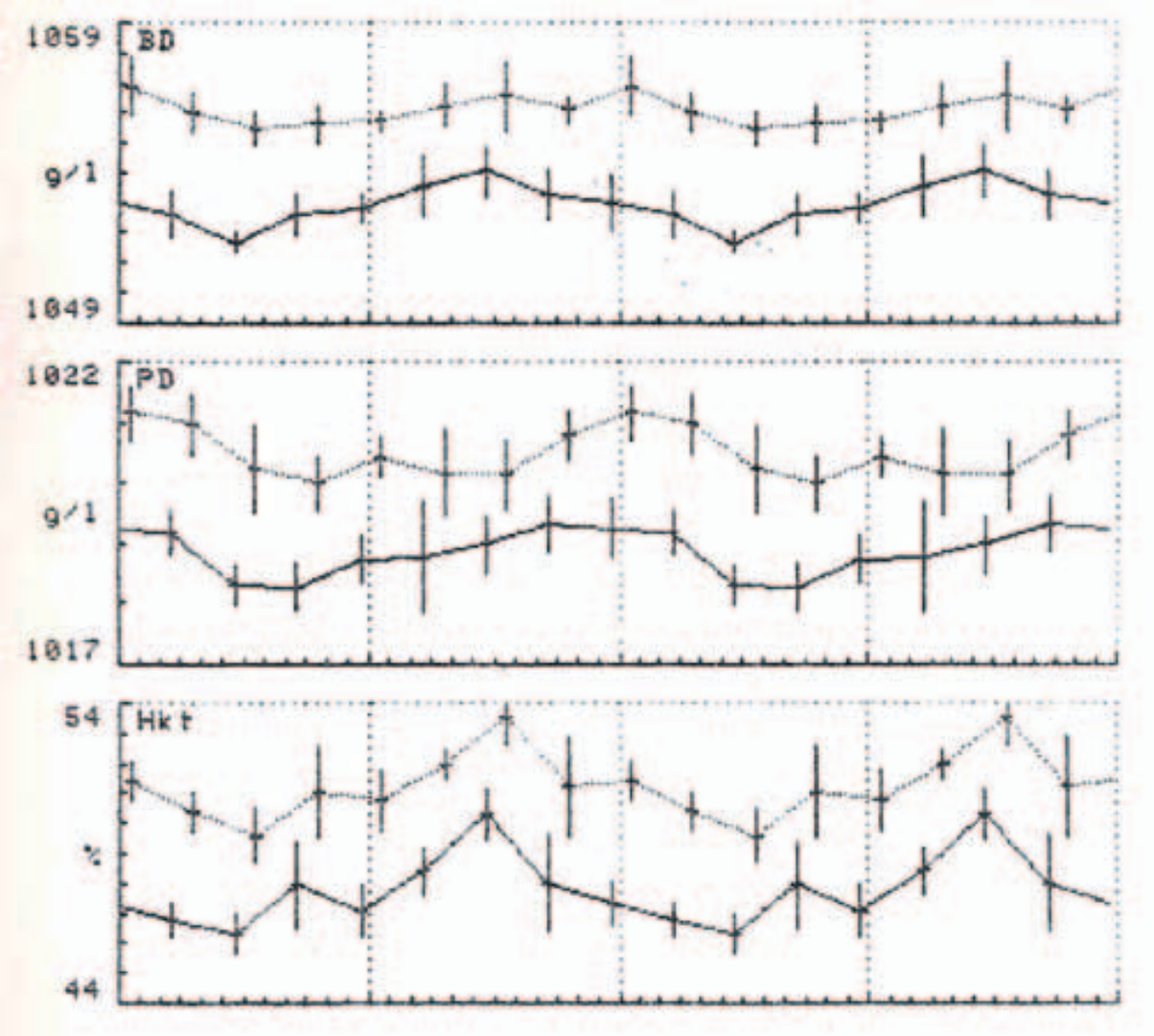
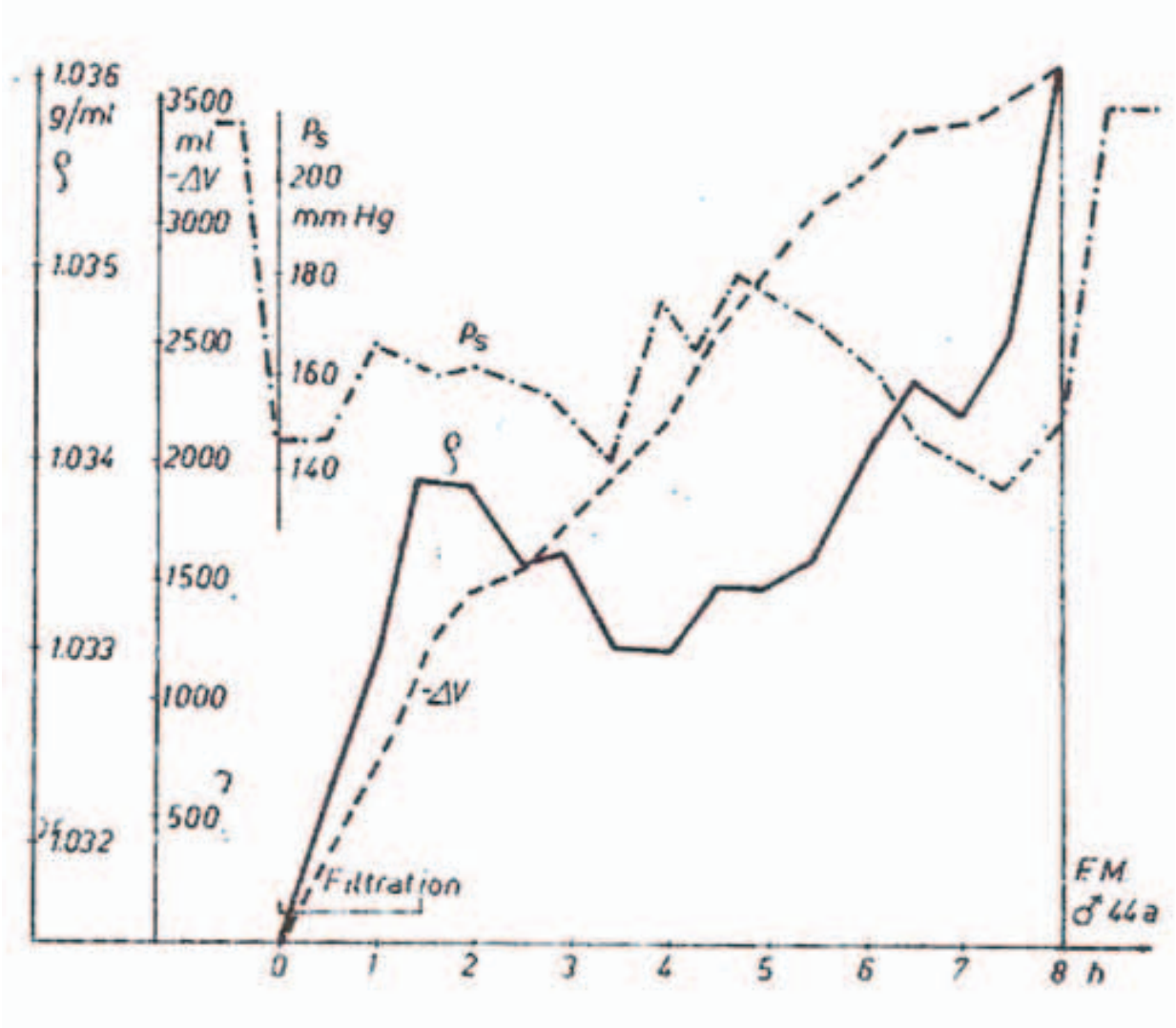


Fig. 1 see text. Abszissa: hours starting from 0 to 24 h and then repeat 24 hrs. Density in g/l. The rise of blood density in morning hours is remarkable.

Fig. 2 demonstrates one of our early recordings, which was done during the time course of a hemodilution treatment. The abscissa is given in hours of treatment and measurement of blood density during the hemodilution. The thick line represents the blood density. The dashed line shows the amount of removed fluid. And the dash-dotted line shows the course of the systolic pressure. This first experience (2) in 1977 led since then to an increased application of this technique. The marked increase of the blood density during loss of fluid by hemodilution can be seen.



Figh. 2. Record of density (rho) Fluid loss DeltaV and systolic blood pressure (ps) during 8 hours hemodilution

The following fig. 3 from (4) – so far – is unique. The four lines show oscillations (here: the ordinate shows the variation, not the absolute values) of the arterial blood of a voluntary person during different frequency of breathing. The oscillations of the blood density are clearly synchronized with the respiration periods.

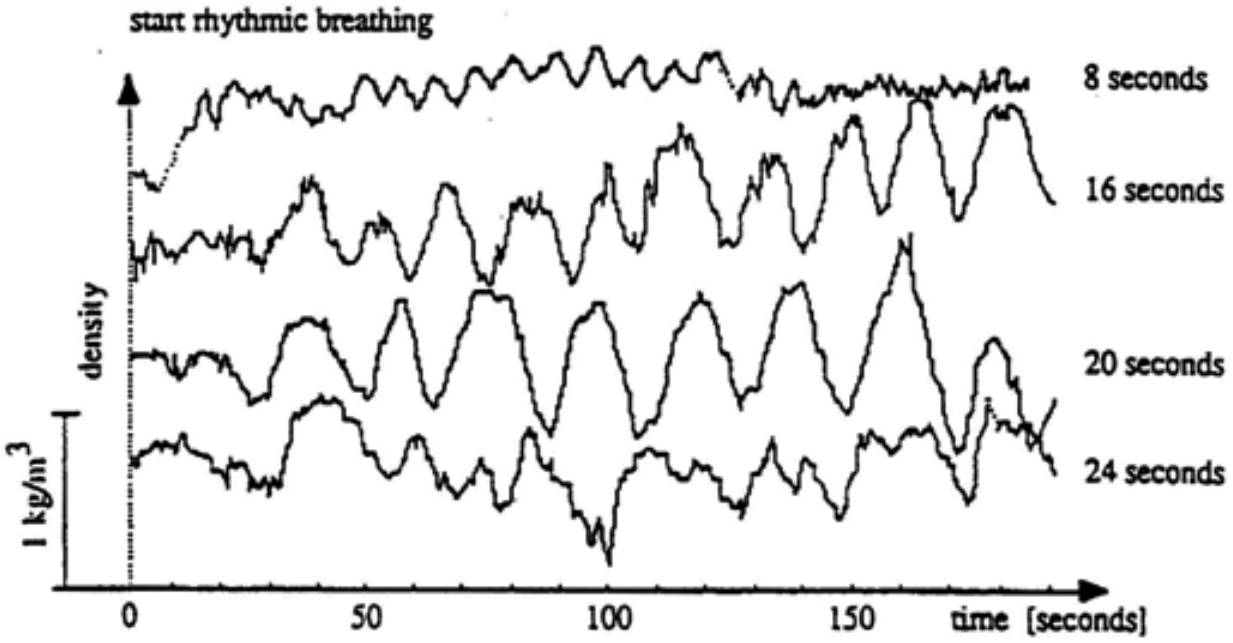


Fig. 3. Variation of arterial blood density is synchronized with breathing periods. Four examples ars shown in the Figure (The ordinate does not show the absolute Values).

THE NUMBERS IN SECONDS ARE THE PERIODS OF BREATHING.

This result is interesting, because during breathing apparently the diameter of the small vessels in the lung is varying. One possible explanation of this phenomenon indicates, that the so called Fahraeus-Lindqvist effect in the capillaries is responsible for the variation of the blood density during breathing. This effect indicates that in capillaries the hematocrit is the smaller the smaller the diameter of the capillaries. During breathing the capillaries in the alveoles can be assumed to change their diameter periodically. Another explanation attributes the fluid shift between capillaries and interstitial tissue a role in the generation of the variation. The latter influence of a different mechanism appears specially interesting because of its possible influence in pathological situations, like interstitial edema.

CONCLUSION

It should be pointed here, that the problems discussed in this short note are but a small and incomplete part of the possible applications of the method and of the particular viewpoint. Besides the possibility of a more detailed quantitative analysis of transcapillary fluid shifts, we have already in our first observations in human beings demonstrated several possibilities of clinical applications. Since the time of our early experiments the application of the recording of the density of blood and other fluids has markedly grown.

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PREVENTIVE CARDIOLOGY CONCERNS AVOIDANCE OF PERSONAL AND SOCIETAL HEALTH-RELATED AND NATURAL CATACLYSMS

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Preamble

Before Sputnik in 1957 and Vostok in 1961, it seemed justified to call human extraterrestrial exploration futuristic at best. Yet Konstantin Tsiolkovsky wrote his "The exploration of cosmic space by reaction devices" in 1903. Robert H. Goddard published "A method for reaching extreme altitudes" in 1919. When the senior author lectured in Washington at a meeting of NASA in the early post-Sputnik era and the USA also had a tennis ball-sized satellite in space, his talk was interrupted by the announcement that the Russians had just placed a truck-sized vehicle into space. Nonetheless, historians can be myopic: an editor in 1997, because of their association with cosmism, called both the father of by-then Sputnik and Vostok-documented spaceflight, Tsiolkovsky, and the father of heliobiology, Alexander Leonidowich Chichevsky, occult (1, 2).
By the same token, both Theodore Janeway (3), who did not wish to see a patient before he had data sufficient to examine periodic variations in 1904 and Frederic C. Bartter (4) who wanted a cosinor analysis of each patient's time series by 1974 are mostly forgotten, even if they were distinguished opinion leaders in their time. Many preventive cardiologists may regard as futuristic at best the proposition made at a prior symposium in Brno, a very few years ago, that human blood pressure should be monitored around the clock for 7 days as a start, with continued monitoring when abnormality is found, and that blood pressure be monitored from womb to tomb once affordable unobtrusive instrumentation becomes available, integrated into a system for automatic data analysis, in order to prevent cerebro-, cardio-, reno-vascular diseases, strokes in particular. It is against this background that a draft of a resolution to be integrated into a proposal to the UN and WHO goes yet further.

Resolution at the World Forum "Natural Cataclysms & Global Problems of the Modern Civilization; Geocataclysm - 2011"

Given that physicists have started the monitoring of various physical signals in different geographic locations on earth and eventually in extraterrestrial space and have made their recordings available for every one to access;
Given that this initiative has been invaluable to learn more about how the environment affects life on earth and to provide warnings so that timely countermeasures can be instituted (examples include the

recording of air and water quality for health reasons, the use of corrosion sensors for surveilling the structural integrity of bridges and other constructions, the monitoring of space weather concerned as yet only with blackouts and interruptions in radio communication, and the monitoring of gravitational waves for earthquake prediction);
Given that biomedical variables analyzed and interpreted in a chronobiological perspective, combined with the continuous monitoring and recording of solar and interplanetary as well as geomagnetic activity, have already served as valuable indicators of biospheric activities, of great impact and direct action in social upheavals as well as in terror attacks and other important events in human history, quite apart from being of direct personal self-help in computer-aided healthcare benefit;
Given that the required monitoring is accessible, cheap and acts as a global as well as a local eye, i.e., as a glocal window in both space and time; and
Given that physiological, pathological and epidemiological data to be accumulated could be organized and analyzed retrospectively as well as prospectively in repeated systematic passes over the accumulating information on a dedicated website, with aims similar to those of NASA, NOAA and RAND, making the data available to everyone and including educational materials to ease the transdisciplinary communication among the entire scientific community;
It is proposed to complement and integrate transdisciplinarily endeavors limited thus far to physics by including the systematic monitoring of biomedical and socio-ecological variables that can also serve as valuable markers of environmental integrity and provide warnings of environmental threats, and by making the information available on a dedicated website;
Thereby to achieve the double purpose of monitoring the environment by a most sensitive set of biospheric magnetometers while also receiving as a hardly negligible dividend a transformation of a costly spotcheck-based medicine into an improved self-help-based cost-effective cyber- healthcare with emphasis on prevention that no longer flies blind to the variabilities in us and around us and of their critical interactions, far beyond interfering with communications only among us, by resolving altered communications in us, as harbingers of both natural and human-made as well as personal cataclysms.

Commentary

After the Italian city of L'Aquila was devastated by an earthquake on 6 April 2009, and more than 300 people lost their lives, it is being asked whether those concerned about panic, who failed to warn the public, were at fault (5). Concern about unwarranted false alarms possibly also underlies the lack of response of Japanese authorities to their own scientists and to the forecast placed on 9 March 2011 by the Global Network for Forecasting of Earthquakes (GNFE) on the www.seismonet.org website. That information was also communicated two days before the 11 March 2011 Sendai earthquake directly to all members of GNFE. Concern about future catastrophes prompted the same undersigned forecasters from Baku to organize and hold a World Forum on "Natural Cataclysms and Global Problems of the Modern Civilization" from 19–21 September 2011 in Istanbul, Turkey (www.2011.geocataclysm.org) (6), advocating the extension of already ongoing sequential analyses of data not only from physical, but also biospheric monitoring, so that the many anecdotal antecedents of earthquakes reported for animals in nature (7) can be complemented by objective numerical data collection ongoing for other reasons in physiology or other experimental laboratories (8) and in data from the self-monitoring public (9, 10).
Half-hourly around-the-clock blood pressure (BP) and heart rate (HR) monitoring is now feasible for severe disease prevention, Figure 1, advocated again in Istanbul as a feature of self-help in health care (10). The same data can be used along with those from purely physical monitoring for forecasting

earthquakes. This is not wishful thinking, as documented in Figure 2. On the top left of this figure are data from monitoring mice in a laboratory during a span bracketing the 12 May 2008 Sechuan earthquake. Antecedents are obvious, as noted elsewhere (8). On the top right, an increase in BP for 2 days is seen during the 7 days centered on the Sendai earthquake in 13 patients who happened to be monitored at half-hourly intervals around the clock, each for at least 7 days, one of them for decades, as advocated by a series of earlier international consensus meetings (10). The objective changes before an earthquake reported in Istanbul, including those on top of Figure 2, were statistically significantly different from any changes in several control populations, as also shown in Figure 2.

Thus, beyond earthquake prediction by purely physical means, these findings are in keeping with the possibility that one may learn from a biospheric complement to seismologic monitoring, as an added measure that may be a largely cost-free dividend of ongoing endeavors by a self-surveilling public and in pharmaceutical companies. Some affordable, unobtrusive instrumentation is already available for the half-hourly automatic monitoring advocated for human populations, as used during the Sendai earthquake (9). It serves for the detection of vascular variability disorders that are otherwise undiagnosed and can be treated and reduced in frequency of occurrence, if not eliminated. Figure 1 shows risks that exceed that of a high BP (10), and continuous surveillance may possibly also have dividends in endeavors for understanding earthquakes, Figure 2, if not for their prediction.

The bottom right of Figure 2 shows, with personal disasters such as strokes, human-made cataclysms such as crime, terror and aggression that, among others, share 50-year cycles with earthquakes, as seen on the bottom left of Figure 2. It is re-emphasized that similar periods in themselves are not sufficient evidence for any association. They gain meaning when subtraction and/or addition of a component in space weather leads to corresponding damping or amplification of a human marker variable, as shown in Figures 3 and 4, concerning a transyear band also found as an about 1.44-year component in earthquakes, Figure 2, bottom left. Figure 5 shows that the about–50-year cycle also characterizes tsunamis, hardly surprising in view of their association with earthquakes, yet as the bottom section on the right of Figure 2 shows, the quindecennian is also found in physio-pathological variables.

As noted above, the evidence in the figures will be part of a recommendation by the World Forum (of Istanbul) to the World Health Organization and the United Nations for the extension of an existing global network for the preparedness for dealing with natural disasters, while also including measures for understanding and avoiding personal health cataclysms, such as a massive stroke or human-made disasters such as terrorism, that further may lead to data contributing a better understanding and better risk assessment in the case of natural disasters.

As to the analysis of the last 331 earthquakes summarized at the bottom of Figure 2, one finds, among other solar activity, a spectral component of about 50 years (11) known by economists as the Kondratiev cycle (12), which also characterizes other earthly natural and human affairs (13, 14), in keeping with earlier claims of an association of weather in space with earthquakes (15), deserving further scrutiny of the role of space weather and/or geomagnetism in physiology, Figure 6 (16–20) and in various cataclysms, perhaps by an effect via mood and vigor and other mental function, in keeping with Figure 7.

This is also an appeal to physiological and pharmaceutical laboratories and to the self-surveilling public for time series bracketing earthquakes, notably in earthquake-susceptible locations. The cycles of the cosmos contribute to natural and human personal and societal disasters, including aggression. Learning about them yields the indispensable control information for anything done in time in science. They are ignored by “baselines” that are a word excusing the disregard of a transdisciplinary spectrum that contributes to sudden cardiac death, to whether we die from our own hand or by the hand of others (20). There is but one unified science, as noted earlier by others (21, 22), also with specific reference to earthquakes (23).

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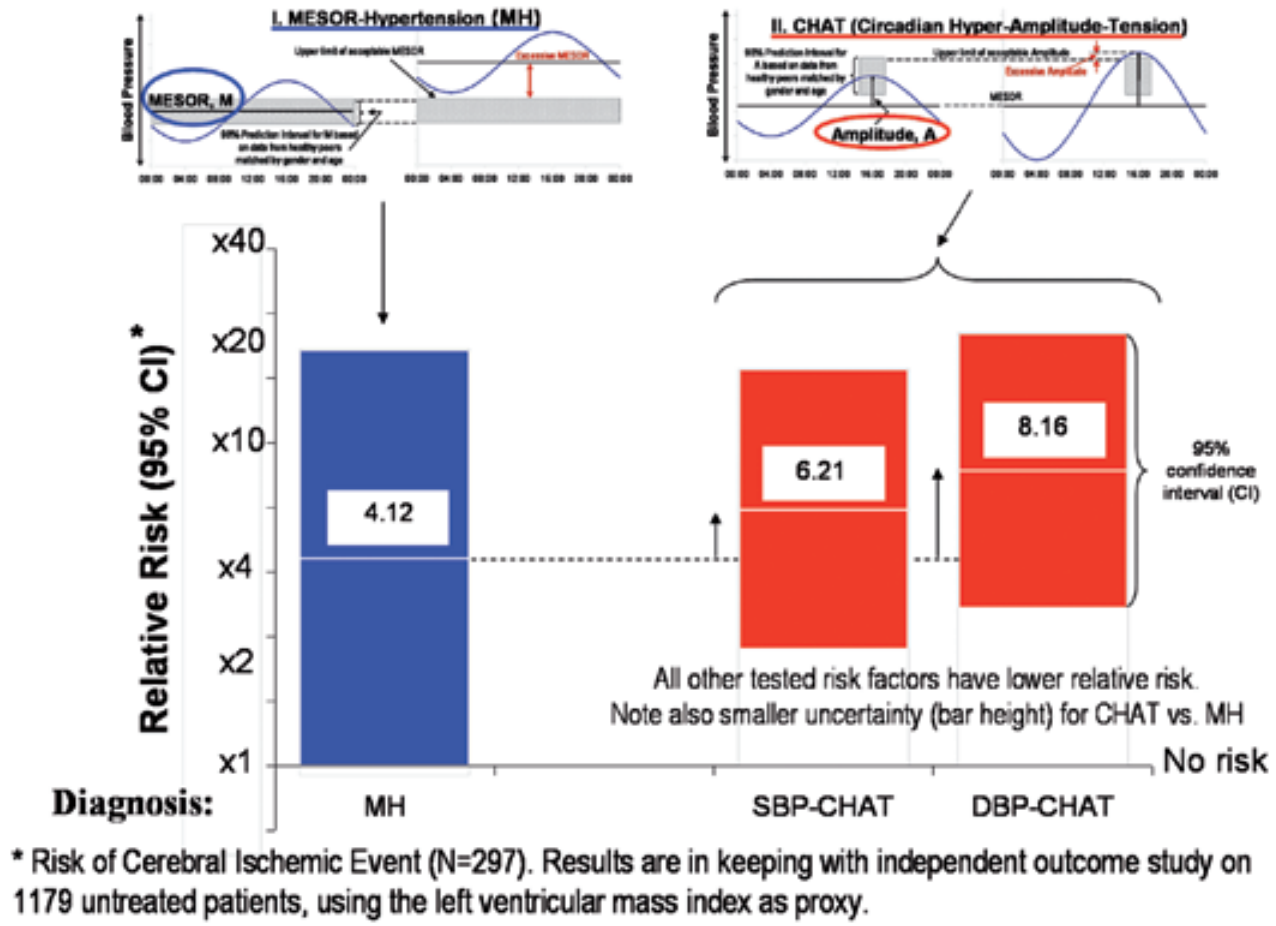


Figure 1. High blood pressure (BP) is a known risk factor for adverse cardiovascular outcomes. In a 6-year prospective study of 297 patients, systolic MESOR-hypertension (MESOR, a rhythm-adjusted mean, is acronym for Midline Estimating Statistic Of Rhythm) was associated with a relative risk of 4.12 (left). In other words, patients with an elevated SBP were 4.12 times more likely to suffer an adverse event than normotensive individuals. The uncertainty of this relative risk, gauged by its 95% confidence interval (height of bar) is barely above the no-risk line. By comparison, an abnormal circadian pattern of BP characterized by an excessive swing (CHAT, brief for Circadian Hyper-Amplitude-Tension) is associated with an even larger relative risk of 6.21 (systolic CHAT) or 8.16 (diastolic CHAT), their 95% confidence intervals being well above the no-risk line. The diagnosis of CHAT and of other Vascular Variability Disorders (VVDs) requires the around-the-clock monitoring of BP and heart rate, preferably for a minimum of 7 days at the outset. It cannot be obtained from single measurements typically taken in the physician's office as is current practice today. © *Halberg*.

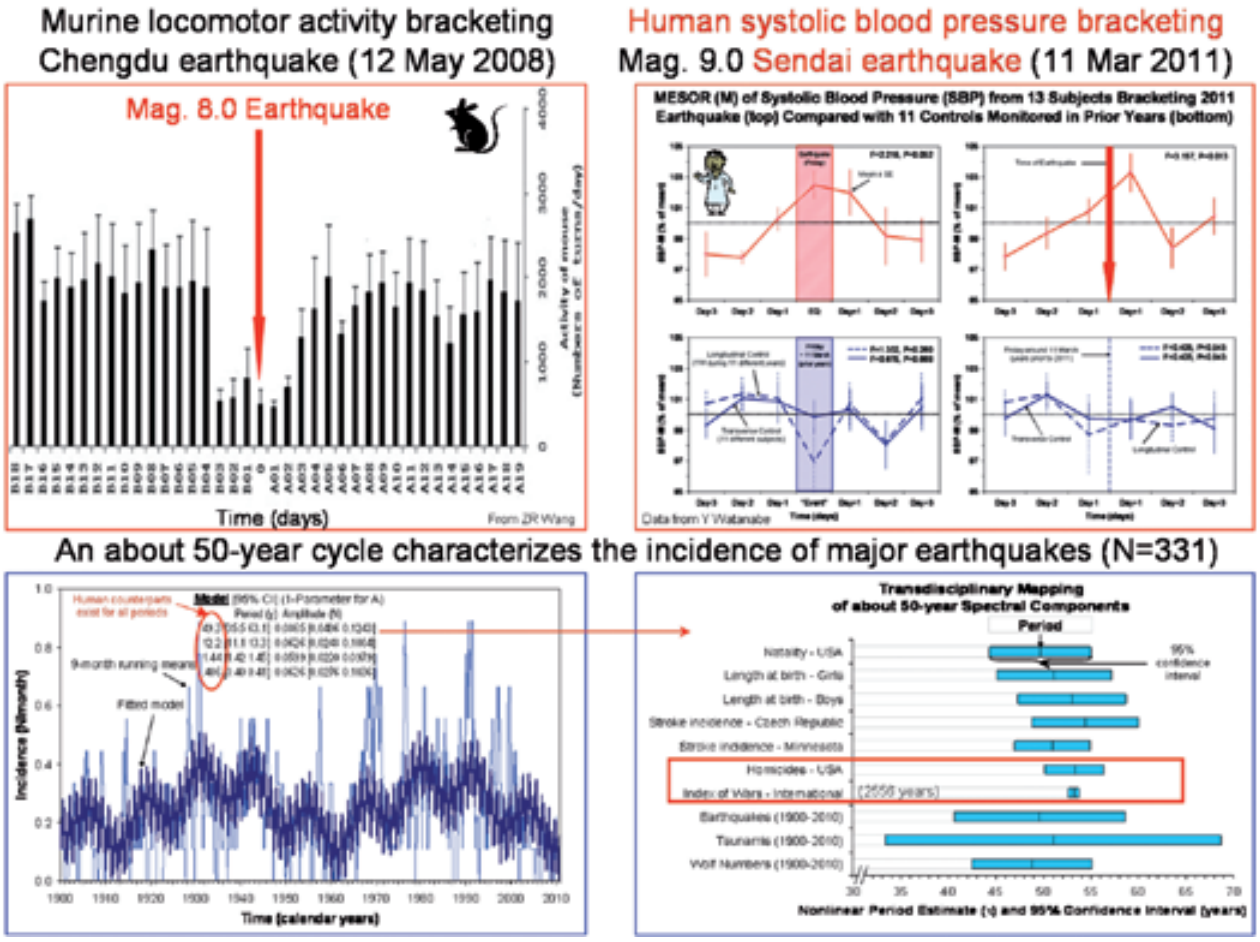
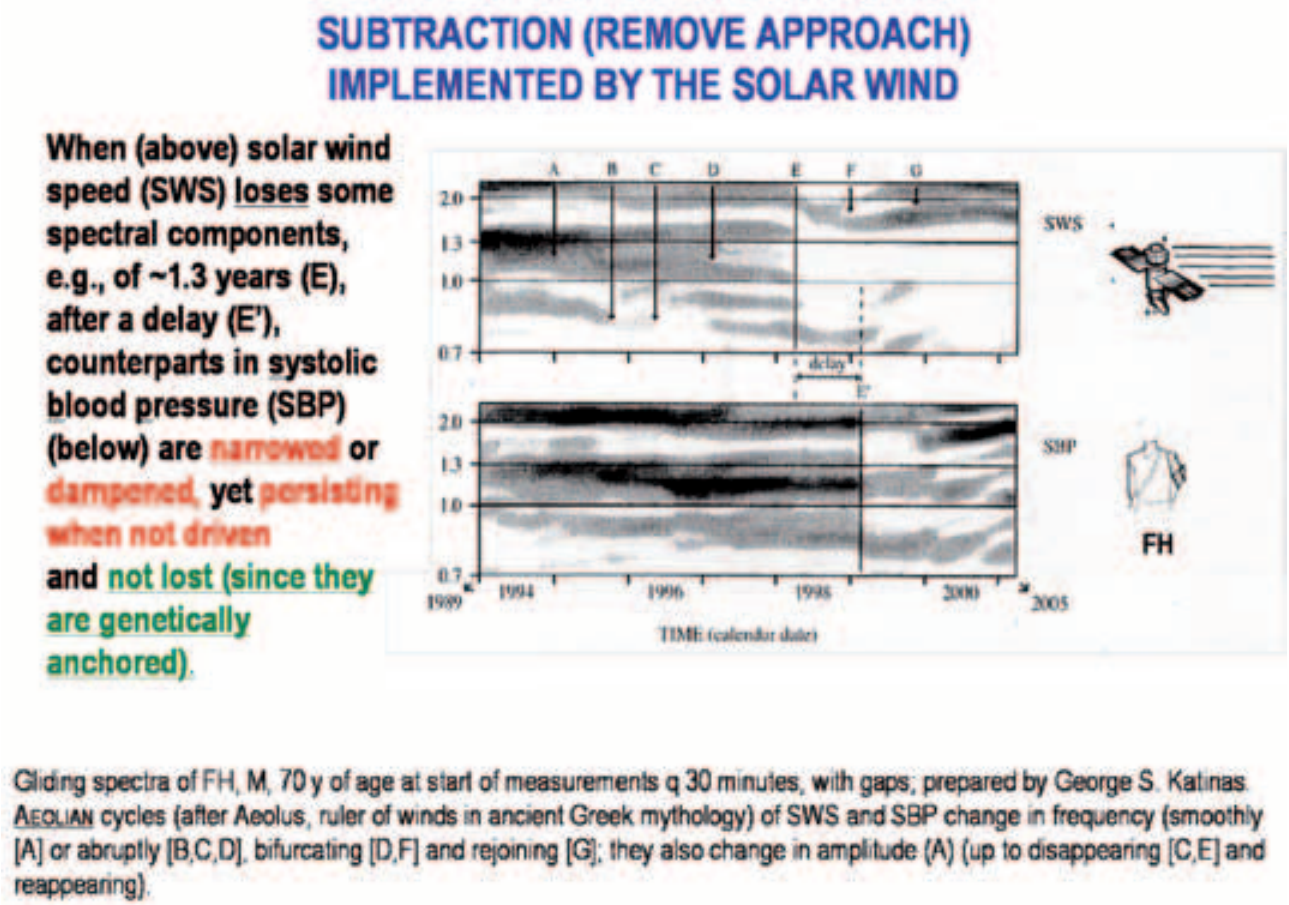


Figure 2. Proposed biospheric contribution to the understanding, if not prediction of earthquakes. Upper left: Locomotor activity of mice telemeterd around the clock was statistically significantly decreased starting 3 days prior to the magnitude 8.0 earthquake in Chengdu, China on 12 May 2008 (8). Upper 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 ambulatory data from 13 Japanese (9). 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 (11). Lower right: The most 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 (11). © *Halberg*.



Gliding spectra of FH, M, 70 y of age at start of measurements q 30 minutes, with gaps; prepared by George S. Katinas. AEOLIAN cycles (after Aeolus, ruler of winds in ancient Greek mythology) of SWS and SBP change in frequency (smoothly [A] or abruptly [B,C,D], bifurcating [D,F] and rejoining [G]; they also change in amplitude (A) (up to disappearing [C,E] and reappearing).

Figure 3. The about–1.4-year component detected in the incidence of earthquakes, known as a 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 of a man (FH) who monitored himself around the clock for over 23 years (with interruptions), as seen in the bottom gliding spectral window. 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. © *Halberg*.

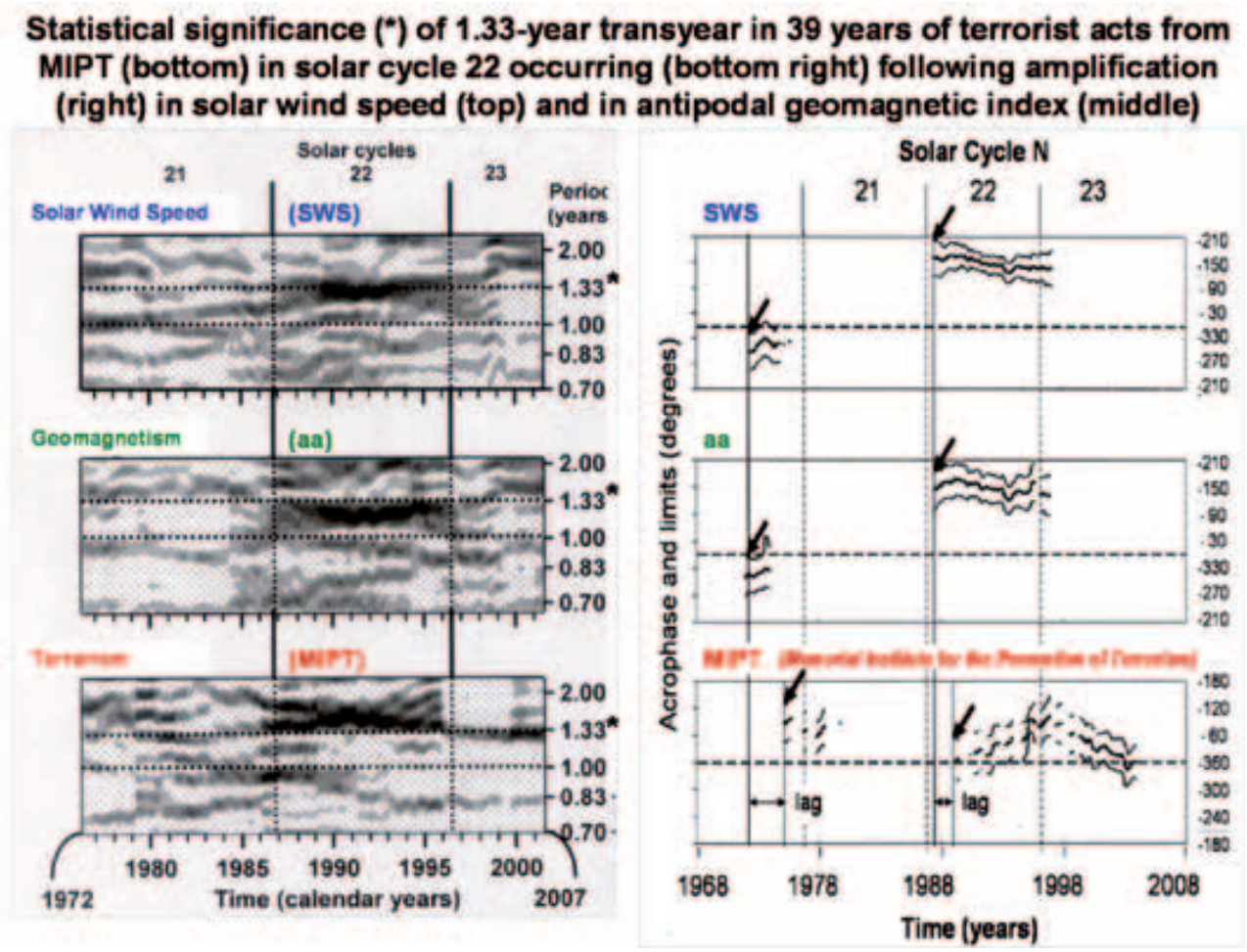


Figure 4. A transyear common to solar wind speed (top), the antipodal geomagnetic activity index aa (middle), and the incidence of international terrorist acts (bottom), all three apparent as dark bands in the gliding spectral windows (left) are particularly prominent during solar cycle 22. The phase behavior at the average period (right) further indicates that the transyear in terrorism follows with a lag the transyears in solar wind speed and aa, persisting after 1998 when it is no longer detected with statistical significance in solar wind speed or aa (phases are displayed with their 95% confidence intervals only when the transyear is detected with statistical significance). © *Halberg*.

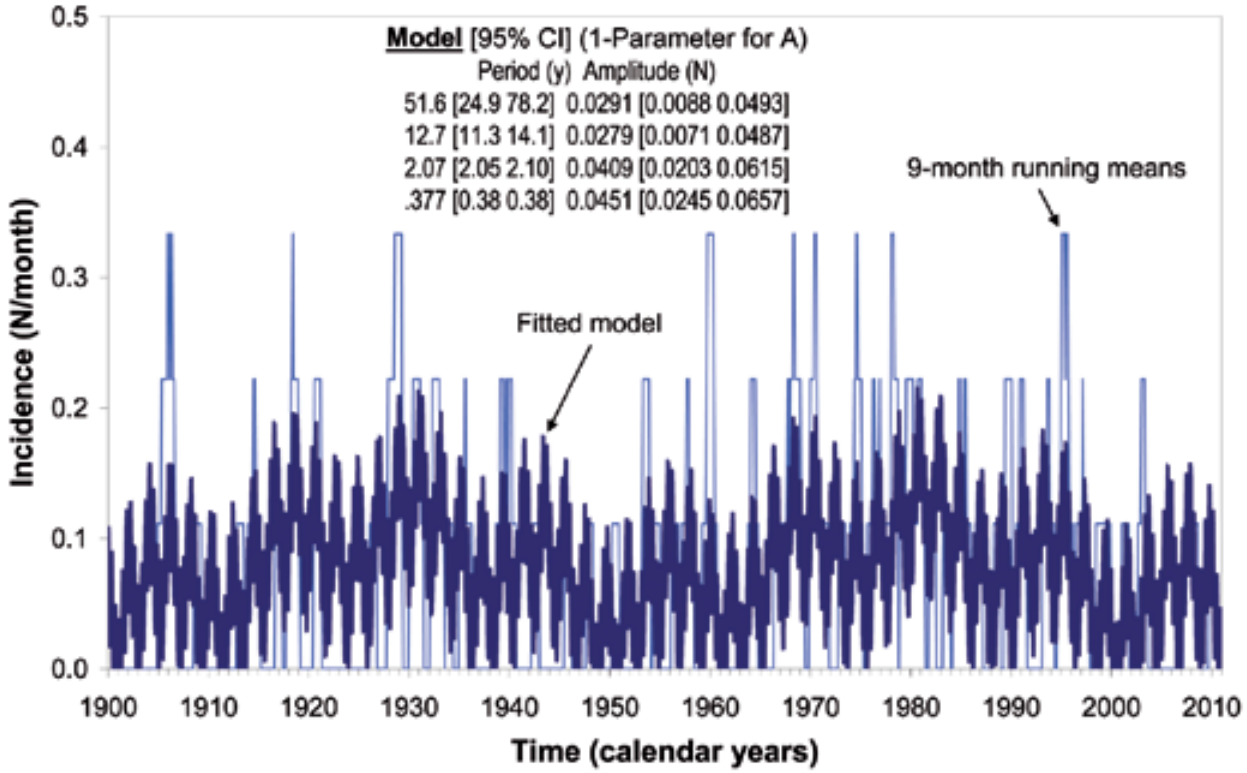


Figure 5. The pervading presence of Aeolian about–50-year (quindecennian) cycles in tsunamis as in earthquakes is noted by their presence in natality, in neonatal anthropometry as well as in the incidence of strokes and homicides and wars. © *Halberg*.

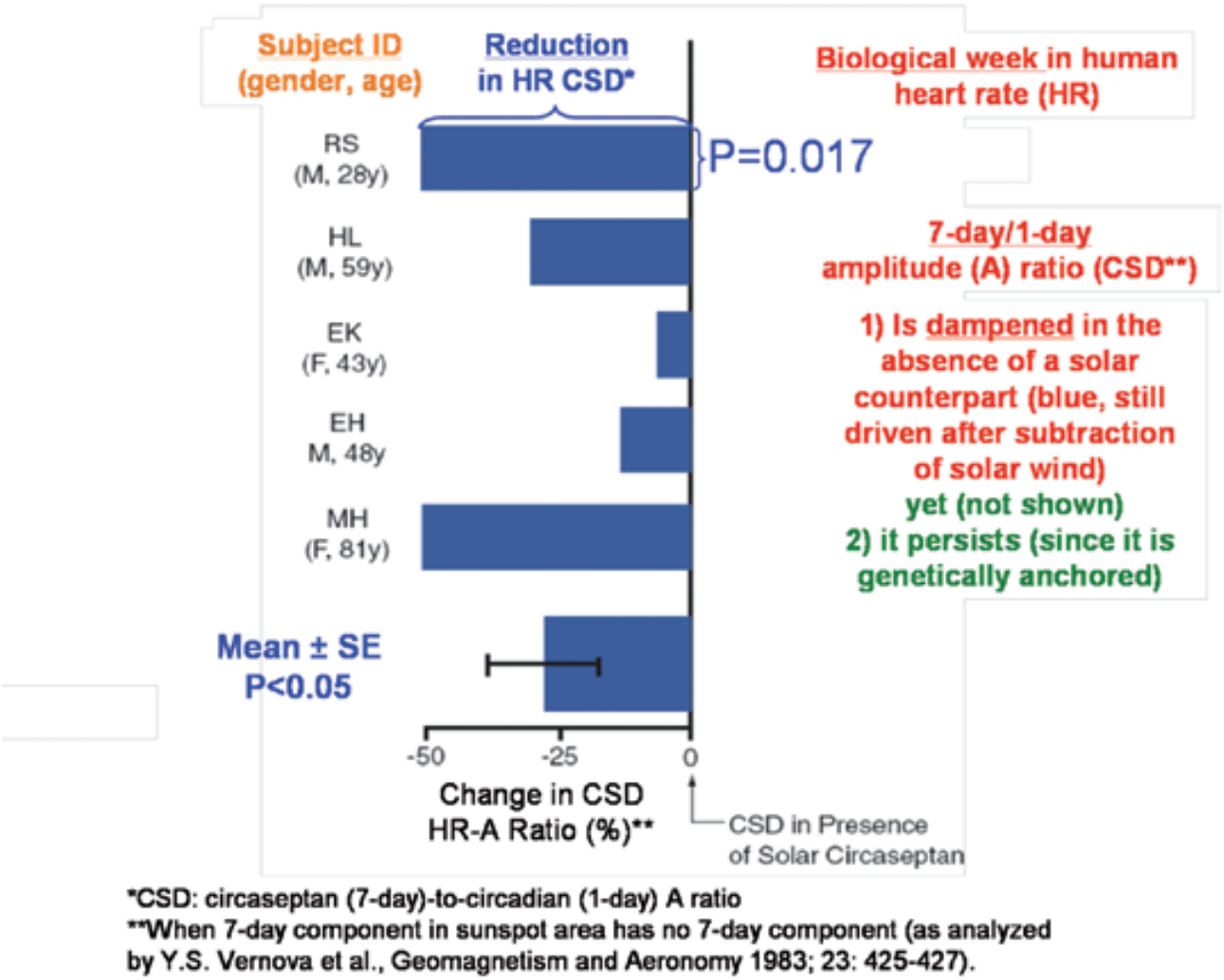


Figure 6. An about–7-day spectral component in the heart rate of five men is less prominent when the solar wind loses its counterpart of corresponding length. Implied, but not shown, is the persistence in the biosphere of an about–7-day component that can be amplified (driven) by a reciprocal component in solar activity. The approach by remove-and-replace in the study of circadian rhythms (16–18) is here extended to the circaseptan component, as it was extended to an addition and/or subtraction approach in Figures 3 and 4 in the transyear band (19, 20). © *Halberg*.

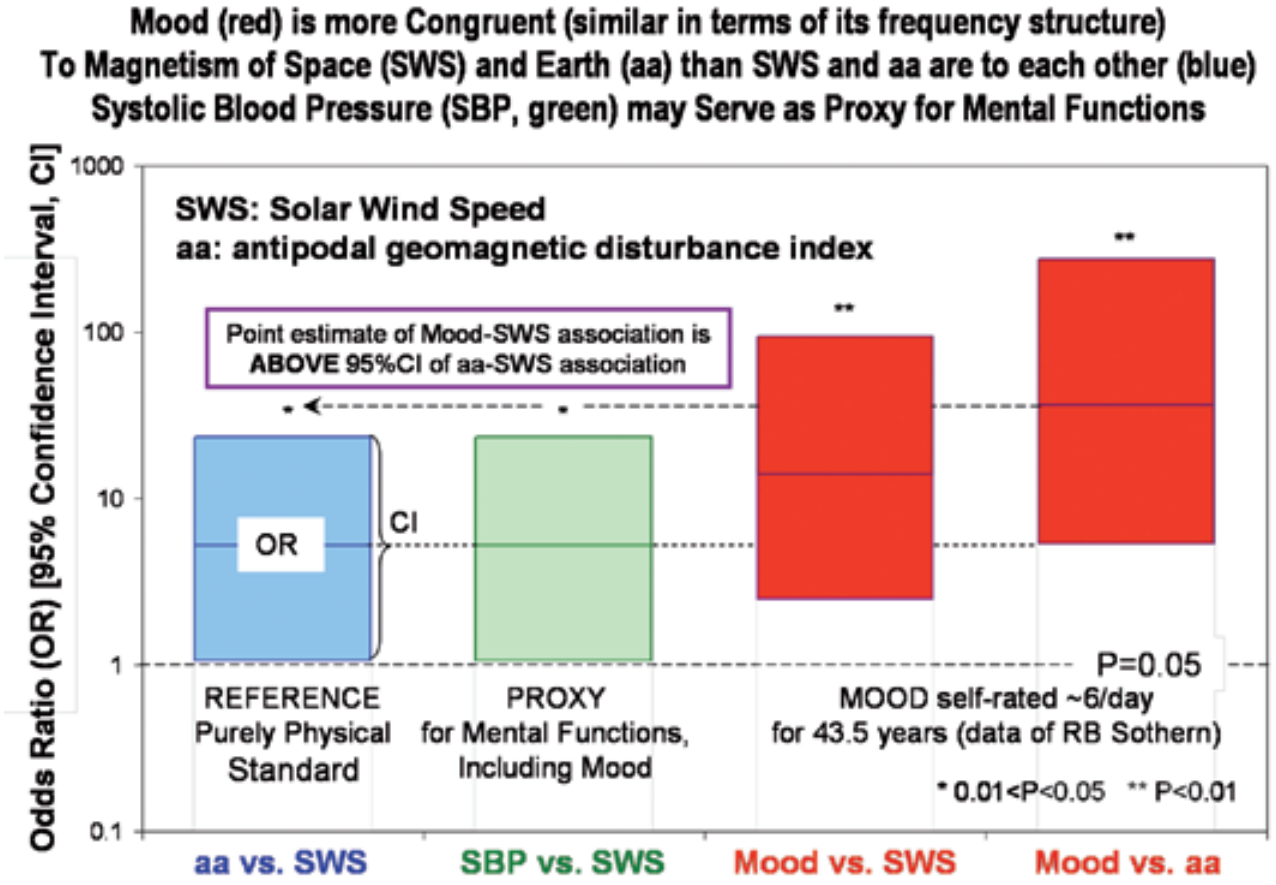


Figure 7. Congruence is a measure of similarity of time structures of two or more variables, gauged by the number of shared frequency components in a given spectral range. In the range of one cycle in 2.5 years to 3 cycles per year, statistical significance for the anticipated congruence between the antipodal geomagnetic index and solar wind speed is barely reached, the 95% confidence interval of the odds ratio just above the detection level (left). By comparison, mood assessed 5 to 6 times a day during waking for over 43 years by a clinically healthy man (RBS) has a much stronger congruence with solar wind speed or aa (last 2 columns to the right) than aa has with solar wind speed (left). Systolic blood pressure self-measured at the same times by RBS may serve as a proxy as it shows a congruence with solar wind speed (second column from left) of similar extent as does aa (left). © *Halberg*.

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MULTIPLE CIRCADIAN PERIODS IN A LADY WITH RECURRING EPISODES OF ADYNAMIC DEPRESSION: CASE REPORT

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Abstract
JF, studied while 61 and 62 years of age, reports selenosensitivity with half-yearly recurrent downtimes for over 20 prior years in herself and recent concurrent milder episodes in her daughter FT and contemporaneous unusual behavior of her granddaughter LT, 3 years of age. We here record multiple circadian desynchronization during episodes of 2–3 months of downtimes recurring twice a year in her about-daily waking fraction, self-rated vigor-wellness, and wrist activity, in (first self-measured, thereafter automatically recorded) systolic (S) and diastolic (D) blood pressure (BP) and heart rate (HR), in urine volume and in salivary cortisol, aldosterone, dehydroepiandrosterone (DHEA), testosterone, estradiol and melatonin, sampled around the clock at 4-hour intervals and determined in 11,702 hormone assays. In monthly summaries during the first 14 lunar months, JF, but not FT, showed the double tidal period, τ, in non-linearly extended cosinor analyses of vigor-wellness (in the computer output, not input) in the first month of the first two investigated episodes and in several other variables in the first month of some subsequent episodes. So did LT in one of three longer than 7-day records of her around-the-clock measured DBP.
Overall, in her daily wake fraction, JF exhibited an ~24.0-hour (h) τ, an ~24.22-h, "desynchronized from society" (free-running [1–3]?) τ, reported as intrinsic or endogenous on unacceptable sleep-wake schedules in prior forced desynchronization studies by others (4, 5), an ~24.8-h (double tidal) τ and a ~24.4-h τ. All τs with a CI (95% confidence interval) not covering 24.0 h may be the expression of a compromise (tug-of-war) arrived at by the interacting pulls with differing relative intensities of the moon and sun/society. As far as the waking fraction is concerned, the coexistence of JF's 4 τs cannot be regarded as pathogenic, since four similar τs were also found in the sleeping-waking of a clinically healthy man, living for ~3 years on a self-selected schedule (6).

Our prior interpretation that in JF the 24.0-h τ (the sun and society) on the one hand, and the 24.8-h τ (i.e., earth tides, the lunidian) on the other hand, are in a tug-of-war with the moon's pull strong during the first month of illness (7), stands, yet the apparent domination of the 24.0-h τ during inter-episode spans of relative wellness is now qualified by the detection of a τ differing from both the 24.0-h societal and the lunidian τ found for salivary cortisol, DHEA, estradiol and melatonin, which points to a block in the 24-h synchronizability of some of JF's important variables, while testosterone and aldosterone may have been 24-h synchronized during relative wellness by JF's treatment with 50 mg of spironolactone on arising and at bedtime.

During downtimes, a pull by tides could act perhaps by gravity-induced changes in the magnetism of the earth's crust (8, 9). In any event, the familial incidence of selenosensitivity reported anecdotally is validated objectively by the unfakeable computer output (in analyses) of a double tidal τ of ~24.8 h documented as extremely rare in controls and not reported earlier as consistent in humans and certainly not repeatedly in several variables of the same person. Prior linear cosinor and other tests on his and others' important data by Miroslav Mikulecky, professor emeritus of medicine and statistics (10), had the lunidian τ in the computer input to the single cosinor, a fully acceptable procedure that is here complemented by letting the τ be a parameter to be estimated by the nonlinear cosinor.

Background

JF's self-rating scale of vigor/wellness describes her problems: 0: multiple symptoms / not able to get out of bed; 10: multiple symptoms / bed - chair - bathroom; 20: multiple symptoms / very minor accomplishment [prepare simple meal]; 30: multiple symptoms / sedentary accomplishment [limited computer work]; 40: multiple symptoms / increased accomplishment with limitation; 50: multiple symptoms / push for productivity followed by post-exertion strain; 60: short spurts of productivity requiring pacing; 70: productivity + minor dysautonomia or headache; 80: productivity or rest with no symptoms at all; 90: high productivity; 100: high productivity + euphoria. If improvement has taken place, but symptoms do not yet rank the next number, 5 is added). Early results objectively confirmed her selenosensitivity since they revealed the 24.8-h double tidal τ in two consecutive episodes and were compatible with a beat in two desynchronized circadian rhythmic variables (7).

Results

Figure 1A (top row) shows a chronobiologic serial section of original self-ratings of vigor/wellness of JF, 61-year-old at the start of investigation. A twice yearly downtime is obvious, starting in the shaded lunar cycles, and is in keeping with the earlier record in the updated Table 1. Figure 1A (row 2) shows, as the lower curve, the time course of the average (MESOR, M, i.e., the Midline-Estimating Statistics Of Rhythm, usually more accurate and more precise than the arithmetic mean). The time course of the circaseptan (Figure 1A, row 2) amplitude (A, a measure of one-half of the predictable extent of change within a cycle) is shown as the distance between the two curves obtained from the fit of a 168-h cosine curve. Results (shaded lunar cycles 4 and 11, respectively) suggest that an ~7-day component is amplified during the initial lunar month of the first adynamic episode but not in that of the second episode. Rows 3 and 4, and, for comparison, rows 5 and 6 of Figure 1A, stem from the fit of a 24.0-h and a 24.8-h cosine, respectively, as shown by vertical brackets on the right. The time course of these components' acrophase (ϕ) is shown in Figure 1A (rows 3 and 5), providing information related to the timing of overall high values recurring in each cycle. When nearing midnight (0° or 360°), ϕs are doubly plotted. The upward slanted delaying time course of the 24-h ϕs (row 3) suggests a τ longer than 24.0 h. A horizontal time course of ϕs (row 5) indicates a good fit of the 24.8-h curve. Note, within the shaded columns denoting episodes of adynamia (with slanted ϕs in row 3, by contrast to more or less horizontal ϕs in row 5), that a 24-h component is demonstrable ($P<0.05$) only during the

first episode of lunar cycle 4 (horizontal dashed line in rows 4 and 6 corresponds to P=0.05), but that it is not consistently significant in lunar cycle 11. Synchronization with the lunar-tidal day of 24.8 h is documented by the outcomes of a complementary (more global) nonlinear analysis of monthly data. Its results are inserted numerically in this figure in row 5 as τ estimates of 24.838 h and of 24.866 h, with their CIs in parentheses. During most of lunar cycle 4 (row 6, as in row 4), P<0.01 (the bottom line in rows 4 and 6 corresponds to P=0.01). In the weekly intervals analyzed in Figure 1A, a circadian rhythm (P<0.05) is very rarely found, except for the first month of the span of lunar synchronization in cycle 4 (by contrast to monthly intervals used for the inserted nonlinear results). This finding is shared by FT's self-ratings (not shown), indicating in both women the absence of a circadian vigor rhythm, except during JF's downtimes when it is synchronized by the moon.

Figure 1B (top two rows) shows the time course of ϕs of two chronobiologic serial sections combined with the numerical results of a nonlinear extended cosinor analysis of JF's urine volume. The P-values (row 3) testing the "no 24.8-h or similar rhythm" assumption are mostly below 0.05. The 24-h ϕs (top row) from the fit of a 24-h cosine curve reveal a horizontal time course in the first lunar cycle examined during wellness and a delaying (upward) time course during the episode which started at the beginning of lunar cycle 2. In the second lunar cycle examined, JF's nonlinear cosinor analyses showed the 24.8-h (double tidal) τ. When a 24.8-h τ is fitted, the time course of ϕs (row 2) is horizontal, validating the lunidian τ for urine volume. In all cases, the τs fitted to monthly intervals were statistically significant, an outcome which substantiates the need for the combined glocal (global and local) analysis in time by varying the length of the intervals used for analyzing a data series.

Figure 1C shows the coexisting τs (above) and their As (below) during adynamic depression for urine volume (left) and excretion rate (right). In the absence of a laboratory and of monitoring instrumentation, urine volume can to some extent serve as a proxy for coexisting τs (Figure 1C top) with alternately dominant amplitudes (bottom).

Figure 2A shows that during the first month of an episode, the double tidal τ of 24.8 h can dominate the spectrum, even though a second peak of 23.78 h with a CI covering 24.0 h is also present. Figure 2B shows the time course in JF's circulation of coexisting and wrangling two τs, with the moon (diamonds) pulling harder during depression, in an unfakeable computer output.

Figure 3A also summarizes in the τ domain the changing dominance of the society/sun during wellness and the appearances of results from the pull of the tides during variables of the blood circulation (SBP, DBP and HR) based on mostly hourly data and the results of non-overlapping monthly spans of 4-hourly salivary hormone collections. Outliers in testosterone, aldosterone and HR notwithstanding, the data are in keeping with a tug-of-war between the moon and society with a slight overshoot in the first adynamic episode (shaded), with most variables in synchrony with each other most of the time. But we encountered quite a surprise in the ϕ domain in an inquiry that first aimed at comparing endocrine behavior for the two weeks before the full moon (FM) with that during two weeks after the full moon. The results in Figures 3B-G and Tables 2–4 show the desirability of the full set of endocrine determinations insofar as the results after a full moon, as compared to before a full moon, seemed to differ first in two sets of monthly determinations. Next, they seemed to differ as a function of depression vs. relative wellness, Table 3. Neither finding was subsequently consistent, Table 4, yet the full set of data in Tables 2–4, analyzed in Figure 3B-G, led to an un-anticipated result in the ϕ domain, apart from a consideration of data before vs. after the full moon. A comparison of data in episodes with a mostly oblique time course of ϕs and the prior implicit assumption of 24-h synchronization during wellness did not hold. For four hormones, there is clearly desynchronization, less prominent than that during depression, also during wellness, as seen in the figures.

For the results in Figure 3E, chronobiologic serial sections were applied to data at 4 h intervals on the salivary hormones of JF by the fit of a 24.0-h cosine curve to intervals of 24 h displaced with an

increment of 24 h. A smooth longitudinal time course of circadian ϕs was prepared wherein any 360° jumps were eliminated. Sequences of ϕs were then plotted separately for each lunar moon (centered on full moon, the day of full moon serving as time zero) during times of wellness or illness. There were five spans during adynamic depression (FM 12, 13, 18, 19 and 24) and eight (remaining) spans during apparent wellness. A linear trend was fitted to the sequences of ϕs during each lunar month, and the dominant circadian τ derived therefrom. In order to better visualize the difference in the behavior of the circadian ϕ between illness and wellness, ϕ sequences were averaged across the five spans of illness and the eight spans of wellness, after normalization. Because there were differences in the average circadian ϕ of a given variable among the different spans that may inflate the error term, the ϕ on the day of full moon was set to zero and ϕs on the 14 days prior to and following the day of full moon determined relative to the ϕ on the day of full moon. After such normalization, the ϕs of a given variable were averaged for each day of the lunar month, separately for the totals of five months of illness and the eight months of wellness. These average ϕs and their standard error are shown in Figure 3E-G.

A ϕ delay is readily seen during illness, corresponding to an average circadian τ of ~24.58 h for cortisol, 24.54 h for DHEA, 24.53 h for melatonin, 24.32 h for aldosterone, 24.39 h for estradiol and 24.12 h for testosterone. For five hormones, the deviation from 24.0 h is significant ($P<0.05$), while it is of borderline significance for testosterone, as shown by the P-values from the regression lines in Figures 3E–3G. In the case of aldosterone and estradiol, the quadratic term of a second-order polynomial is also statistically significant, indicating that there was a faster ϕ delay before full moon and a slower ϕ delay after full moon for these two hormones.

During wellness (in the absence of adynamic depression), the regression line also shows a statistically significant ϕ delay in the case of cortisol, DHEA, melatonin and estradiol, suggesting that for these variables, the dominant circadian τ may also be somewhat longer than 24.0 h. The regression lines correspond to a circadian τ of 24.11 h for cortisol, 24.14 h for DHEA and to 24.13 h for melatonin and estradiol, close to the partly built-in "free-running from the 24.0-h society's" circadian τ, clearly different (by non-overlapping CIs) from the precise 24.0-h synchronized schedule. Spironolactone, with anti-androgenic and anti-aldosterone effects, used by JF twice daily, on arising and at bedtime in a 50 mg dose, could have synchronized selectively testosterone and aldosterone, as seen during apparent wellness.

Discussion

A pull of the moon is suggested by the repeated finding of a 24.8-h τ in JF's vigor during the first month of two consecutive episodes as well as by this τ in her HR, urine volume and salivary aldosterone (not shown), attesting objectively to seleno-sensitivity in JF. The double tidal τ was also found in a record of DBP of JF's granddaughter LT. We have seen a near 24.8-h τ in the telemetered intraperitoneal temperature of rats kept in continuous light of low intensity in the presence (11), but not in the absence of the suprachiasmatic nuclei (SCN) (12).

The desynchronization of a single variable in humans, of SBP only, yet not of oral temperature or activity, in an afebrile month of a boy with recurrent fever was found during apparent wellness (13). The coexistence of multiple behavioral circadian τs in the human circulation, endocrines, vigor, wrist activity and other variables of JF as well as in her daily awake fraction may not have been similarly demonstrated earlier. Yet, again in a single variable, sleep-wakefulness, the τs found in JF's wake fraction are replicated by a clinically healthy man while he lived on a self-selected schedule, apparently in good health, Table 5 (6). Hence in themselves the prevalence of coexisting multiple circadian τs in sleep-wakefulness need not be pathogenetic. We need to explore multiple variables for their behaviors, which can differ among variables, Figures 3B-G, and among downtimes (not shown here) which in turn happen to differ further after music therapy (14). The inter-variable differences

limit the value of urine volume to a first exploration as a proxy for some of the desynchronizations. All results on all variables are in keeping with the assumption that the moon and society (the latter in synchrony with the sun) wrangle during downtimes, even when the mechanisms underlying their interactions are unknown but point to the adrenal cortex (7). It is tempting to conclude that the moon pulls mainly during episodes of depressive adynamia, yet the sun does not fully synchronize four important circadianly variable hormones during relative wellness, as shown by the studies in the ϕ domain (Figures 3E and F).

Overall, in the light of Figures 3E-G, JF may be partly internally as well as partly externally 24-h desynchronized, even during wellness, as documented at least for cortisol, DHEA, melatonin and estradiol, with τs close to those reported as free-running on forced (but synchronizing) unacceptable routines of sleeping and waking (4, 5) versus 24-h synchronized testosterone and aldosterone. Smith et al. (5) report (with ethnic differences) an intrinsic 24.2-h τ, while Duffy et al. (4) found (with a sex difference) an intrinsic τ of 24.15 ($\pm$ 0.21) h, very close to the τs here noted for cortisol, DHEA, estradiol and melatonin. Both groups (4, 5) thoroughly review the pertinent literature. New in Figures 3E-G, based on 11,700 hormone assays, are differences among endocrines even during relative wellness, since salivary testosterone was apparently fully 24-h synchronized overall, as was aldosterone, perhaps because JF was on twice-daily 50 mg of spironolactone. Certainly, JF is a case for extending the scope of laboratory technology from single samples to time scales that have a spectrum of τs much broader than the circadian region examined herein (15, 16).

On the basic side, in hamsters with unilaterally ablated suprachiasmatic nuclei (SCN) kept in continuous light, the splitting of a circadian activity rhythm was avoided, as if two τs may stem from the separate SCNs found during desynchronization (17). Pickard and Turek (17) note further that the τ of the new circadian activity rhythm following unilateral SCN ablation differed from the τs of the split rhythm and of that preceding the split. These authors suggested an interaction between the bilaterally paired suprachiasmatic nuclei in the generation of the circadian rhythm of activity. An interaction of the two nuclei described as subtractive coupling was also found by us earlier in the core temperature rhythm of rodents after unilateral SCN ablation (12, 18, 19). De la Iglesia et al. (20), in turn, using a model for non-invasively dissociating the circadian oscillator network in vivo (21), found two motor activity rhythms that reflect the separate activities of two oscillators in anatomically defined ventrolateral and dorsomedial SCN subdivisions. Welsh et al. (22) found multiple autonomous circadian oscillators discussed by Reppert and Weaver (23).

Whether the multiple τs and the different endocrine behaviors stem from the SCN or the periphery remains one of the many problems for further study. So is the question of JF's half-yearly recurrence of downtimes, Table 1. Other τs modulating circadians may be expressed in JF, the near-half-yearly τ in particular (24). On the critical medical side, the possible molecular basis of the likely familiar aspects of JF's problems is being explored at the NIH, with particular focus on cryptochrome (25; cf. 26). Steven Reppert considered the possibility that humans could have cryptochrome heavily expressed in the retina, as a light-sensitive magnetoreceptor, since the human version of cryptochrome 2 restored geomagnetic orientation in cryptochrome-deficient fruit flies (24; cf. 23). Also from a practical viewpoint, the familial genetic background notwithstanding, the possibility of a post-traumatic stress syndrome is best considered by magnetoencephalography (27).

Event trauma is limited to an accident in 1969 in which JF's car was totaled and three people in two other vehicles were killed. The event continues to live in her emotions with a genuine distaste for travel on two-lane highways. Downtimes were not detected until 1990, however. JF also had a brief span of unconsciousness after a fall from a horse, 7 or 8 years ago. An MRI at that time showed no damage, but brain pain and tingling during the downtime, which began several days after the fall, was greater than usual.

The family has also considered the possibility of trauma from the intense years of travel as a Christian missionary, when she dealt with a different group of people and slept in different places each week, with the demands of trying to meet the practical and professional needs during the fewer than 48 h she was at home each week. Perhaps the physical push to accomplish the needed during the at home times did have an impact, thus causing increased sensitivities to magnetics. An emotional impact of her profession on JF is supported by the reoccurring stress dreams that JF has during times of high magnetic disturbance that involve her trying to get luggage packed to get to the airport in time.
The possible merits of a systematic attempt at synchronization by light and melatonin are indicated, preferably with the concomitant sampling of marker rhythms, whatever the underlying mechanism may be. That the moon must be considered as affecting living matter was advocated by many and documented recently by Miroslav Mikulecky, among others (10, 28; cf. 29–38), even though the topic is contested (39). It seems more difficult to separate lunar and solar effects by their about-monthly cycles, although an attempt has been made to compare in neonates the association of frequencies found in their physiology with the rotation of the sun around its axis in ~27-days at its equator on the one hand and with lunar τs on the other hand (40). The difference between 24.0 and 24.8 h between the societal and solar day on the one hand and the lunidian τ on the other hand is here regarded as decisive. The underlying mechanisms of selenosensitivity, being investigated at the NIH, remain to be elucidated at the molecular level.

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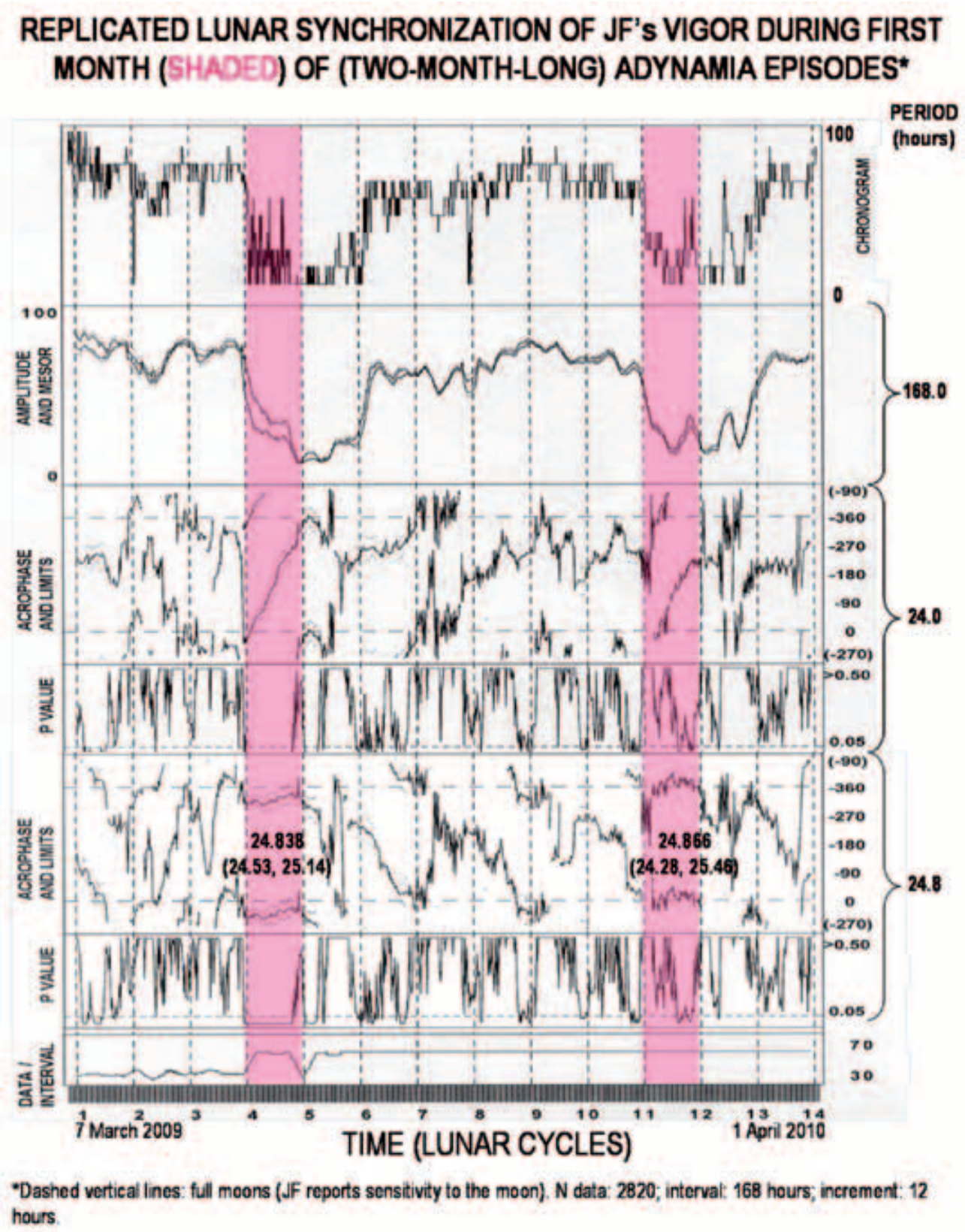


Figure 1A. Self-rated vigor-wellness of JF during the first 14 lunar months of study. © Halberg.

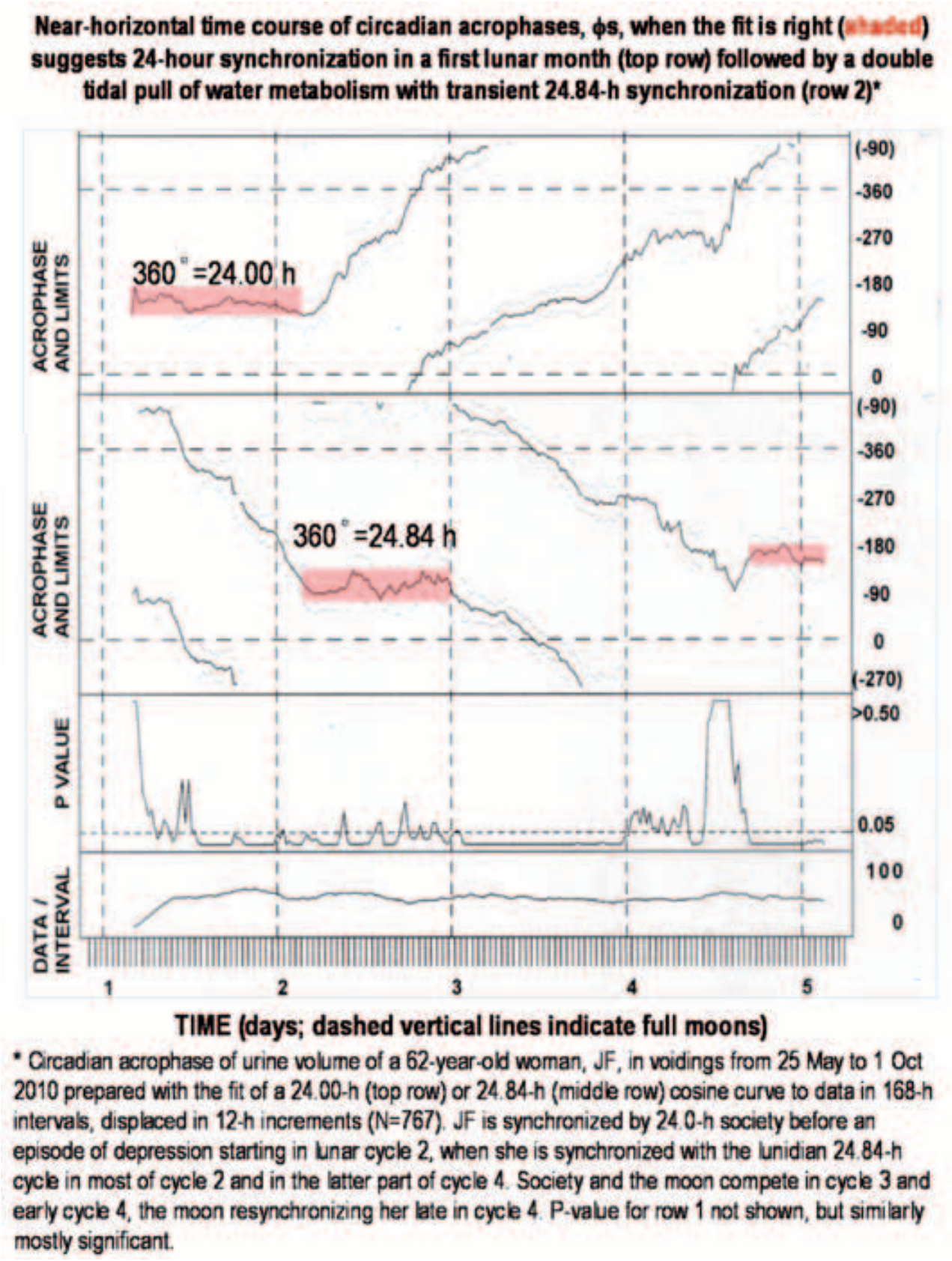


Figure 1B. Chronobiologic serial sections suggest 24-h synchrony during wellness in a first lunar cycle and desynchronization thereafter with a 24.84-h τ in the first month of desynchronization. Subsequently, the ϕ advances, i.e., the τ shortens until it reaches a 24-h length. © Halberg.

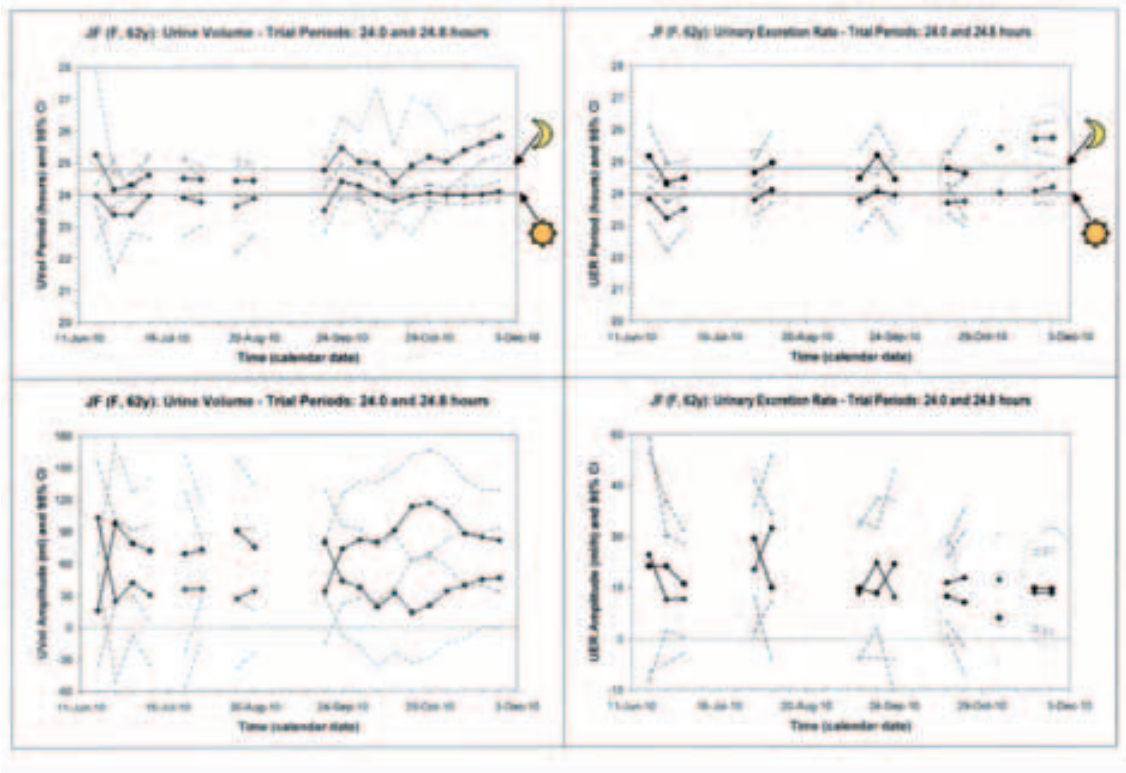


Figure 1C. Alternately dominating coexisting circadian (~24.0-h and longer) τs in the urine volume (left, top) and excretion rate (right, top) as seen from their amplitudes (bottom). © Halberg.

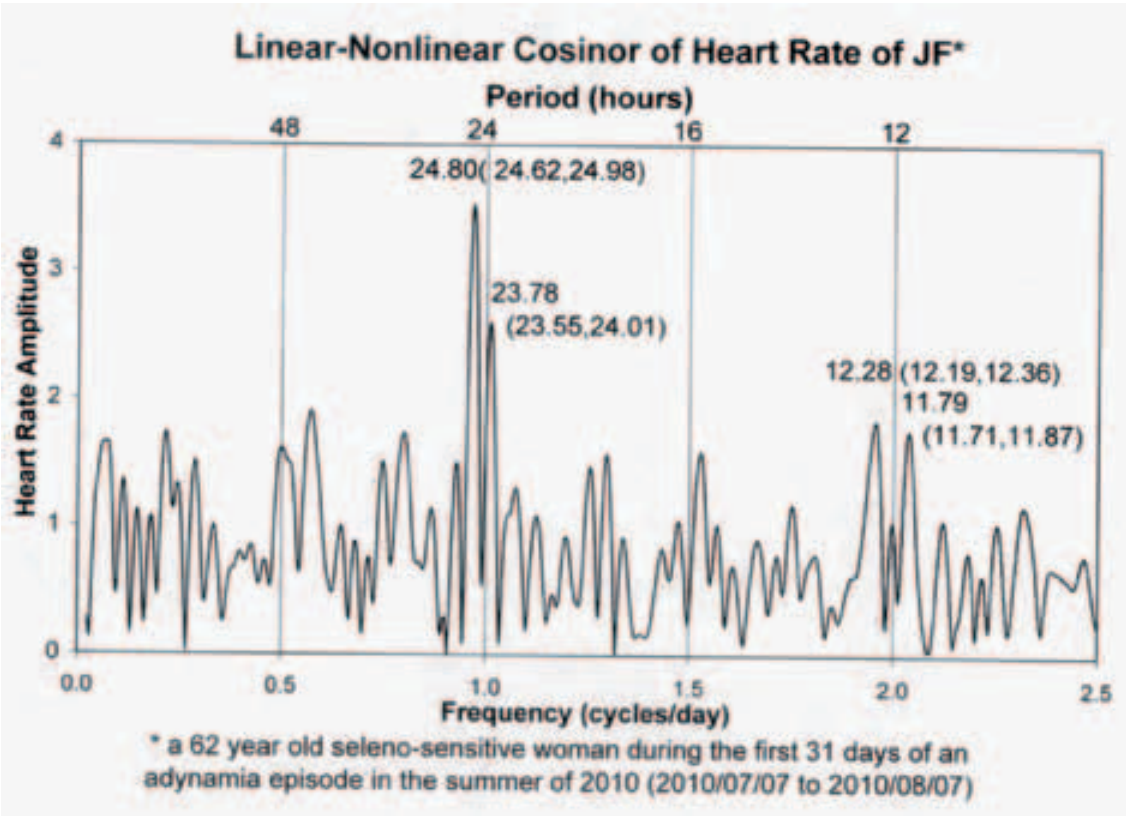


Figure 2A. Coexisting separate circadian τs in JF's HR during an episode of depression with adynamia. © Halberg.

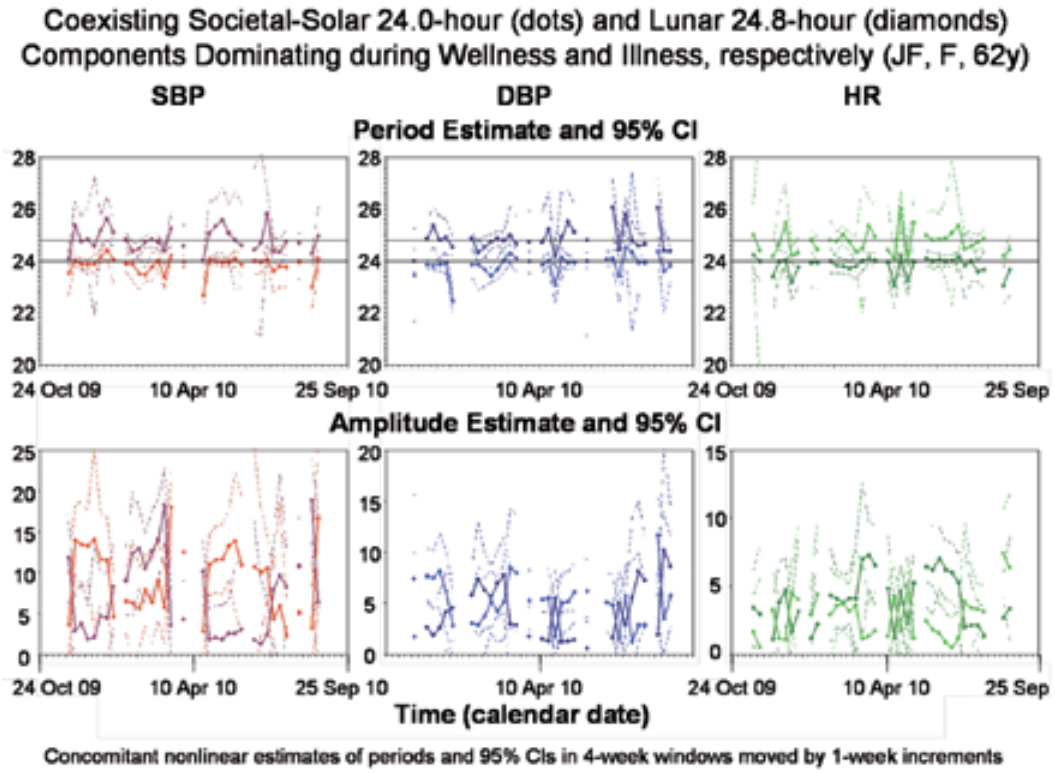


Figure 2B. Time course of two separate circadian τs in JF's circulation. © Halberg.

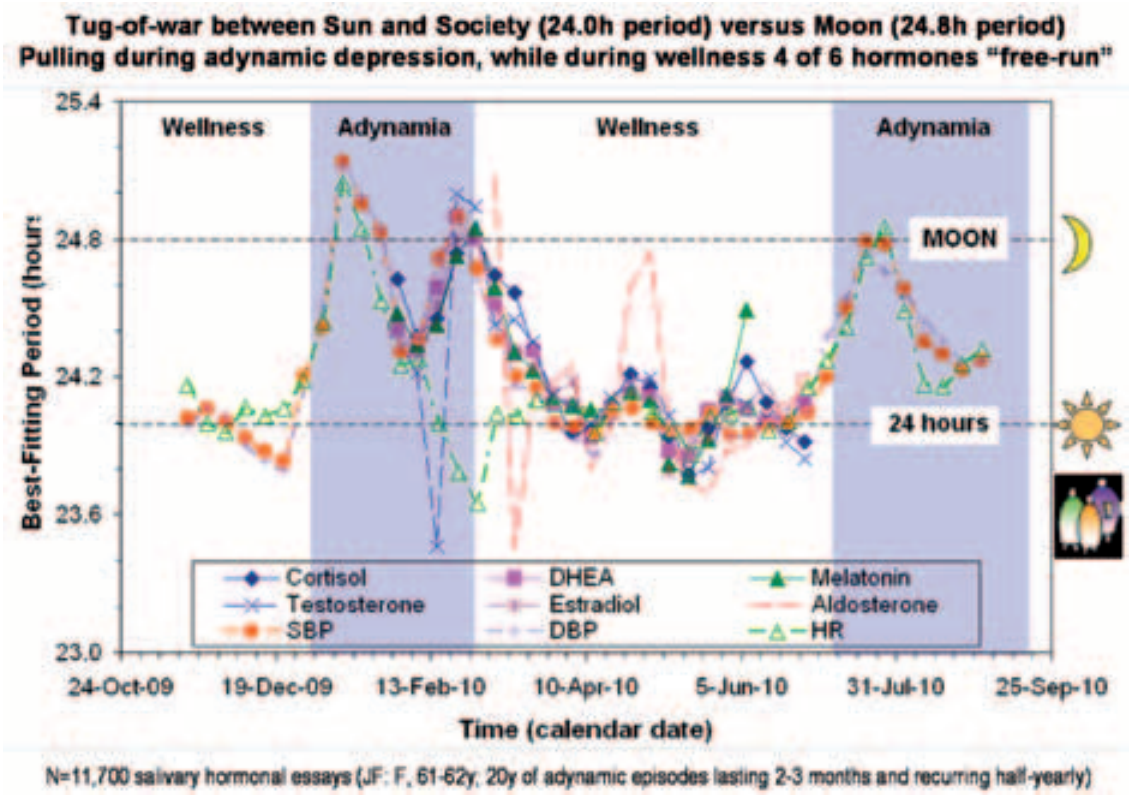


Figure 3A. Wrangling between the moon on the one hand and society/sun on the other hand in JF's endocrines as in her circulation, with the pull of the tides lengthening the dominant τ during depression. © Halberg.

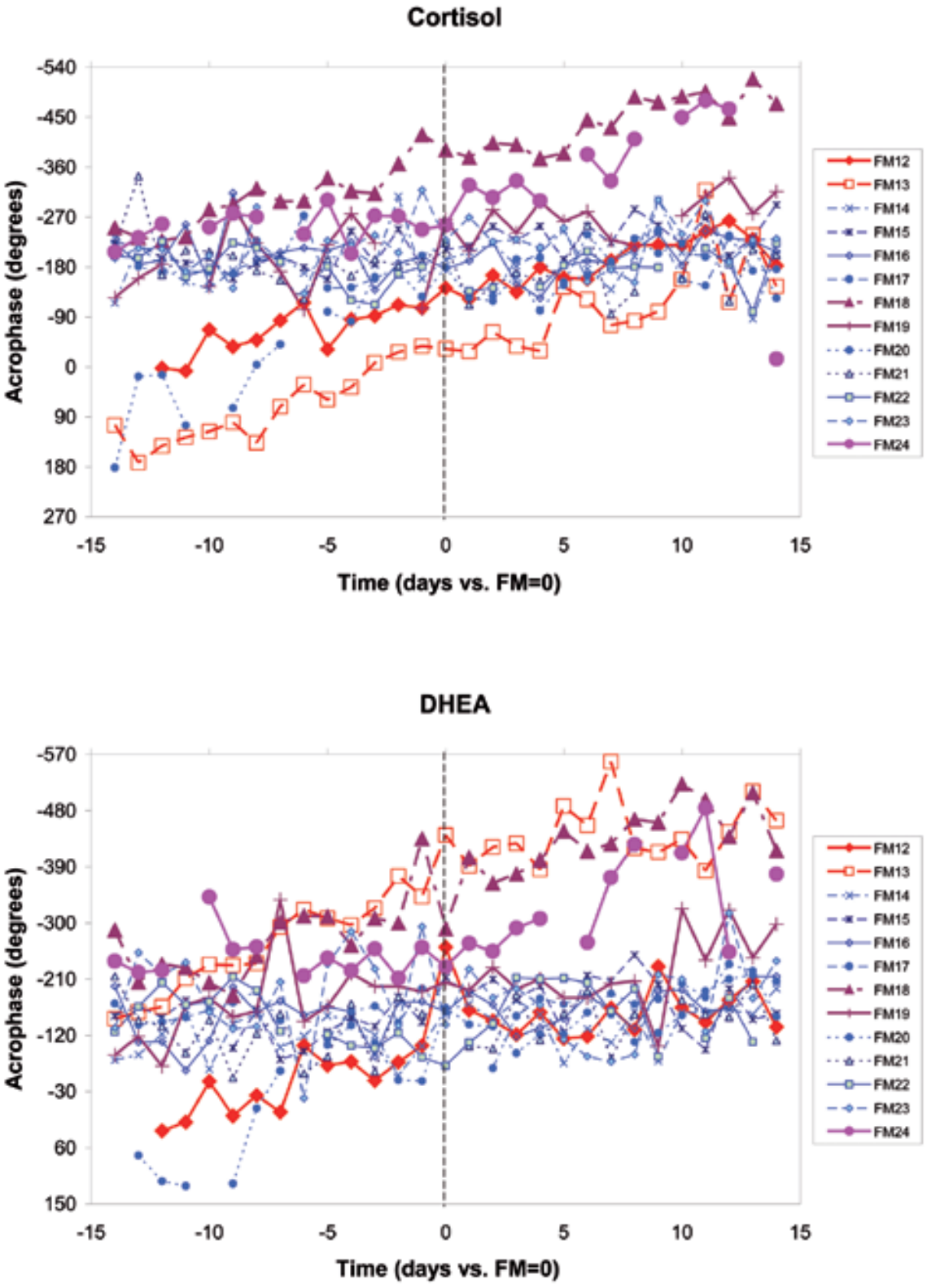


Figure 3B. Time course of ϕs for two weeks before (–1 to –15 days) and after (+1 to +15 days) the full moon (=0) for JF's salivary cortisol and DHEA. © Halberg.

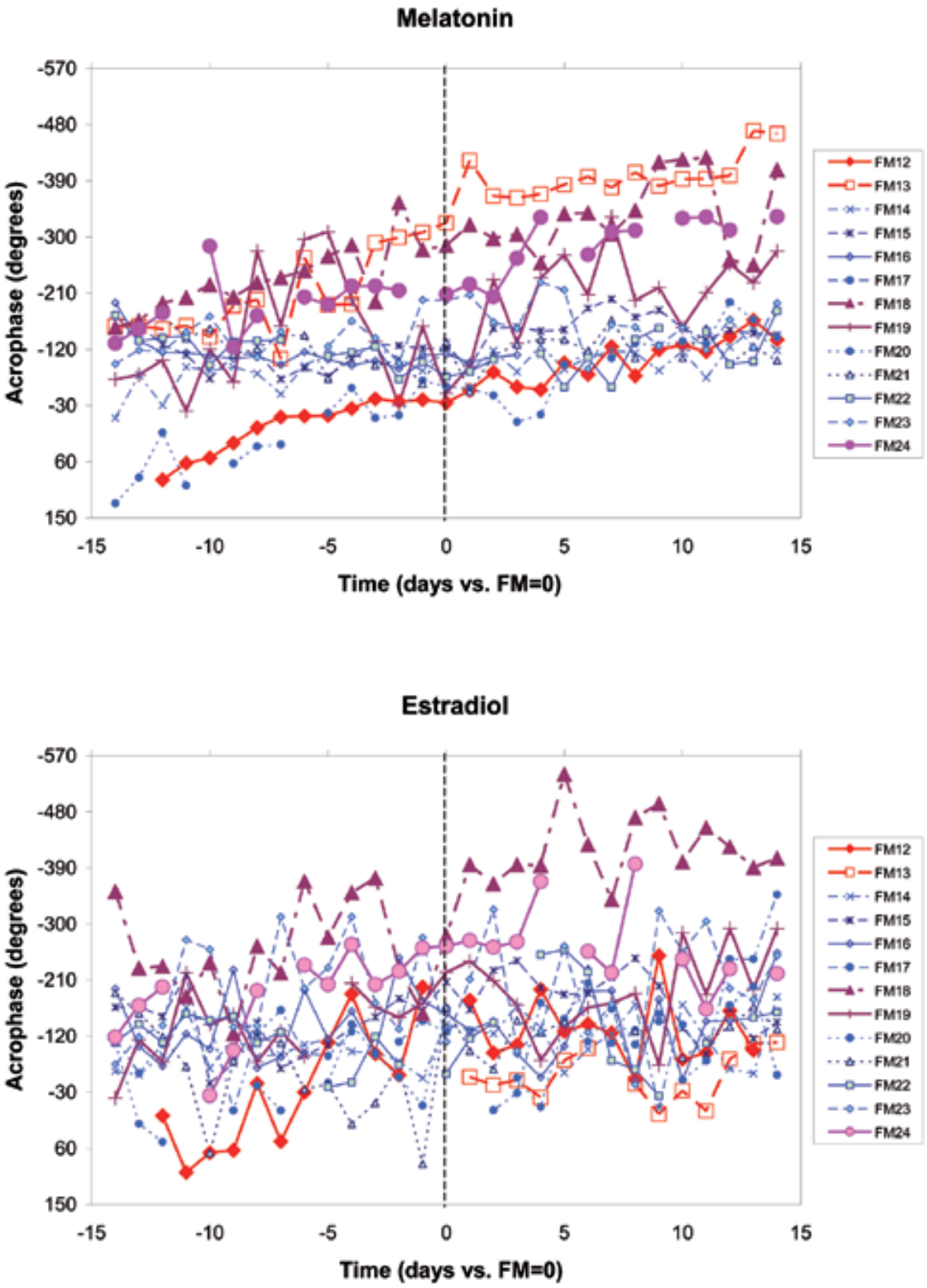


Figure 3C. Time course of ϕs for two weeks before (–1 to –15 days) and after (+1 to +15 days) the full moon (=0) for JF's salivary melatonin and estradiol. © Halberg.

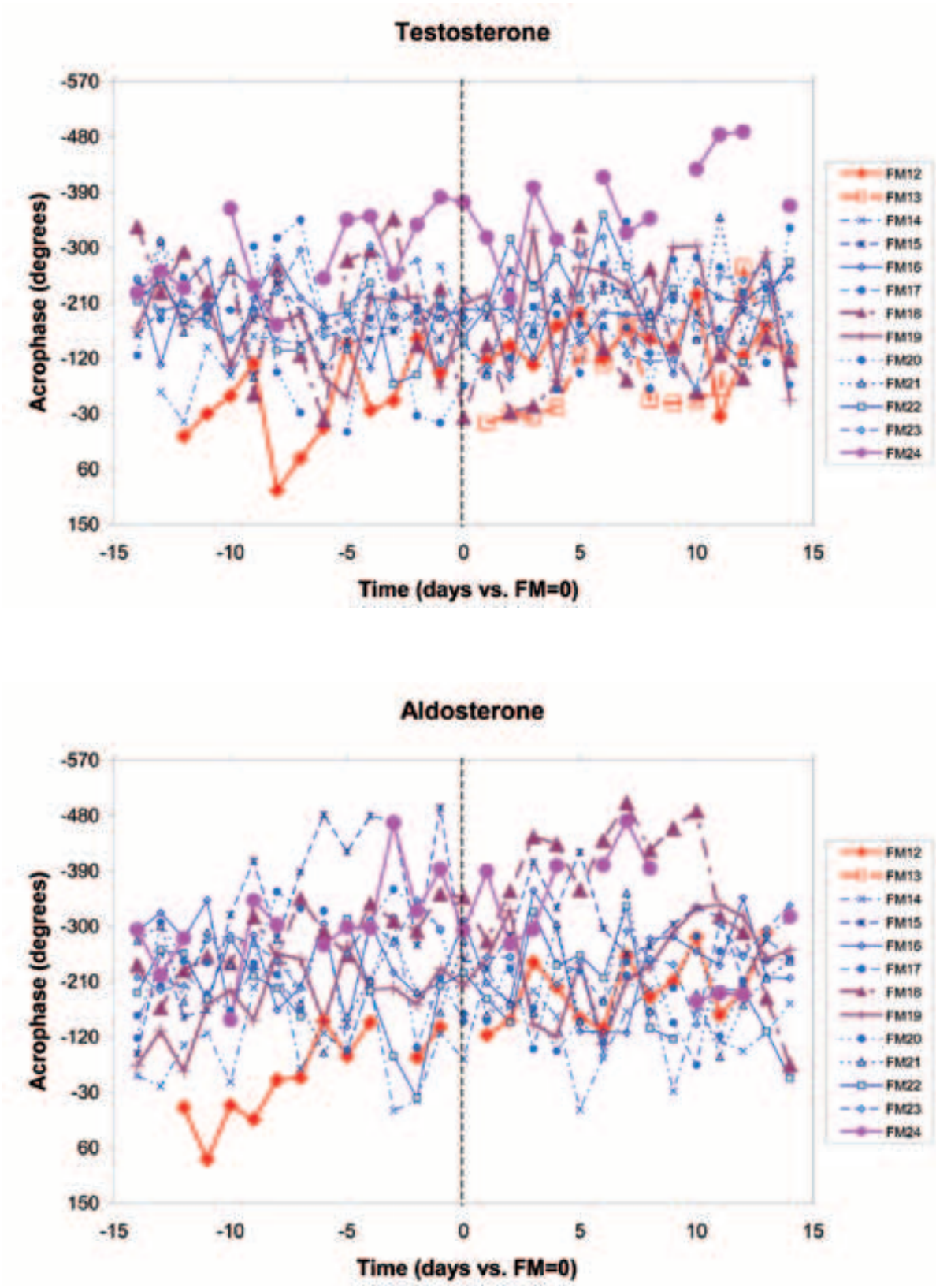


Figure 3D. Time course of ϕs for two weeks before (–1 to –15 days) and after (+1 to +15 days) the full moon (=0) for JF's salivary testosterone and aldosterone. © Halberg.

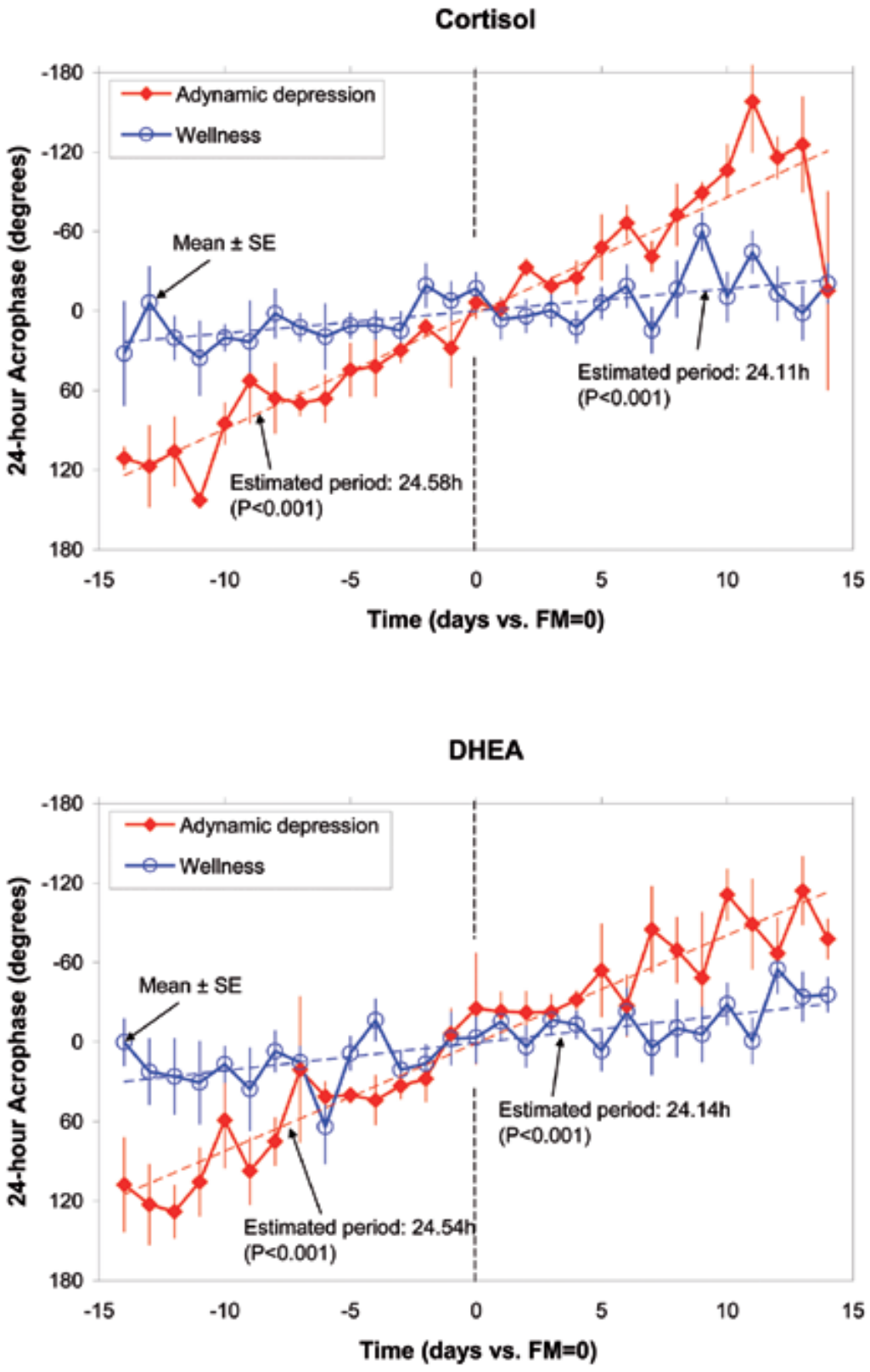


Figure 3E. Oblique (desynchronized) time course of JF's ϕs during depression is much less prominent during wellness, but present in salivary cortisol and DHEA. © Halberg.

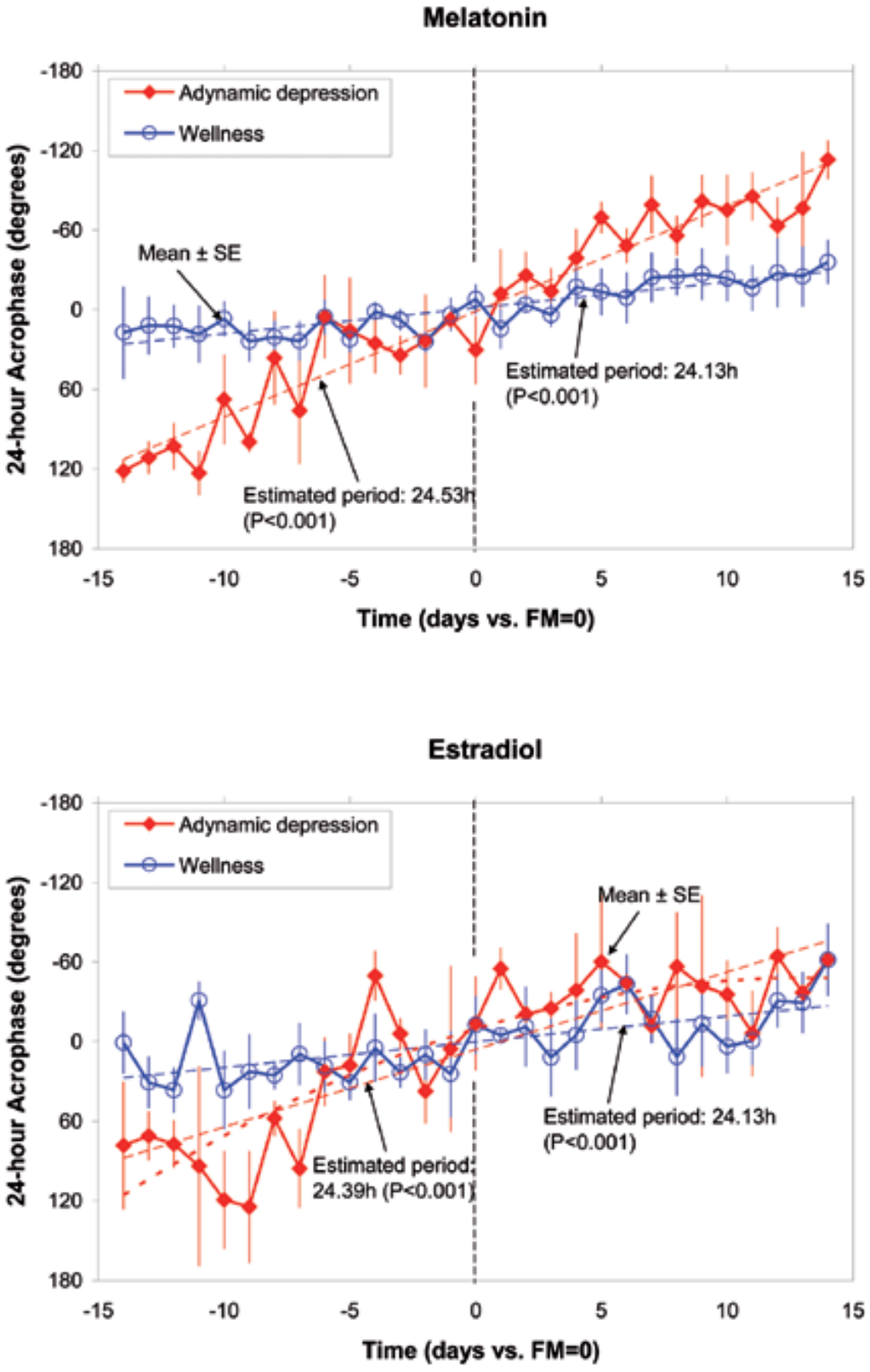


Figure 3F. Oblique (desynchronized) time course of JF's ϕs during depression is much less prominent but present in salivary melatonin and estradiol. © Halberg.

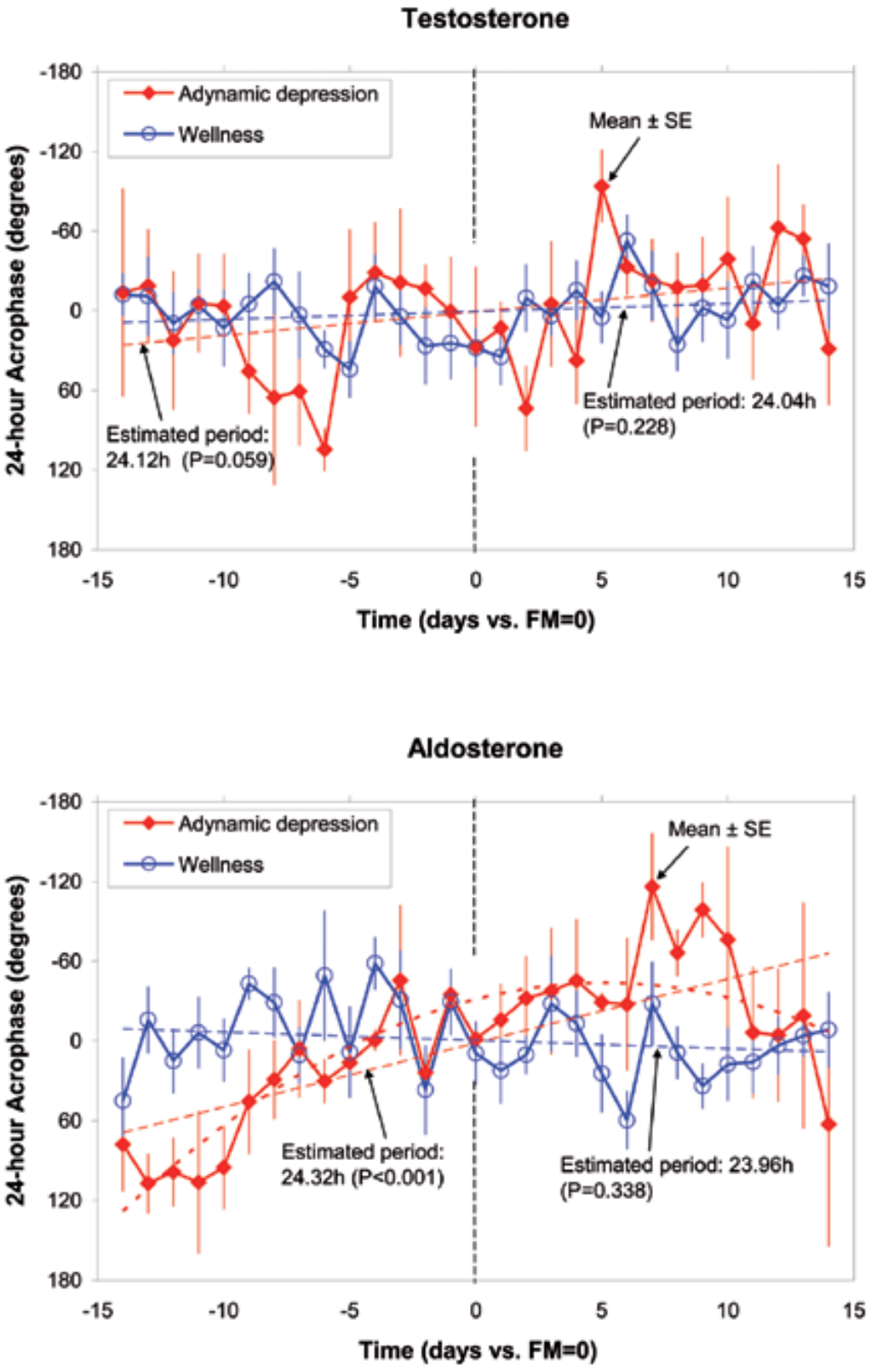


Figure 3G. Oblique (desynchronized) time course of JF's ϕs present during depression is not seen in testosterone and aldosterone during wellness, presumably because of selective synchronization by twice-daily spironolactone. © Halberg.

Table 1: Recorded recurrent adynamia
Start-end dates and length (weeks) of spans of adynamia when recorded in winter (W) and summer (S). f: date of full moon; n: date of new moon

	2002	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
W	-	01.18 f 02.17 f (4)	01.12 02.20 n (5)	01.05 02.15 (5)	12.25 n 02.14 n (7)	01.03 f 03.03 f (8)	01.08 n 02.21 f (6)	12.26 n 02.23 n (8)	01.02 f 02.28 f (8)	01.04 n 03.05 n (8)
S	06.09 08.07 (8)	06.15 f 08.12 f (8)	06.17 n 08.18 n (8)	06.20 f 08.09 (7)	06.04 08.28 (11)	05.31 f 08.12 n (10)	? 08.18 f (?)	06.09 f 08.08 f (8)	07.08 09.16 (10)	07.07 09.13* (10)

*“I have concluded that Sept 1 was a false end to the downtime. I had five functional days, but the last eight [i.e., 09.06-09.13] have been horrible again!“ (JF, personal communication, 14 September 2011)

	FM	Period (h)	14 days Before FM SE	r	P	Period (h)	14 days After FM SE	r	P	Comparison ΔPeriod	"SE"	ΔPeriod(%)
Cortisol	12	24.68	0.13	0.836	<0.001	24.51	0.10	0.813	<0.001	-0.15	0.23	0.61
DHEA	12	25.05	0.24	0.798	0.001	23.97	0.18	-0.041	0.884	-1.07	0.41	4.28
Melatonin	12	24.69	0.08	0.934	<0.001	24.51	0.07	0.898	<0.001	-0.18	0.15	0.72
Testosterone	12	24.60	0.39	0.437	0.155	24.00	0.25	-0.004	0.989	-0.60	0.64	2.44
Estradiol	12	25.47	0.34	0.810	0.001	23.86	0.27	-0.151	0.621	-1.61	0.61	6.34
Aldosterone	12	25.10	0.26	0.819	0.002	24.48	0.25	0.507	0.077	-0.61	0.50	2.45
Cortisol	13	24.96	0.11	0.926	<0.001	24.88	0.23	0.724	0.002	-0.08	0.34	0.32
DHEA	13	25.21	0.09	0.963	<0.001	24.19	0.19	0.263	0.344	-1.02	0.29	4.06
Melatonin	13	24.85	0.17	0.811	<0.001	24.39	0.11	0.668	0.004	-0.46	0.28	1.83
Testosterone	13							0.578	0.030			
Estradiol	13					24.15	0.17	0.255	0.401			
Aldosterone	13											
Cortisol	14	24.28	0.16	0.434	0.106	23.87	0.19	-0.189	0.500	-0.41	0.35	1.69
DHEA	14	24.09	0.14	0.176	0.529	24.04	0.14	0.088	0.756	-0.05	0.28	0.19
Melatonin	14	24.36	0.10	0.725	0.002	24.07	0.09	0.219	0.433	-0.29	0.18	1.20
Testosterone	14	24.81	0.17	0.813	0.001	24.00	0.09	-0.014	0.960	-0.81	0.27	3.27
Estradiol	14	24.06	0.13	0.128	0.650	23.87	0.20	-0.168	0.551	-0.18	0.33	0.76
Aldosterone	14	23.98	0.30	-0.021	0.941	23.89	0.26	-0.115	0.682	-0.09	0.56	0.36
Cortisol	15	24.02	0.11	0.040	0.888	24.14	0.12	0.327	0.235	0.13	0.23	0.53
DHEA	15	24.07	0.15	0.128	0.664	23.75	0.16	-0.409	0.130	-0.32	0.31	1.33
Melatonin	15	23.95	0.10	-0.145	0.606	24.10	0.10	0.263	0.344	0.16	0.20	0.65
Testosterone	15	23.94	0.15	-0.110	0.709	23.96	0.14	-0.082	0.773	0.02	0.29	0.08
Estradiol	15	24.09	0.21	0.125	0.657	23.58	0.15	-0.615	0.015	-0.51	0.36	2.12
Aldosterone	15	25.19	0.43	0.607	0.016	23.83	0.24	-0.189	0.500	-1.36	0.67	5.40
Cortisol	16	23.83	0.17	-0.273	0.325	24.28	0.12	0.551	0.033	0.45	0.26	1.88
DHEA	16	24.14	0.16	0.228	0.414	24.21	0.11	0.489	0.064	0.08	0.27	0.31
Melatonin	16	23.78	0.08	-0.606	0.017	24.03	0.21	0.111	0.689	0.26	0.30	1.09
Testosterone	16	23.91	0.24	-0.103	0.715	24.24	0.17	0.358	0.190	0.33	0.41	1.36
Estradiol	16	24.24	0.22	0.280	0.312	24.24	0.23	0.277	0.318	0.00	0.46	0.02
Aldosterone	16	23.72	0.27	-0.274	0.322	24.02	0.31	0.020	0.942	0.30	0.59	1.26
Cortisol	17	23.97	0.15	-0.060	0.859	23.98	0.19	-0.037	0.899	0.00	0.34	0.01
DHEA	17	24.04	0.09	0.119	0.686	24.36	0.15	0.558	0.038	0.32	0.24	1.35
Melatonin	17											
Testosterone	17	23.87	0.22	-0.161	0.566	24.01	0.27	0.009	0.975	0.14	0.49	0.57
Estradiol	17	24.13	0.18	0.214	0.463	24.92	0.30	0.662	0.010	0.78	0.48	3.25
Aldosterone	17	23.97	0.27	-0.027	0.923	24.30	0.26	0.319	0.267	0.33	0.53	1.38

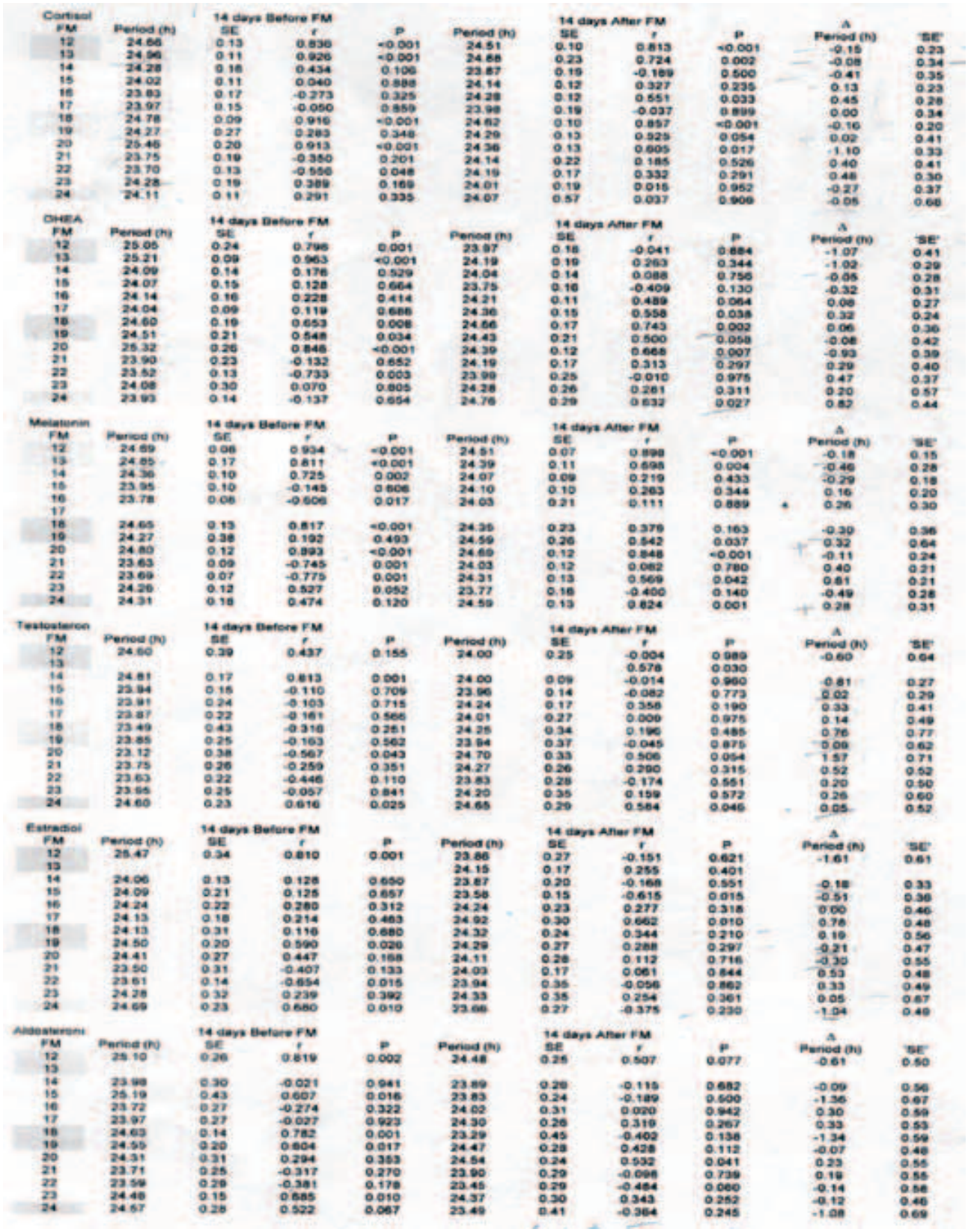
Table 2: When 4-h endocrine salivary sampling around the clock for 6 months does not suffice, shortening of circadian period (τ) of 6 hormones in 2-week intervals after full moons (FM) vs. before FM in JF's episode of depression (shaded FM) vs. wellness, does not hold in the next 9 months (see Table 3)

*Period estimated from phase behavior: FM number 12 refers to the 12th FM investigated on JF, a 61-year-old woman at start of study. The first FM was on March 11, 2009, at 02:40 Universal Time and the 12th bracketed by the start of hormone assays on January 30 at 06:19. Note dangers of extrapolating from limited data since during FM 12–14, 15 out of 15 comparisons in a downtime and in the month thereafter revealed a shortening following FM. In the case of FM 15, 3 hormones had shorter periods and 3 others had longer ones. In FM 16 and 17 all periods lengthened or did not change after FM. It is tempting to attribute the shortening after FM to depression in FMs 12 and 13 and to interpret FM 14 as a transient aftereffect on the basis of 6 months of 4-hourly assays of 6 hormones. Table 3, however, does not show these differences in behavior in episodes vs. during relative wellness. Shading of FM indicates episodes of adynamic depression.

Cortisol	18	24.78	0.09	0.916	<0.001	24.62	0.10	0.857	<0.001	-0.16	0.20	0.64
DHEA	18	24.60	0.19	0.653	0.008	24.66	0.17	0.743	0.002	0.06	0.36	0.24
Melatonin	18	24.65	0.13	0.817	<0.001	24.35	0.23	0.379	0.183	-0.30	0.36	1.22
Testosterone	18	23.49	0.43	-0.316	0.251	24.25	0.34	0.196	0.485	0.76	0.77	3.23
Estradiol	18	24.13	0.31	0.116	0.680	24.32	0.24	0.344	0.210	0.19	0.56	0.78
Aldosterone	18	24.63	0.14	0.782	0.001	23.29	0.45	-0.402	0.138	-1.34	0.59	5.43
Cortisol	19	24.27	0.27	0.283	0.348	24.29	0.13	0.525	0.054	0.02	0.41	0.08
DHEA	19	24.51	0.21	0.548	0.034	24.43	0.21	0.500	0.058	-0.08	0.42	0.31
Melatonin	19	24.27	0.38	0.192	0.493	24.59	0.26	0.542	0.037	0.32	0.64	1.33
Testosterone	19	23.85	0.25	-0.163	0.562	23.94	0.37	-0.045	0.875	0.09	0.62	0.37
Estradiol	19	24.50	0.20	0.590	0.026	24.29	0.27	0.288	0.297	-0.21	0.47	0.87
Aldosterone	19	24.55	0.20	0.604	0.017	24.47	0.28	0.428	0.112	-0.07	0.46	0.30
Cortisol	20	25.46	0.20	0.913	<0.001	24.36	0.13	0.605	0.017	-1.10	0.33	4.31
DHEA	20	25.32	0.26	0.846	<0.001	24.39	0.12	0.668	0.007	-0.93	0.39	3.68
Melatonin	20	24.80	0.12	0.893	<0.001	24.69	0.12	0.848	<0.001	-0.11	0.24	0.42
Testosterone	20	23.12	0.38	-0.567	0.043	24.70	0.33	0.506	0.054	1.57	0.71	6.80
Estradiol	20	24.41	0.27	0.447	0.168	24.11	0.28	0.112	0.716	-0.30	0.55	1.23
Aldosterone	20	24.31	0.31	0.294	0.353	24.54	0.24	0.532	0.041	0.23	0.55	0.95
Cortisol	21	23.75	0.19	-0.350	0.201	24.14	0.22	0.185	0.526	0.40	0.41	1.68
DHEA	21	23.90	0.23	-0.132	0.652	24.19	0.17	0.313	0.297	0.29	0.40	1.22
Melatonin	21	23.63	0.09	-0.745	0.001	24.03	0.12	0.082	0.780	0.40	0.21	1.70
Testosterone	21	23.75	0.26	-0.259	0.351	24.27	0.26	0.290	0.315	0.52	0.52	2.20
Estradiol	21	23.50	0.31	-0.407	0.133	24.03	0.17	0.061	0.844	0.53	0.48	2.26
Aldosterone	21	23.71	0.25	-0.317	0.270	23.90	0.29	-0.098	0.739	0.19	0.55	0.82
Cortisol	22	23.70	0.13	-0.556	0.048	24.19	0.17	0.332	0.291	0.48	0.30	2.04
DHEA	22	23.52	0.13	-0.733	0.003	23.99	0.25	-0.010	0.975	0.47	0.37	1.99
Melatonin	22	23.69	0.07	-0.775	0.001	24.31	0.13	0.569	0.042	0.61	0.21	2.59
Testosterone	22	23.63	0.22	-0.446	0.110	23.83	0.28	-0.174	0.551	0.20	0.50	0.86
Estradiol	22	23.61	0.14	-0.654	0.015	23.94	0.39	-0.056	0.862	0.33	0.49	1.39
Aldosterone	22	23.59	0.29	-0.381	0.178	23.45	0.29	-0.484	0.080	-0.14	0.58	0.59
Cortisol	23	24.28	0.19	0.369	0.169	24.01	0.19	0.015	0.952	-0.27	0.37	1.10
DHEA	23	24.08	0.30	0.070	0.805	24.28	0.26	0.261	0.311	0.20	0.57	0.84
Melatonin	23	24.26	0.12	0.527	0.052	23.77	0.16	-0.400	0.140	-0.49	0.28	2.03
Testosterone	23	23.95	0.25	-0.057	0.841	24.20	0.35	0.159	0.572	0.26	0.60	1.07
Estradiol	23	24.28	0.32	0.239	0.392	24.33	0.35	0.254	0.361	0.05	0.67	0.19
Aldosterone	23	24.48	0.15	0.685	0.010	24.37	0.30	0.343	0.252	-0.12	0.46	0.47
Cortisol	24	24.11	0.11	0.291	0.335	24.07	0.57	0.037	0.909	-0.05	0.68	0.19
DHEA	24	23.93	0.14	-0.137	0.654	24.76	0.29	0.632	0.027	0.82	0.44	3.44
Melatonin	24	24.31	0.18	0.474	0.120	24.59	0.13	0.824	0.001	0.28	0.31	1.17
Testosterone	24	24.60	0.23	0.616	0.025	24.65	0.29	0.584	0.046	0.05	0.52	0.19
Estradiol	24	24.69	0.23	0.680	0.010	23.66	0.27	-0.375	0.230	-1.04	0.49	4.20
Aldosterone	24	24.57	0.28	0.522	0.097	23.49	0.41	-0.364	0.245	-1.08	0.69	4.39

Table 3: As compared to Table 2, a different behavior of the endocrines in relation to the full moon (FM) is seen, notably during JF's downtimes (shaded FM) *

*9 increases out of 19 in FMs 18, 19 and 24 (rather than 0 in depression). The data of Tables 2 and 3 led to Figure 3B.



Cortisol		14 days Before FM				14 days After FM			Δ	
FM	Period (h)	SE	r	P	Period (h)	SE	r	P	Period (h)	'SE'
12	24.66	0.13	0.836	<0.001	24.51	0.10	0.813	<0.001	-0.15	0.23
13	24.96	0.11	0.926	<0.001	24.88	0.23	0.724	0.002	-0.08	0.34
14	24.28	0.18	0.434	0.106	23.87	0.19	-0.189	0.500	-0.41	0.35
15	24.02	0.11	0.040	0.888	24.14	0.12	0.327	0.235	0.13	0.23
16	23.83	0.17	-0.273	0.325	24.28	0.12	0.551	0.033	0.45	0.28
17	23.97	0.15	-0.050	0.859	23.98	0.19	-0.037	0.899	0.00	0.34
18	24.78	0.09	0.916	<0.001	24.62	0.10	0.857	<0.001	-0.16	0.20
19	24.27	0.27	0.283	0.348	24.29	0.13	0.525	0.054	0.02	0.41
20	25.46	0.20	0.913	<0.001	24.36	0.13	0.605	0.017	-1.10	0.33
21	23.75	0.19	-0.350	0.201	24.14	0.22	0.185	0.526	0.40	0.41
22	23.70	0.13	-0.556	0.048	24.19	0.17	0.332	0.291	0.48	0.30
23	24.28	0.19	0.389	0.169	24.01	0.19	0.015	0.952	-0.27	0.37
24	24.11	0.11	0.291	0.335	24.07	0.57	0.037	0.909	-0.05	0.68

DHEA		14 days Before FM				14 days After FM			Δ	
FM	Period (h)	SE	r	P	Period (h)	SE	r	P	Period (h)	'SE'
12	25.05	0.24	0.798	0.001	23.97	0.18	-0.041	0.884	-1.07	0.41
13	25.21	0.09	0.963	<0.001	24.19	0.19	0.263	0.344	-1.02	0.29
14	24.09	0.14	0.176	0.529	24.04	0.14	0.088	0.756	-0.05	0.28
15	24.07	0.15	0.128	0.664	23.75	0.16	-0.409	0.130	-0.32	0.31
16	24.14	0.16	0.228	0.414	24.21	0.11	0.489	0.064	0.08	0.27
17	24.04	0.09	0.119	0.686	24.36	0.15	0.558	0.038	0.32	0.24
18	24.60	0.19	0.653	0.008	24.66	0.17	0.743	0.002	0.06	0.36
19	24.51	0.21	0.548	0.034	24.43	0.21	0.500	0.058	-0.08	0.42
20	25.32	0.26	0.846	<0.001	24.39	0.12	0.668	0.007	-0.93	0.39
21	23.90	0.23	-0.132	0.652	24.19	0.17	0.313	0.297	0.29	0.40
22	23.52	0.13	-0.733	0.003	23.99	0.25	-0.010	0.975	0.47	0.37
23	24.08	0.30	0.070	0.805	24.28	0.26	0.261	0.311	0.20	0.57
24	23.93	0.14	-0.137	0.654	24.76	0.29	0.632	0.027	0.82	0.44

Melatonin		14 days Before FM				14 days After FM			Δ	
FM	Period (h)	SE	r	P	Period (h)	SE	r	P	Period (h)	'SE'
12	24.69	0.08	0.934	<0.001	24.51	0.07	0.898	<0.001	-0.18	0.15
13	24.85	0.17	0.811	<0.001	24.39	0.11	0.698	0.004	-0.46	0.28
14	24.36	0.10	0.725	0.002	24.07	0.09	0.219	0.433	-0.29	0.18
15	23.95	0.10	-0.145	0.606	24.10	0.10	0.263	0.344	0.16	0.20
16	23.78	0.08	-0.606	0.017	24.03	0.21	0.111	0.889	0.26	0.30
17										
18	24.65	0.13	0.817	<0.001	24.35	0.23	0.378	0.163	-0.30	0.36
19	24.27	0.38	0.192	0.493	24.59	0.26	0.542	0.037	0.32	0.64
20	24.80	0.12	0.893	<0.001	24.69	0.12	0.848	<0.001	-0.11	0.24
21	23.63	0.09	-0.745	0.001	24.03	0.12	0.082	0.780	0.40	0.21
22	23.69	0.07	-0.775	0.001	24.31	0.13	0.569	0.042	0.61	0.21
23	24.26	0.12	0.527	0.052	23.77	0.16	-0.400	0.140	-0.49	0.28
24	24.31	0.18	0.474	0.120	24.59	0.13	0.824	0.001	0.28	0.31

Testosteron		14 days Before FM				14 days After FM			Δ	
FM	Period (h)	SE	r	P	Period (h)	SE	r	P	Period (h)	'SE'
12	24.60	0.39	0.437	0.155	24.00	0.25	-0.004	0.989	-0.60	0.64
13							0.578	0.030		
14	24.81	0.17	0.813	0.001	24.00	0.09	-0.014	0.960	-0.81	0.27
15	23.94	0.15	-0.110	0.709	23.96	0.14	-0.082	0.773	0.02	0.29
16	23.91	0.24	-0.103	0.715	24.24	0.17	0.358	0.190	0.33	0.41
17	23.87	0.22	-0.161	0.566	24.01	0.27	0.009	0.975	0.14	0.49
18	23.49	0.43	-0.318	0.251	24.25	0.34	0.196	0.485	0.76	0.77
19	23.85	0.25	-0.163	0.562	23.94	0.37	-0.045	0.875	0.09	0.62
20	23.12	0.38	-0.567	0.043	24.70	0.33	0.506	0.054	1.57	0.71
21	23.75	0.26	-0.259	0.351	24.27	0.26	0.290	0.315	0.52	0.52
22	23.63	0.22	-0.446	0.110	23.83	0.28	-0.174	0.551	0.20	0.50
23	23.85	0.25	-0.057	0.841	24.20	0.35	0.159	0.572	0.26	0.60
24	24.60	0.23	0.616	0.025	24.65	0.29	0.564	0.046	0.05	0.52

Estradiol		14 days Before FM				14 days After FM			Δ	
FM	Period (h)	SE	r	P	Period (h)	SE	r	P	Period (h)	'SE'
12	25.47	0.34	0.810	0.001	23.86	0.27	-0.151	0.621	-1.61	0.61
13					24.15	0.17	0.255	0.401		
14	24.06	0.13	0.128	0.650	23.87	0.20	-0.168	0.551	-0.18	0.33
15	24.09	0.21	0.125	0.657	23.58	0.15	-0.615	0.015	-0.51	0.36
16	24.24	0.22	0.280	0.312	24.24	0.23	0.277	0.318	0.00	0.46
17	24.13	0.18	0.214	0.483	24.92	0.30	0.662	0.010	0.78	0.48
18	24.13	0.31	0.116	0.680	24.32	0.24	0.344	0.210	0.19	0.56
19	24.50	0.20	0.590	0.026	24.29	0.27	0.288	0.297	-0.21	0.47
20	24.41	0.27	0.447	0.158	24.11	0.28	0.112	0.716	-0.30	0.55
21	23.50	0.31	-0.407	0.133	24.03	0.17	0.061	0.844	0.53	0.48
22	23.61	0.14	-0.654	0.015	23.94	0.35	-0.056	0.862	0.33	0.49
23	24.28	0.32	0.239	0.392	24.33	0.35	0.254	0.361	0.05	0.67
24	24.69	0.23	0.680	0.010	23.66	0.27	-0.375	0.230	-1.04	0.49

Aldosteron		14 days Before FM				14 days After FM			Δ	
FM	Period (h)	SE	r	P	Period (h)	SE	r	P	Period (h)	'SE'
12	25.10	0.26	0.819	0.002	24.48	0.25	0.507	0.077	-0.61	0.50
13										
14	23.98	0.30	-0.021	0.941	23.89	0.29	-0.115	0.682	-0.09	0.56
15	25.19	0.43	0.607	0.016	23.83	0.24	-0.189	0.500	-1.36	0.67
16	23.72	0.27	-0.274	0.322	24.02	0.31	0.020	0.942	0.30	0.59
17	23.97	0.27	-0.027	0.923	24.30	0.26	0.319	0.267	0.33	0.53
18	24.63	0.14	0.782	0.001	23.29	0.45	-0.402	0.138	-1.34	0.59
19	24.55	0.20	0.604	0.017	24.47	0.28	0.428	0.112	-0.07	0.48
20	24.31	0.31	0.294	0.353	24.54	0.24	0.532	0.041	0.23	0.55
21	23.71	0.25	-0.317	0.270	23.90	0.29	-0.096	0.739	0.19	0.55
22	23.59	0.29	-0.381	0.178	23.45	0.29	-0.464	0.060	-0.14	0.58
23	24.48	0.15	0.585	0.010	24.37	0.30	0.343	0.252	-0.12	0.46
24	24.57	0.28	0.522	0.067	23.49	0.41	-0.364	0.245	-1.08	0.69

Table 4: Consistent differences in each of 6 hormones of circadian periods before vs. after consecutive full moons*

*See also Tables 2 and 3, studies that led to Figure 3B.

Table 5: Free-running circadian fading while coexisting lunar pull competes with 24-hour environment on a self-selected schedule (JFC)

Calendar date		PERIOD	AMPLITUDE
1: 1990/02/19	Lunar	24.872(24.830,24.914)	0.02513(-0.0070,0.0573)
to 1991/04/28	Compromise?	24.409(24.384,24.435)	0.04117(0.0089,0.0734)
	Free-running	24.222(24.210,24.235)	0.07921(0.0468,0.1116)
	Societal	24.008(24.004,24.011)	0.31605(0.2838,0.3483)
	Tidal	12.421(12.411,12.431)	0.02615(-0.0059,0.0582)
	Semidian	12.007(12.001,12.013)	0.04105(0.0090,0.0731)
2: 1991/04/28	Lunar	24.898(24.832,24.964)	0.12744(0.0707,0.1842)
to 1991/09/23	Compromise?	24.707(24.671,24.743)	0.25208(0.1973,0.3068)
	Free-running	24.488(24.434,24.541)	0.10274(0.0552,0.1502)
	Societal	24.011(23.992,24.030)	0.22758(0.1815,0.2736)
	Tidal	did not converge	—
	Semidian	—	—
3: 1991/09/23	Lunar	24.862(24.852,24.872)	0.34858(0.3089,0.3882)
to 1992/03/08	Compromise?	24.523(24.468,24.579)	0.06108(0.0212,0.1009)
	Free-running	did not converge	—
	Societal	23.997(23.984,24.011)	0.22362(0.1841,0.2631)
	Tidal	12.432(12.416,12.448)	0.04969(0.0106,0.0888)
	Semidian	did not converge	—
4: 1992/03/08	Lunar	24.942(24.896,24.989)	0.15133(0.0960,0.2067)
to 1992/07/14	Compromise?	24.451(24.394,24.508)	0.11847(0.0630,0.1739)
	Free-running	—	—
	Societal	23.987(23.967,24.006)	0.32099(0.2660,0.3760)
	Tidal	12.432(12.398,12.465)	0.04960(-0.0051,0.1042)
	Semidian	11.982(11.951,12.012)	0.05028(-0.0044,0.1049)
5: 1992/07/14	Lunar	24.789(24.782,24.797)	0.31836(0.2798,0.3569)
to 1993/03/11	Compromise?	24.474(24.438,24.510)	0.06218(0.0236,0.1008)
	Free-running	—	—
	Societal	24.009(23.997,24.022)	0.17892(0.1405,0.2173)
	Tidal	12.352(12.328,12.376)	0.02358(-0.0147,0.0619)
	Semidian	12.001(11.988,12.013)	0.04128(0.0030,0.0796)
All (3yr) data	Lunar	24.836(24.833,24.838)	0.10606(0.0854,0.1268)
1990/02/19	Compromise?	24.432(24.427,24.436)	0.05643(0.0357,0.0772)
to 1993/03/11	Free-running	24.260(24.252,24.268)	0.03253(0.0118,0.0533)
	Societal	24.001(24.000,24.001)	0.25443(0.2337,0.2751)
	Tidal	12.414(12.410,12.418)	0.01728(-0.0034,0.038)
	Semidian	11.999(11.997,12.001)	0.03204(0.0113,0.0527)

All available data were analyzed as a whole (bottom 6 rows) and then divided into five subspans according to visual inspection of characteristics of 24-h and 24.84-h fits in serial sections, suggesting similarities within the spans and differences among them. Initial τ guesses for the 6 nonlinearly searched τs were 24.84, 24.43, 24.26, 24.00, 12.42 and 12.00 h. Results were omitted if they did not converge to a τ fitted to the data, in which case the analysis was redone after removal of these components from the model, to yield results summarized herein. Some τs converged well but the CI of the A covered zero, as apparent from a negative sign inside the last column's first, fourth and fifth rows, for the case of lunar and tidal associations in the first subspan (top) where the societal 24-h day predominates. The lunar (double tidal) effects converge invariably thereafter. Note that overlaps of zero by the CI of the A are very small. The near-lunar (double tidal) cycle's A is invariably positive and in 2 of 5 sections has the largest A when the moon dominates over society in clinical health.

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INFRADIANS IN HUMAN BLOOD PRESSURE, HEART RATE AND BODY WEIGHT DURING 35 YEARS OF AGING

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Abstract. In once-daily morning measurements of systolic (S) and diastolic (D) blood pressure (BP) and body weight (BW) and in a 17-year series of heart rate (HR) of a treated hypertensive man (WRB), we assess putative infradian cycles (with periods, τs, >28 hours). We analyze separately the aging of the 7-day (septan) Midline-Estimating Statistic of Rhythm (MESOR) and amplitude by applying the nonlinearly extended cosinor to intermediate computations (imputations), by fitting 7-day cosine curves to consecutive non-overlapping 14-day sections of the original data. Some of the τs found are a putative mimicry of cycles in solar activity, but for causal relations a subtraction (and/or addition) approach will be essential and is illustrated for another case.
Background. Chronomics, a cartography of chronomes (time structures, consisting of rhythms, trends and chaos) in and around us, has yielded a few pages of an as-yet fledgling atlas of transdisciplinary rhythms that cover a wide range of frequencies: some are photic in origin, such as about 24-hour (circadian) and about-yearly (circannual) cycles, now broadly recognized as partly built-in entities in their own right; others are non-photic components found in particle radiation from the sun and the galaxy, partly in helio-geomagnetics, gravity, UV flux, and/or possibly in other measurable weather in extraterrestrial space.

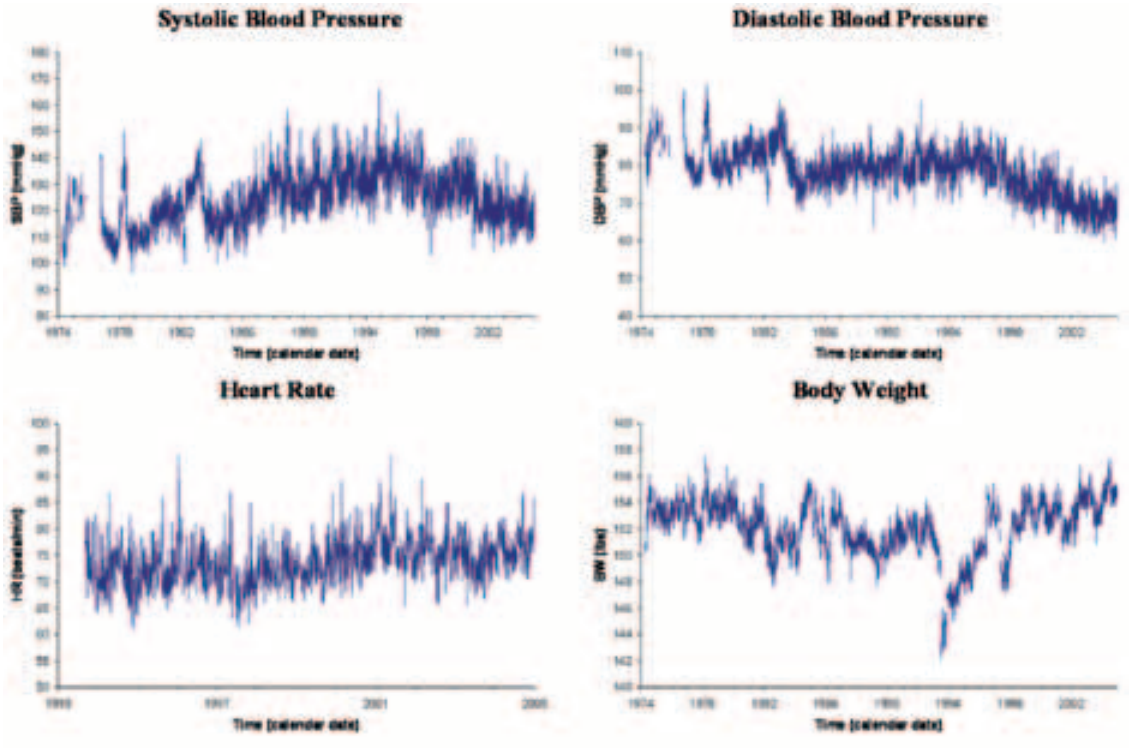

Figure 1. Time plots of original data of WRB cannot be interpreted in terms of the uncertainties of any τs characterizing them. © *Halberg*

Pairs of τs in two or more aligned time series, congruent insofar as they have some overlying or at least partly overlapping CIs (95% confidence intervals) of their τs are seen when these series are analyzed with the extended linear-nonlinear cosinor (1–3). Congruence is found, for instance, among helio-geomagnetic activity indices themselves and among some of these and vascular spectral components, notably in BP and HR (studied over decades around the clock), in the spectral regions, among others, of 1 cycle in I. about 7-days, the circaseptans (4); II. about 5 months, the quinmensal (5, 6); III. the transyears (longer than [beyond = trans] a calendar year) (7); IV. the Horrebow-Schwabe sunspot cycle of about 11 years (8, 9); V. a global cycle of about 17 years (10); VI. the Hale sunspot bipolarity cycle of about 22 years (11); and VII. the tridecadal BEL of about 30–40 years currently extensively documented (12–20). The uncertainties of these cycles are mapped as yet in only a few longitudinal around-the-clock series of measurements, and this investigation, to our knowledge is the first to do such cartography on single values/day, collected on awakening, subject to qualifications (19).

Earlier (7, 21–24; cf. 25–28), we had focused upon transyears (components with τs longer than one year but shorter than 1.9 years). These can be far-transyears (1.2 years ≤ [τ - CI] < [τ + CI] < 1.9 years) with the CI of τ within these limits or near-transyears (1.00 year < [τ - CI] < [τ + CI] < 1.20 years) with the entire CI of τ within these limits. We had also focused on quinmensals (5, 6), slightly shorter than a half-year, predicted by Wolff (29),found by other physicists in solar flares (30, 31). Congruent transyear τs of the solar wind's speed (33, 34) were detected in physiology (22–24, 35, 36). They were discovered in sudden cardiac death in some locations and in cardiac arrhythmia during some time spans during some solar cycle stages (7, 37). Near-transyears found in biology (37) prompted us to discover them in the solar magnetism, solar wind and geomagnetics (38; cf. 37).

Results after 30 years (39). A physician (WRB) began self-monitoring BW, SBP and DBP when he was a few months short of 52 years of age and continued for 35 years. During the most recent 17 years, he also recorded his HR. WRB had started hypotensive therapy (chlorthalidone 50 mg/d) in June 1972 and had a good, sustained BP response. He began recording frequent serial BP values on graph paper in April 1974, since he planned to reduce the dosage and wanted to know the effects of such reduction. This graphing of his data helped him to arrive at self-medication decisions. A first set of extended cosinor analyses was presented earlier (39). Here, we focus on the broader spectrum, including the transtridecadal BEL noted previously.

Table 1: Para-tridecadal periods with the concomitant fit of a linear trend in the 30-year series*

Variable (units)	Period (years)	Double amplitude, 2A
Diastolic blood pressure (mmHg)	31.68 [23.94, 39.42]	9.24 [5.26, 13.22]
Body weight (lbs)	41.23 [31.25, 51.20]	6.62 [3.60, 9.62]

* Decreasing trend in DBP, increasing trend in BW (not shown).

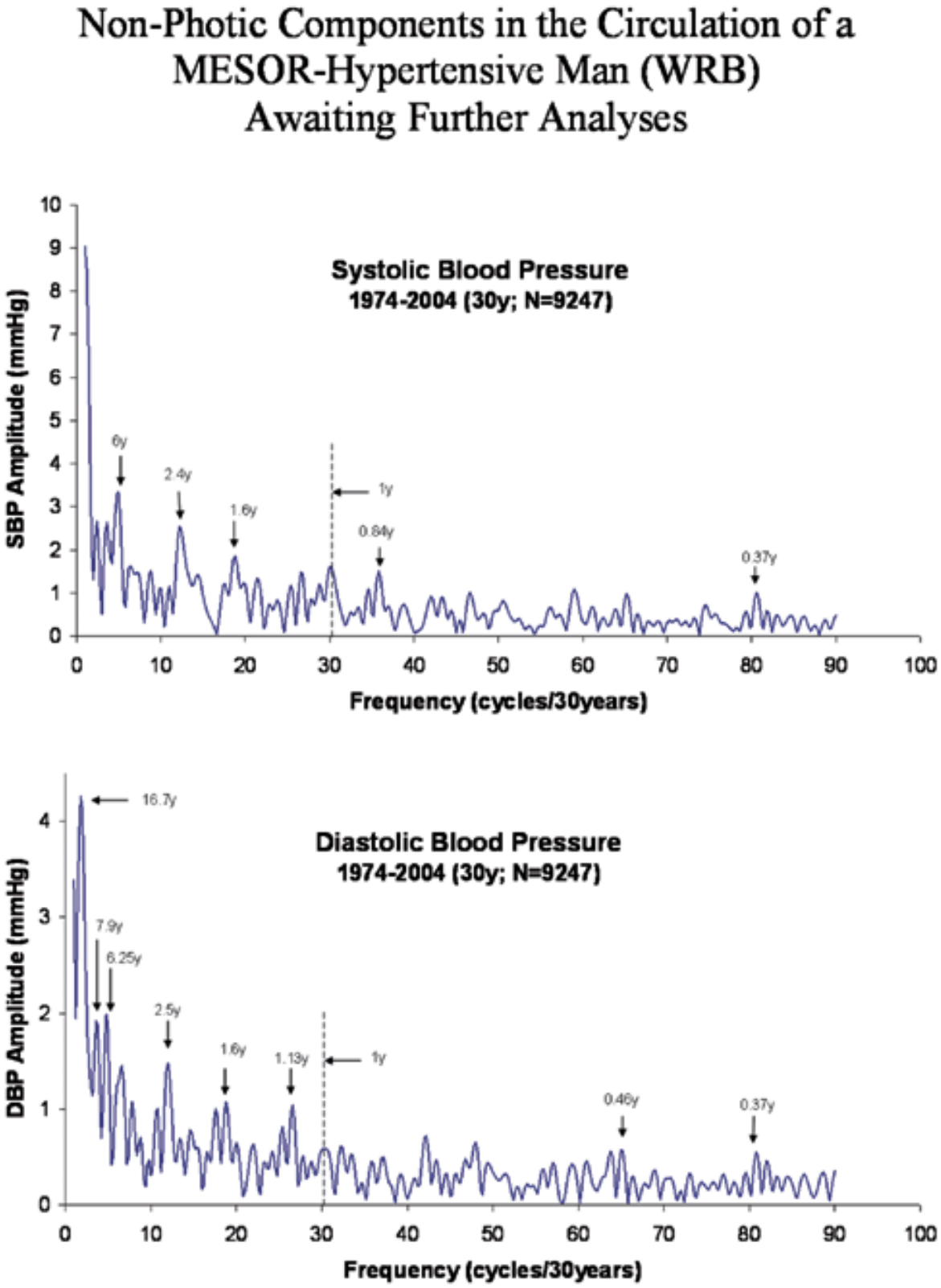

Figure 2. Linear least squares spectra of blood pressure of WRB: first 30 years. © Halberg.

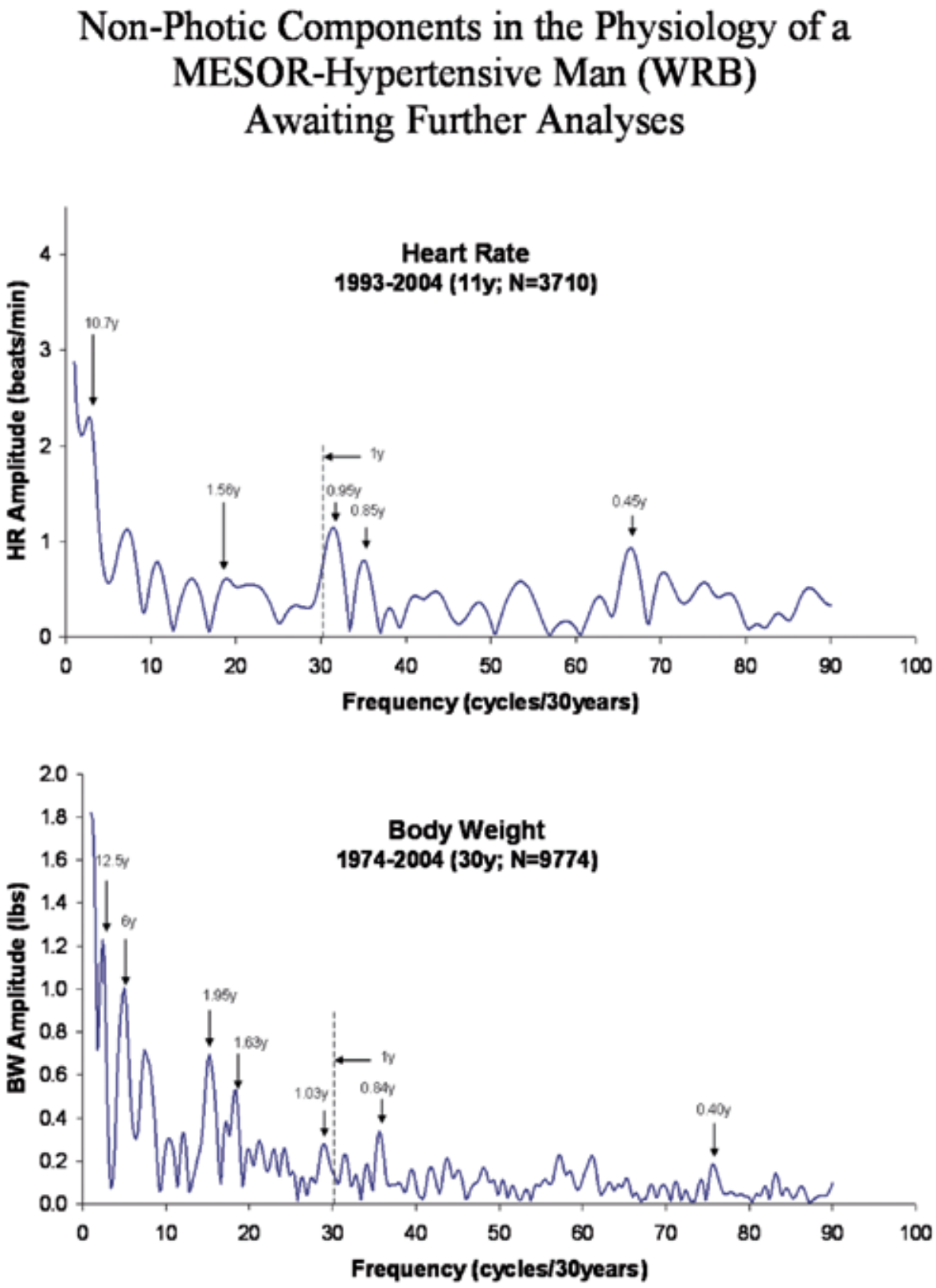

Figure 3. Linear least squares spectra of heart rate and body weight of WRB: first 30 years. © tHalberg.

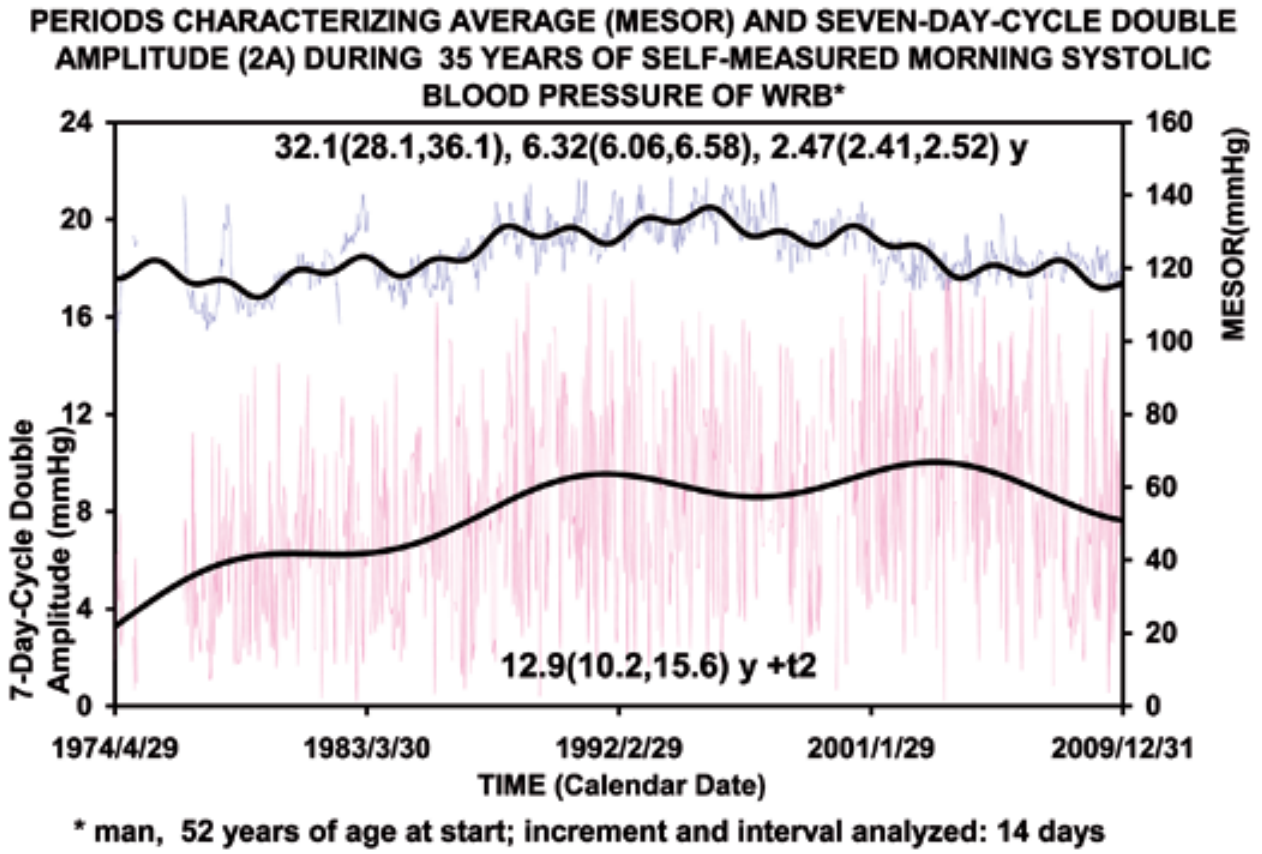

Figure 4. Different periods approximate the time course of the MESOR (upper curve) and the double circadian amplitude (lower curve) in systolic blood pressure of WRB during 35 years. © Halberg.

The about 30-year component in SBP and DBP and a component also qualifying as a para-tridecadal by a CI of the τ covering part of the 30–40 year range constituted an exciting new finding on a revisited forgotten yet vindicated BEL periodicity (33; cf. 5–13, 34, 35).

Figure 1 displays the original data covering the first 3 decades for SBP, DBP and BW. Eyeballing sees changes that differ in BW from those in BP, but objective analyses are needed, although the naked eye rules out linear increases or decreases with age. Accordingly, Figures 2 and 3 show cosinor spectra. Figure 2 (top) shows for SBP, among other components, a far-transyear of 1.6-year length, with an amplitude numerically larger than that of the calendar-yearly component, which is also present in the least squares spectrum. As seen in Figure 2 (bottom), DBP also shows a far-transyear of 1.6-year length and a near-transyear of 1.13-year length, both much larger in amplitude than the calendar-yearly component. The most prominent component in DBP has a τ of about 16.7 years, the possible signature of a global Makarov and Sivaraman (10) cycle. A cis-half-year, as the quinmensal (about 5-month) component was originally called, is further seen in SBP (Figure 2, top) with a τ of about 0.37 year as well as in DBP along with a second quinmensal of 0.46-year length. For HR, Figure 3 (top) shows a relatively broad band in the spectrum with a peaklet at 1.56 years, and another component in the neighborhood of the calendar year, a near-cisyear, and further a quinmensal at a τ of 0.45-year length. BW (Figure 3, bottom) shows a far-transyear of 1.63 years and a near-transyear of 1.03 years, along with a peaklet at 0.4 year, a quinmensal, and no calendar-yearly component. Other anticipated non-photic components seen in Figures 2 and 3 suffice to suggest that non-photic effects were prominent in several variables in the subject investigated, awaiting nonlinear analysis.

The putative mimicry of a circadecadal Horrebow-Schwabe cycle in HR is of 11.7 years, whereas in BW it is of 12.5 years, Figure 3.

Linear-nonlinear analyses by the extended cosinor (1–3), using 35 years as trial τ, yielded a clear tridecadal spectral component only for SBP, the τ [CI] being estimated as 30.56 [29.24, 31.87] years and the double amplitude (2A) as 18.06 [16.92, 19.20] mmHg, hardly a trivial extent of change. For BW, the τ was 28.14 [26.66, 29.63] years and the 2A was 3.58 [3.34, 3.84] lbs. Analyses did not converge for DBP, perhaps because this variable was characterized by a decreasing trend with age, apparent in Figure 4. Using a slightly different model that includes a linear trend with the BEL cycle and a trial τ of 32.17 years, results were compatible with the presence of a BEL cycle in all 3 variables investigated on the 30-year series, as shown in Table 1, since for body weight the CI of τ is well within the 20–30-year range.

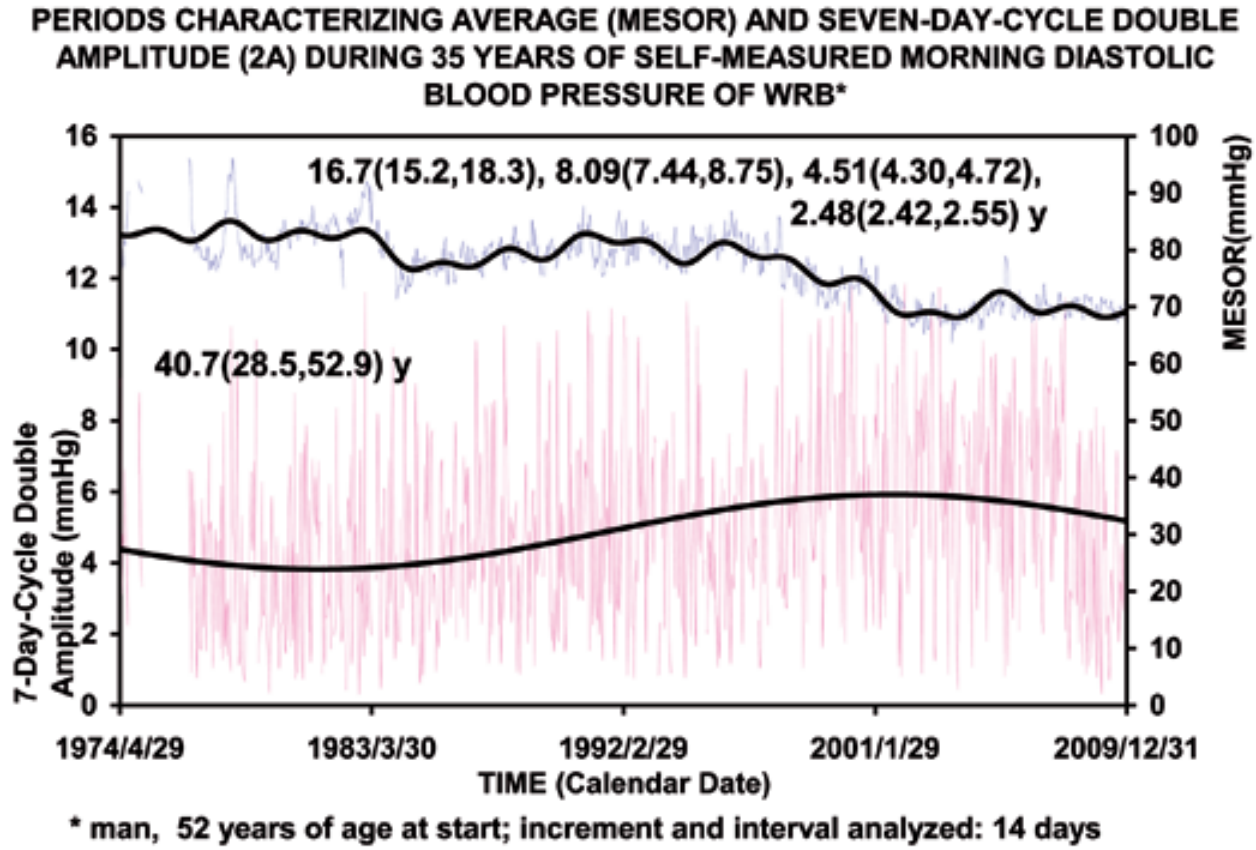

Figure 5. Different τs approximate the time course of the MESOR (upper curve) and the double circadian amplitude (lower curve) in diastolic blood pressure of WRB during 35 years. © Halberg.

Results after 35 years. Table 2 summarizes analyses on the original data of 30 years of morning measurements that included 3 components with a τ whose CI overlapped the 30–40-year range. This para-tridecadal τ could be reproduced after the addition of 5 additional years of data in the MESOR (M) of SBP. A para-tridecadal remained prominent, as also seen by the naked eye in Figure 4 (upper curve), along with a 6.3-year τ (which could mimic a third harmonic of the about 22-year Hale cycle and a 2.47-year τ that was also found in the MESOR of DBP. An about 12.9-year τ was found with a parabolic trend (t^2) in the 7-day (septan) amplitude (used instead of the circadian amplitude that could not be determined in single measurements/day).

Table 2A: Analyses on a time series of 30 years length

	29 Apr 1974 [HR: 13 Sep 1993] - 31 Dec 2004 (~31 years; HR: ~11 years)	
	Trial τ: ~35 years	
Variable	τ [95% CI]	A [95% CI]
SBP	30.56 [29.24, 31.87]	9.03 [8.46, 9.60]
DBP (+ LT)	31.68 [23.94, 39.42]	4.62 [2.63, 6.61]
HR	—	—
BW (+ LT)	41.23 [31.25, 51.20]	3.31 [1.80, 4.81]
	Trial τ: 15 years	
	τ [95% CI]	A [95% CI]
SBP	12.55 [11.73, 13.37]	2.66 [1.93, 3.39]
DBP	16.29 [15.79, 16.79] converges to 31.68 years with LT	4.29 [3.89, 4.68]
HR HR (+ LT)	12.68 [10.68, 14.68] 5.90 [5.34, 6.45]	2.25 [1.76, 2.75] 1.70 [1.13, 2.27]
BW BW (+ LT)	12.52 [12.18, 12.87] 12.58 [12.20, 12.96]	1.23 [1.08, 1.38] 1.23 [1.07, 1.39]
	Trial τ: 7 years	
Variable	τ [95% CI]	A [95% CI]
SBP	6.14 [6.00, 6.28]	3.39 [2.66, 4.11]
DBP DBP (+ LT)	6.21 [6.05, 6.37] 6.26 [6.08, 6.44]	2.01 [1.55, 2.47] 1.55 [1.17, 1.94]
HR HR (+ LT)	converges to 12.68 y ears converges to 5.90 years	
BW BW (+ LT)	6.06 [5.96, 6.16] 6.09 [5.98, 6.19]	1.01 [0.86, 1.17] 1.05 [0.89, 1.22]

Table 2B: Analyses on a longer 35-year series (5 additional years)

	29 Apr 1974 [HR: 13 Sep 1993] - 31 Dec 2009 (~36 years; HR: ~16 years)			
	Trial τ: 35 years		Trial τ: 35 years + linear trend (LT)	
Variable	τ [95% CI]	A [95% CI]	τ [95% CI]	A [95% CI]
SBP	31.92 [30.38, 33.47]	8.06 [7.55, 8.57]	—	—
DBP	—	—	22.06 [21.23, 22.90]	2.85 [2.51, 3.18]
HR	22.36 [17.96, 26.75]	2.48 [2.12, 2.84]	—	—
BW	24.23 [23.62, 24.84]	1.77 [1.64, 1.89]	24.40 [23.71, 25.09]	1.76 [1.63, 1.90]
	Trial τ: 15 years		Trial τ: 15 years + LT	
	τ [95% CI]	A [95% CI]	τ [95% CI]	A [95% CI]
SBP	13.32 [12.35, 14.29]	1.83 [1.17, 2.49]	13.87 [12.67, 15.07]	1.76 [1.06, 2.46]
DBP	18.40 [17.88, 18.92]	4.27 [3.86, 4.87]	Converges to 22.05	
HR	converges to 22.36		—	—
BW	13.25 [12.91, 13.59]	1.14 [1.01, 1.27]	13.24 [12.84, 13.64]	1.14 [1.00, 1.29]
	Trial τ: 7years		Trial τ: 7years + LT	
	τ [95% CI]	A [95% CI]	τ [95% CI]	A [95% CI]
SBP	7.92 [7.58, 8.85]	1.99 [1.35, 2.63]	7.60 [7.28, 7.91]	2.11 [1.44, 2.78]
DBP	7.44 [7.18, 7.69]	1.62 [1.17, 2.06]	6.34 [6.18, 6.50]	1.31 [0.97, 1.66]
HR	7.62 [7.00, 8.24]	1.26 [0.83, 1.70]	5.69 [5.32, 6.05]	1.30 [0.88, 1.71]
BW	6.65 [6.55, 6.76]	0.92 [0.79, 1.06]	6.62 [6.51, 6.73]	0.92 [0.77, 1.97]
	Trial τ: 6 years		Trial τ: 6 years + LT	
	τ [95% CI]	A [95% CI]	τ [95% CI]	A [95% CI]
SBP	6.08 [5.94, 6.20]	2.84 [2.19, 3.48]	6.02 [5.89, 6.15]	2.94 [2.26, 3.62]
DBP	6.04 [5.85, 6.21]	1.46 [1.00, 1.91]	6.34 [6.18, 6.50]	1.31 [0.97, 1.66]
HR	converges to 7.62		5.69 [5.32, 6.05]	1.29 [0.88, 1.71]
BW	converges to 6.65		converges to 6.62	

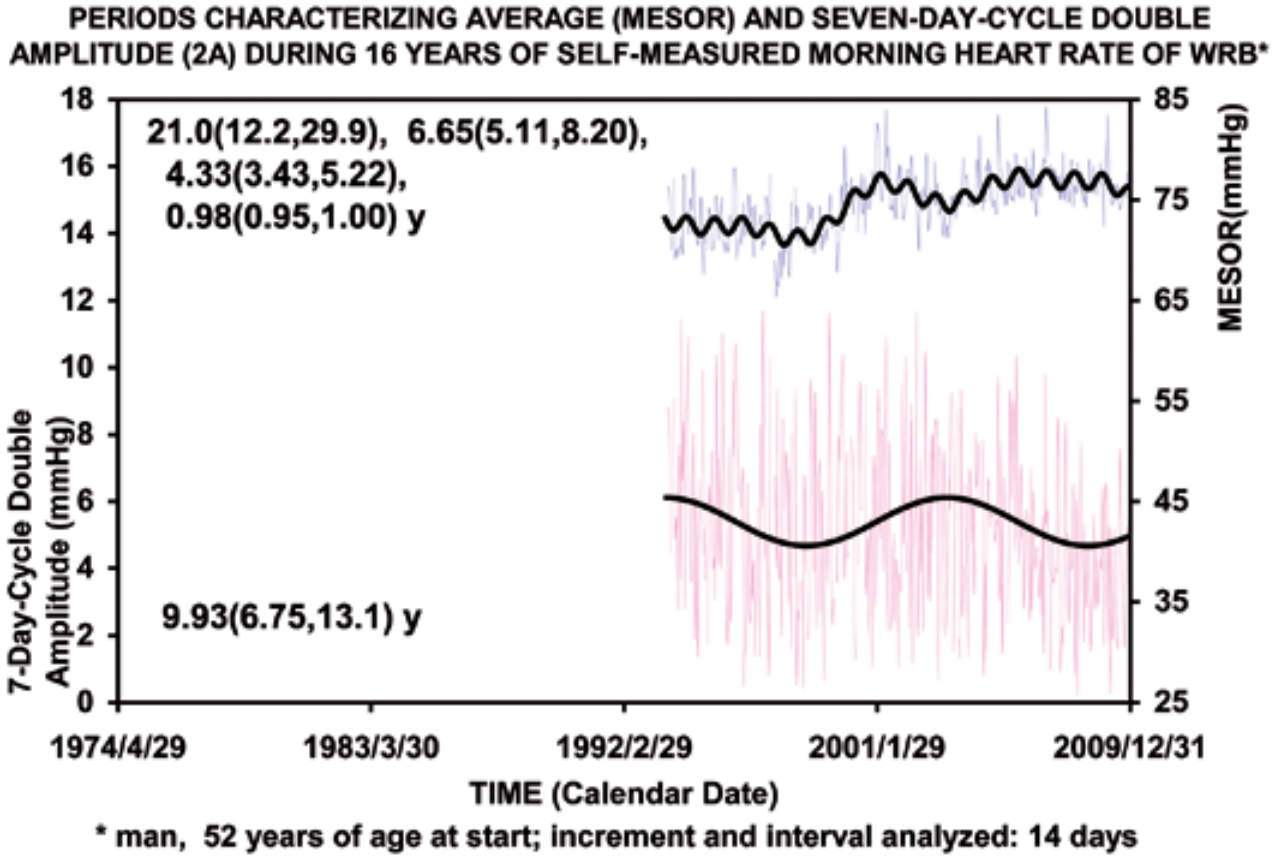

Figure 6. Different τs approximate the time course of the MESOR (upper curve) and the double circadian amplitude (lower curve) in heart rate of WRB during 35 years. © Halberg.

In the (septan) double amplitude of SBP, the trend could be part of a long cycle. For DBP (upper curve of M), Figure 5, a τ longer than the ~11-year Horrebow-Schwabe and shorter than the about 21-year Hale cycle predominated, possibly a 16.7-year signature of the Makarov and Sivaraman global cycle (10). For those in the physics community who have never heard of Makarov and Sivaraman, the finding of their τ in the biosphere could be taken as evidence for validating this τ which may also be found as a peaklet in sunspot numbers. In the 7-day double amplitude of DBP, a para-tridecadal cycle seems possible. The M in DBP showed added τs, some of which could be harmonics of the Hale and Horrebow-Schwabe cycles. In the shorter series of HR, a Hale cycle mimicry characterizes the MESOR, along with its third harmonic, a further possible harmonic of the Horrebow-Schwabe cycle and a yearly component. The double amplitude of the 7-day cycle shows a putative signature of the Horrebow-Schwabe cycle, Figure 6. Figure 7 shows a multitude of τs for BW, possibly related to a multitude of factors.

The limits of a para-tridecadal cycle have been redrawn to specify that it suffices if the CI of the τ approaches the 30–40-year range, the interpretation of a τ of 25.9 years, with CI extending to 28.7 years, should prompt the search for concomitantly congruent environmental τs. Particularly noteworthy, in the M of BW, are a far-transyear of 1.70 years and a 1.04-year near-transyear with a CI that does not overlap the precise yearly τ in WRB, who happens to be very sensitive to cold and thus to the seasons. The 7-day double amplitude of BW in turn exhibits a Horrebow-Schwabe cycle mimicry. With circadecadals or cycles that are multiples and submultiples of 10 years, which might be signatures of the physical solar system, extreme caution is indicated by reliance not on point estimates of the τ, but only on CIs of τs and the putative global τ between the decadal and didecadal one makes

almost every τ with a wide CI fit a solar equivalent so that addition and subtraction approaches become indispensable; until they are available, the description of mimicry does not allow any inference of causal relations among external and internal periodicities.

Discussion. The yearly progression of seasons in a mid-continental climate is anticipated to have a profound effect on our lives, and is expressed in some measures of body function, as in the HR MESOR in Figure 6. Before doing any statistical analysis on the question of the importance of the about-yearly rhythm, WRB felt sure from taking many measurements over 30 years that on a cold day, when his body felt chilled, his BP would tend to be higher than otherwise. Despite modern heating/air conditioning systems, when it is cold outside, he often feels cold inside as well. For at least as long as he kept records, moderate to marked winter chilling of his body resulted in Raynaud's phenomenon, spasms of the arterioles

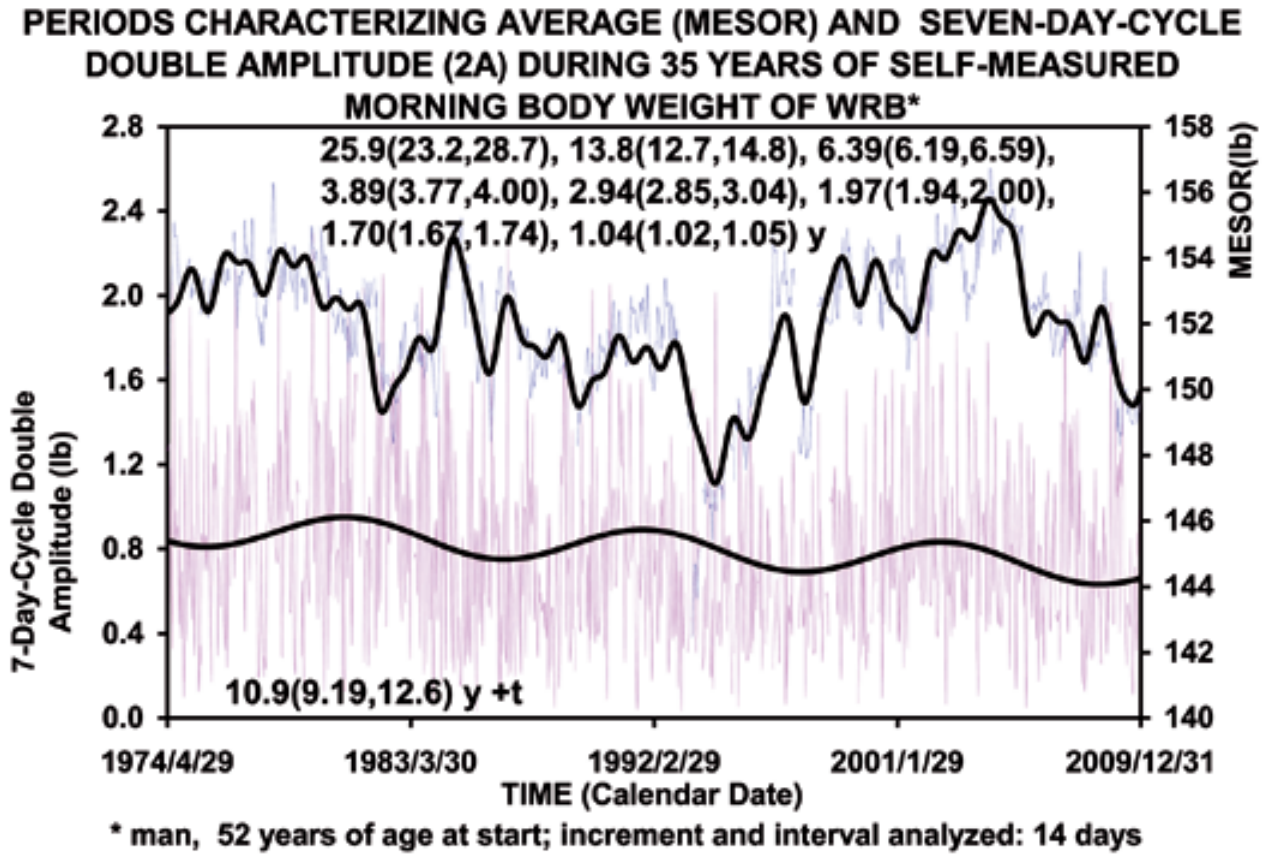

Figure 7. Different τs approximate the time course of the MESOR (upper curve) and the double circadian amplitude (lower curve) in body weight of WRB during 35 years. © Halberg.

in some or all of his fingers, leading to a dead white appearance lasting from minutes to (rarely) hours after warming up. This never occurred while he took BP readings, but is symptomatic of his autonomic nervous system's sensitivity to cold. This seasonality notwithstanding, transyears can be present, and overall no yearly component was detected in a global analysis of WRB's BW and not even in the 7-day amplitude of his HR. In a MESOR (chronome-adjusted mean)-normotensive younger colleague who started measurements at 20.5 years of age (RBS), the yearly component was most prominent in SBP and DBP. In RBS, an about 33-year cycle has been documented (18; cf. 16, 17, 19, 20). In FH (7), another elderly man (also under hypotensive treatment), a circannual component was absent in SBP, a variable characterized only by transyears.

In WRB's series, the BEL cycle is consistently demonstrated for SBP and DBP. The BEL was originally documented in climate as an alternation of hot, dry and wet cold spans that was said to have driven people to emigrate from Europe to North America, and westward within North America (40–42). It persists in an analysis of temperature data measured since Brückner's time to that of this writing (20), and is thus pertinent as a background to discussions of climate change. It relates to economics (43) and to military-political affairs (44) as well as to international battles (45) and thus to diseases of society, as our meta-analyses (20, 23) of invaluable data compiled by the scholarship of Alexander Leonidovich Chizhevsky (44) and Raymond Holder Wheeler (45) reveal. It is noteworthy that if the τs of the physical solar system are built into the biosphere, they could be desynchronized from their environmental counterpart. Whether synchronized or not, a subtraction-addition approach is indicated to see whether the physiological spectral component is damped when the environmental counterpart happens to be lost or amplified reappears or increases in amplitude (7).
Before generalizing from two elderly cases, WRB and FH (20), and two younger adults at start of monitoring, RBS and YW (46), many more time series will have to be collected, in the footsteps of Santorio (47), who hung a scale from the ceiling of a room in his house, on which he reportedly carried out all his activities including eating, sleeping, work, excretion and sex. His data, including those on his changes of weight, led to the discovery of insensible perspiration, could not be retrieved. RBS's, FH's, YW's and WRB's data in turn allow the demonstration of otherwise "insensible" effects of the cosmos in our physiology. These results can be complemented not only by nonlinear analyses on FH's data (1987–2009) but also by a remove-and-replace approach, as presented elsewhere (7). A major question revolves around selective congruence. Do different physiologic variables in RBS, YW, WRB and FH show congruence with environmental cycles of differing lengths during the same multidecadal spans, and what may putative underlying mechanisms be for this selective assortment (23, 48)? An approach by remove-and-replace, or at least by subtraction and/or addition of intensity, is recommended for all studies on solar-human associations and remains to be done in our data and in those of others whenever possible (49).

Acknowledgement and comment
All his co-authors thank Dr. William R. Best (WRB), not only because the data analyzed herein are his. We are pleased to clarify at the outset that WRB's motivation, which has now continued for over 3.5 decades, constitutes a model for the public at large, when some voices suggest that one need not measure blood pressure at all and instead could be treating all comers with antihypertensive drugs regularly. We are in the same situation as diabetology was in the middle of the 20th century, when a lonely voice in Iowa advocated a strict control of blood sugar at one extreme, while others in New York disregarded all control of glycemia at the other extreme, and the majority were in the middle of the road, as is the case today once we substitute "Minnesota" for "Iowa" and "pressure" for "glucose". The time of monitoring of vascular variability disorders is also likely to come.
The senior author (FH) is further indebted to WRB for his publication of his studies on the response to epinephrine in 1952 (50) wherein he documented a decrease in the count of circulating eosinophil cells in patients who had had their adrenals removed, a finding that torpedoed the epinephrine test of adrenal cortical function. The latter finding was in agreement with studies of the same response to epinephrine (decrease in eosinophil count) in adrenalectomized and gonadectomized mice of both sexes, where ectopic adrenal cortical tissue next to the vertebral column and in the large ligaments or in the scrotal fat had also been removed by FH.
FH reported his inability to confirm the epinephrine test in mice to his then department head, the late George W. Thorn, Hersey Professor of Medicine at Harvard. Thorn admired FH's sticking to his guns, but said that all the others could not be wrong. In the case of the epinephrine test, the majority at the

time was clearly wrong (50). So are all those who fail to recognize Vascular Variability Disorders (VVDs). We need not repeat the maladies of the past, such as the failure to scrub before surgery. Measuring and interpreting chronobiologically blood pressure series may be cumbersome, like scrubbing for antisepsis. Nonetheless, in a computer era self-surveillance could soon be implemented by everyone continuously, whether or not he has a VVD and as a feature of universal preventive health care it may allow even the mapping of infradian, e.g., transtridecadal cycles (51) and perhaps some new information thereby concerning the health of individuals and societies (52, 53).

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BLOOD PRESSURE AND HEART RATE VARIABILITY GAUGING HEALTH, THE MIND, LOADS AND HUMAN AFFAIRS (ASSESSED BY A SYSTEM FOR A CHRONOBIOLOGICALLY-INTERPRETED ABPM REPLACING THE BLOOD PRESSURE CUFF IN PROVIDERS' OFFICES)

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Preamble

It is an anachronism to do no more than determine, at each physical examination, what the blood pressure (BP) or heart rate (HR) may be at a given moment. We need not ignore what happened inside or outside the physiological range in the past and, in particular, since the person was last seen, when for instance there was a change in medication. BP behavior in any situation encountered in life is a gauge of load (1). Eventually, preventive cardiology, as part of a wider transdisciplinary science and a still broader culture (2), may recognize that monitoring the ECG around the clock and for longer than a day or even a week need not be reserved for patients near or in fibrillation and that a continuous registration of vital signs from womb to tomb has advantages that call for proper tools such as a polychronor planned and developed in part by Siemens in the 1970s (3). Technology that records HR from the ear is already available (4, 5), and in-the-ear unobtrusive devices have been proposed for recording BP and the EEG as well (6).

Figure 1 shows elevations in BP while we think hard, drive through a tornado warning, or exercising (7). All of these responses to such activities and any others require a reference standard for deciding whether a value is elevated or within limits. These norms change predictably along the 24-hour scale, as seen in Figure 1, as well as along other, notably much longer as well as shorter scales. Some variability is predictable and assessable, as we map, in addition to the about 24-hour variation (Figure 2, left) and about-yearly rhythms (Figure 2, middle), cis-half-years, about-half-yearly rhythms, near-transyears and far-transyears, as well as cycles with periods of about one to several decades.

A systematically changing set of reference values is best obtained for a given person during wellness. This is the most immediate reason for continuous monitoring by everybody, once unobtrusive, affordable instrumentation becomes available. This availability at low cost depends solely on the recognition of the need, since the technology is available, to monitor BP for the purpose of surveillance. The BP monitoring of mice in laboratories, primarily of pharmaceutical companies interested in developing new drugs, can and should be extended for those who care to use these drugs. An FDA-approved automatic monitor of BP on the wrist is already available, albeit at an all-too-high cost (8). Another, no less significant reason for monitoring is that our environment also changes and its dynamics can be assessed quantitatively, as many aspects already are. We advocate that human and other animals' BP and HR be also monitored for continued surveillance of environmental effects. Both

the physical and social time structures around us impart their features to our healthy physiological and altered pathological and epidemiological dynamics (9). Chronomes (time structures; from Gk chronos = time and Gk nomos = rule) consist of cycles embedded in and arising from deterministic and other chaos and trends. Some of the trends may be parts of cycles longer than the time series on hand. The cycles are aeolian in space and time, so named after Aeolus, mythical Greek ruler of the winds. They have characteristics that change as a function of time, their amplitude increasing and decreasing, sometimes below the noise level, and the frequency drifting, sometimes to the point of merging with other neighboring signals. They hence require analyses in space and time, i.e., they have to be specified for geo- or cosmo-graphic location in space and analyzed in the longest available time series as a whole (globally) as well as in sections (locally in time).

The sections chosen for analysis are best systematically varied in length, preferably by complementary methods or sets of methods, that combine both aims glocally, i.e., GLObally and loCALLY. This can be done on the one hand by varying the parameters of a single approach, e.g., the interval lengths in moving spectrograms (10) or the time-frequency parameters of wavelets (11), or, on the other hand, as a set of multiple methods such as the global extended linear-nonlinear cosinor with gliding spectra and with chronomic serial sections. Preferably, some redundancies not withstanding, all these methods may well be used.

All of the cycles tested thus far are transdisciplinary, found in the lithosphere and biosphere, including an anthroposphere. We propose that they can serve for a further step, namely to organize Vernadsky's noosphere into a chronousphere (portmanteaued from Gk chronos = time, Attic Gk nous = mind, and Gk sphairos = sphere or, in our context, also globe) (2). The transdisciplinary cycles constitute an extension of the electromagnetic cycles with congruent, e.g., overlapping CIs (95% confidence intervals) of their periods, which offer themselves as organizing features, constituting a system.

Any physical, biological or other variable can be studied in a general as well as specific diagnostic or therapeutic medical context. In the general context, a variable can be informative with respect to many human and environmental affairs (2). Such a broad view is particularly warranted in the case of BP and HR. One of us (FH) first learned about the ranges of variability in the counts of certain blood cells that stain with a pink dye (eosin) (12). Next, he mapped the variability of epileptic seizures and electroencephalograms, and then after solving several puzzles, had the opportunity to be first in documenting the about 24-hour rhythms of RNA and DNA formation (13), at a time when nucleic acid was believed to be THE constant feature of organisms (12). What started with blood cell counts resulted in scientific tools, if not disciplines, as branches of a unified science (2):

1. Chronobiology is the study of time structures in living matter. Time structures in and around us consist of deterministic and other chaos, trends and cycles (14), the former two components contributing to the variability of the latter. In physiology, cycles lead us into the normal range, which is otherwise covered by the curtain of ignorance of homeostasis, Figure 2. Rather than following the "constancy" of the aging Claude Bernard (15), we agree with the younger Bernard's recognition of the "extreme variability of the internal environment" as one of his major discoveries (in response to an inquiry by a journal) (16). Variability, when present, serves for new diagnoses that single spotchecks cannot detect, Figure 3, and renders old diagnoses less unreliable. Abnormal variability in BP and HR is resolved by computer in time series collected automatically in a proposed cyber-healthcare (17), as suggested by others for the 2020s without specifically proposing the replacement of single spotchecks by continuous monitoring (18). This has been implemented for BP and HR in the light of data from the 20th century (19) that recognized a high risk of a stroke occurring within 6 years associated with a circadian overswing, exceeding the risk of a high BP. The goal of determining and treating harbingers of severe cerebro-, cardio-, reno-vascular disease (CVD) has been implemented as a model for elsewhere in two Japanese towns, Urausu and Tosa City, by Prof. Kuniaki Otsuka

(20–23), beyond the plans of the former mayor of Roseville, Minnesota, Dan Wall (24). Without clinically applied chronobiologic diagnoses, many millions worldwide (25) with Vascular Variability Anomalies (VVAs) (more than those with only high BP, also a VVA) are at a high risk of CVDs, comparable to (and, in particular, in the case of coexistent VVAs, much larger than) the risk of CVD associated with a high BP not complicated by other VVAs (14, 17, 26). The promise of chronobiology lies in the prevention of personal cataclysms such as massive strokes within 6 years (Figures 4A and 4B) that otherwise, as in current practice, remain undetected.

2. Chronomics aligns and studies interactions among time structures in and around us by a remove-and-replace (or at least by an addition-and-subtraction) approach, done by the sun at a certain frequency while recording any amplification or damping of a corresponding biospheric frequency component. Without clinically applied chronomics, the mirroring of environmental, including solar and interplanetary cycles in the human circulation would have remained unknown (9). The promise of chronomics lies in clarifying factors underlying human-made (9, 27) and natural (28) cataclysms, in order to develop countermeasures to disasters such as crime, terrorism or war, or to evade natural disasters like earthquakes, preferably by the study of data collected in chronobiology for personal self-surveillance (17).

3. Chronobioethics. Diseases of nations, such as international battles in the past 2556 years, exhibit periods that are counterparts of cycles in the solar system (27), as noted for military-political affairs by Alexander Leonidovich Chizhevsky (28–33) and Suitbert Ertel (34). The demonstration in BP of about 21-year Hale (35) bipolar cycles can be a starting point for focus on ills of society by focus on individuals for chronobioethics. Just as a micro-organism can multiply to produce a lethal toxin, so can a mentally ill individual, by infecting a population, produce both crime and terror. Starting with focus upon the psycho-physiological mechanisms of cycles underlying diseases of nations, complex relations will have to be resolved, perhaps the major task of applied societal biomedicine, if humanity is to meet the extremist challenges of our time.

Vascular Variability Anomalies (VVAs)

Transient circadian VVAs can be physiological responses to tasks and encounters in everyday life (1). They are best analyzed glocally, that is, a 24-hour cosine curve is fitted to 7-day or longer BP and HR profiles as a whole (globally) and further to 24-hour or systematically longer sections (locally). Local VVAs on single or a few days are more likely responses to transient loads, Figure 5, than global VVAs that may occur beyond the span of time during which long-term loads persist, Figure 6. Monitoring BP and HR should be accompanied by a diary to detect the association of loads with VVAs, so that the loads yielding strain are identified and activities associated with them are avoided as far as possible. Globally, single or a few days of a VVA (e.g., out of a 7-day record) are often outweighed by acceptable days without VVAs when the record is analyzed as a whole. VVAs become Vascular Variability Disorders (VVDs) when they persist after the cessation of short- and long-term loads in several consecutive glocally analyzed 7-day profiles.

When several VVDs coexisted in a first 6-year study on 297 patients, they raised the risk of a severe event such as a stroke in 6 years from less than 5% to up to 100% (17, 19; cf. 25, 26). In this study and others, the numbers of subjects involved compensate to some extent for the individual record's brevity (of 48 hours). Chronobiometry, on a small scale, detected these abnormalities in individuals' records worldwide via a project on The BIOsphere and the COSmos, BIOCOS (corne001@umn.edu). The development of affordable unobtrusive instrumentation and a manned international website for education, analyses and research can greatly extend these endeavors on a much broader scale, Figure 7. Whereas adverse events in the first study of severe outcomes such as brain or heart attacks or kidney disease were assessed (17, 19), in a second study, around-the-clock BP and HR profiles were

complemented by an assessment of the left ventricular mass index (LVMI) as a surrogate outcome measure (26). In the second study, one-fourth (24.6%) of 1,177 untreated, presumably normotensive subjects had MESOR-hypertension (MH), an elevation above gender- and age-matched peer limits of the MESOR (M, Midline-Estimating Statistic Of Rhythm, usually more accurate and more precise than the arithmetic mean), obtained by curve-fitting with the cosinor, also yielding other characteristics that can be deviant. Among the 289 subjects diagnosed with MH on the basis of 24-hour records, 137 (47.4%) had one or more VVAs.

The current screening in health care fails to detect VVDs other than hypertension. Some VVDs can occur in the absence of high BP, in very few patients with excessive pulse pressure (EPP), in more patients with a circadian overswing (CHAT, short for Circadian Hyper-Amplitude-Tension), in yet more with odd circadian timing (ecphasia), and in 87 patients with a deficient HR variability (DHRV), that is for a total of 182 subjects, representing 15.5% of the study population (which could amount to 10.5 million people in the US population). In a third study, with survival as outcome, summarized 28 and 42 years after the examination (36), those with a circadian overswing (CHAT) were all dead when some of those without this VVD were alive (P=0.011), Figure 8.

Consensus of Brno

On the basis of these three and other investigations, a consensus was guided by two preeminent cardiac physiologists, both university department heads, one (Thomas Kenner) also a president of the University of Graz (Austria), the other (the late Bohumil Fiser) a Czech minister of health and WHO board member. It documents the great limitations to any inference concerning the individual of a chronobiologically-uninterpreted record from ambulatory BP monitoring (ABPM) covering only 24 hours. The consensus advocates for everybody in health, for load assessment, continuous, preferably lifetime BP and HR monitoring by replicated chronobiologically-interpreted (C)-ABPM (17). Once the diagnosis of a VVA is made, a change in lifestyle is indicated. In the case of a VVD, non-drug or drug treatment is recommended, again with continued monitoring. Sometime, in persons receiving hypotensive medication, a change in medication can eliminate the VVA. Hence, in the case of all hypotensive drug use, systematic change in treatment kind and timing for its optimization is recommended first, and thereafter, C-ABPM is continued for surveillance of treatment effects. The consensus concluded that the BP cuff in the provider's office or in the care recipient's home is to be replaced by a system of chronobiologic monitoring, preferably via a cell-phone, for assessment of strain and of CVD antecedents, for the objective optimization of drug or other treatment, and thereafter for treatment surveillance. The aim of all anti-hypertensive treatment is to return any and all altered BP or HR characteristic, as soon as detected, into the acceptable range.

The consensus implements the desire of pioneers

In 1904, Theodore C. Janeway (37), an opinion leader at Johns Hopkins University (Baltimore, Maryland, USA), concluded that "… 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 [note plural]. 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". Indeed, before Janeway, Zadek (38, 39) had data allowing the cosinor validation of about 3.5- and 7-day as well as daily variation (40). The late Frederic C. Bartter (41) (of Bartter syndrome fame; director first of the Hypertension-Endocrine Branch of the [US] National Institutes of Health [NIH] and later of the NIH Clinical Center) wrote regarding his patient whose BP was diagnosed differently by two physicians who saw him at different times of day: "By conventional standards, this patient is clearly normotensive every morning [one of the earlier diagnoses]. Yet the

blood pressure determined each day at 6 in the afternoon provides especially convincing evidence that this patient is a hypertensive. [The other diagnosis by the care provider who saw this patient in the morning; material in ( ) is our addition.] ... My [Bartter's] 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." These visionary statements will be more readily implemented with modern instrumentation for data collection and chronobiologic analysis, once limitations of the status quo are clarified.

Status quo

Today's practice, often with casual single BP measurements by a trained professional at yearly or even longer intervals, determines whether the pressure is elevated above arbitrary fixed limits at the given moment. This is done when small devices for BP telemetry can be implanted for a lifetime in small laboratory animals like mice (to develop new drugs) or for other research purposes and routinely in cars' tires as a safety measure. There is indeed an FDA-approved wristwatch-size automatic BP recorder to remove undue obtrusiveness, albeit as yet costly (8). Implicit to the status quo are the tacit beliefs that BP is constant, that any variability in BP stems solely from measurement error, activity or emotions, and that the latter and sleep- and wakefulness-associated changes fully account for the extensive literature reporting on prominent about 24-hour or circadian rhythms (42; cf. 43). There are, however, gender differences, changes as a function of age and, what is novel, a broad spectrum of partly built-in infradian rhythms (with periods longer than 28 hours) up to decades-long cycles (9) characterizing circadian characteristics such as the MESOR (M), double amplitude (2A, a measure of predictable extent of change within a cycle), and acrophase (ϕ, a measure of timing of overall all values recurring in each cycle). All these parameters have an uncertainty, usually gauged by the 95% confidence interval (CI). Currently, in a diagnostically important range of pressures, the acceptability of a BP measurement depends on whether the individual is seen by the provider at one or another clock-hour, Figure 9 (44), as was the case in a patient seen by one physician in the morning, who diagnosed him as normotensive, while another physician, who saw him later in the day, diagnosed him as hypertensive (41). He was hospitalized at the US National Institutes of Health, and his BP fluctuation confirmed the wide within-day fluctuation.

When, in current practice, ABPM is recommended, it is limited to 24 or to 48 hours and remains uninterpreted chronobiologically. When ABPM is done for 30 days, one can find, in the case of a neurosurgery resident, on different days at the same clock-hour and on the same day of the week, measurements compatible with hypertension, normotension and hypotension, Figure 10. Currently, data collected around the clock are examined in terms of 24-hour, daytime and nighttime means and standard deviations (SD), sometimes complemented by an estimate of the day-night ratio (DNR) (45). The DNR, its current general use notwithstanding, is documented as too crude an approximation of the circadian variation (19, 26). It can fail (46) or even mislead (47; cf. 48) when the alternative chronobiologic analysis works, Figure 11. Against this background, improvements are desirable (17). Arbitrary fixed limits or "targets" like 120 mmHg in systolic "pre-hypertension" or 140 mmHg in systolic "hypertension" need to be replaced with limits of circadian characteristics derived from curve-fitting and stacking, the latter time-specified as prediction intervals and qualified by gender, age and when possible by geographic/ethnic setting. Chronobiologically- and chronomically-interpreted

ABPM (C-ABPM) on subjects in clinical health served to derive time-specified reference limits along the 24-hour scale, separately for each gender in different age groups, computed as 90% prediction limits expected to cover, on the average, 90% of the population of Caucasians in Europe and North America (49, 50). These reference standards served thus far worldwide until geographic and ethnic differences are further investigated.

The least squares fit by cosinor of a 2-component model, consisting of cosine curves with periods of 24 and 12 hours served to adequately approximate the circadian waveform of BP and HR in most people. The period is not listed in the usual sphygmochron (Figure 12), which is a summary of a C-ABPM, when the CI of the circadian period covers 24 hours. (When the period's CI does not cover 24 hours, a glocal analysis of all detected circadian components is indicated.) Estimates are obtained for the MESOR (usually more accurate and more precise that the arithmetic mean), and for the double amplitude (2A) and acrophase (ϕ) of each component (Figure 12, left). Gender- and age-specified reference values for M, 2A(24h) and ϕ(24h) are also derived as 90% prediction limits, eventually to be improved by restriction to a database needed to retain only time series on long-lived disease-free individuals, in order to have reference values to detect VVAs. One of the VVAs is thus far hardly explored, but includes, in our experience, a first case of (a lady with) circadian multifrequentia. Figure 13 shows the time course of the dominant period among several circadian components in addition to a 24.0-hour-synchronized component, the time course of the multiple circadians being shown for BP and HR in Figure 14.

By assessing circadian characteristics and by relying on reference values that account for the prominent circadian variation as well as for gender and age differences, new questions can be asked that are more refined than just asking whether or not a BP value is elevated or too low. Deviations from circadian norms can affect the MESOR, among other rhythm characteristics. MESOR-hypertension, MH, is diagnosed when M is above the upper 95% limit of gender- and age-matched peers; MESOR-hypotension, Mh, when it is below the lower 5% limit. By corresponding criteria, an odd timing (circadian ecphasia) or odd period (ec- or dysfrequentia) can be diagnosed, Figure 3.

An elevation of the 2A(24h) above the upper 95% prediction limit of peers has been associated in a first study in Japanese subjects with an increase in cardiovascular disease risk larger than that of a high BP (MH), Figure 15-IIA,B (17, 19), even among MESOR-normotensive subjects, Figure 15 II-C (left column). This condition has been called CHAT (Circadian Hyper-Amplitude-Tension) and may sometimes be amenable to treatment, notably when it is iatrogenic, by a change in treatment timing (51). An odd timing of the circadian rhythm of BP but not of HR (circadian BP ecphasia), found, e.g., in patients with non-insulin-dependent diabetes mellitus, is also associated with a large increase in CVD risk. It has been related to the presence of autonomic system dysfunction (7, 17). MH, CHAT, BP ecphasia and ecfrequentia, i.e., an altered circadian period, are further examples of VVAs. Circadian ecfrequentia may occur physiologically when the dominant period is desynchronized from 24.0 hours, with a 95% CI not covering 24.0 hours in a subject on a self-selected odd sleep-wake schedule (52) (when multiple circadian periods may be found in sleep-wakefulness), or in recurrent adynamic depression when multiple periods may be found both in the circulation and in the endocrines (53), or when the circadian rhythm may be lost (circadian arrhythmia insofar as the assumption of a zero circadian amplitude cannot be rejected).

VVAs also include an excessive pulse pressure (above 60 mmHg) and a deficient HR variability (defined as HR-SD < 7.5 beats/min), all in a 24-hour/7-day record replicated in the absence of a load. These VVAs have been shown to be largely independent and additive. When two or more VVAs coexist in replicated 24-hour/7-day records to form a Vascular Variability Syndrome (VVS), the CVD risk is increased, Figures 4A and 4B (7, 17), as demonstrated in several outcome studies. This paper is a plea to those who possess outcome studies with ABPM limited to one or a few days to compare

the relative merits of their approach with that here advocated themselves and/or to send their data to the BIOCOS project (corne001@umn.edu) for such a comparison.

Measuring BP variability and strain in health

By keeping detailed diaries, it is possible to associate specific changes in measures of circadian BP and HR variability, including the M, with external events resulting in conflict or grief, Figure 16A (54), anger, worry, exercise and alcohol consumption, to cite just a few examples, or with associations of VVAs with visitors, parties, holidays and other events, sometimes but not always loads, Figures 1, 5 and 6 (1). Giving a party was associated in one subject with a VVA, while attending a party by the same subject had no such effect (while other circumstances, such as ethanol consumption, were similar; 1). One important application in this context is to use ABPM as a tool to assess strain and factors underlying its occurrence so as to determine lifestyle modifications that may help control VVAs after the cessation of loads, Figure 6 (1). It cannot be overemphasized that a physiological VVA or the putative pathology of a VVD can occur in the normal range, Figure 16B (1).

Screening for Vascular Variability Disorders (VVDs) leads to a refined diagnosis

It has been recommended that ABPM be performed for a minimum of 7 days at the outset (17), to be complemented by another week-long profile whenever abnormality is detected and to rely on continued surveillance once abnormality is detected, in view of the day-to-day, week-to-week and even longer variability in BP and HR associated with a sometime selectively assorted set of infradian rhythms. Around-the-clock monitoring for a lifetime is the method of choice for everybody for strain assessment. The term strain is used to denote the response to loads ("stressors", or rather "stress"), gauged by endpoints of circadian and other rhythms, rather than relying on spotchecks ignoring such endpoints. This assessment is particularly relevant for patients in need of treatment for the optimization of therapy by timing at the outset (17, 55–59), for surveillance of continued treatment efficacy and for earliest detection and correction of any undesired iatrogenic effect.

Timely institution of timed treatment targeted to the individual patient's diagnosis

Optimizing the timing of treatment in view of the chronodiagnosis of individual patients has been called chronotheranostics (60). Not all anti-hypertensive agents can reduce an excessive circadian amplitude of BP (17, 61). The same dose of the same drug administered to the same patient for month-long spans (each monitored for the last week) can exacerbate systolic CHAT and induce diastolic CHAT when it is given at one circadian stage (in relation to the time of awakening) but eliminates CHAT when it is given at another circadian stage (51, 62). A different timing of the administration of a given medication to each individual in a group according to the time of high BP excess in a previously monitored record has been shown to be associated with a greater efficacy, to have fewer side effects and to require a lesser dose, thus being also less costly, as compared to a group on traditional scheduling three times a day or at some clock-time without personalized checking of the time and/or kind of abnormality (58, 59; cf. 56).

Cost-effectiveness of continued surveillance by ABPM

The modest, already documented technological change to an automatic monitor once it becomes affordable makes continued ABPM available to the lay public on a very broad scale. Conditions involving billions of people, now unrecognized by both patients and care providers, could be detected, Figures 4A and 4B (17, 25), thereby allowing a shift from the emphasis on the treatment of overt disease to a truly primary prevention prompted by the diagnosis of pre-hypertension (14, 17), pre-diabetes (46, 63) and a pre-metabolic syndrome (all associated with the presence of VVAs or VVDs)

before the onset of target organ damage (14, 17), thereby reducing the incidence of morbid events such as strokes, heart attacks, kidney disease and retinopathy.

Website

The building of a dedicated manned website for the analysis of weeklong and preferably lifelong profiles of BP and HR would help reduce cost since health professionals would only be called upon once there is a need for intervention, the surveillance being part of self-help taught in schools (17). The cost of analyses would also be reduced, the data management being fully automated, including the construction of data archives serving for the longitudinal follow-up of individual subjects. These databases could be further mined for the identification of new VVDs and for refining the reference values.

Basic science: physiological responses to the environment near and far may become pathology

The databases collected for self-help in health care could also be mined for answering a host of novel questions related to the influence of the environment on human physiology and psychology. Apart from the circadian rhythm, BP and HR are characterized by many other cycles, some related to light and temperature such as about-yearly rhythms and others sharing the frequencies of the solar wind and/or geomagnetic activity, Figure 17 (64, 65). The mapping of about 5-month cycles (64, 66), of transyears with periods longer than 1.0 but shorter than 1.9 years (67) as well as the about 10.5-year Horrebow-Schwabe cycle, the about 21-year Hale cycle, the about 33-year Brückner-Egeson-Lockyer (BEL) (68) and the about 50-year Kondratieff cycle has already started in several longitudinal records spanning decades (69). Some lessons concerning the development of MESOR-hypertension have already been learned that may see practical applications (70). Magnetic storms have been associated with a decreased HR variability (71, 72), a risk factor for coronary artery disease. Shielding susceptible patients or screening the population as a whole for VVAs and in particular for a deficient HRV in candidates for space travel come to mind. Systolic BP seems to be an infradian marker of solar wind speed (67).

The human body is a readily available physiological laboratory and BP and HR are biomarkers that can unveil important physiological responses to seemingly benign life events, revealing strain, CVD risk increase, pre-disease and disease. Thereby a new window on life in the cosmos is found. Organisms are open systems with the environment, subject to photic as well as non-photic, the latter rather unstationary (aeolian) solar influences, which may be in the normal range. Hence, they are neglected in current spotcheck- (pseudo-) evidence-based health care. Chronobiology and chronomics are more complex yet inexpensive and cost-effective. A system for 7-days of monitoring and analysis for evading a stroke and perhaps a social upheaval or natural disaster, i.e., an earthquake, is worth considering as a good trade (17).

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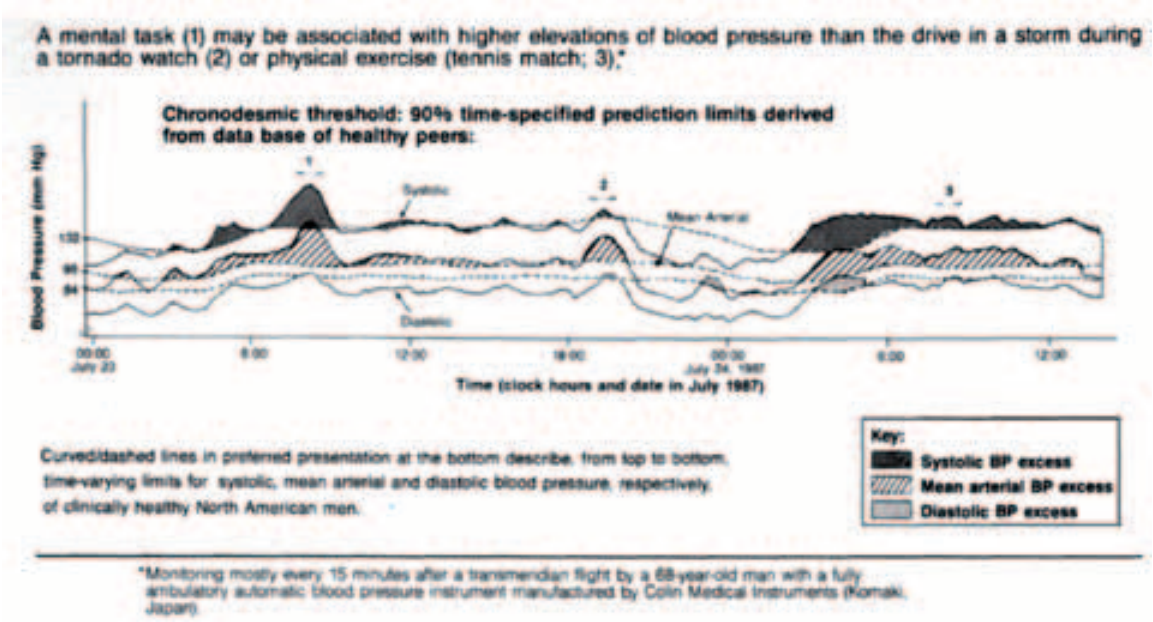


Figure 1. Short-term responses as blood pressure elevations in association with different activities, as in this figure, can be assessed in the light of time-varying limits (chronodesms) and can be complemented by reference to parameters of a broad spectrum of infradian as well as circadian rhythms, including CHAT. © *Halberg.*

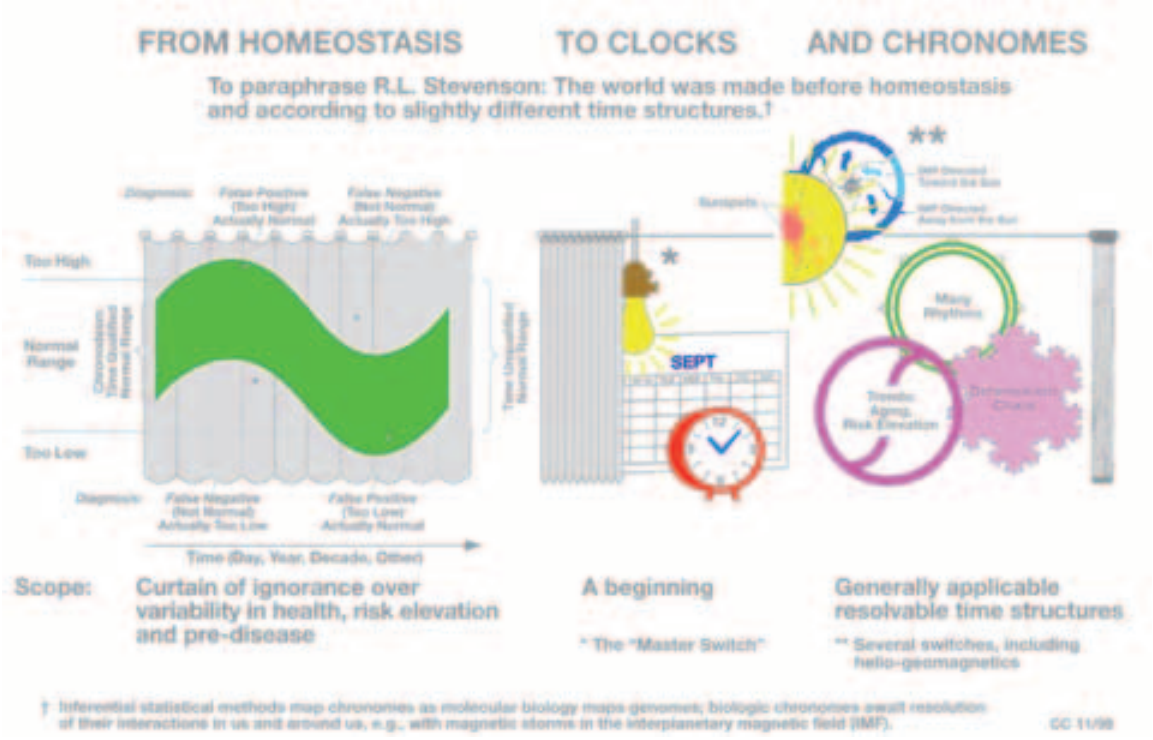


Figure 2. A curtain of ignorance, drawn by the concept of homeostasis over normal variability (left), is only partly lifted by biological clocks and calendars and awaits further exploration of nonphotic spectral components originating in the cosmos. The same data serve for the prevention of individuals' life-threatening events and for an understanding of societal illnesses. © *Halberg.*

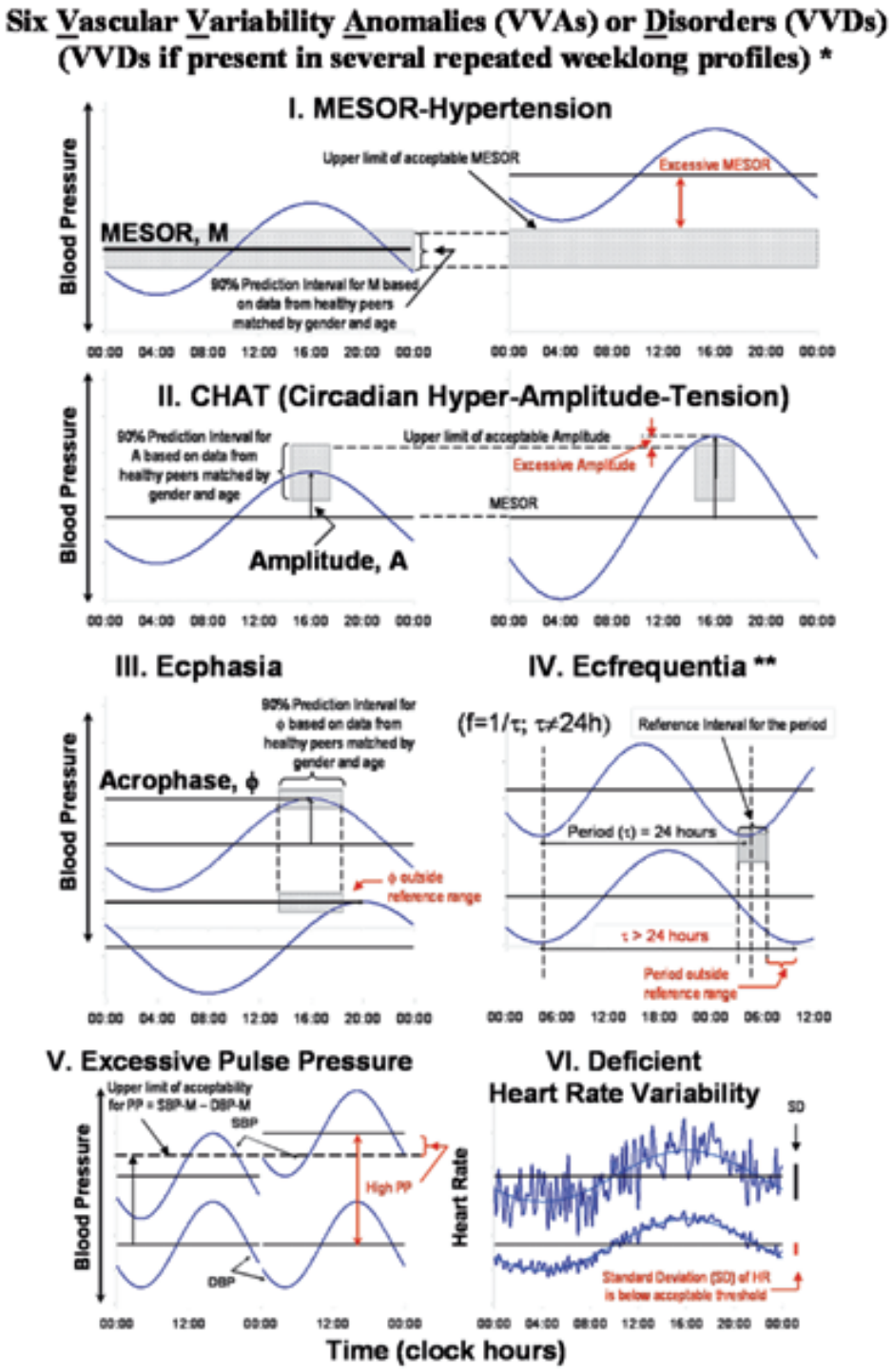


Figure 3. Abstract definitions of VVAs: I. MESOR-hypertension; II. CHAT; III. Ecphasia; IV. Ecfrequentia; V. excessive pulse pressure; and VI. Deficient HR variability. These VVAs are diagnosed when the subject's values exceed the upper 95% prediction limit of healthy peers matched by gender and age (I-IV), when the pulse pressure is above 60 mmHg (V), and/or when the standard deviation of HR is below 7.5 beats/min (VI). © *Halberg.*

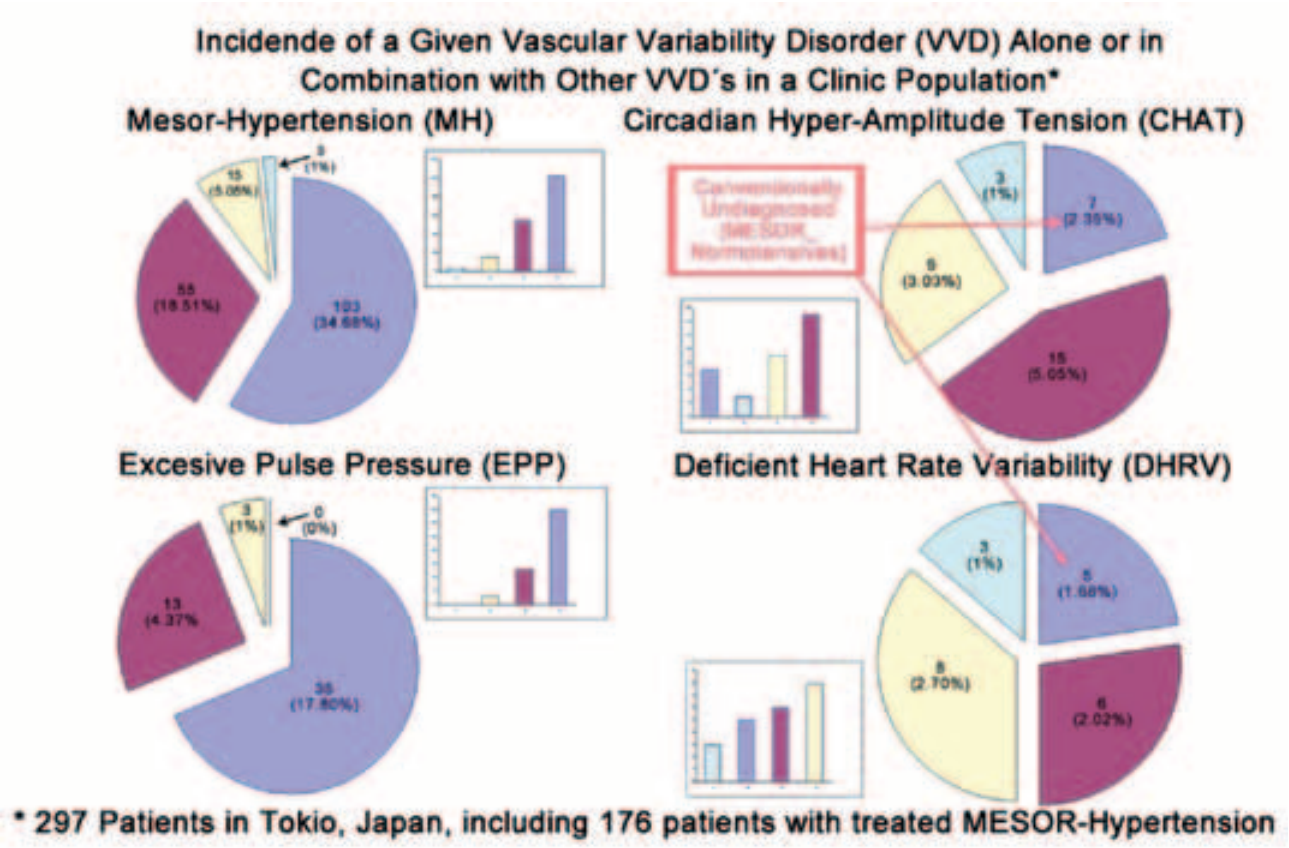
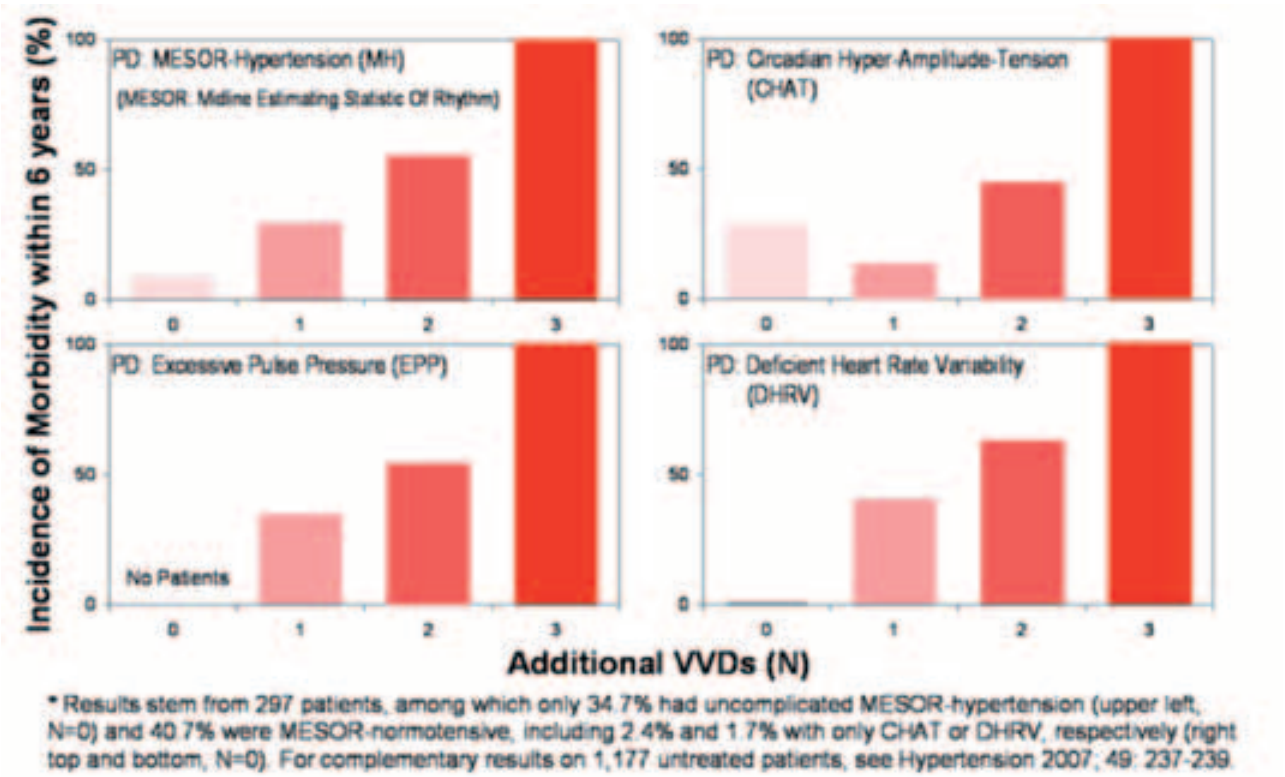


Figure 4.A.

Figure 4. The incidence of VVAs was assessed in a clinic population of 297 patients. BP and HR of each subject were monitored around the clock for two 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), CHAT, and a 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 six months for six years, to estimate the relative risk associated with each VVA alone (primary diagnosis, PD) or in combination with 1, 2, or 3 additional VVAs. 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 VVA, present alone or in combination with one or more additional VVAs. The 176 patients with MH were broken down into 103 (34.7% of the population of 297 patients) with uncomplicated MH, 55 (18.5%) with MH complicated by one additional VVA, 15 (5.1%) and 3 (1.0%) with MH complicated by two or three additional VVAs. In the last group, all three patients had a morbid outcome within six years of the BP monitoring. Ambulatory BP monitoring over only 48 hours, 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%) had additional VVAs 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 VVAs. This proportion may be smaller when VVAs are diagnosed on the basis of 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 suggests that treating these conditions may translate into reducing morbidity and/or mortality from vascular disease. Another lesson 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). This is an alternative to a polypill, given without a chronobiologic diagnosis that as yet neither detects nor treats VVDs and VVSs. A. Incidence of a given VVA alone or in combination with other VVA(s) and corresponding risk, assessed by actual outcomes within 6 years. B. Risk associated with each VVA alone or complicated by 1 to 3 additional VVAs. © *Halberg.*

Figure 4.B.



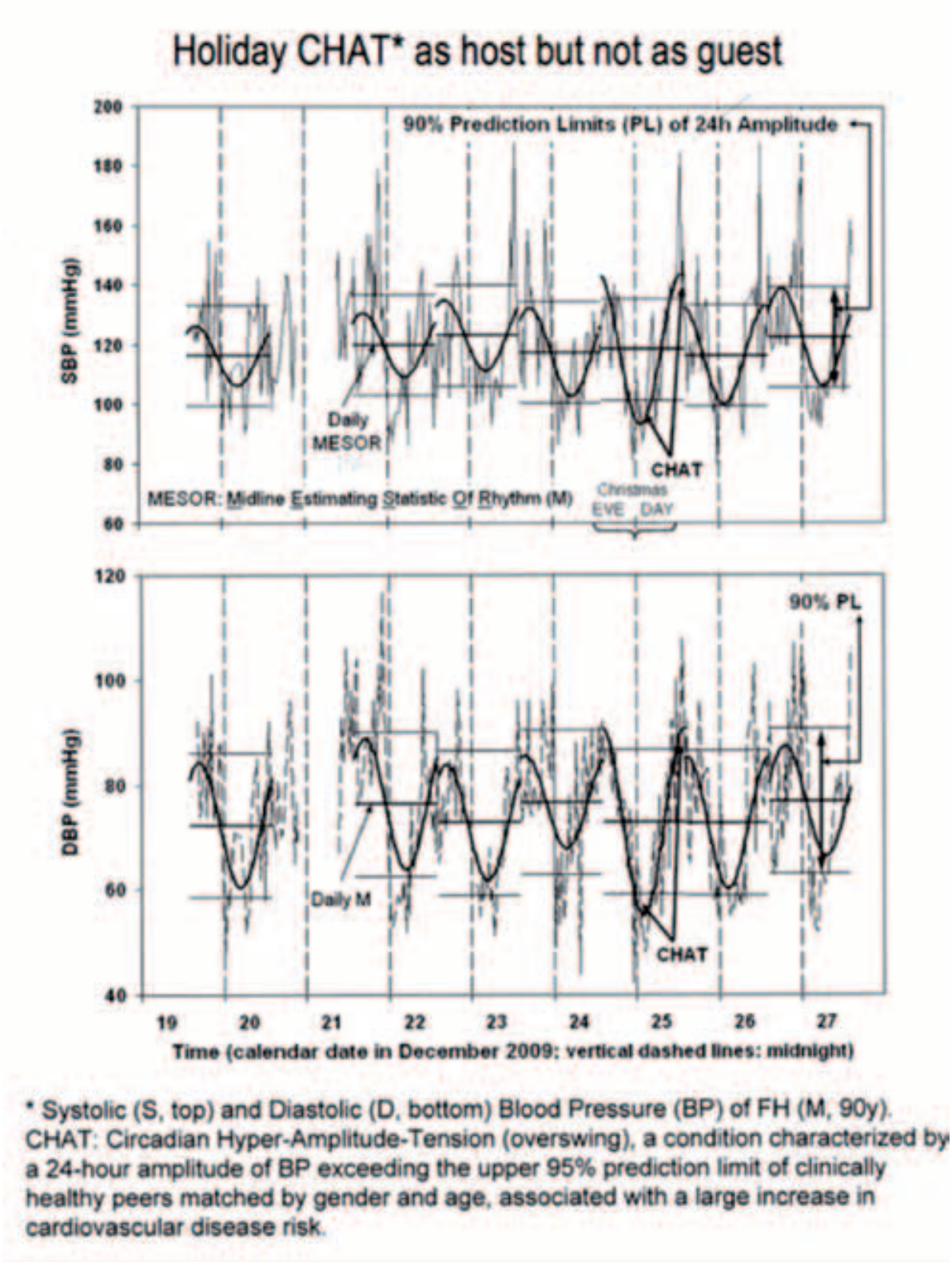
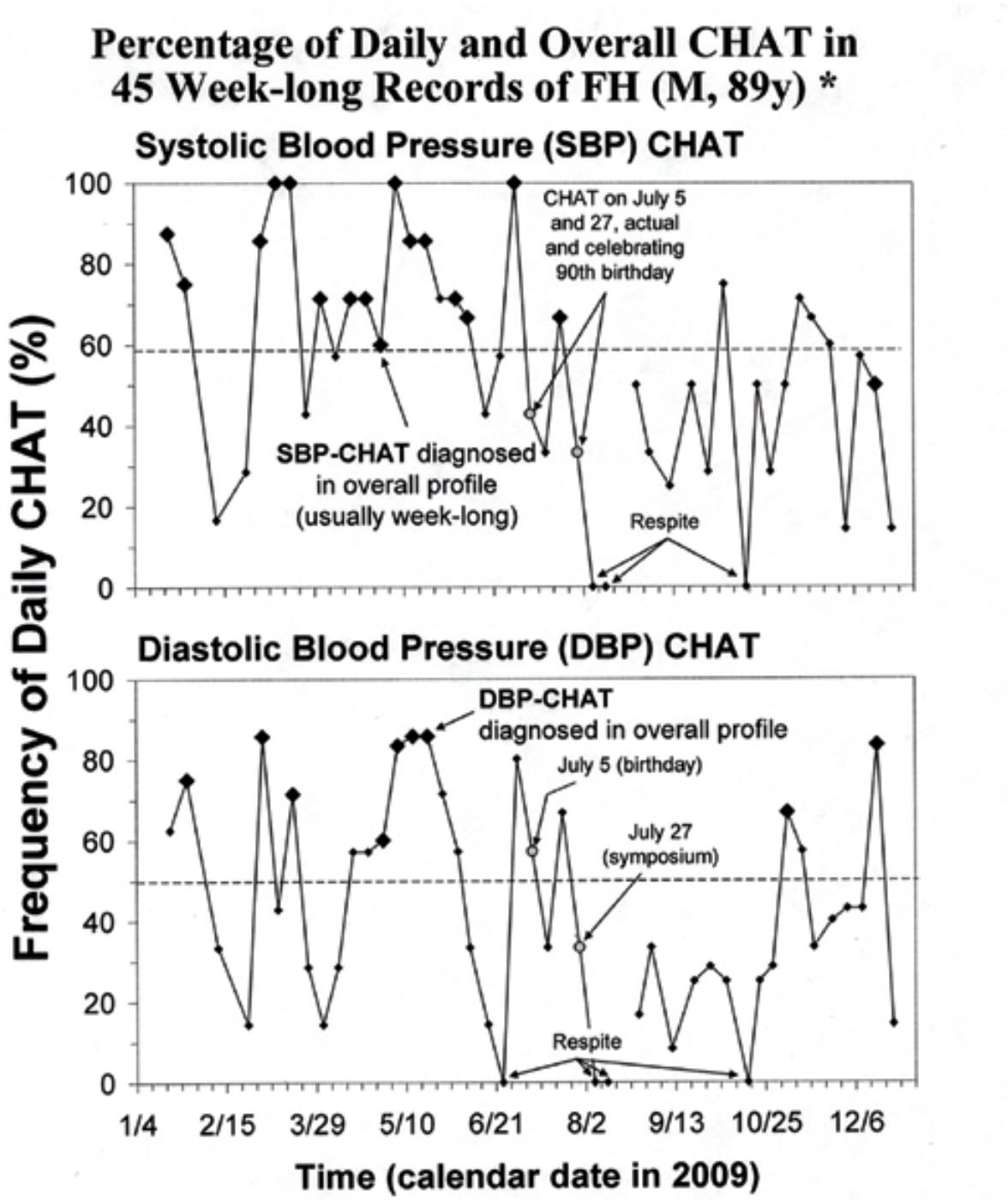


Figure 5. FH attended parties on both Christmas Eve (host), and Christmas Day (guest). As host, he could not follow his favorite task of writing. In the capacity of a guest, he took the liberty of unobtrusively doing some professional homework. The latter, but not the former role, was acceptable. Situational 24-hour transient CHAT, as here recorded, was limited to a single 24-hour span. It is smoothed out by the fit of a fit of a 24-hour cosine to 7 days of observations as a whole. © *Halberg.*



* Large diamonds indicate that CHAT was detected in overall record, irrespective of the percentage of the daily occurrence of CHAT (Circadian Hyper-Amplitude-Tension, "overswing"), a condition characterized by a 24-hour amplitude of blood pressure (in a 2-component model consisting of cosine curves with periods of 24 and 12 hours) exceeding the upper 95% prediction limit of clinically healthy peers matched by gender an age, associated with a large increase in cardiovascular disease risk. Whereas occasional daily CHAT is found in many usually week-long profiles, it is present overall in only a few records, day-to-day changes in MESOR and circadian acrophase contributing to a reduction in the 24-hour amplitude estimated from the entire records.

Figure 6. CHAT during about 5 months of preparation for a symposium is lost in the last two post-symposium records, each of 1-week duration. It would seem that after 14 days of normalcy, one could dispense with monitoring. © *Halberg.*

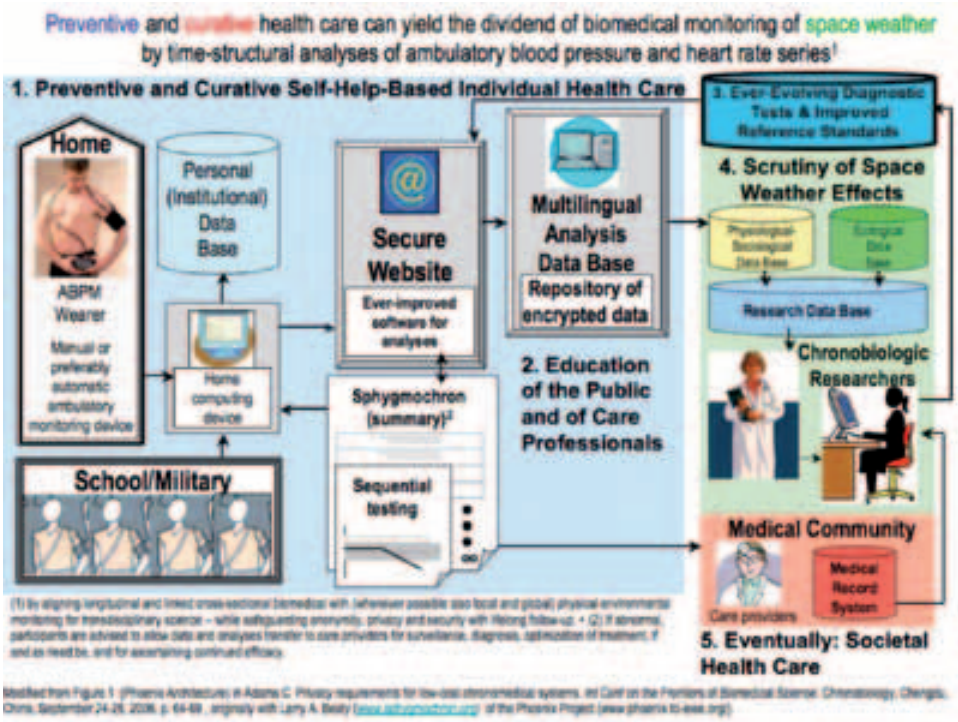


Figure 7. The Phoenix Group of volunteering electrical and electronic engineers from the Twin Cities chapter of the Institute of Electrical and Electronics Engineers (http://www.phoenix.tcieee.org) is planning on developing an inexpensive, cuffless automatic monitor of blood pressure and on implementing the concept of a website (www.sphygmochron.org) for collection and analysis of data collected with these instruments. © *Halberg.*

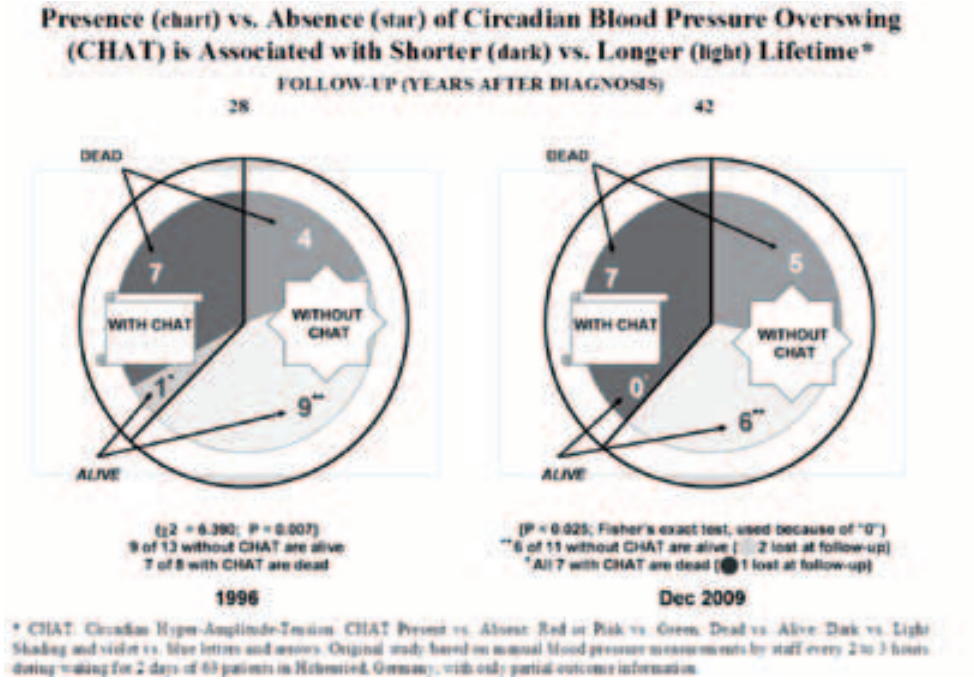


Figure 8. 42 years after a 48-hour BP profile at 2- to 3-hour intervals during the waking hours, on 63 patients, among those available to follow-up, nearly 50% of those without a circadian BP overswing, CHAT, are alive, while all with CHAT are dead. © *Halberg.*

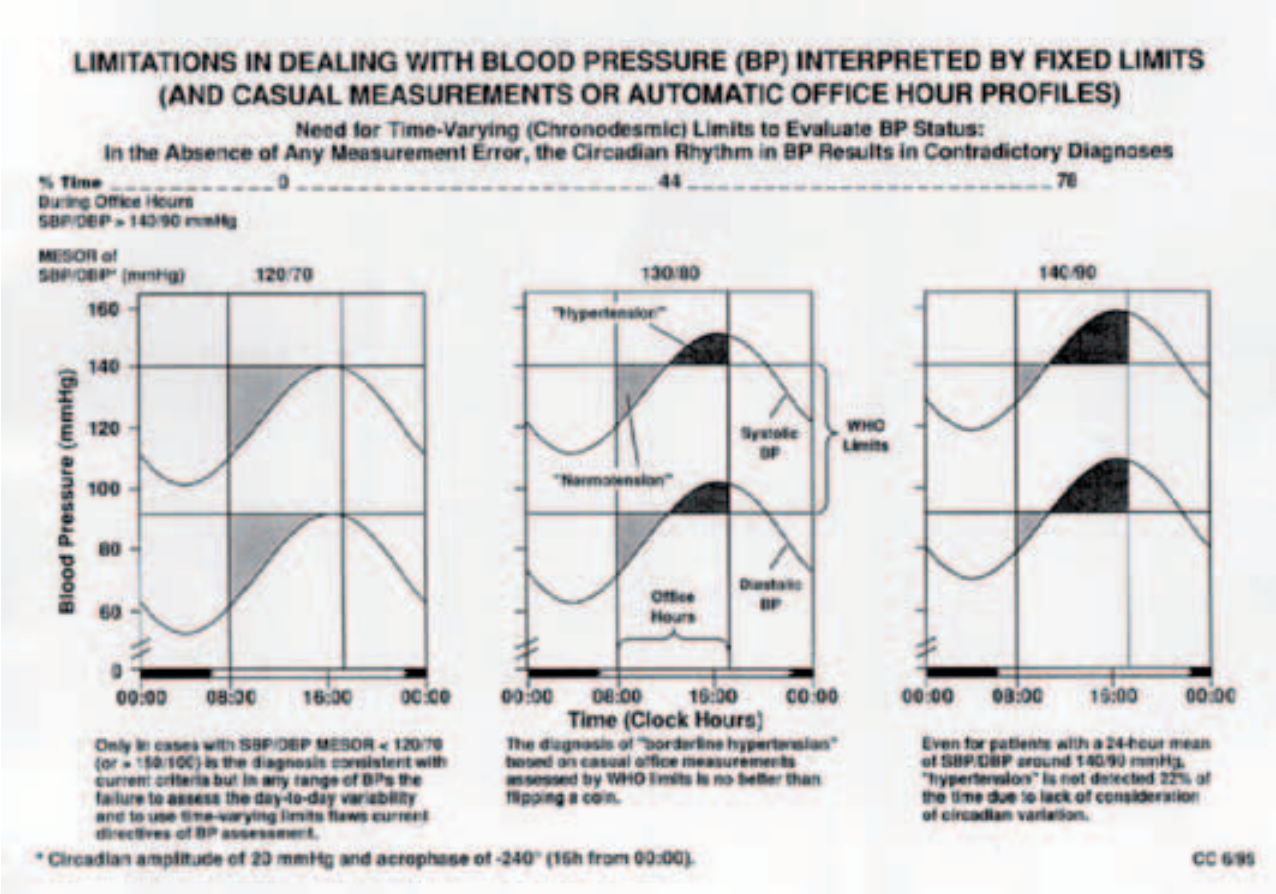


Figure 9. The diagnosis of high BP today can depend upon the time of day of the visit to a care provider. Abstract illustration, validated in Figure 2, in dealing with casual measurements of BP during office hours interpreted by fixed limits, insofar as the circadian rhythm in BP can, in itself, even in the absence of measurement error, result in contradictory diagnoses. Computations here 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). Left: Only in cases with SBP/DBP MESORs <120/70 (or >150/100) mmHg is the diagnosis consistent with current criteria, but in any intermediate range of BP MESORs, failure to assess day-to-day variability and to use time-varying limits, flaws current directives of BP assessment. Center: The diagnosis of "borderline hypertension" based on casual office measurements assessed by WHO limits is no better than flipping a coin. Right: Even for patients with a 24-hour mean of SBP/DBP around 140/90 mmHg, "hypertension" is not detected 22% of the time because of the lack of consideration of the circadian variation. Fixed thresholds can be replaced by time-varying reference standards (chronodesms). One can rely on series of BP measurements for at least 7 days; they should be repeated but are a practical start. © *Halberg.*

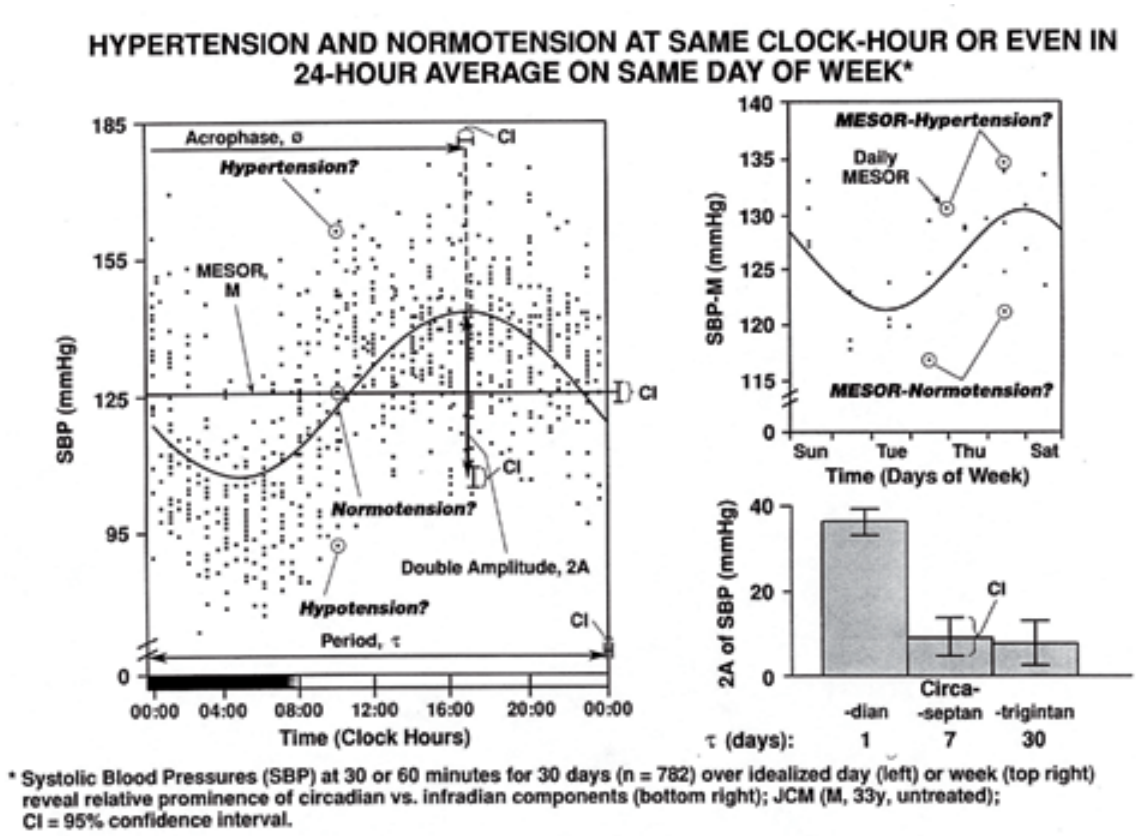


Figure 10. Single measurements from an automatic around-the-clock monitoring for 30 days, stacked along an idealized 24-hour scale, can be compatible with the diagnosis of normotension, hypertension and hypotension, underscoring the need for systematic chronobiologically-interpreted long-term self-surveillance (left). Even 24-hour averages on different days can be compatible with MESOR-hypertension or MESOR-normotension (right, top). In part, the day-to-day differences are accounted for by an about weekly pattern (right, bottom). © *Halberg.*

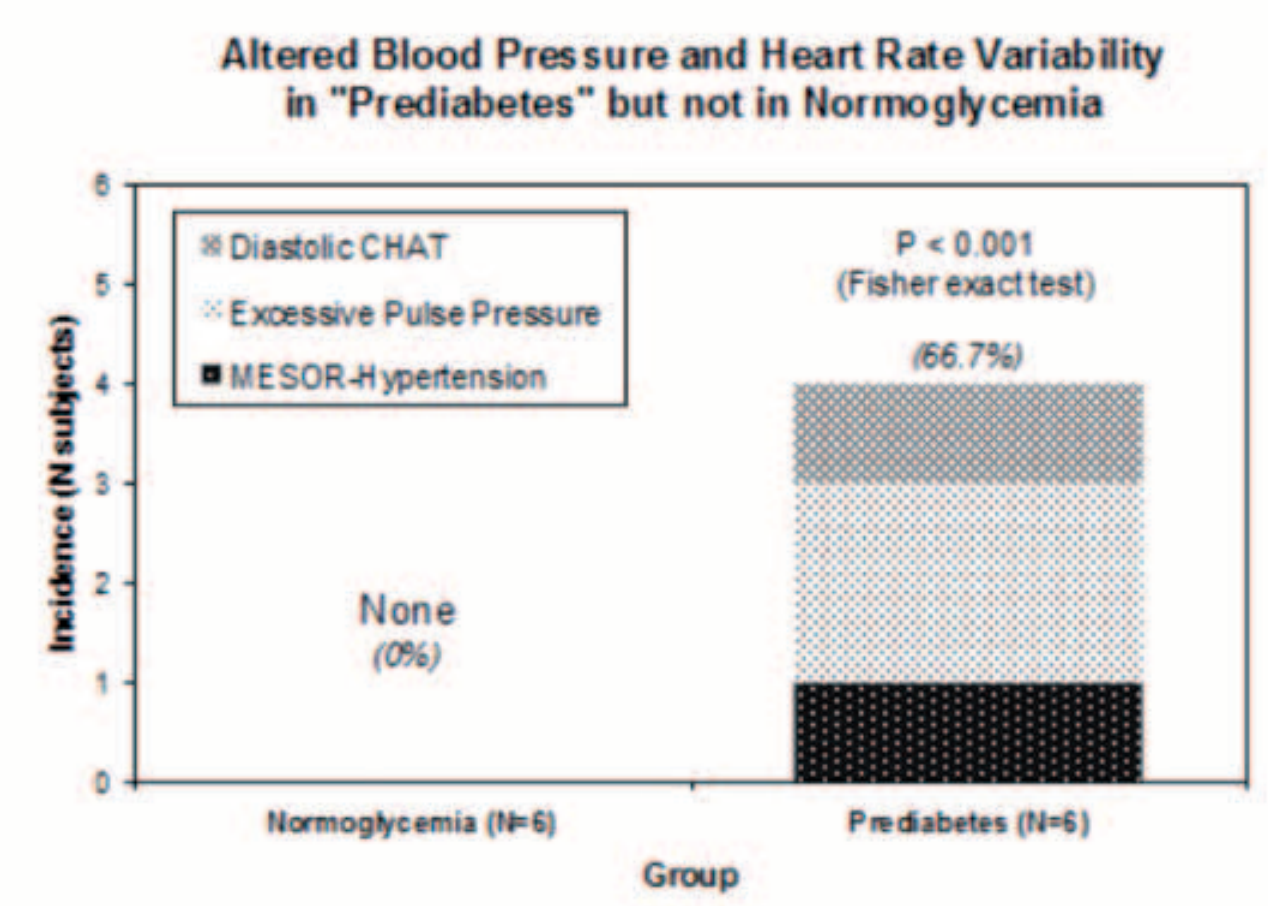
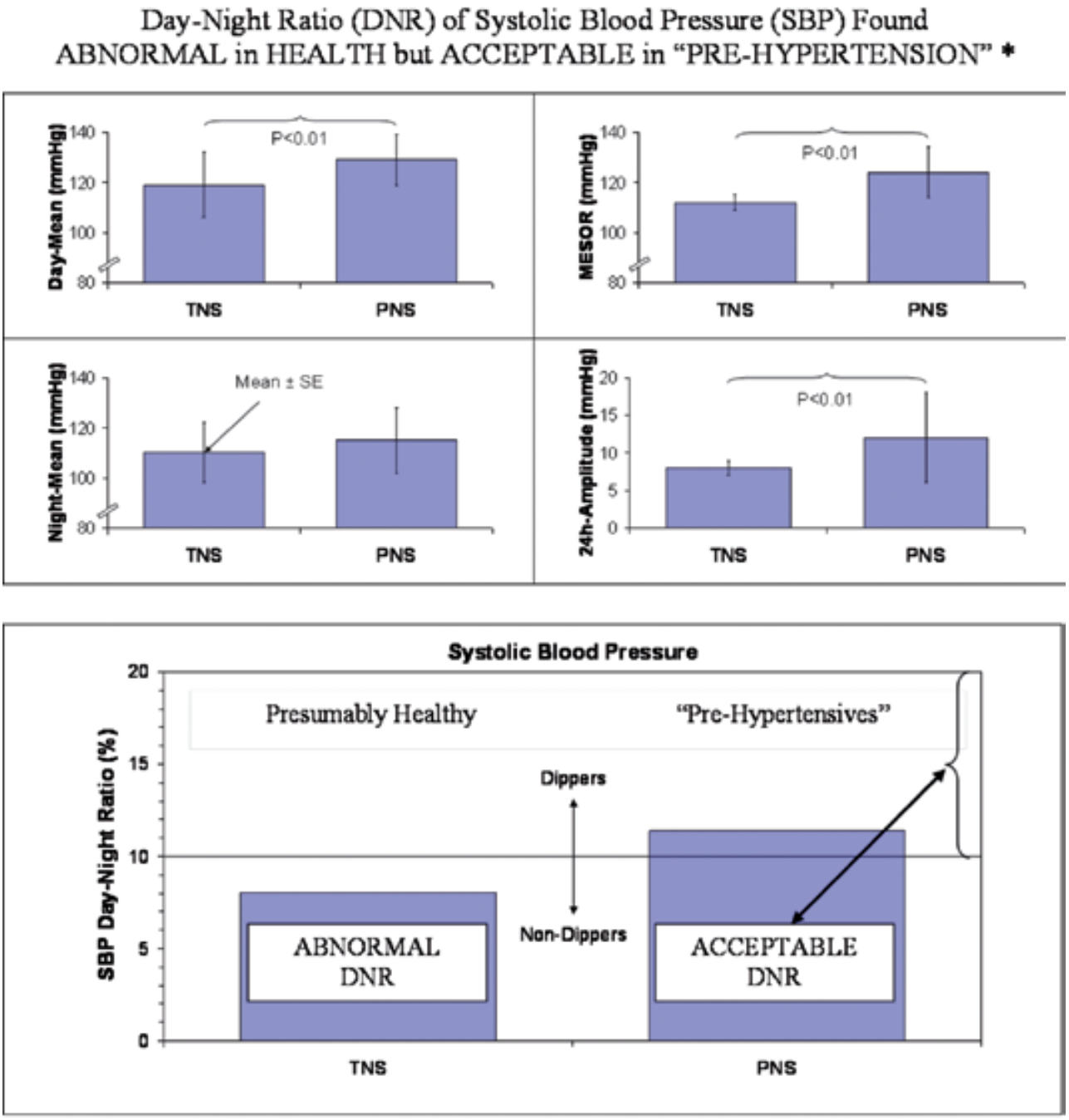


Figure 11. A.

Figure 11. A. With the relatively small sample sizes of 6 patients with a moderately elevated fasting glucose and a slightly abnormal glucose tolerance versus 6 individuals with acceptable corresponding results (healthy controls), all undergoing 7-day/24-hour ambulatory BP and HR monitoring, analyses indicate that a chronobiological approach works when a classification in terms of "dipping" based on the day-night ratio (DNR) fails to detect abnormality. Indeed, chronobiologically, no abnormality was detected in the light of time-specified reference standards qualified by gender and age among the 6 controls, but 4 of the 6 pre-diabetic patients showed one or more VVAs ($P<0.001$). By contrast, in both groups, there were two patients with a DNR > 20% ("excessive dipping") and one patient with a DNR < 10% ("non-dipping"). It was thus impossible to discriminate the group of patients with pre-diabetes from the healthy controls in terms of "dipping", when a chronobiological interpretation worked (46). B. Circadian parameters and day-night ratios (DNRs) of systolic BP are compared between groups of presumably healthy MESOR-normotensive subjects and pre-hypertensive subjects with incipient signs of minimal change hypertensive retinopathy (47; cf. 48). Minimal retinal alterations, presumably reflecting an increased vascular disease risk, are associated with a higher MESOR and a larger circadian amplitude of SBP ($P<0.01$). A classification in terms of dipping, based on the DNR of SBP, however, is misleading, as the pre-hypertensive patients as a group are "dippers" with a DNR between 10% and 20%, but the MESOR-normotensive controls as a group are non-dippers, with a DNR of SBP below 10%. © *Halberg.*



** Comparison of "Truly Normotensive Subjects" (TNS) and "Putatively Normotensive Subjects" (PNS) with Incipient Signs of Hypertensive Retinopathy. Data from P Cugini et al. (27). Minimal retinal alterations, presumably reflecting an increased vascular disease risk, are NOT associated with abnormal DNR, but rather with the chronobiologically predicted elevation in circadian BP amplitude (middle, right).t*

Figure 11. B.

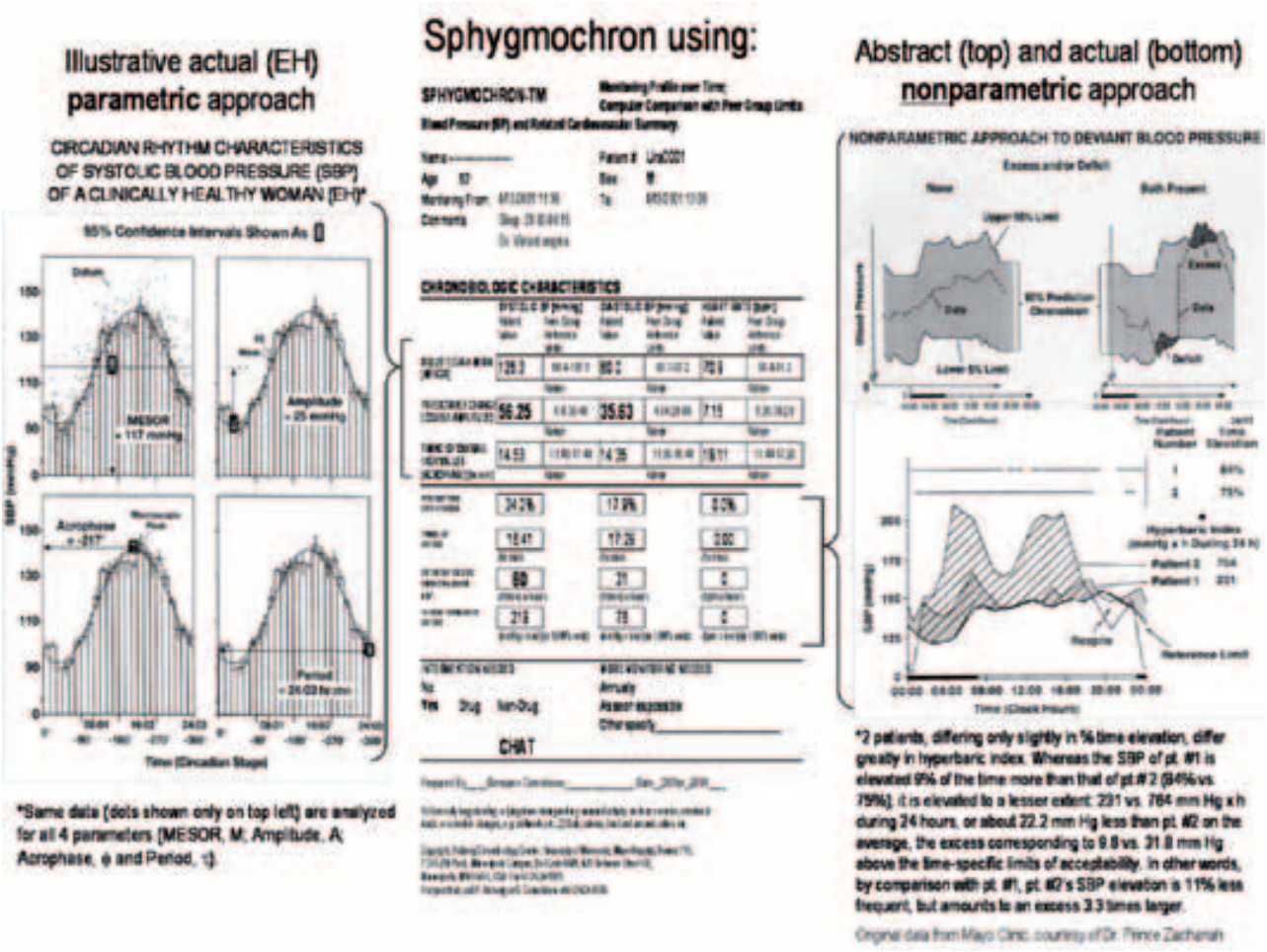


Figure 12. Illustrative parametric (left) and non-parametric (right) approach bracket a sphygmochron (middle) from a MESOR-normotensive man with CHAT, a first tentative diagnosis requiring additional monitoring. BP and HR data covering preferably at least 7 days are downloaded into a computer for analysis and the (dominant) circadian period is determined to check whether its CI (95% confidence interval) overlaps 24.0 hours (not shown). If so, the following results are provided (since the 1990s and currently cost free from corne001@umn.edu) for the patient as well as for the care provider:

1. A list of actual measurements and the times at which they were obtained.
2. A plot of data as a function of time, shown together with the time-specified prediction intervals (PIs) of acceptability for systolic and diastolic BP and HR characteristics.
3. A data summary, and a report of any BP and/or HR excess in consecutive 3-hour intervals. This part of the report may be accompanied by a "rhythmometric summary", which is just a more technical form from which the information is derived to prepare the:
4. "Sphygmochron". A sample "sphygmochron" (center) illustrates how results are being reported. First, above, the participant's name is kept confidential; a codename is used instead. Gender and age are listed, along with the date and time at which monitoring started, and for how long data were collected. The numerical report consists of two parts labeled "Characteristics" (parametric results) and "Indices of Deviation" (non-parametric results). In each case, results are shown for SBP (when the heart contracts) on the left, DBP (when the heart relaxes) in the middle, and HR on the right. Under "parametric results", a mathematical model of a smooth curve is fitted to the data to assess their circadian variation, which is primarily characterized by four numbers shown in the left-hand section of the graph, one of which, the period, covers 24.0 hours with its uncertainty, so that the other three

estimates are given from the fit of a 24-hour cosine curve. One characteristic, called the "MESOR", is the average value around which values fluctuate. It is very similar to the mean value, but yields more reliable results when the data are not collected at precisely regular intervals, and has a smaller error when the data are equally spaced. Another characteristic, called the "double amplitude", is a measure of the predictable change occurring within a day, from the overall low values found usually during sleep to the high values during the daily active span. The third characteristic, called the "acrophase", is a measure of the time when overall high values are likely to recur each day. For each of the three characteristics ("parameters"), the participant's value is compared to a range of acceptable values, derived from data provided by clinically healthy people of the same gender and age group as the participant. In the example shown here, the average SBP, DBP and HR are within acceptable limits, as are the acrophases and the double amplitude of HR. This is not the case, however, for the double amplitudes of SBP and DBP, which exceed their respective upper 95% prediction limits, leading to the diagnosis of CHAT. Under "non-parametric results", the participant's data are compared by computer with time-specified reference values, also derived from chronobiological archives on clinically healthy subjects matched by gender and age. For this analysis, all data are stacked over an idealized 24-hour day. Whenever a given person's profile exceeds the limits of acceptability of peers, the data are marked as being excessive or deficient. The "percentage time of elevation" reports the relative incidence of excessive values during a 24-hour day. It is common to have occasional high values, but in the example herein there is reason for concern. The next item, the time of excess, becomes useful when treatment should be timed prior to the peak in excess. Excessive values may either be barely above the limit or in turn can be very much higher than the limit. It is therefore important to express the extent of deviation by the "area under the curve", that is the area between the values when they exceed the limit and this limit itself. Empirically, it has been shown that excess up to about 50 (mmHg x hour during 24 hours) may still be acceptable and accountable for by daily worries and/or physical activities. In the case summarized, the SBP excess (HBI) is 60 mmHg x hour during 24 hours (bold). If confirmed in the next 7/24 profile, this may be a reason for treatment.

An abstract illustration of excess and deficit (top right) is accompanied by two actual cases that are similar in terms of percent time elevation (bottom right). They are very different in terms of hyperbaric index, however. In patient #2, although the percent time elevation is 9% smaller than that in patient #1, the hyperbaric index is several times larger. The "timing of excess" can be used as a guide to time the administration of non-drug or, if need be, of drug treatment once there is BP excess above 50 (mmHg x h during 24 hours) and/or an elevation in MESOR, taking into account the chronopharmacokinetics of the drug prescribed. When, e.g., a tentative diagnosis of MESOR-normotension with CHAT is made, with insight into information provided on the questionnaire given to the participant with the monitor, as a first step, additional analyses may be carried out. Additional monitoring is recommended to check on any abnormality detected during the first monitoring, and if confirmed, the need for intervention is reported to the person monitored so that it can be reported to the health care provider. In one case summarized elsewhere, the follow-up 7-day monitoring showed that CHAT persisted for both SBP and DBP, while the MESORs were again acceptable. Thus, the diagnosis of CHAT with MESOR-normotension was confirmed. Consultation with a health care provider was strongly and urgently recommended. In two cases of CHAT without an elevation of the BP MESOR, when such recommendations were ignored, catastrophic disease and high cost occurred, a myocardial infarction in a man or eclampsia in a pregnant woman with pressures of 115/67 mmHg (SBP/DBP), leading to the delivery of a very premature boy hospitalized for 26 months at a cost of $1 million U.S. (references in 7). © *Halberg.*

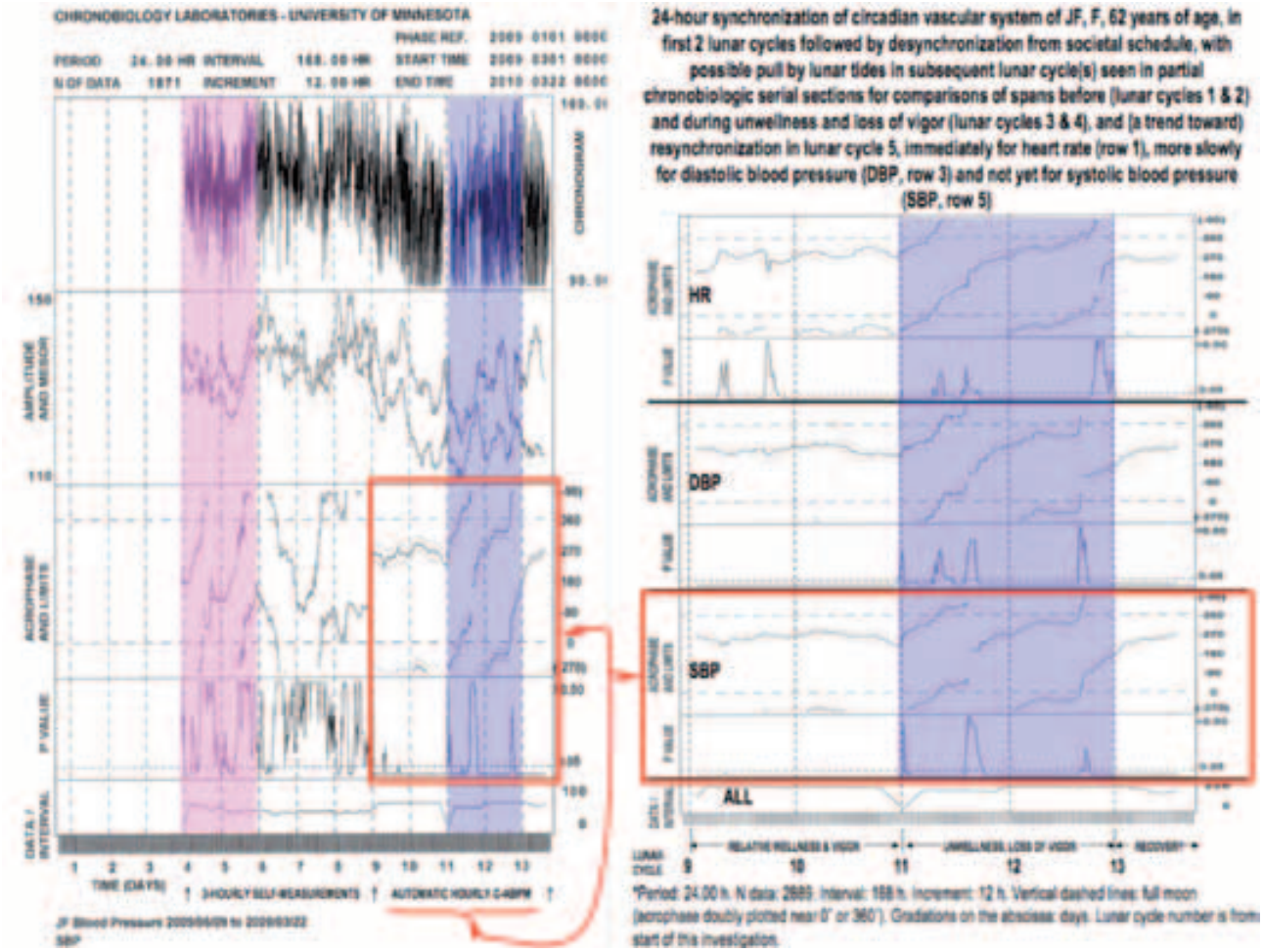


Figure 13. Left: A chronobiologic serial section of SBP of JF shows original data in the top row. They are self-measured in lunar cycles 4–8, automatically recorded by ABPM in and after cycle 9. These are interpreted chronobiologically (temporally locally) in weekly intervals. P-values in cycles 4–8 (fourth row) indicate that the dominant circadian rhythm is not consistently demonstrable in the case of self-measurements. Most P-values are above the dashed horizontal line (P=0.05). By contrast, in cycles 9–13 showing analyses of the denser automatic measurements including nightly values (see top row's now lower values), most P-values hug the bottom line (P≤0.01), documenting the indispensability of continuous ABPM monitoring, if false or incomplete diagnoses are to be forestalled in this case (and in others, not shown). Right: For cycles 9–13 only, acrophases (ϕs) of HR and DBP are shown for comparison with those of SBP. Note in cycle 11 a lengthening of the circadian period, seen as delaying obliquely ascending ϕs, scanning 24 hours (= 360˚) in cycles 11 and 12, with 24-hour resynchronization of HR, seen as horizontal ϕs, but not yet of DBP and SBP with still oblique ϕs during cycle 13. © *Halberg.*

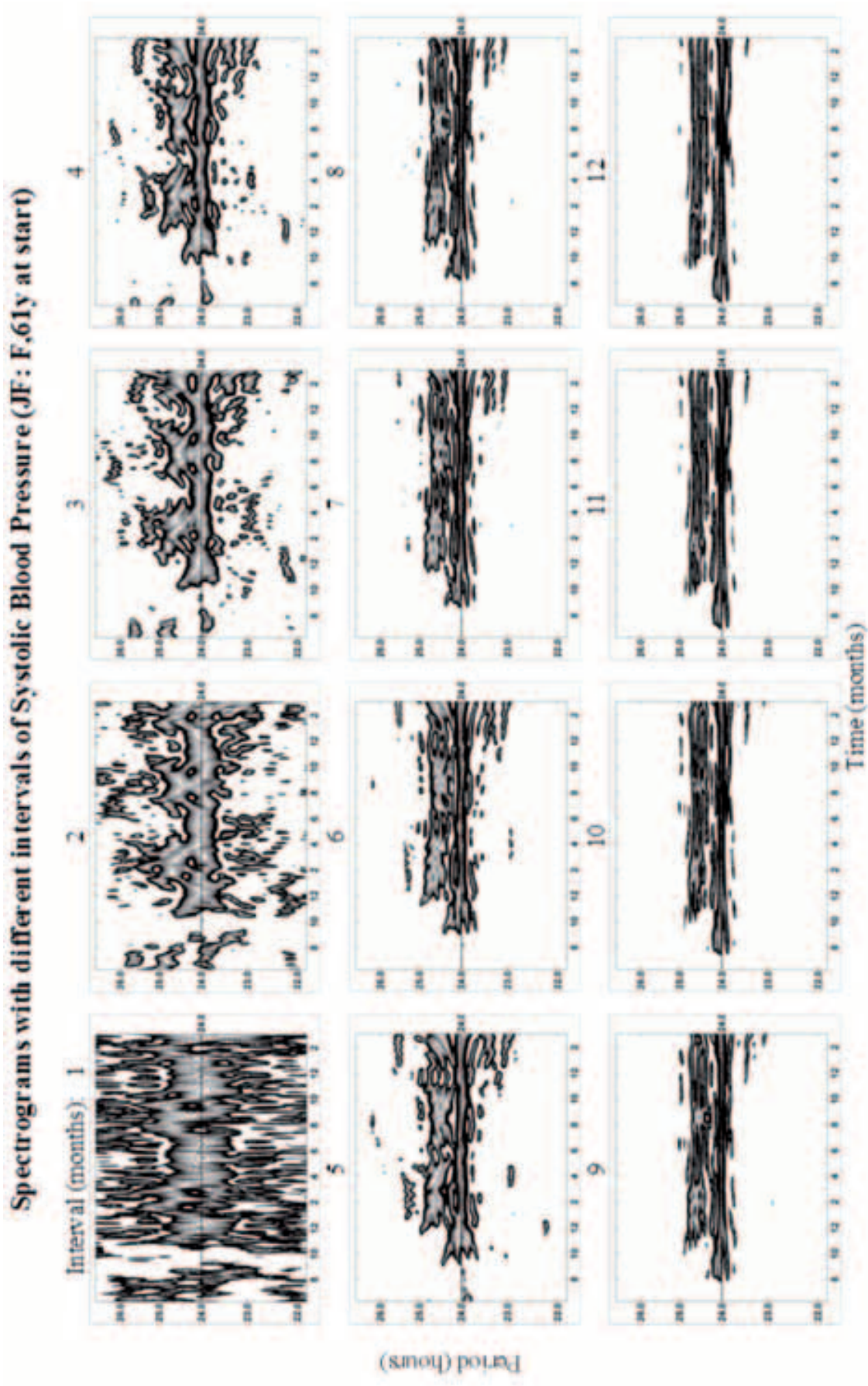


Figure 14. Spectrograms of SBP of JF, a woman 61 years of age at start of around-the-clock measurements analyzed with intervals ranging from 1 to 12 months (10). The presence of multiple periods is more clearly seen with an interval of 12 months (bottom right) than with shorter intervals, but with a loss of detail in the long intervals. Temporally local alterations (during episodes of adynamic depression, not indicated) are better seen with shorter intervals (top row). © Halbergt.

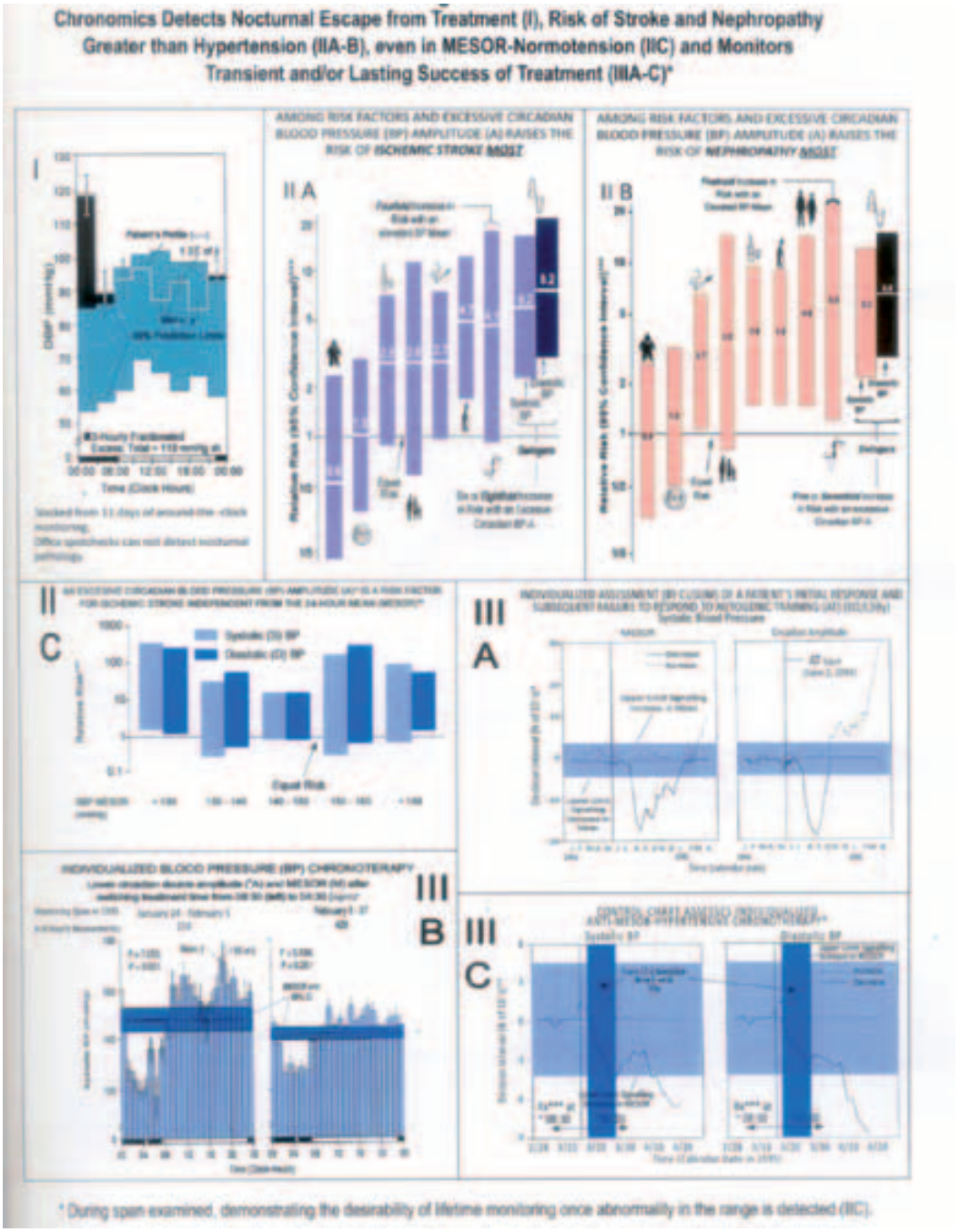


Figure 15. Illustrative results support the need for continued surveillance and for a chronomic analysis of BP records. I. Nocturnal hypertension: data stacked from 11 days of around-the-clock monitoring. Office spotchecks cannot detect nocturnal pathology. II A: Among risk factors, an excessive circadian BP amplitude (A) raises the risk of ischemic stroke most. II B: Among risk factors, an excessive circadian BP-A raises the risk of nephropathy most. II C: An excessive circadian BP-A is a risk factor for ischemic stroke independent from the 24-hour mean (MESOR). III A: Individualized assessment (by CUSUM) of a patient's initial response and subsequent failure to respond to autogenic training (AT) (EO, F, 59y). III B: Individualized BP chronotherapy. Lower circadian BP- 2A and MESOR (M) after switching treatment time from 08:30 (left) to 04:30 (right). III C – Control chart assesses efficacy of individualized chronotherapy. © *Halberg*.

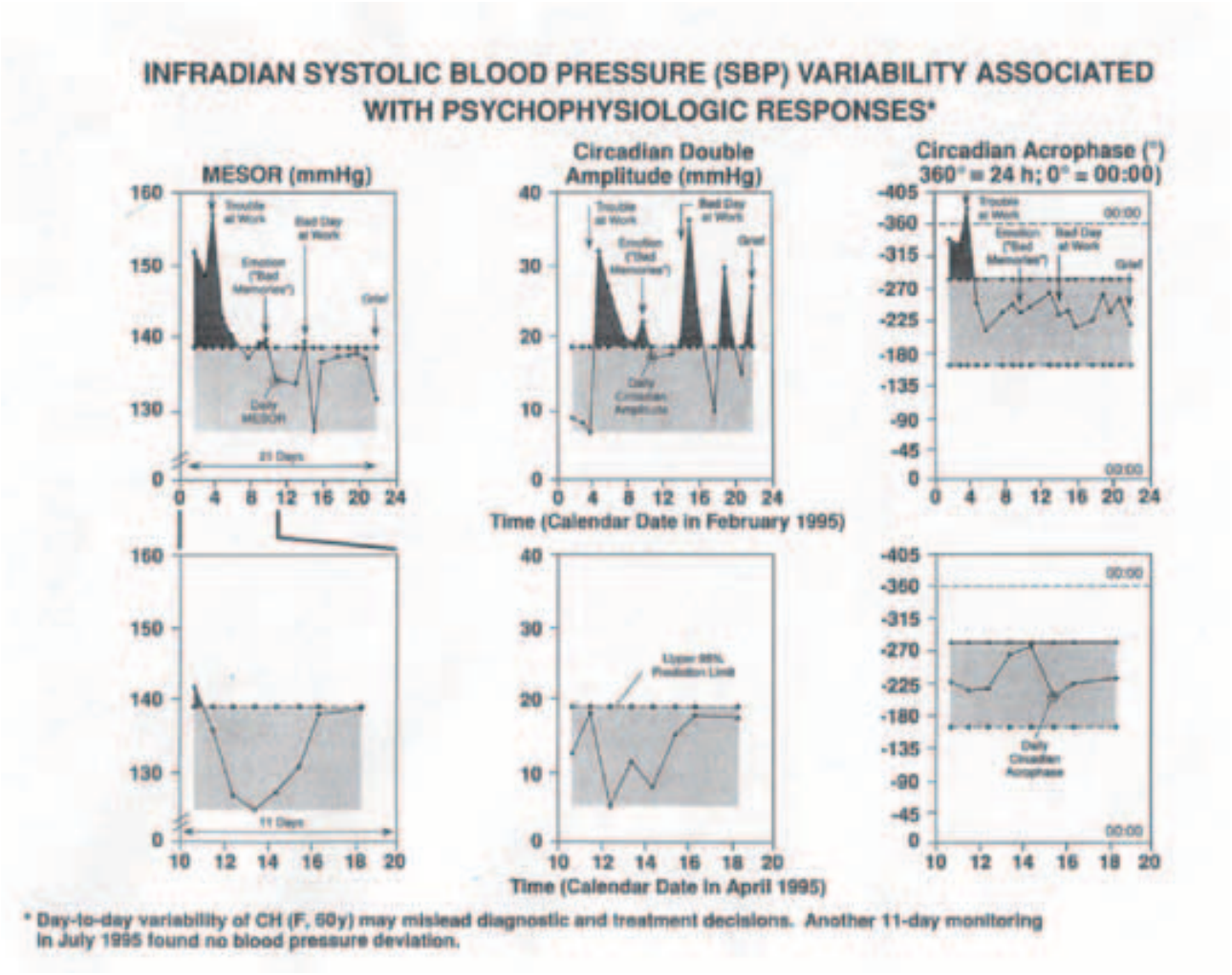


Figure 16. A.

Figure 16. A. MESOR-hypertension is detected for the first 5 days but not for the next 16 days in February (top left) or for another 11-day record in April (bottom left) in the case of a 60-year old woman (CH). The circadian amplitude is acceptable for the first 3 days in February, but is intermittently excessive in February (top middle) but not in April (bottom middle). The circadian acrophase is 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 longer than 24 hours to obtain a reliable diagnosis (17). B. Abnormality can occur while most or all measurements lie within acceptable limits. Average profiles of systolic (left) and diastolic (right) BP of FH (M, 90y) are within time-specified 90% prediction limits of healthy peers matched by gender and age (top). The fit of a 24-hour cosine curve to the data reveals the presence of CHAT for both SBP and DBP (bottom). © *Halberg.*

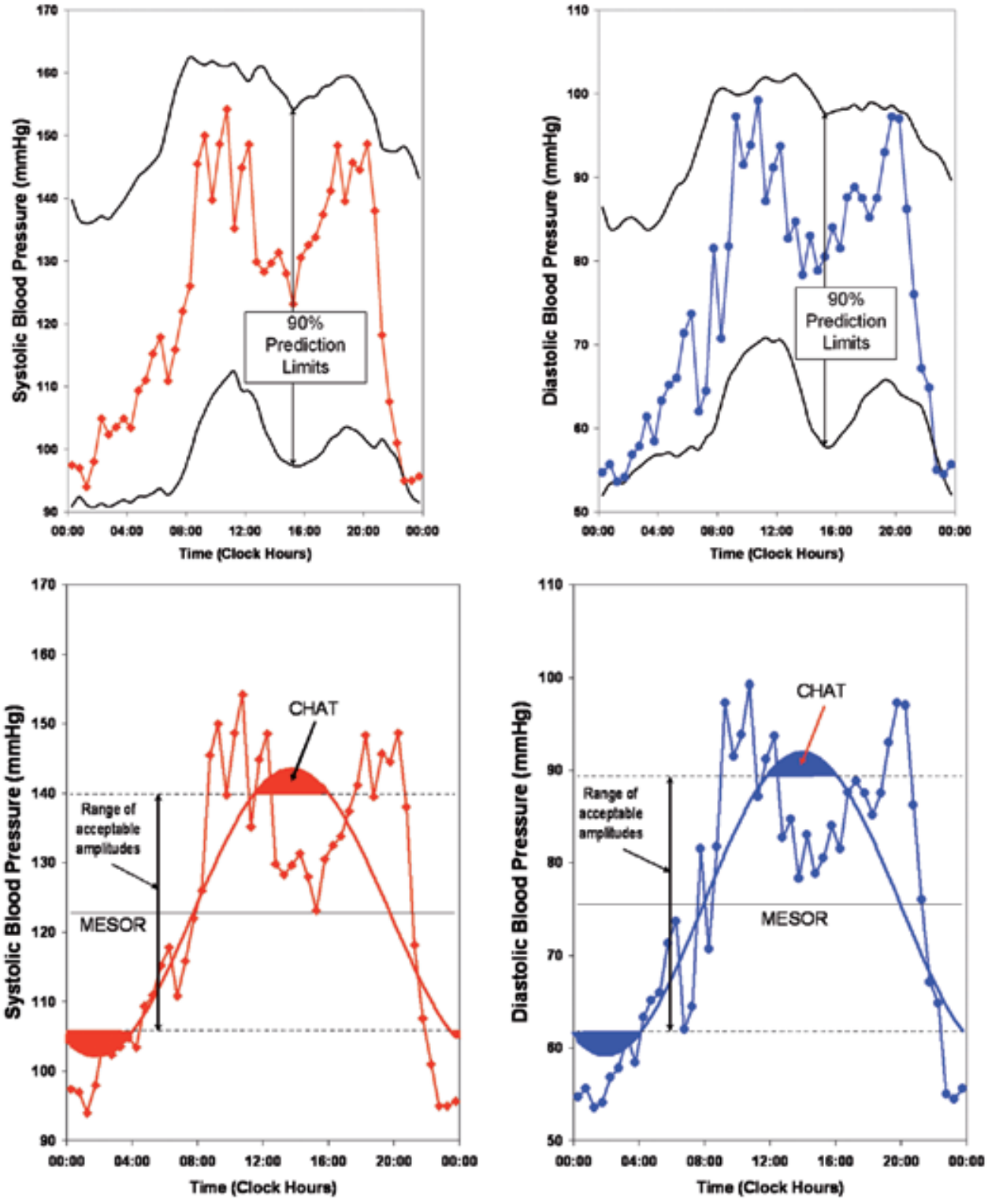

Systolic Blood Pressure (mmHg)
Diastolic Blood Pressure (mmHg)
90% Prediction Limits
Time (Clock Hours)
CHAT
Range of acceptable amplitudes
MESOR

Figure 16. B.

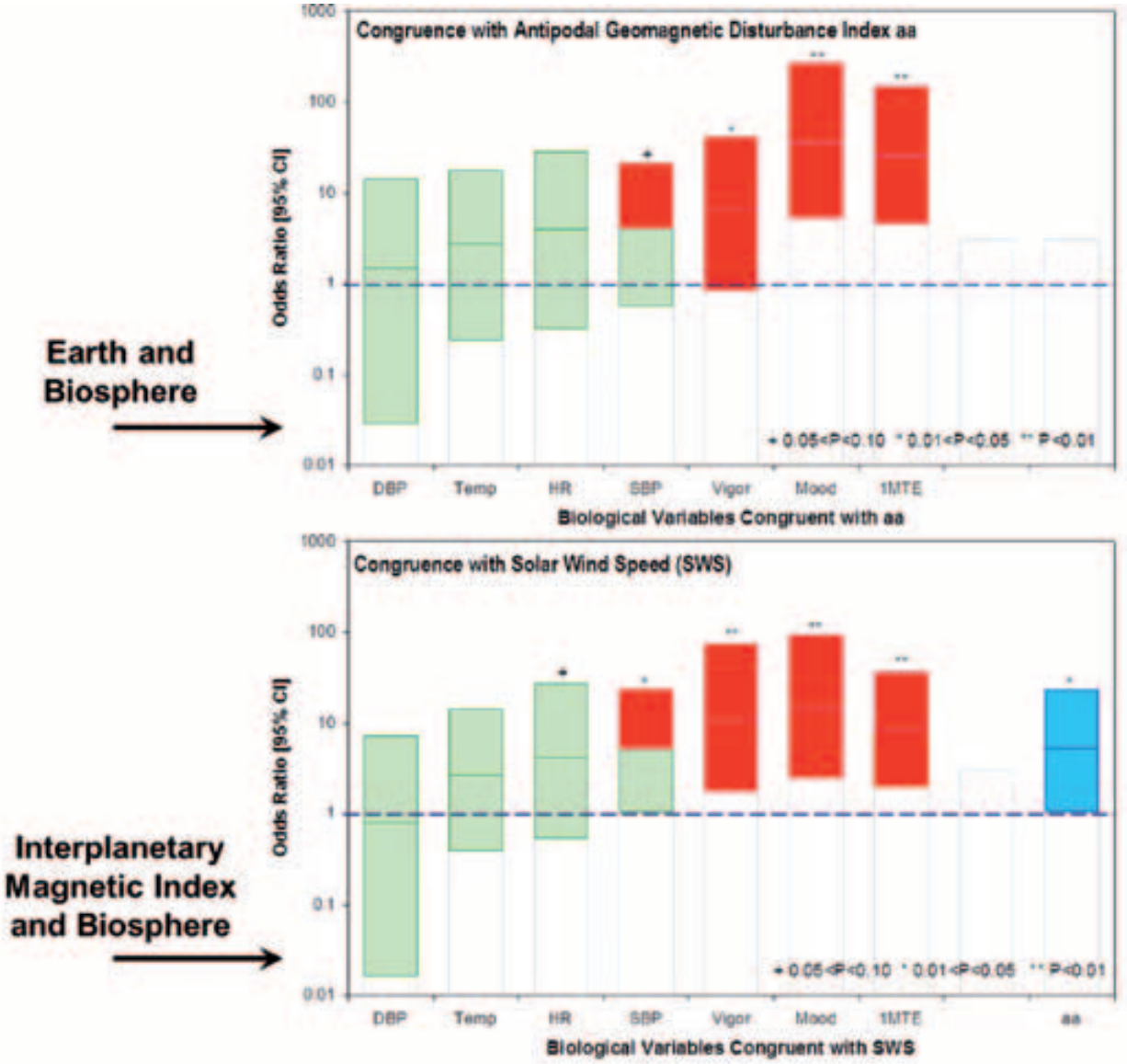


Figure 17. Human mental functions (vigor, mood and 1-minute time estimation) are as closely associated with our cosmos as is the well-known association of the sun's and the earth's magnetism (extreme lower right). Systolic (S) BP monitoring for preventive health maintenance provides data that, as a dividend, 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 CIs of 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), SBP, diastolic (D) BP 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) (64, 65). 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, 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 CIs computed using Fisher's exact test, used since the null hypothesis was rejected in some, yet not all cases. © *Halberg.*

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AN 11-YEAR CYCLE IN MATERNAL MORTALITY?

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Abstract. The detection of cycles in us, corresponding to the known average length of cycles around us, is an indispensable, but in itself insufficient step for the study of shared frequencies and of their possibly corresponding behavior. With the qualification that even similar cycles in and around us, in themselves, are not evidence for an association, we here report a hint that human pregnancy, like the human baby, may be influenced by interplanetary and/or terrestrial magnetism, a probability deserving further investigation by examining, when the opportunity arises, whether an amplification, damping or disappearance of an environmental spectral component, is associated (perhaps with a lag) with the amplification or damping of the biospheric component.

The fourteen areas of the Republic of Kazakhstan provided, via the program "Motherhood and childhood" of its Ministry of Health, data on maternal mortality, that is on the rate of death among women during pregnancy or within 42 days after the end of any pathological condition associated with pregnancy, excluding accident-related causes. The data were yearly, and each series covered 11 consecutive years, Figure 1. A decreasing trend in the data, Table 1, was removed, as shown in Figure 2. (Before attributing this trend to improved care, longer series will have to examine the possibility that the trend is at least in part contributed by a cycle with a period, τ, longer than the length of the available time series.)

Method. The detrended data were analyzed by single cosinor, first as separate series fitted to a 11-year cosine curve and its harmonics. The amplitudes and acrophases thus obtained were summarized by population-mean cosinor (1–3).

Results. The no-undecennian-rhythm assumption was rejected (P=0.007), as seen from Figure 3, displaying the average data from the 14 areas, together with the 11-year cosine curve, its characteristics being obtained by population-mean cosinor. The second harmonic, with a 5.5-year period, was also found to be statistically significant (P=0.024). The corresponding composite model is shown with the data in Figure 4, providing an improved approximation of the data.

Discussion. It has previously been reported that the human baby is a very sensitive magnetometer, exhibiting, for instance, putative solar periods, Figure 5 (4; cf. 5, 6). Figures 6A and 6B show the time course of Wolf's sunspot numbers during the span for which data on maternal mortality are available. It appears to the naked eye that the fit of an 11-year cycle alone reflects an as-yet also putative cosmic effect better than the added fit of a harmonic. Whether the harmonic reflects an alteration of the waveform and, if so, the factor(s) underlying this alteration are questions warranting further analyses on longer series. Whether the pregnant mother is also influenced by the cosmos, perhaps by factors related, among others, to the about 11-year Horrebow (7)-Schwabe (8) sunspot cycle, must be established by longer series that allow more than cross-correlation and cross-spectra or cross-wavelets, but the fact that short series, of the length analyzed herein, can provide results validated by longer ones, has been documented (9). Long time series covering several decades will be essential to see whether any environmental cycles from space or terrestrial weather influence maternal mortality, among other human affairs (10, 11). Amplifications, damping or lack of detection of the environmental cycles could then be tested for corresponding changes in the biospheric component(s), with the possibility that in the case of disappearance of an environmental cycle, the biospheric component may be damped, but may persist if it is genetically coded (12, 13) and surfaces above the noise level,

as it did in Figures 3, 4 and 6 (while the naked eye fails to reliably detect any cycle in the original or detrended data, shown in Figures 1 and 2).

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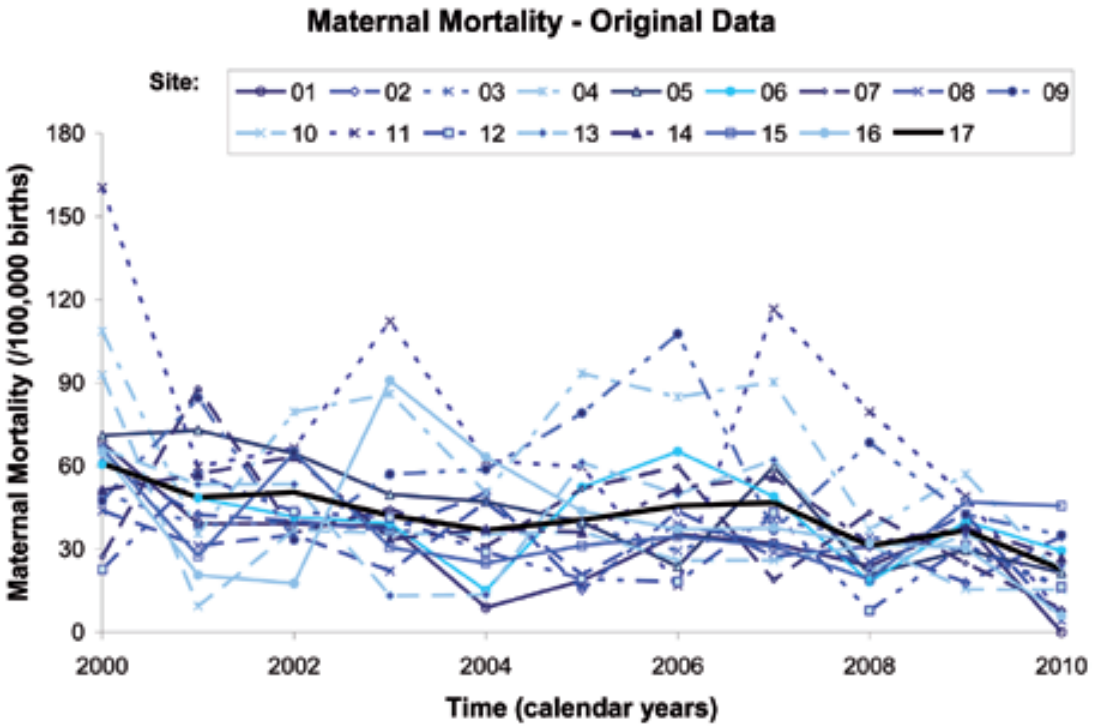

Figure 1. Original yearly data (2000–2010) on maternal mortality from 14 areas of Kazakhstan, for two towns and for the country as a whole. © Halberg.

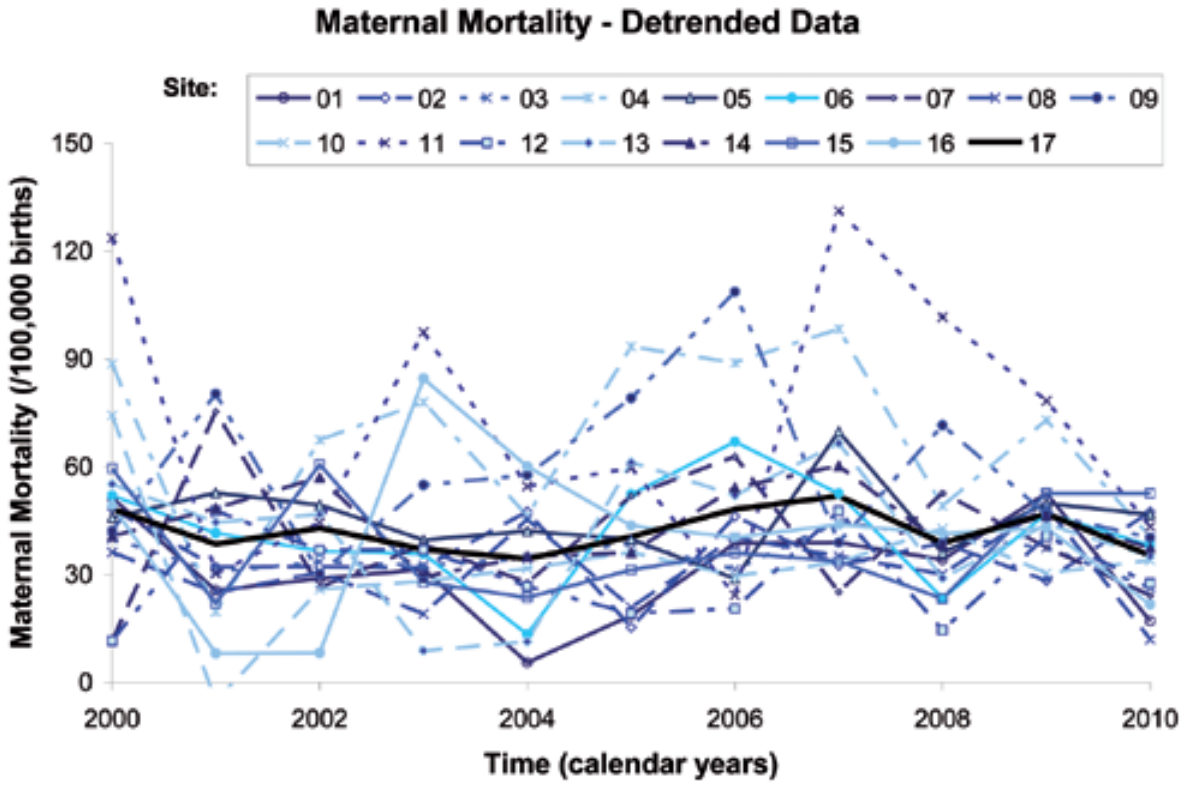

Figure 2. Since maternal mortality decreases numerically in all 16 sites investigated and, with statistical significance, in Kazakhstan as a whole (see Table 1), yearly data were detrended prior to analysis. © Halberg.

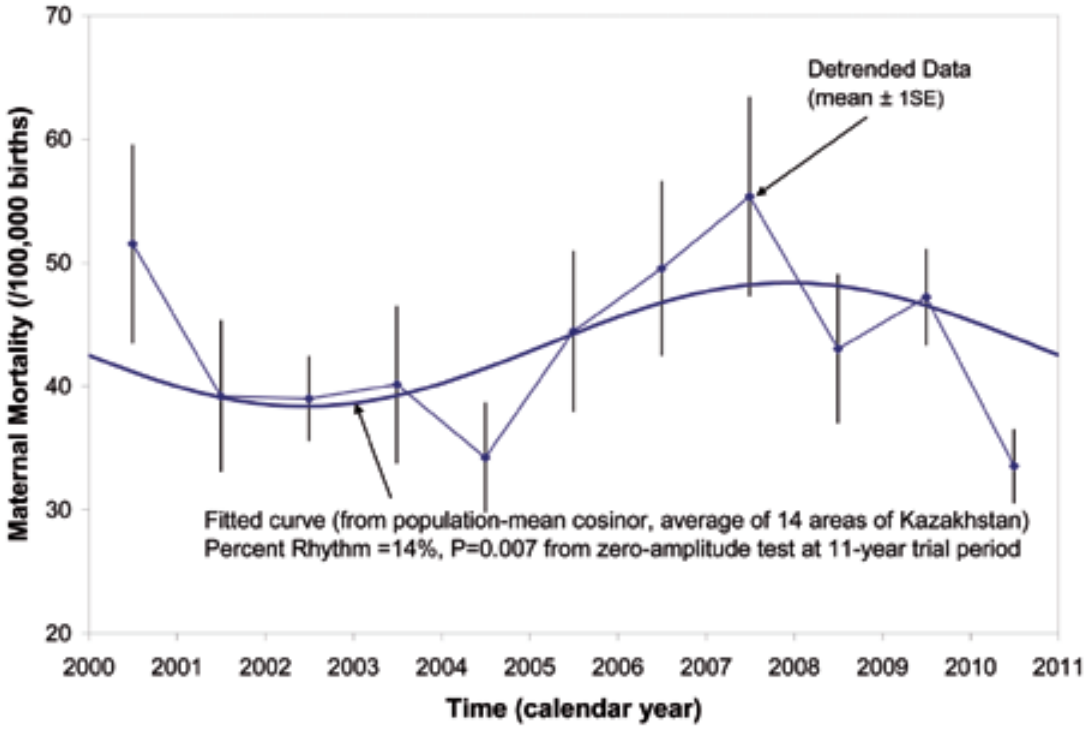

Figure 3. Yearly means and standard errors (SE) of maternal mortality for the 14 areas of Kazakhstan are fitted with a 11-year cosine curve detected with statistical significance by population-mean cosinor. © Halberg.

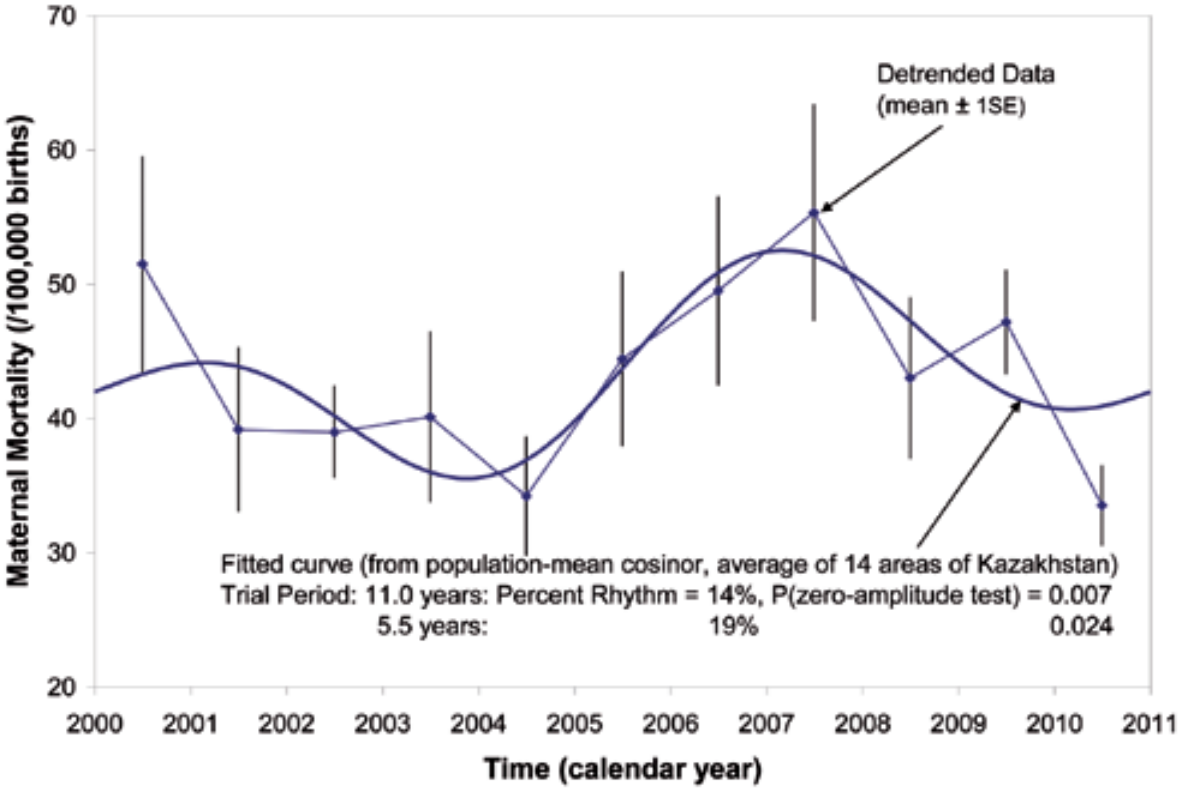

Figure 4. By population-mean cosinor, the second harmonic with a period of 5.5 years was also detected with statistical significance. Accordingly, the yearly means are fitted with the composite model, including cosine curves with periods of 11.0 and 5.5 years. © Halberg.

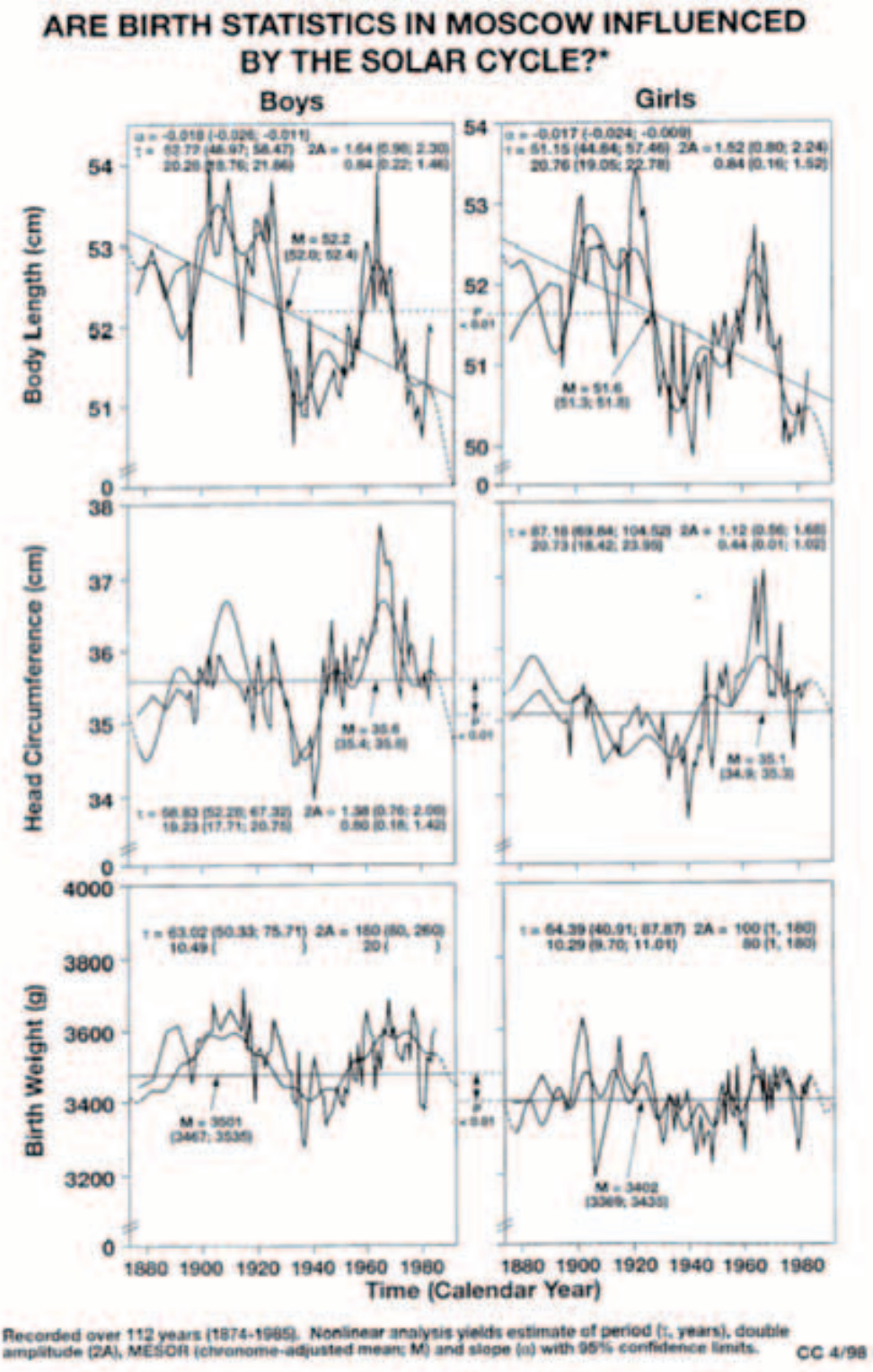

Figure 5. Body length, head circumference and weight at birth in Moscow, Russia, measured between 1874 and 1985 (112 years), is characterized by about 10.5- and/or 21.0-year cycles, which are in keeping with a possible modulation of human morphology by the solar activity cycle. Not shown herein is a para-tridecadal cycle detected by wavelets and validated with the 95% confidence interval of its period (13). © Halberg.

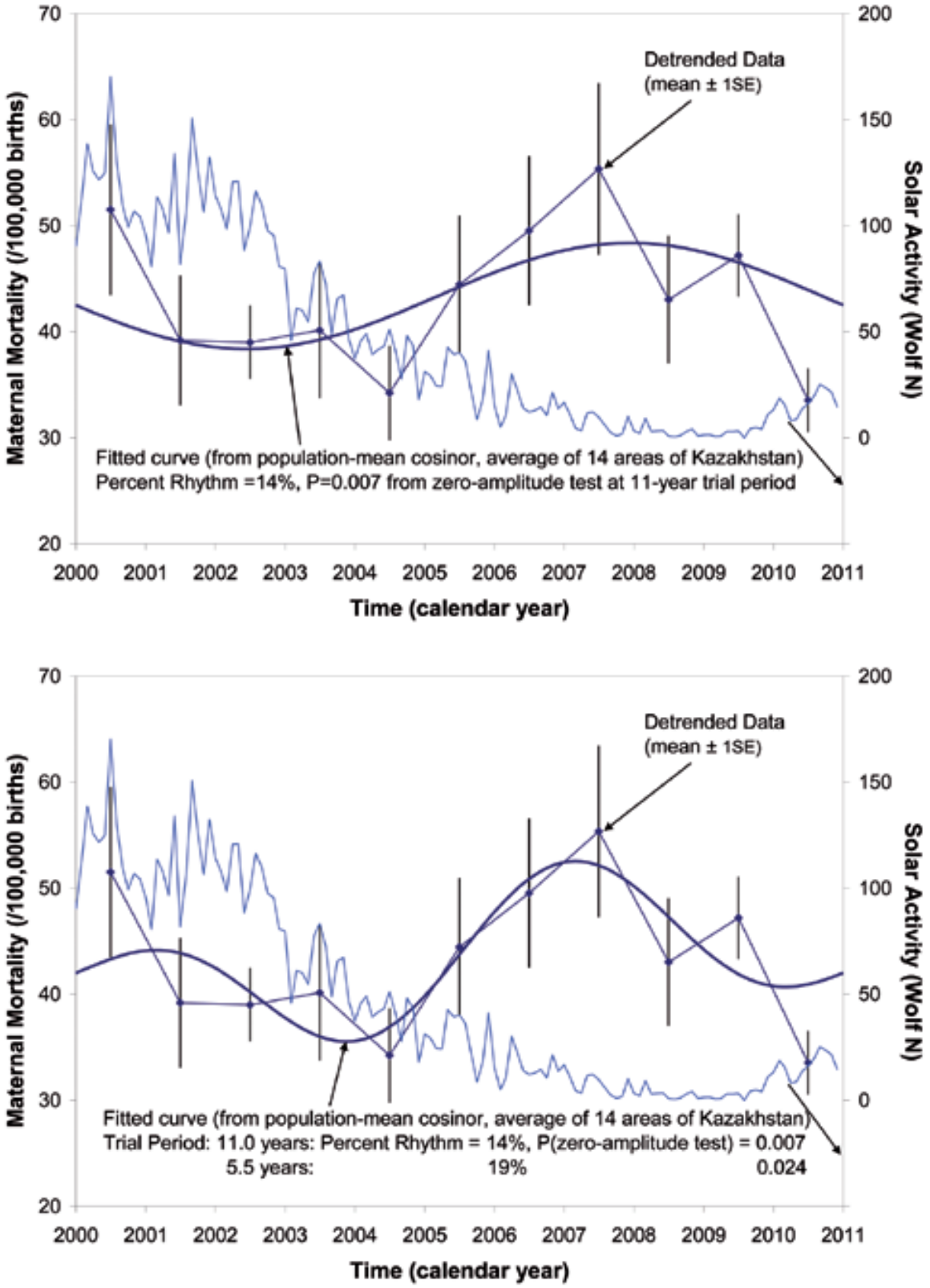

Figure 6. Yearly means of maternal mortality fitted with the 11-year cosine curve are plotted together with monthly Wolf numbers during the same 11-year span. A reverse relation is suggested (A). Validation of this finding will require analysis of similar data over longer spans. The negative relation between maternal mortality and solar activity is less obvious when Wolf numbers are displayed with the composite model including cosine curves with periods of 11.0 and 5.5 years (B). © Halberg.

Table 1: The decreasing trend in maternal mortality in different provinces and two cities (with the status od State importance) of Kazakhstan and periods detected in detrended data*

Geographic location	Site N	r	P	Period (years)
Akmola	01	-0.619	0.042	
Aktobe	02	-0.639	0.034	~2.2
Almaty Province	03	-0.786	0.004	
Atyrau	04	-0.462	0.152	
East Kazakhstan	05	-0.845	0.001	
Jambyl	06	-0.361	0.276	
West Kazakhstan	07	-0.478	0.137	
Karaganda	08	-0.411	0.210	~2.2
Kyzyl-Orda	09	-0.147	0.665	
Kostanay	10	-0.556	0.076	
Mangistau	11	-0.550	0.080	
Pavlodar	12	0.502	0.116	
North Kazakhstan	13	-0.363	0.272	~5.5
South Kazakhstan	14	-0.576	0.063	~5.5
Almaty city	15	-0.294	0.380	
Astana city	16	-0.426	0.191	
KAZAKHSTAN	17	-0.817	0.002	

*Periods from rhythmometric summary revealed 2nd and 5th harmonics of 11 years, each to be statistically significant in two areas, albeit without correction for multiple testing. Note that 8 of the first 14 correlation coefficients (r) are above 0.5 (11 are above 0.4 and 12 are above 0.35).

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HUMAN BABIES: A SLOW-TO-READ, SENSITIVE POPULATION MAGNETOMETER, ALSO READ BY WAVELETS

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Abstract. Wavelet analyses can usefully complement the nonlinearly extended cosinor and prompt focus on para-tridecadals, cycles whose 95% confidence interval of the period falls within the range of near 30–40-year length. They here complement the analyses of nonstationary neonatal somatic cycles. In this case, wavelets served for the resolution of a para-tridecadal for body length at birth during part of the time (after 1930), along with other cycles previously detected in neonatal body length, head circumference, and birth weight. Chronobiological serial sections with the frequency revealed by wavelets in neonatal body length after 1930 document the statistically significant presence of a para-tridecadal of 32.95 years, or with a frequency near it, before 1930 as well. The global approaches by least squares spectra of an entire series and the local gliding windows of sections of the series make this approach glocal, whereas wavelets are glocal in themselves as an addition to the combined glocality of spectral windows of an entire series and sections thereof. Wavelets, in turn, can be complemented by further purely local approaches such as chronomic serial sections at a certain period of interest.
Aim. Application of a set of complex Morlet functions, wavelets with adjustable parameters (1; cf. 2–3), to three anthropometric time series, each covering 112 years (y), serves to compare findings with results (4) obtained earlier by the nonlinearly extended cosinor (5–7), to examine the extent of complementarity between the cosinor and the particular wavelets used in dealing with nonstationary periodicities and to apply wavelets to annual data on the antipodal (aa) geomagnetic index which covers data over a similar span using the same time-frequency parameters as those used for the anthropometric data. The need to vary such parameters is seen in a display of group sunspot numbers.
Background in aa. The geomagnetic aa-index (annual values spanning 130 years) is a global geomagnetic activity index, derived from the local (K) indices from two approximately antipodal observatories, with units of 1 nT. While laboratories providing the data for aa changed with time, current observatories used are Hartland in the UK, operated by the British Geological Survey, and Canberra in Australia, operated by Geoscience Australia. Since it is based on data from only two observatories, it is the simplest of all the 3-hourly planetary indices. Provided averages over 12 hours or longer are used, the index strongly correlates with the ap and am indices, which are derived using data from more extensive observatory networks.
The main advantages of using aa indices are that the time series spans go further back (to 1868) than those of most other planetary index time series. Up-to-date values are also produced and made available on a weekly basis.
General background. The nonlinearly extended cosinor serves for the analysis of a time series as a whole (globally) in combination with moving spectral windows and/or chronobiologic serial sections for examining a component (also locally) in time, i.e., for the changes occurring at a given frequency in sections of the span investigated. Wavelets in turn provide an overall view by glocal (global and local) analyses in time. In the case on hand, the two methods resolve complementary aspects of putative signatures of the cosmos in neonatal anthropometry. Thus analyzed, we found biospheric population rhythms with serially-independent sampling as to individuals, with each set of babies examined in a given year contributing a single measurement to each of three long time series (4), Figure 1. Some of the periods found can also be detected in individuals' longitudinal measurements, actually continued for decades more densely around the clock. Longitudinally in

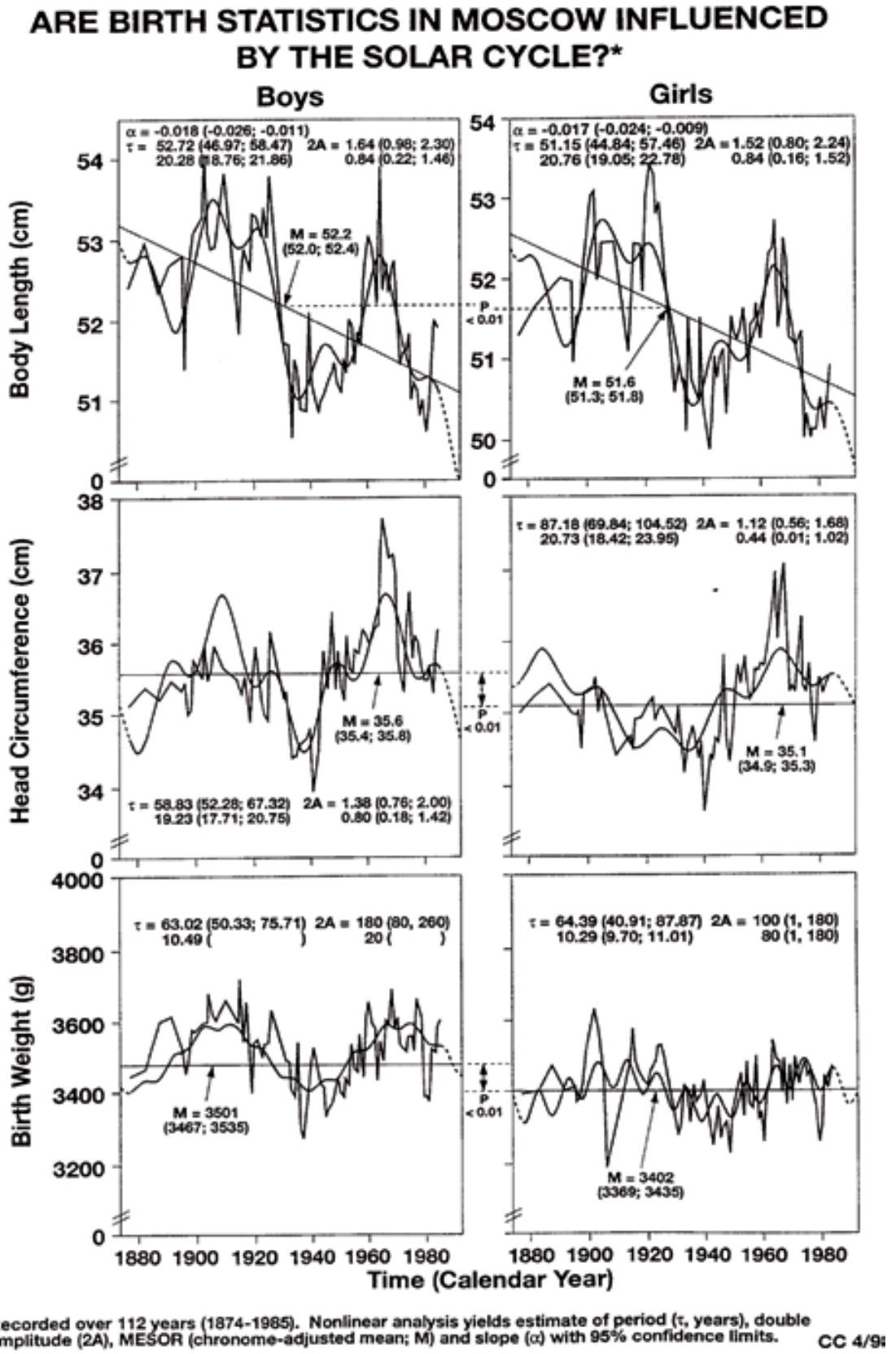

Figure 1. Solar cycles' signatures in a biospheric magnetometer: the human neonate (4). See Figures 2A and 2B for the about 33-year BEL, that was missed until it appeared prominently after 1930 in wavelets, Figure 3. © Halberg.

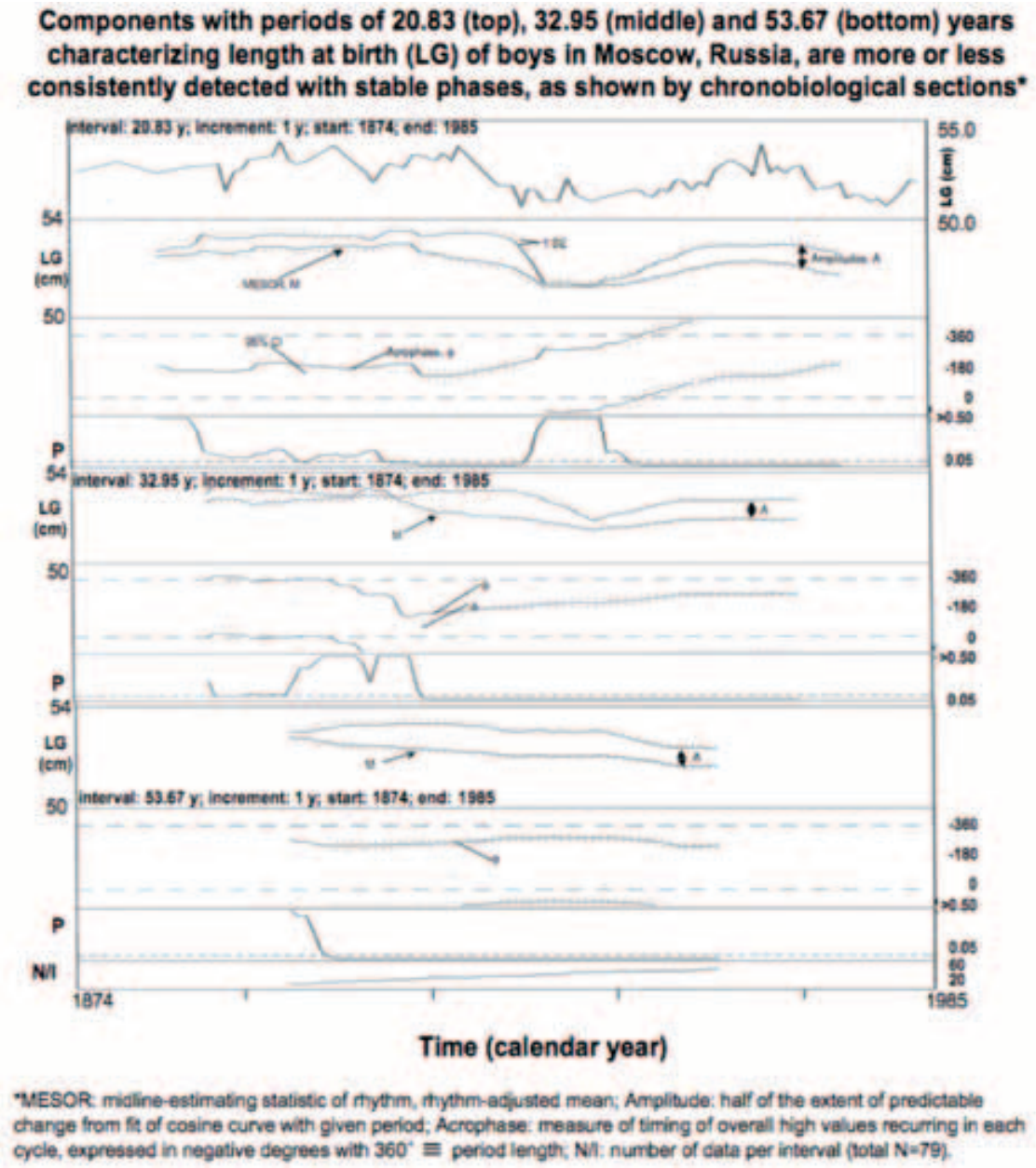

Figure 2A.

single individuals and transversely in populations, humans constitute sensitive magnetometers and still broader cosmometers, revealing, among others, Schwabe, Hale and para-tridecadal Brückner-Egeson-Lockyer (BEL) cycles, Kondratiev's about–50-year periods and near–60-year or longer cycles. All are aeolian, changing in period, amplitude and/or phase. The BEL came to the fore in the neonatal data on body length by the combination of the methods here used and prompted additional extended cosinor analyses and chronobiologic serial sections that glocally showed the intermittency of the BEL. Whether these cycles in us and in the aa index around us evolved with the former mirroring the latter, subtraction and addition by the sun (in amplifying, damping or even losing and regaining a frequency, respectively) tell the extent to which the rhythms in the biosphere of populations still respond to their counterparts in space weather by amplification or dampening but persist in the absence of the environmental cycle, as do some rhythms in individuals (Figure 7 in [8]).

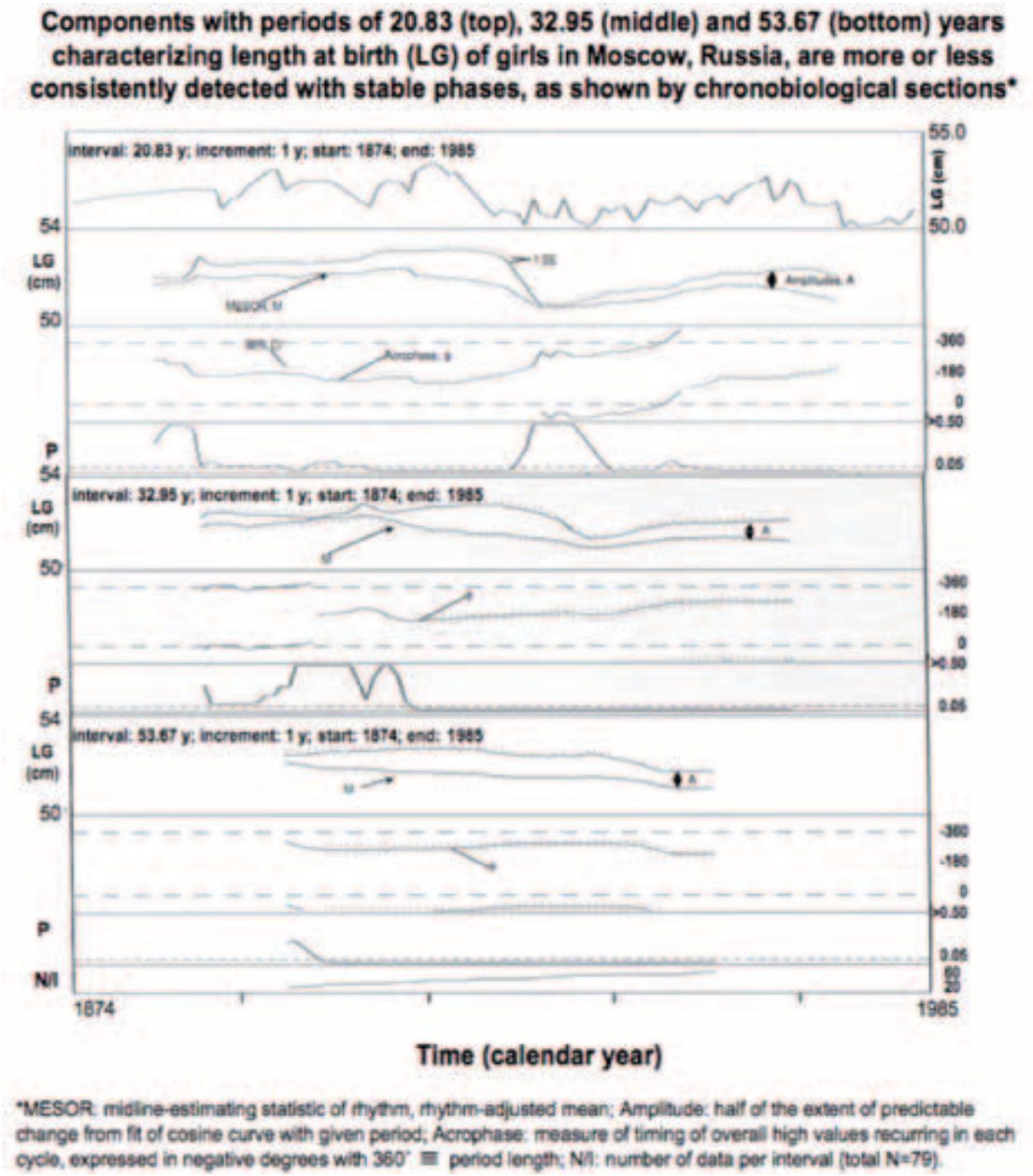

Figure 2B.

Figures 2A and 2B. Body length at birth in boys and girls, respectively, is characterized by 3 main spectral components, some with intermittent reductions in amplitude (distance between the 2 curves in sections 2, 5 and 8). Didecadal (top section) and tridecadal (middle section) but not quindecadal (bottom section) cycles show relatively short spans of aeolian loss of statistical significance in sections 4 and 7 and some drifting acrophases, the latter in keeping with changes in period. © Halberg.

In any event, our methodologic point is that a combination of glocal analyses – global spectra and/or spectral windows combined with gliding spectra and chronobiological serial sections on the one hand and a priori glocal wavelets complement each other in a unified science aimed at analyses after the alignment of anthropometric, biological and cosmophysical mapping, prospectively and in archives. Basic and applied purposes are thus served. First, time structure maps, physical or biological, represent reference values that dynamically define normalcy, including, by the use of certain physiological variables, a quantification of health (8). Second, analyses of physiological recordings aligned with cosmo-helio-geophysical data detect health hazards such as those posed by magnetic storms (9–11). Third, ongoing ontogenetic and phylogenetic mapping (12) may allow hypotheses concerning (if not cosmogeny, then) at least effects from beyond the solar system, if sensitive physiological indices change before a magnetic storm in interplanetary space, as human blood pressure may do, rather than concomitantly with a storm, as may human heart rate, or on the day following a magnetic storm, as human myocardial infarctions seem to do (9, 10; cf. 13). Available impressions from opportunistically available data await systematic ongoing analyses. Fourth, as humans venture further into extraterrestrial space, as on earth away from hospitals, the vascular monitoring for the early detection of disease risk syndromes, as a step toward the timely implementation of countermeasures for reducing risk, becomes a most important task, since illness can jeopardize a mission. Fifth, a cross-sectional human and eventually a longitudinal comparative physiological approach, examining the evolution of the physiological time structures, can lead to testable hypotheses concerning the origins of life. *Omnis cyclus e cyclo.*

Reference data: Anthropometry in Moscow by the late Boris Nikityuk. Body weight and length and head circumference at birth were recorded from random samples of 25–150 babies in Moscow, Russia, over 112 y. The major component published (4) for body weight was of 63.02 y for boys with a CI (95% confidence interval) extending from 50.33 to 75.71 y, Figure 1 (4). In girls, body weight underwent a cycle of 64.39 y (CI: 40.91–87.87 y). Both boys and girls showed an added circadecadal (Horrebow-Schwabe) component of much smaller amplitude which was statistically significant only in girls (10.29; CI: 9.70, 11.01). In birth weight, a major component of variation common to boys and girls is an about 63–64-y cycle, validated nonlinearly.

As to head circumference, the about 60-y component was dominant in boys and a longer periodicity dominated in girls. Other components found in the least squares spectra were circadidecadal signatures of the Hale cycle of sunspot bipolarity (of about 20 years), present in head circumference and body length at birth.

The major component in neonatal body length in both genders was of about 50 years, a Kondratiev cycle reported in economics (14) and found in the incidence of stroke in several geographic locations (10, 15). Table 1 summarizes the periods found in a more recent nonlinearly extended cosinor analysis of body length, prompted by results from wavelets. The table includes a BEL. Figures 2A and 2B show the time course of these several components, including variations in amplitudes and in particular also acrophase drifts that may reflect drifts in periods.

Results from Morlet wavelets. The wavelets in Figure 3 are glocal in that they not only reveal by (arbitrary) colors the relative prominence of different components, but also the time course of the periods that are significant at the 5% level, since the black contour lines are the boundaries of confidence regions at 95%. Note that the ordinate is logarithmic, to resolve a wide range of frequencies to be examined (1, 16). Table 2 shows some of the periods detected by each of the two methods used and reveals a reasonable agreement between them. These can be complemented with focus on specific frequencies in Figures 2A and 2B. The row of P-values in serial sections reveals that the para-tridecadal component is not absent before 1930 but instead is statistically significant at the beginning of the record with a relatively short interruption of the P-values below 5% apparent in

Figure 2A for boys, hardly surprising if the biosphere echoes the nonstationarity of its cosmos. Figure 4 demonstrates a very broad BEL and justifies the increasingly wider definition of the para-tridecadal BEL as an aeolian (nonstationary) band with a widely changing period, τ, and/or phase having a 95% confidence interval of τ around the 30–40-year period range. With this qualification, the display in Figure 4 is in keeping with the analysis of a para-tridecadal in neonatal body length on top of Figure 3, which gains in prominence after 1930 (changing from yellow to pink). Figure 5 in turn presents the best known solar cycle in the band from 9–12 y, generally accepted to change coherently with the variation of geomagnetism.

Methodologic discussion. To cite General Sir Edward Sabine, "... it is certainly a most striking coincidence, that the period, and the epochs of minima and maxima, which M. Schwabe has assigned

Table 1: Period(s), τ, in body length at birth in Russia 1874–1985: data of Boris Nikityuk*

	Boys (overall standard error: 0.44)	Girls (overall standard error: 0.47)
MESOR	52.224 (51.962, 52.687)	51.564 (51.288, 51.840)
Slope	-0.017 (-0.027, -0.008)	-0.015 (-0.025, -0.005)
Adjusted period	53.671 (46.12, 61.23)	53.666 (42.00, 65.33)
Amplitude	0.76 (0.37, 1.14)	0.66 (0.21, 1.11)
Acrophase	–276˚ (–247, –305)	–274˚ (–237, –311)
Adjusted period	32.404 (29.35, 35.13)	33.487 (25.88, 41.09)
Fundamental amplitude	0.38 (-0.00, 0.75) [0.21, 0.54]	0.43 (0.00, 0.87) [0.24, 0.62]
Acrophase	–243˚ (–187, –300)	–207 (–151, –263)
Adjusted period	20.441 (18.31, 22.57)	21.217 (19.18, 23.25)
Fundamental amplitude	0.42 (0.28, 0.55)	0.47 (0.31, 0.62)
Acrophase	–184˚ (–129, –240)	–158˚ (–109, –208)

*95% confidence limits in ( ) are conservative; in the case of a very slight overlap of zero beyond the second decimal, 1-parameter limits are given in [ ].

Table 2: Comparison of some periods (τ) in Figure 1 with periods of wavelets in Figure 3*

τ=52.72, 20.28	WA 53–38,20	τ=51.15,20.76	WA 53–38,20
τ=58.83, 19.23	WA 64,20, 9.8	τ=87.18,20.73	WA 64,20
τ=63.02, 10.49	WA 64,12.6	τ=64.39,10.29	WA 64,12.6,9.8

*There are some little differences on the periodicity values detected by the two methods, but essentially the results are concordant. A 32.4-year component in Table 1 was found after the wavelet result. Wavelet analysis shows strong and **wide bands** (in general better visible in the case of boys), and the exact global peak spectral values are not always easy to point out. The appearance of the near 60-y periodicity band in four of six series analyzed is of interest. Some more localized solar cycle type periodicities are also visible and it is useful to see their time evolution. Future longer time series, on a broader population, will be needed to allow us to better characterize and refine the above detected periodicities.

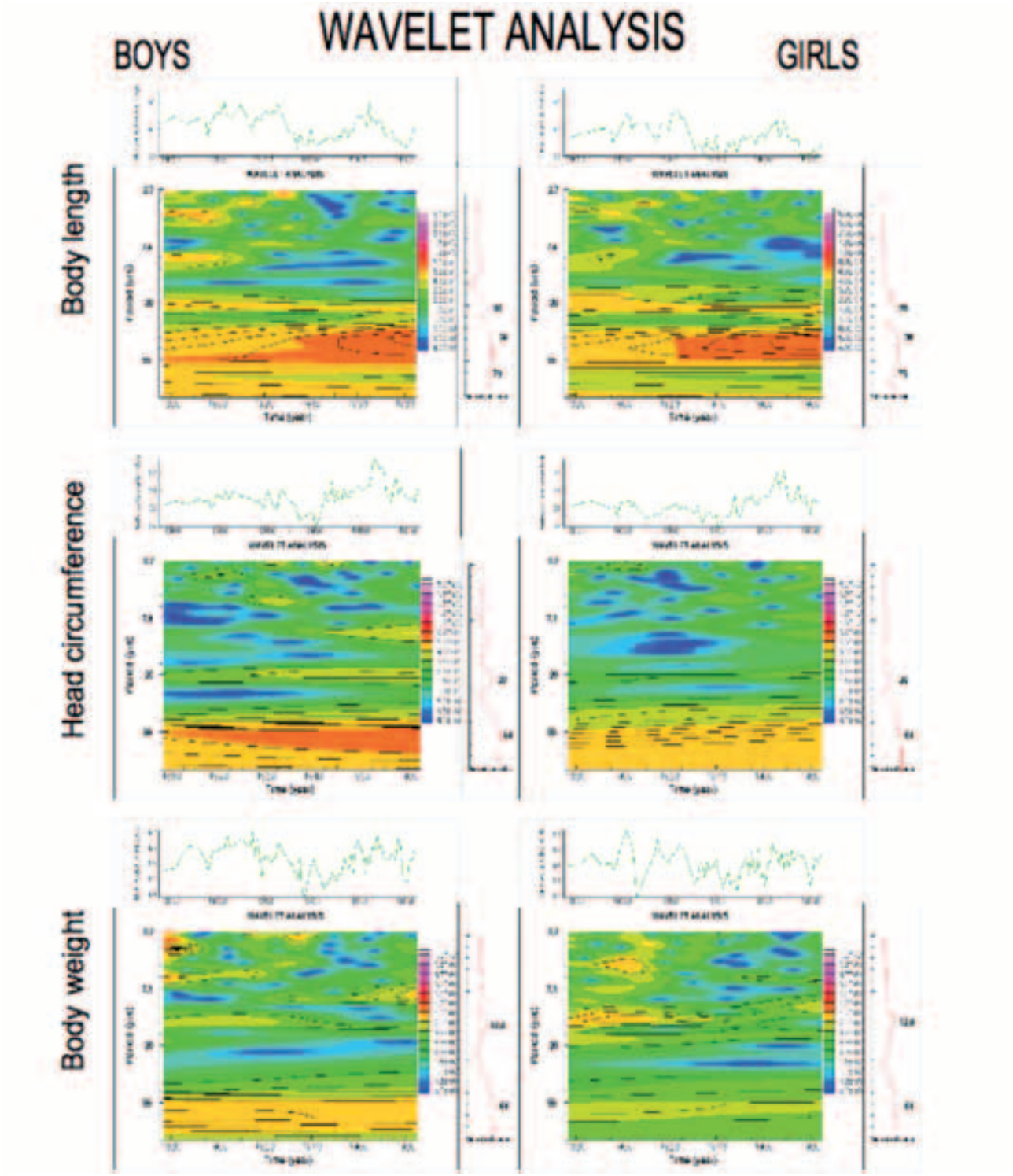

Figure 3. Morlet wavelets of the late Boris Nikityuk's anthropometric data reveal time course, among others, of the signatures of periods listed in Figure 1 and, after 1930, a para-tridecadal signature as well.

to the variation of the solar spots, are *absolutely identical* with those which have here been assigned to the magnetic variations" (17; italics ours). With the data that became available in the interim, however, it is clear that helio- and geomagnetism have not behaved identically. As seen in Figure 6, geomagnetism is sometimes congruent with solar activity, but on occasion it is not. Figure 7 shows the most sensitive reflection of geomagnetism in human mood by the criterion of shared periods. We find that the odds ratio of this association has a CI (95% confidence interval), whose lower limit is above the upper limit of the CI of the association of interplanetary and terrestrial magnetism (18). Figure 5, regarded as an accurate long-term wavelet analysis of Schatten's sunspot data, shows the Horrebow (19)-Schwabe (20), but misses the para-tridecadal BEL (21). When different time-frequency parameters of the same method have not been used, with wavelets or spectrograms (22), different methods may serve the purpose of detecting often "hidden" aeolian cycles.

General discussion. As to the recovery from the Little Ice Age, a prominent geophysicist indicates the need to assess multidecadal periodicities, adding that they are "natural" (Syun-ichi Akasofu's emphasis) phenomena and that they have to be taken into account "in order to determine the contribution of the manmade greenhouse effect" (24). By contrast, "Identifying [multidecadals] correctly and

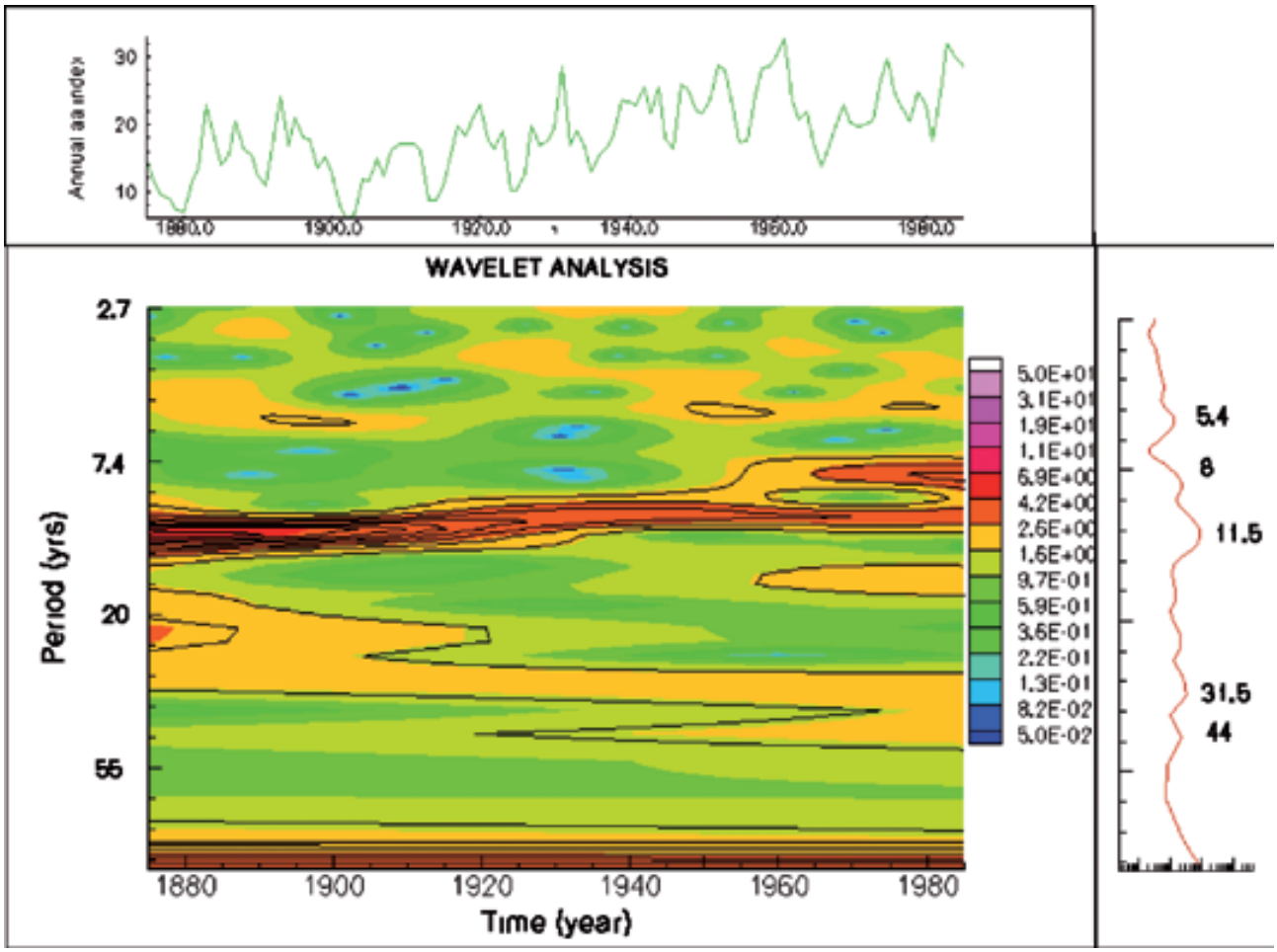

Figure 4. Morlet wavelets reveal, in the antipodal geomagnetic index, the time course of periods centered on 5.4 -(8–11.5) y and 31.5 – 44.0 y. Note the broad yellow band starting near the about 20y Hale cycle and the near 30y BEL cycle, periodicities putatively associated in part with changes with long-term solar activity.

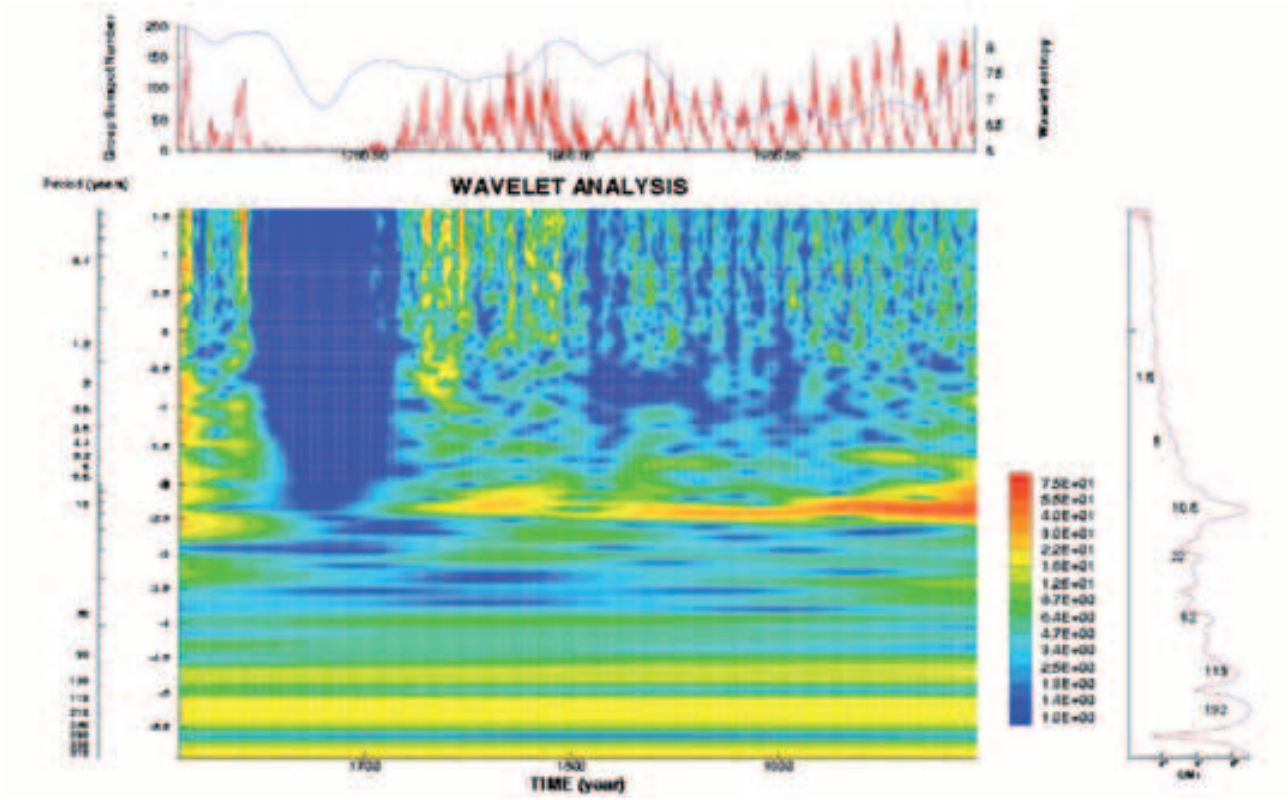

Figure 5. With the particular time-frequency parameters used, an about–10–11y band is seen in group sunspot numbers (Hoyt and Schatten, Solar Physics 1998; 179: 189–217, and Solar Physics 1998; 181: 491–513), but any para-tridecadal trace is largely missed, a demonstration of the need for analyses with different time-frequency parameters.

accurately", also Akasofu's plea, is hardly the explicit concern of others focusing on the length of the solar cycle as an indicator of solar activity associated with climate (25) that reveals a para-tridecadal Brückner-Egeson-Lockyer (BEL) cycle in environmental temperature, human affairs and global warming (23; cf. 26–31), an indispensable control, with notable exceptions (32, 33), is ignored.

Wu et al. write that the variability with respect to the multidecadal trend is not distinguishable from that of white noise (p. 14891), while on p. 14892 we read that "... the overall EMD [empirical mode decomposition] trend and the multidecadal variability appear to be quite stationary in the whole data span" (34). This multidecadal variability is described as the 65y cycle, without concern for its uncertainty, which, in our hands, exceeds 4 y for air temperature 1850–2008, Figure 8 (24). Akasofu's plea regarding natural cycles is exactly ours and was documented in an analysis of multidecadal rhythms including environmental temperature, invited by the journal Geophysical Processes and Biosphere (21). Our paper was published bilingually after translation into Russian by Dr. Alexander Sidorin, to whom the authors are sincerely indebted (a well-intended backtranslation into English by the journal's staff [insisted upon by the editor], however, in some places mirrors neither our views nor our style).

In the year since the first publication of our review, the data on rainfall in Sydney published by Charles Egeson (26) (aka J.J. George) (27) have also been meta-analyzed and published, Figure 9 (27), and other accumulating biospheric data sets have been updated by further (partly meta-) analyses. In particular, the freezing/breakup dates of rivers in (23), among related endpoints, were the concern

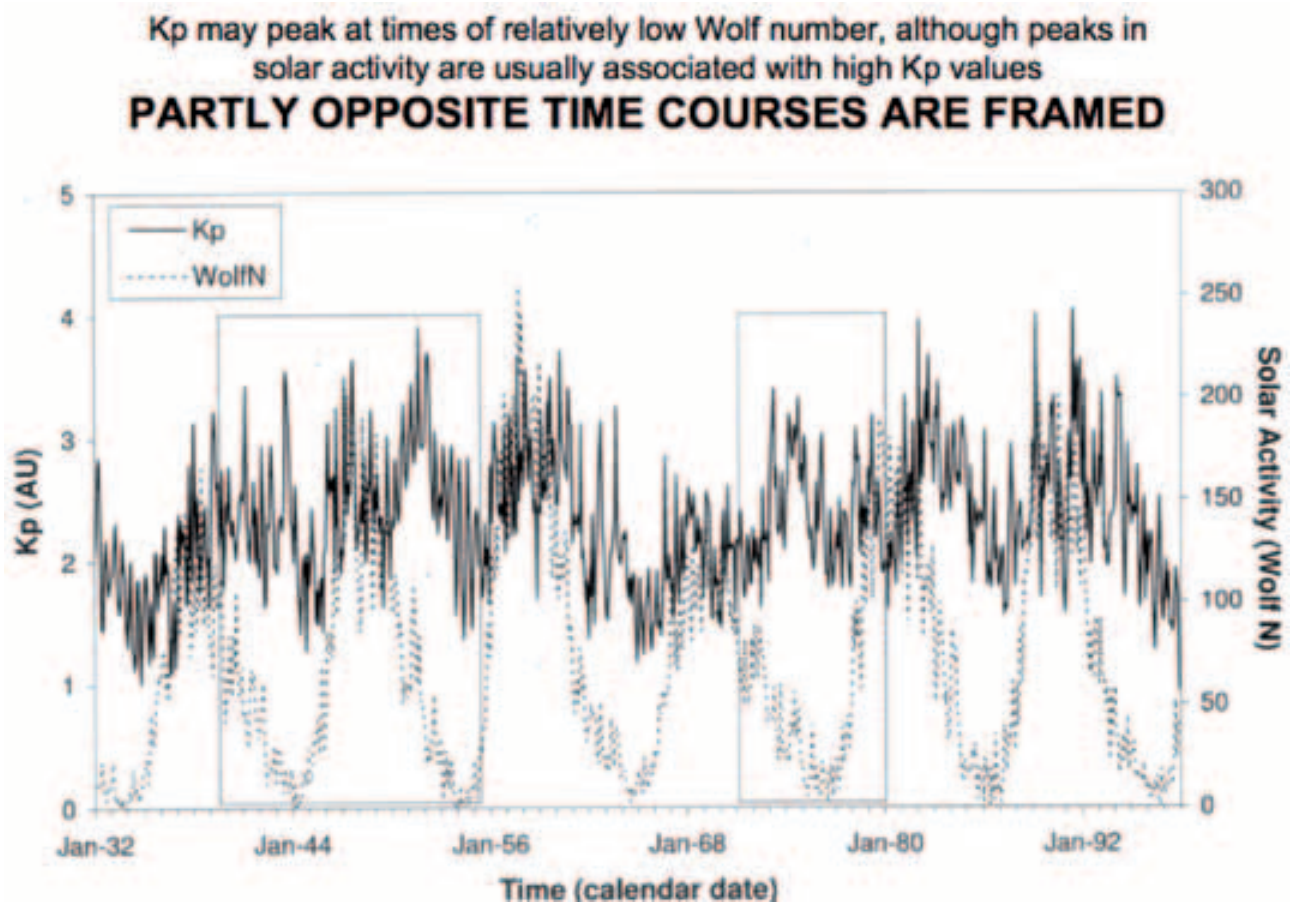

Figure 6. The planetary geomagnetic index Kp is not always congruent with sunspot numbters. © Halberg.

of Edward Brückner (28), who, shortly after Egeson (26), described an about 33- or 35y climate cycle, Figure 10. This periodicity is mostly ignored by those concerned about climate, even including reports (25) that relate specifically to an endpoint such as the length of the circadecadal Horrebow-Schwabe (19, 20) sunspot cycle, undergoing an about–35y cycle, reported shortly after the start of the 20th century by William J.S. Lockyer (29), the son of Sir Norman Lockyer, codiscoverer of helium and founder of the journal Nature (30). Father and son Lockyer followed up on the paper by Egeson (26) and the broader contribution by Brückner (28), promptly confirmed by Liznar (31), the topic of (too few, but important) recent contributions (32, 33). The often misspelled Bruckner (without an Umlaut) (35) or Brickner cycle (36) has a long history of being questioned (37, 38; cf. 39). After other meta-analyses by ourselves (39–41) and in keeping with the initials of the names of the discoverers (in alphabetical order), Brückner, Egeson and Lockyer, we proposed the term „BEL“ (39–41), which was endorsed by a meeting of physicians, other biologists, and solar and other physicists in Moscow (42).

Readers may be interested to know that nonphotic recurrent changes, such as the BEL, are aeolian, coming and going in terms of detectability and, when present, waxing and waning in amplitude and drifting in phase and frequency, bifurcating or splitting into more parts and reuniting, a nonstationary behavior that earned them the title of quasi-periodicity, to which Julius Bartels added an explicit reference to quasi-persistence (43; for review see 44). Exceptions notwithstanding (32, 33, 35), the BEL is today mostly forgotten and indeed it is difficult to define it in terms of a point estimate of its

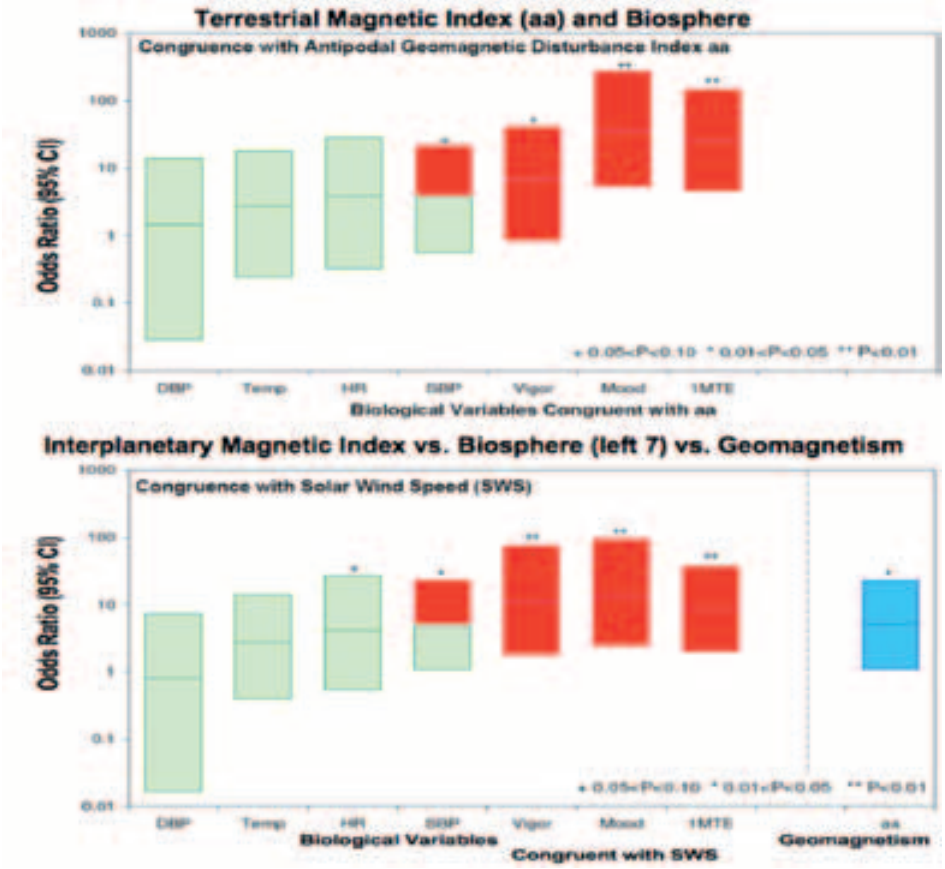

Figure 7. Toward chronoastrobiology. Alexander Leonidovich Chizhevsky (1897-1964): "Peut-être même nos sentiments et nos pensées ne sont-ils qu'un faible écho de ces vibrations du cosmos .... Involontairement, une antique idée nous vient à l'esprit: notre connaissance des phénomènes de la nature ne serait pas autre chose qu'un écho, reçu par nos organes, des processus réels de l'univers"
("Perhaps even our feelings and thoughts are just a weak echo of the vibrations of the cosmos .... Involuntarily an old idea comes to mind: Our knowledge of natural phenomena will not be different from an echo, received by our organs, of the real processes of the universe").
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) (bottom) on human psychophysiology was assessed by means of the congruence of periods, τ, of their spectral components (defined by overlap of the 95% confidence intervals of the 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 5-6 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). Mental functions show higher congruence than somatic functions. Among the latter, systolic blood pressure (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 (23). © Halberg.

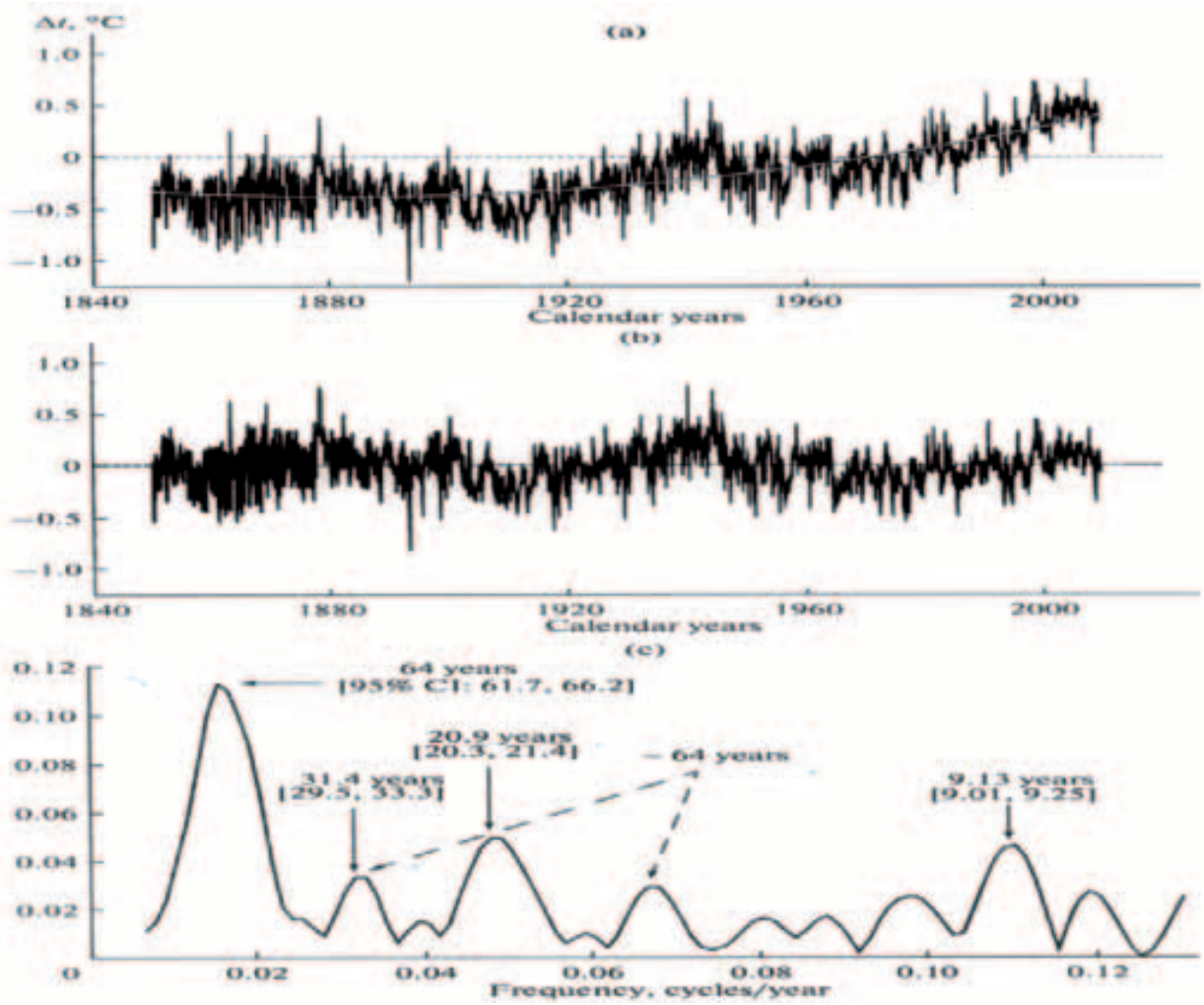

Figure 8. BEL cycle in variations of air temperature for 1850-2008: (a) original data, (b) time series without the trend, and (c) spectrum of time series obtained after trend removal. The dashed arrows in (c) indicate modulation-induced beats of around 64y oscillations (24). © Halberg.

period, which is spread over more than 30–40 y, already in a meta-analysis of Brückner‘s original extensive data (28, 40), Figure 8. Hence the BEL was defined as a cycle with a 95% confidence interval of the period that falls between 30 and 40 y and called a para- (= near, beside) tridecadal cycle. Most recently, we became even more liberal when, with the addition of 5 years of longitudinal data (of WRB), a BEL had a 95% confidence interval of the period extending with its upper limit not quite to 30 years, while it was a clear BEL with only about 30 y of data. We submit for consideration the term „para-tridecadal“, with exact limits for the „para“ to be specified by further experience. The BEL is found not only in environmental temperature records, Figure 8, that undergo cycles rarely considered by scholars in global warming or by those in human military-political, economic and other affairs (45; cf. 21).

This update on the BEL may be complemented in the form of maps with glocality in time, namely a combination of analyses of a record as a whole (globally) and in sections (locally) as well as in space (46). An example of temporal glocality is Figure 10, with global analyses in the middle and local chronobiologic serial sections on the sides. Because of the aeolian nature of multidecadal components, a geographically global and local scrutiny (in space) is best complemented by glocality

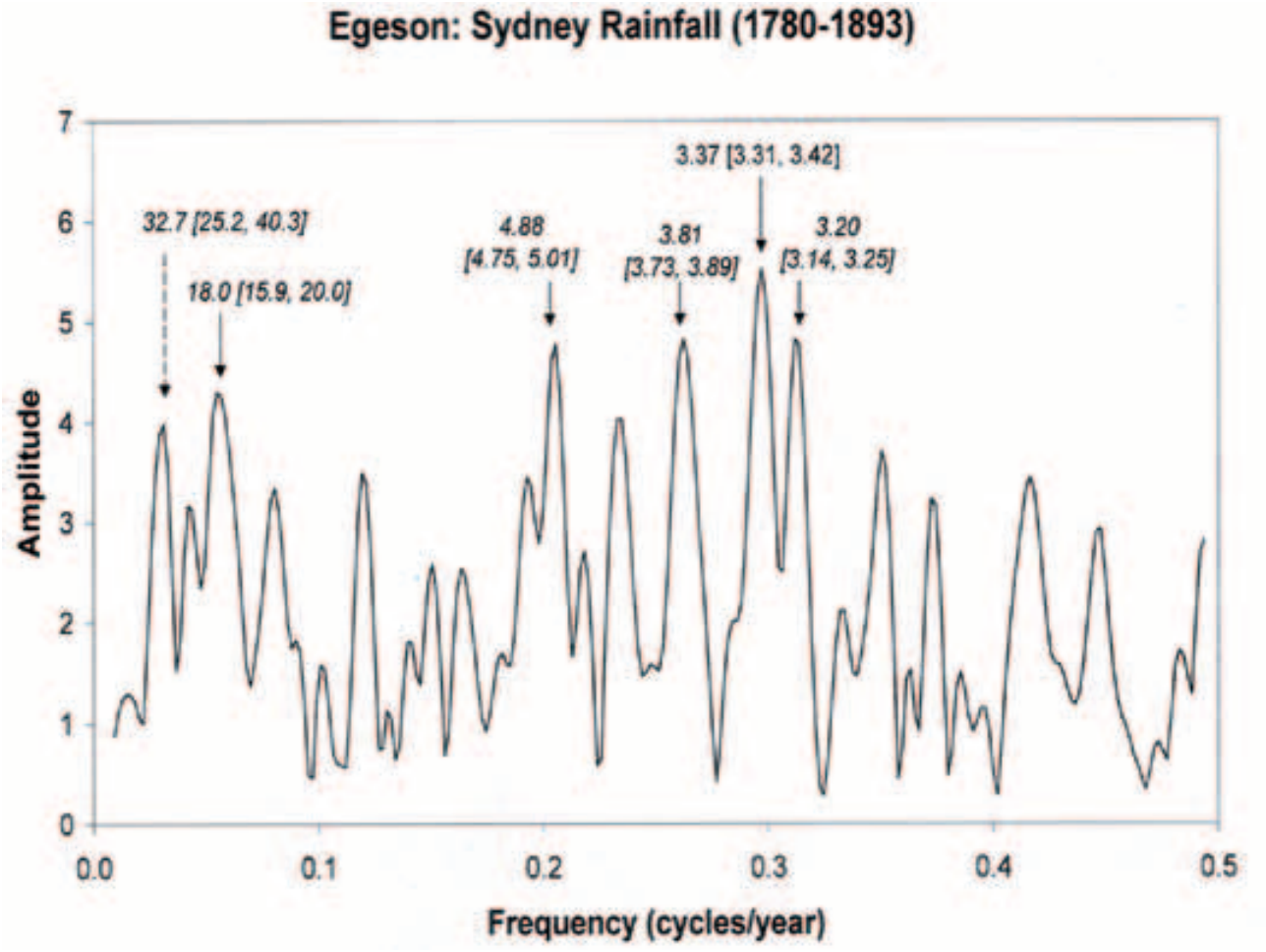

Figure 9. An extended linear-nonlinear cosinor spectrum of data taken off Egeson's graph on rainfall validates his, Francis Bacon's and others', e.g., Brückner's, intuitions. Egeson may have been the first to compile and publish data in support of his proposition. An extended cosinor meta-analysis shows the great uncertainties involved, by ordering 95% confidence intervals of the periods. The 95% confidence interval of the 32.7y estimate extends from 25.2 to 40.3 y with Marquardt's "conservative" method* (47; cf. 27). The confidence intervals are called "ordering" since the assumption upon which they are based may not apply. They are offered until more pertinent procedures that account for nonstationarities become available.
*Marquardt's (1963) algorithm (47) provides three measures of uncertainty of the period estimate and of the other parameters of the fitted model. One is an equivalent of the usual standard error and is called the "1-parameter" approach. Another is called "conservative" in the sense that the corresponding confidence intervals are slightly wider than the "true" or "nonlinear" 95% limits. The nonlinear limits, a third measure, are more complex, but generally do not differ much from the more easily derived "conservative" approximation. In view of the non-stationarities of the biological data analyzed, the approach called "conservative" by Marquardt is actually too liberal and is used in the want of a more appropriate method that accounts for non-stationarities. © Halberg.

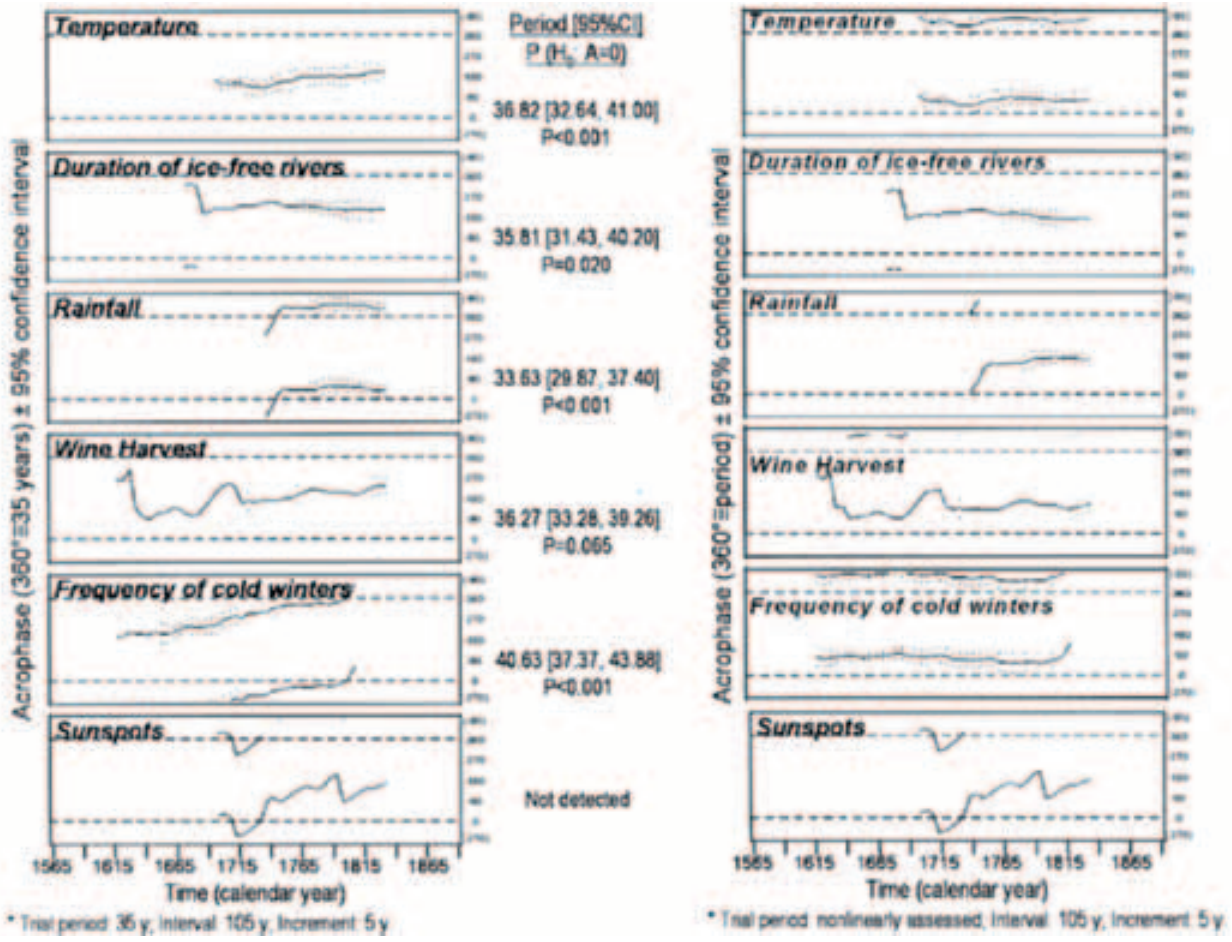

Figure 10. Variations in acrophases of time series from Brückner [1890] calculated with the help of the cosinor method for 35y (left) and near 35y (right) periods of different parameters: (a) air temperature, (b) length of the ice-free period in rivers, (c) rains, (d) wine harvest, (e) frequency of cold winters, and (f) sunspots. The acrophases were estimated in a sliding window of 105 y with a step of 5 y. The central part indicates the values of periods, confidence intervals, and level of statistical significance (see text). © Halberg.

in time, notably when we focus on climate, while we do not forget those responsible for the BEL, Figure 11. The concern for BEL and other cycles related to changes in climate may be far from trivial as large-scale human population collapses on the long-term scale have been associated with the synergistic effects of climate-related subsistence shortage and population growth (45).

Conclusion. Meta-analyses by a set of Morlet wavelets visualize the time series of the several spectral components isolated earlier by the nonlinearly extended cosinor which we owe to the late Donald Marquardt (47), which is complemented by wavelets as an approach to glocality in time. In data on body length at birth, the approach by wavelets revealed a component of about 38 y after 1930, also detected, as a 33y band with its uncertainty by the extended cosinor. Moreover, when the time course of this trans-tridecadal is followed by chronomic serial sections, it is also revealed to be statistically significant before 1930 with one interruption, in keeping with its intermittent nonstationary aeolian behavior. The serial section complements the wavelet by focus upon a specific frequency. Before conclusions concerning causality can be reached, the wavelets of environmental cycles and/or gliding spectra, spectrograms or serial sections will have to seek opportunities for a subtraction and addition

approach, which depends upon cooperation by the environment (44, 48).
Footnote. Part of the general discussion was submitted on February 27, 2011, to the journal Natural Science by GC and FH under the title "Para-tridecadal cycles in environmental temperature, human affairs and global warming".

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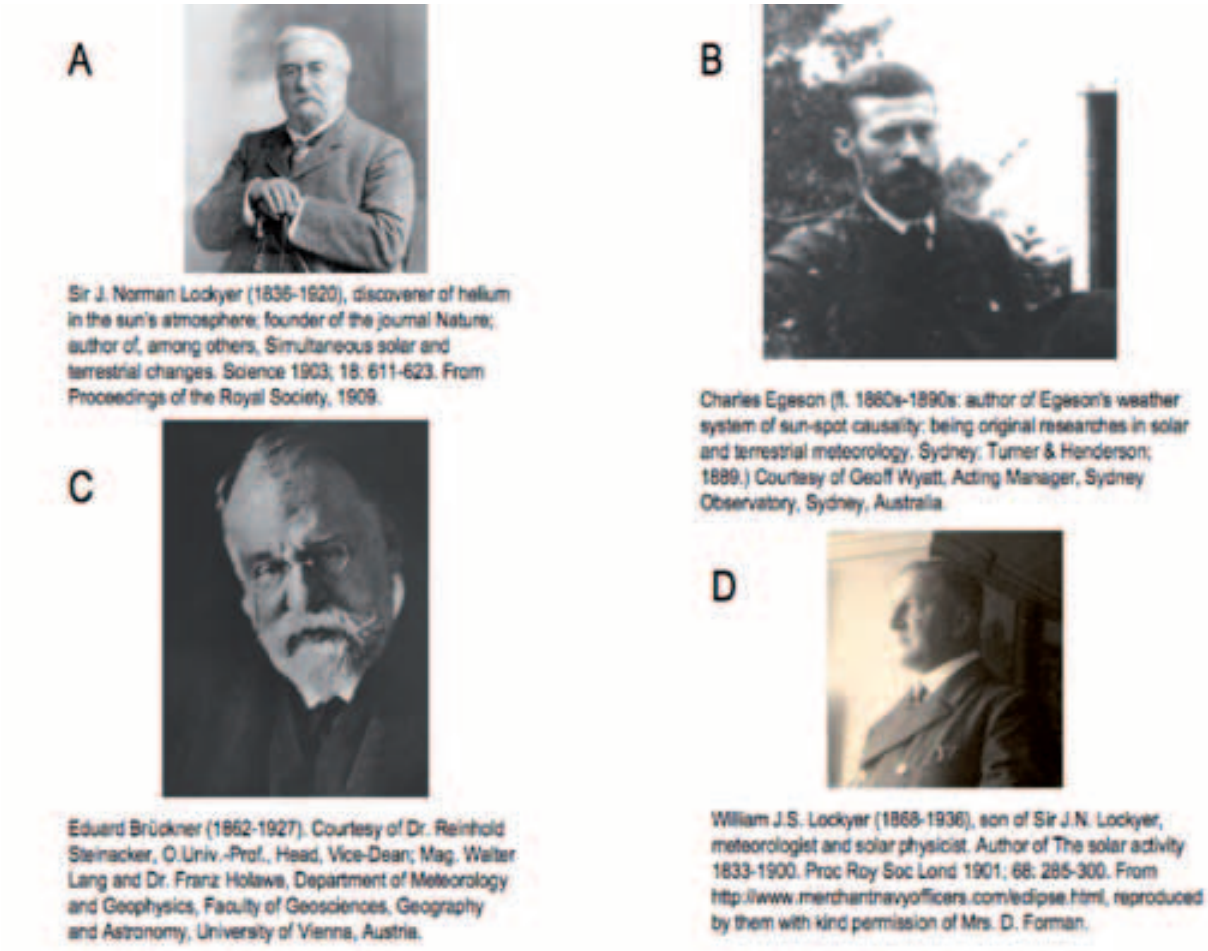

Figure 11. The history of these investigators is given elsewhere (39).

Imaging in time by phase synchronization reveals wide spectral-biospheric resonances beyond short rhythms. ("Wenn man über kurze Rhythmen hinausgeht") In memoriam – lost future: Dr.-Ing. habil. Dr. rer. nat. Barbara Schack: 1952–2003. Neuroendocrinol Lett 2003; 24: 355–380.

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THE CHRONOMICS TRIAL: REPORT OF A 3-MONTH PILOT STUDY.

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Abstract

The Chronomics Trial is designed to test the evolutionary diet/tissue hypothesis (De Meester, 2009), i.e. that a return to the original balanced (1:1) ratio of polyunsaturated fatty acids (PUFAs) and/or to a corresponding 25% proportion of ω6 highly unsaturated fatty acids (HUFAs) in plasma/serum total lipids (ω6:ω3 PUFAs = 1:1 and/or %ω6 in HUFAs = 25) (www.columbus-concept.com) can possibly reduce the risk of developing chronic degenerative diseases to near zero at the population level. The longitudinal study is to be conducted in three different age groups of healthy subjects living in Southern Poland (adolescents, adults, elderly), with a focus on biomarkers and clinical/psychological symptoms of the development of cardiovascular and psychological diseases.

This, herein reported, 3-month (3-m) pilot study was carried out on 5 family-related subjects + 4 family-acquainted subjects (external references) to test the protocol designed for the 4-y-long psychosomatic intervention trial involving 90 subjects, distributed evenly over 3 subgroups of 30 adolescents, 30 adults & 30 elderly. The pilot study has yielded results in terms of a potential for the alteration of tissue fatty acid composition (Omega–6 Status, Ω6S, %ω6-HUFAs in total blood fatty acids) back to its envisaged evolutionary standard (*Columbus Hypothesis: ω6:ω3-PUFAs = 1:1 and/or %ω6-HUFAs = 25*) in samples of a modern Western human population. The main observation was

that: (i) age & gender, (ii) body mass composition & index, and (iii) metabolic rate & lifestyle do not appear to substantially influence the:

"ΔΩ6S = –7.5 units/(g ω–3 HUFA)/day"

response of modern Western blood/tissue fatty acid composition – expressed here as the ω–6 status (Ω6S) or the proportion of ω–6 fatty acids in total blood lipids HUFA – to ω–3 HUFA (PUR3) supplementation in the presence of an agent for reducing epigenetic-genomic effects (a "blunter") (LIPISTASE). Within the 3-m pilot study, all subjects in the adolescent & elderly subgroups on the 6 pills a day (~2.7g ω–3 HUFA (PUR3)/day), in association with 2 tablets LIPISTASE/day, have had their Ω6S reduced by some 20%, with no reduction in blood concentration of ω–6 HUFA. In the adult group, the three individuals were on a ~1.0, 3.6 & 4.5g ω–3 HUFA (PUR3)/day intervention program. They respectively had their Ω6S decreased and/or stabilized at 67.5, 48.0 & 41.0%, thus confirming the generality of the blood/tissue titration method observed in the adolescent & elderly groups. All subjects reported subjective mind- and body-wise health improvements concerning cognition, concentration, communication, breathing, general feeling, relief of dizziness and pain. The first adult subject reported slight improvement in his annual episode of seasonal allergy whereas the next two reported feelings of "rejuvenation" in all senses. Medical, biochemical & socio-psychological analyses did confirm those self-assessed subjective improvements. In all three subgroups, prolonged ω–3 HUFA (PUR3) intake appears to maintain the new status, not to further reduce it. The results of the 3-m Pilot Chronomics Study not only refine the size of the problem in terms of the daily intake of ω–3 HUFA (PUR3) needed to reverse the Omega–6 Status (Ω6S) from 75 to 50% (3.35g ω–3 HUFA (PUR3)/day) and then eventually from 50 to 25% (3.35g ω–3 HUFA (PUR3)/day) in the blood-tissue of a modern Western population, but also indicates benefit from promoting the approach and from doing so in the presence of a "blunter" (LIPISTASE) of inter-individual genotypic variance.
A reduction in daily intake of omega–6 fatty acids from plant & animal origins could help a long way in reducing the currently determined daily intake of ω–3 HUFA (PUR3) needed to continue with, and/or to maintain post-intervention, the evolutionary selected blood/tissue ratio. In this respect, foods responding to the Columbus Concept (Wild Foods for Health™; www.columbus-concept.com) appear to be acceptably designed.

More generally, its small sample size notwithstanding, the efficacy if not the safety of the Chronomics Trial protocol seems satisfactory.

Introduction

The Columbus Concept (www.columbus-concept.com) emanates from a research project initiated in 1995 in a family-owned egg-processing company located in Belgium, in yet another 2nd world war sadly famous town, Bastogne, Ardennes Region (http://en.wikipedia.org/wiki/Mardasson_Memorial). The Battle of the Bulge has left the place with scares and opportunities for Humanity to progress. A pioneer in Egg Science & Technology, the family company surely consisted of two generations of the De Meester family. Eventually, the brands remain: Belovo, Columbus, OvoLife, BNLfood (www.bnlfood.com).
For those who still think or believe that non-essential nutrients – such as cholesterol, saturated & mono-unsaturated fats, glucose and carbohydrates, and the like, accounting for the bulk (~90%) of the daily energy intake – are primary risk factors in diet-ill health relationships, the best advice to convey probably resides in: "keep reading, evaluating, questioning, arguing, disputing facts commonly

regarded as established". As someone once said, "I cannot teach you anything, I can only help you think". Good points to start from that refreshed perspective are the long-standing, well-documented, evidence-based, unbiased scientific open access site maintained by Uffe Ravnskov (www.ravnskov.nu/uffe) and the more recent yet similarly scholarly blog developed by Michel de Lorgeril (http://michel.delorgeril.info/).

It is Artemis Simopoulos who once inspired nutritionists to take a new look at human nutrition, pointing out the evolutionary fact that Homo sapiens' genetic pattern evolved on a diet that was basically balanced in essential fats (Omega–6/3 ~ 1). Michael Crawford came on postulating the hypothesis from an earlier observation that free-roaming non-domesticated animals in the African Savannah keep responding to the same evolutionary principle, namely that in the original diet Omega 6 and Omega 3 fatty acids were equally represented. Such a basic consideration may prevent obesity. Donald McNamara established the fact that dietary and blood cholesterol were not related to CVD and Harumi Okuyama concluded on saturated fats being a non-issue unless associated with modern plant/animal fats exceedingly rich in omega–6 fatty acids. William Lands developed mathematical models to predict risk of death from CHD based on population-based observational data related to total blood proportion of omega–6 highly unsaturated fatty acids (omega–6 status) and Jing Kang engineered fat–1 mice to show that tissues naturally tend in their constant search for homeostasis to balance omega–6/3 fatty acid composition in cell membranes. Claudio Galli developed a reliable bench methodology for fatty acid analyses of blood collected from fingertips whereupon William Harris & Clemens von Schacky went on deriving a complementary clinical approach (omega–3 index) based on fatty acid analyses in red blood cells.

The Columbus Concept (De Meester, 2009) was born, by which it is hypothesized that the most single common roots of all chronic degenerative diseases causing 85% of all deaths world wide is an eicosanoid-derived uncontrolled inflammatory process at tissue level, "The Tissue is The Issue", and that a return to the original balanced (1:1) ratio of polyunsaturated fatty acids (PUFAs) and/or to a corresponding 25% proportion of ω6 highly unsaturated fatty acids (HUFAs) in plasma/serum total lipids (ω6:ω3 PUFAs = 1:1 and/or %ω6 in HUFAs = 25) can possibly reduce the risk of developing chronic degenerative diseases to near zero at population level.

The Chronomics Trial will test-validate the evolutionary diet/tissue hypothesis from a broadened psycho-somatic approach recognizing the importance of the mind stress → body strain response in the biological cascade leading to tissue injury, which if not taken care of at the level of cell membrane fatty acids eventually transform into chronic inflammation and the inception of non-communicable diseases (fig.1). The sympatho-vagal balance and vascular rhythms of the autonomic cardiovascular regulation are promising tools to solve the long disputed psychosomatic gap. Especially sympatho-vagal balance obtained from beat-to-beat monitoring on task-force monitors and circadian (daily) rhythms obtained from 7/24 continuous monitoring of SBP, DBP and HR appear to accurately and reliably probe mind stress-induced body strain. Circadian Vascular Variability Disorders (VVDs) are also established independent risk factors (reliable predictors) of cardiovascular diseases. Circaseptan (weekly) rhythms have a strong social component that may also reflect mind stress-related body strain. In the Chronomics Trial, circadian, circaseptan and other infradian vascular rhythms and disorders will be studied from a socio-psychological perspective with the aim of capturing the physiological determinants of currently and widely used socio-psychological tests, with the far-reaching contemplated objective of developing a new era of evidence-based socio-psychology. The Chronomics Pilot Study carried out over the last 6 months of 2010 provides tangible evidence that such relationship does exist. The 3-month pilot study reported here was aimed at sizing the challenge and testing the feasibility and safety of returning blood/tissue omega–6 status from current 75% to contemplated 25% in a subgroup (a family extending over 3 generations, fig.2) of the Silesian Polish Society, as well as at

assessing new sets of psychosomatic markers (vascular variabilities of blood pressure & heart rate) and symptoms (sympatho-vagal balance of the autonomic cardiovascular regulation) for systematic follow-up along the contemplated Chronomics Trial (fig.3). The protocol of the Chronomics Trial is financially supported by the TsimTsoum Institute (www.tsimtsoum.net); it was initially submitted for granting to the EU Commission under FP7-Health–2010 (FP7–259825–1; OCT 29, 2009) and then to the Polish NCN (Narodowego Centrum Nauki) under NZ5_9: Prevention of Human Diseases (2011/01/B/NZ5/01369; JUN 20, 2011).

Materials & Methods

SUPPLEMENTS: (i) PUR3 (BioSeutica USA, Inc, 6369 Mill Street, Suite 202, Rhinebeck NY 12572, USA; www.bioseutica.com): min 90% lc-omega–3 fatty acid ethyl ester, min 40% EPA, min 15% DHA, mixed tocopherols 0.15-0.25%, pesticides max 1 mg/kg, dioxine max 1.5 pg Teq/g, heavy metals max 0.1 mg/kg each (Cd, Hg, Pb), Anisidine Value max 20, peroxide value max 10 meq/kg, acid value max 2 mg KOH/g. Coating: Gelatin 160 Bloom, Glycerol 85%, Sorbitol-Lsg 70%. One pill: 500 mg; (ii) LIPISTASE (Exichol SA, Bioresearch, Biopôle, Corniche Str. 4, 1066 Epalinges, Switzerland; www.exichol.com): containing a combination of micronutrients – essential fatty acids, minerals & vitamins, yeast-fungi-land & marine plant extracts – involved in lipid metabolism (El Kochairi et al., 2011), destined to blunt epigenetic/genomic variabilities vs lipid metabolism. List of ingredients - all ingredients present at less than 1 mcg (microgram) per pill.

Scientific Name	English Translation	Source
Oleum Brassica napus oleifera	Canola (Rapeseed) Oil	Grain
Oleum Olea	Olive Oil	Fruit
Oleum Vitis vinifera	Grapeseed Oil	Fruit
Oleum Oenothera biennis	Primrose Oil	Grain
Cocos nucifera	Coprah	Fruit
Crithmum maritimum	Marine Criste	Flower
Allium sativum	Garlic	Flower
Vitis vinifera	Vine	Fruit
Fucus vesiculosus	Sea wrack	Algua
Palmaria palmata	Sea weed	Algua
Chondrus crispus	Irish Moss	Algua
Lentinus edodes	Shiitake (mycelium)	Fungi

Supplementation was recommended to follow individual eating habits: two pills three times a day PUR3 at breakfast, lunch and dinner, and one pill two times a day LIPISTASE at breakfast and dinner. Monthly fingertip samplings were taken with no consideration of fasting and timing.

METHODS & INSTRUMENTS: (i) body mass composition (table 1): Maltron Body Composition Analyser BF–907, Maltron International Ltd, PO Box 15, Rayleigh, Essex SS6 9SN, United Kingdom (www.maltronint.com). Bioelectrical impedance analysis is a rapid, non-invasive and low cost method for measuring body fat and body water; (ii) general medical assessment (table 2): standard routine blood & urine analyses performed at local public laboratories; (iii) psychological health (table 3): polish version of the Eysenck's Personality Questionnaire EPQ-R (Eysenck et al., 1985; Brzozowski & Drwal, 1995). The EPQ-R has 4 subscales: Neuroticism, Extroversion, Psychoticism and a scale which measures social approval, also known as the lie scale. The EPQ-R consists of 100 questions.

The subject has to decide if the items describe him or if they don't (YES or NO); (iv) parameter of the autonomic cardiovascular regulation (table 4) & hemodynamic parameters (table 7): Task Force Monitor, CNSystems Medizintechnik AG, Reininghausstraße 13, 8020 Graz, Austria (www.cnsystems.at); (v) circadian amplitudes of blood pressures & heart rate (table 5): TM–2430 Ambulatory Blood Pressure Monitor, A&D Co, Ltd, 3–23–14, Higashi-Ikebukuro, Toshima-ku, Tokyo 170-0013 Japan (www.aandd.co.jp), equipped with standard TM–2430-06A adult left-arm cuff, recorder, casing & belt, 3 AA batteries. Once a month 350 records of SBP, DPB, HR at 30 min intervals around the clock (7–10 days). Doctor Pro3 Application Software with data communication cable AX-KO3057–200 for Windows PC (2000 Professional, XP Professional / Home Edition, Vista). Sphygmochron (Halberg Chronobiological Center (Minneapolis, MN, USA), one time-structure profile containing detailed analysis & interpretation of 7/24 stacked recorded data (http://www.msi.umn.edu/~halberg/); (vi) endothelial function & arterial stiffness (table 6): Endo-PAT2000, Itamar Medical Ltd, 9 Halamish St, PO Box 3579, Caesaria 38900, Israel (www.itamar-medical.com). Peripheral arterial tone (PAT) is a rapid, non-invasive and low cost method for measuring endothelium-mediated changes in vascular tone; (vii) blood fatty acid profiles (tables 8a,b,c): Fluka #11312 Blood Collection Kit, Sigma-Aldrich Co, 3050 Spruce St., St. Louis, MO 63103, United States (www.sigmaaldrich.com), containing 100 dipstick matchboxes, antioxidant BHT-solution, dessicant packs, foil barrier ziplock bags. FAsTEST SRL, Viale Tunisia, 38, 20124 Milano, Italy (www.fastest.it) with detailed analysis & interpretation of total blood lipids fatty acids distribution. The omega–6 status (Ω6S), defined as the proportion of omega–6 in total blood highly unsaturated fatty acids (HUFA) was used to index pre-supplementation vs post-supplementation fatty acid composition.

Results

Characterization of subjects

The five family-related subjects were the mother B2 (1966), her two m/f twin children A1 & A3 (1993) and her two parents C1 (1938) and C3 (1939). Each age group included external references with no family connection, i.e. one female adolescent A2 of similar age (1992) as the two family children, two adults respectively older B3 (1961) and younger (1984) then the family mother, and one elderly older C2 (1933) than the two family grand parents (fig.1). The nine subjects received ample oral and written information about the scope of the study and voluntarily signed a formal agreement on the day of initiation of the study, i.e. Aug 15, 2010. Consents of parents were requested and obtained on the same day for the three children (< 18 years of age) enrolled.

Analyses of Body Mass Composition did not identify any obesity-related risks within the group. Most values were within norms notwithstanding obvious differences in lifestyle and body fat between and across age groups (tab.1). The two sportive twin children A1 & A3 differed from each other body-wise, in size (height: 158 & 184 cm, weight: 53 & 77.5 kg), composition (fat: 17.9 & 9.7%, water: 60.0 & 66.1%) and resting metabolic rate (RMR: 1417 & 2076 kcal); their mother B2 was intermediate in size (height: 175 cm, weight: 60 kg) and exhibited normal age-related changes in body composition (fat: 20.5%, water: 58.2%) and resting metabolic rate (RMR: 1375 kcal). The two grand parents C1 & C3 (height: 168 & 175 cm, weight: 70 & 82 kg) presented similarly normal values for their age, in body composition (fat: 34.0 & 18.8%, water: 48.3 & 59.5%) and resting metabolic rate (RMR: 1221 & 1615 kcal). With the external references, the ranges of body variables extended broadly as follows: age (17 to 77 yr), height (158 to 190 cm), weight (51 to 82 kg), body fat (4 to 34%), body water (48.3 to 70.3%), BMI (19.6 to 26.8), RMR (1124 to 2076 kcal), TDE (1163 to 3013 kcal).

Tab.1. Body Mass Composition: Oct 10, 2010 (2/3rd of study).

	A1	A2	A3	B1	B2	B3	C1	C2	C3
Age (yr)	17	18	17	49	44	26	72	77	72
Height (cm)	158	160	184	190	175	185	168	158	175
Weight (kg)	53	51	77.5	80	60	82	70	60	82
Weight R (kg)	51–56	50–58	78–85	88–97	60–70	78–90	59–70	51–61	78–86
Body Fat (%)	17.9	19.0	9.7	4.0	20.5	16.3	34.0	33.3	18.8
Body Fat R (%)	16–22	23–29	12–18	15–21	26–32	18–24	28–34	28–34	17–23
Water (%)	60.0	59.2	66.1	70.3	58.2	61.2	48.3	48.8	59.5
Water R (%)	55–62	50–57	58–65	55–62	47–54	54–61	45–52	45–52	53–60
BMI	21.2	19.9	22.9	22.2	19.6	24.0	24.8	24.0	26.8
RMR (kcal)	1417	1388	2076	2007	1375	2000	1221	1124	1615
ADE (kcal)	482	272	937	937	482	885	91	39	984
TDE (kcal)	1899	1660	3013	2944	1857	2885	1312	1163	2599

A: Active; N: Normal; S: Sportive; BMI: Body Mass Index; RMR: Resting Metabolic Rate; ADE: Average Daily Energy; TDE: Total Daily Energy.

General Medical Assessments of the subjects (blood: Tab.2a & urine: Tab.2b) were performed upon completion of the study (B3 was not available). Most parameters were within norms or borderline except for a number of medically relevant items as follows: (i) blood sedimentation rates were exceeding norms in B1 (16 mm/hr), B2 (14 mm/hr), even more so in C1 (39 mm/hr); (ii) hematocrytes were low in B1; (iii) MCV was low in A3; (iv) Glucose was high in C3 (medically treated for type–2 diabetes); (v) potassium & sodium were on the high side in A2 & A1, respectively; (vi) calcium was abnormally high in the elderly group C (2.35 to 2.55 mmol/l); (vii) fibrinogen was a bit low in A1; (viii) creatinin was on the low side in B1; (ix) vitamins 25-OH D3 & B12 were high or above norms in the multi-vitamins & minerals supplemented subgroup A1, A3, B1 & B2; (x) triglycerides were low in both A3 & B1; (xi) HDL & TC were exceeding norms in B1, and (xii) total cholesterol was above norms in B1, C1 & C3. In urine analyses, a neutral pH was found in B2 and traces of protein were detected in A2.

Tab.2a. General Medical Assessment – Blood: Jan-Feb 2011 (completion of study)

Blood	Norms	Units	A1	A2	A3	B1	B2	C1	C2	C3
Type/Formula	(i)		A+	B+	A-	A+	O+	nd	nd	nd
Sedimentation	(ii)	mm/hr	5	3	1	16*	14*	39*	11	4
Hematocrytes	(iii)	%	36.3	35.3	41.2	39.6*	38.2	43.0	41.2	nd
Hemoglobin	(iv)	g%	12.4	12.4	14.8	14.2	13.3	13.8	14.2	nd
Red cells	(v)	10E6/mm^3	4.12	4.08	5.22	4.57	4.63	5.01	4.51	nd
White cells	(vi)	10E3/mm^3	4.0	9.1	5.4	6.0	5.4	7.6	8.0	nd
MCV	(vii)	µm^3	88.8	86.5	78.9*	86.7	82.5	85.0	91.4	nd
MCH	(viii)	pg	30.1	30.4	28.4	31.1	28.7	28.0	31.6	nd
MCHC	(ix)	%	33.9	35.1	35.9	35.9	34.8	32.0	34.5	nd
Thrombocytes	(x)	10E3/mm^3	236	311	253	173	260	244	298	nd
Index Anizo	(xi)	%	13.2	13.2	12.6	12.4	13.3	13.9	13.0	nd
Glucose	(xii)	mg/dl	87	92	84	94	nd	87	109	133*

Uric acid	(xiii)	mg/dl	3.6	4.3	4.7	3.8	2.5	5.3	4.0	nd
Bilirubin total	(xiv)	mg/dl	0.51	0.45	0.60	0.72	0.44	0.50	0.50	nd
Ferritin	(xv)	ng/ml	19	54	45	184	21	55	112	271
Magnesium	(xvi)	mg/dl	2.1	1.8	1.7	2.1	2.2	1.9	1.9	2.1
Potassium	(xvii)	mmol/l	4.5	5.2*	5.1	4.6	4.9	4.75	4.3	4.24
Sodium	(xviii)	mmol/l	147*	142	141	142	142	139	138	137
Calcium	(xix)	mmol/l	1.14	1.18	1.08	1.10	1.11	2.35*	2.25*	2.55*
Fibrinogen	(xx)	g/l	1.89*	2.29	2.33	3.32	2.94	3.91	2.77	2.65
Creatinin	(xxi)	mg/dl	0.66	0.79	0.85	0.69*	0.81	1.15	0.88	nd
25-OH D3	(xxii)	ng/dl	41.1*	24.0	42.7*	41.1*	36.1*	nd	nd	nd
B12	(xxiii)	pg/dl	471	456	754	975*	714*	438	340	399
CRP	(xxiv)	none	nd	nd	A	A	nd	nd	nd	nd
Triglycerides	(xxv)	mg/dl	nd	nd	56*	40*	nd	91	nd	101
Cholesterol LDL	(xxvi)	mg/dl	nd	nd	125	133	nd	141	nd	142
Cholesterol HDL	(xxvii)	mg/dl	nd	nd	60.1	77.3*	nd	43.0	nd	60.0
Cholesterol Tot	(xxviii)	mg/dl	nd	nd	196	218*	nd	202*	nd	222*
Prolactin	(xxix)	ng/dl	nd	28.2	nd	nd	nd	nd	nd	nd

(*)Out of norms, as follows: (i) None; (ii) M:1–8; F:1–12, (iii) M:45–52; F:38–48; C:35–43, (iv) M:14–16.6; F:12–15; C:10.9–15, (v) M:4.3–5.9; F:3.9–5.5; C:3.8–5.5, (vi) M&F:4–10; C:5–17, (vii) 82–94, (viii) 28–32, (ix) 32–36, (x) 150–400, (xi) 11.5–14.5, (xii) 75–115, (xiii) M:3.0–7.0; F:2.5–6.0, (xiv) 0.2–1.0, (xv) M:30–400; F:13–150, (xvi) 1.60–2.55, (xvii) 3.5–5.1, (xviii) 136–145, (xix) 1.0–1.3, (xx) 2.0–4.0, (xxi) M:0.7–1.4, F:0.6–1.3, (xxii) 20–32; (xxiii) M:174–878; F:191–663; (xxiv) Absent A, (xxv) M:60–115, F:40–140, (xxvi) <135, (xxvii) M:30–70; F:30–85, (xxviii) 140–200, (xxix) M:3–25; F:5–35.

Tab.2b. General Medical Assessment – Urine: Jan-Feb 2011 (completion of study)

Urine	Norms	Units	A1	A2	A3	B1	B2	C1	C2	C3
Color	(xxx)	None	Y	Y	Y	Y	Y	Y	Y	Y
pH	(xxxi)	None	H	H	H	H	H/O*	H	H	H
Density	(xxxii)	g/l	1030	1030	1026	1028	1014	1008	1020	1008
Protein	(xxxiii)	None	A	T*	A	A	A	A	A	A
Sugar	(xxxiv)	None	A	A	A	A	A	A	A	A
Urobilinogen	(xxxv)	Unspecified	N	N	N	N	N	N	N	N
Ketonic bodies	(xxxvi)	None	A	A	A	A	A	A	A	A
Red cells	(xxxvii)	wpw	0–1	0	0	0	0	0–1	nd	nd
White cells	(xxxviii)	wpw	1–2	8–10	0–1	0–2	1–2	3–5	2–6	0–1

(*)Out of norms, as follows: (xxx) Yellow, (xxxi) Acidic, (xxxii) 1005–1030, (xxxiii) Absent A, (xxxiv) Absent A, (xxxv) not specified – within norms N, (xxxvi) Absent A, (xxxvii) <5, (xxxviii) <10. Y:Yellow, H:Acid, H/O:Neutral, T:Traces.

General Health Questionnaires (GHQ12 & 28) revealed no anomalies within the group, with all subjects but the adolescents scoring at 0 on both scales except for B1 scoring at 1 in the GHQ28 test. Adolescents (A1, A2, A3) scored 1 & 5, 0 & 11, 3 & 2 in GHQ12 & 28 tests, respectively. Eysenck

Personality Questionnaire – Revised (EPQ-R) revealed a relatively heterogeneous distribution of psychological traits within the group, except for the two grand parents C1 & C3 (tab.3).

Tab.3. Eysenck Personality Questionnaire – Revised (EPQ-R)

	A1	A2	A3	B1	B2	B3	C1	C2	C3
Neuroticism	5	9	4	2	1	3	5	4	3
Extroversion	8	4	9	1	4	8	5	8	6
Psychoticism	7	3	3	8	6	4	5	3	6
Lie Scale	1	8	6	10	1	2	6	5	7

1–10 sten scales

The parameters of the autonomic cardiovascular regulation obtained on the Task Force Monitor (St Anna Hospital, Brno) under conditions of spontaneous Φ1 and controlled Φ2 (0.33 Hz) breathing (tab.4) led to the general observation that subjects appear not to fit norms to various extents with, as general trends across all variables, A1, A3, B2, C3 in opposite direction to B1 & C1 (save perhaps for B1 under controlled breathing); (i) in the range of low frequency (LF) and of low-to-high frequency ratio (LF/HF) of heart rate variability (HRV), power spectral density (PSD), and Sympatho-Vagal Balance (SVB), A1, A3, B2 & C3 are clearly down expected range, whereas B1 & C1 are clearly up; (ii) in the high frequency range of HRV, all subjects but C1 were clearly under norms, with C3 extremely so, which renders the two elderly grand-parents opposite extremes on that specific variable.

Tab.4. Parameters of the Autonomic Cardiovascular Regulation (ACR): Nov 4, 2010 (end of study).

Parameter	Abbr.	Unit	Norms	Φ	A1	A3	B1	B2	C1	C3
Baroreflex Sensitivity	BRS	ms/ mmHg	>9.3	1	10.0	15.0	33.2	7.3	36.8	6.4
				2	28.3	10.0	11.7	12.2	42.9	2.5
Heart Rate Variability (LF)	LF-RRI	ms^2	>750 <1590	1	147	479	4269	84	3964	7.0
				2	68	114	329	104	3986	4.0
Heart Rate Variability (HF)	HF-RRI	ms^2	>775 <1175	1	344	405	467	232	1390	25.0
				2	930	153	178	110	1790	19.0
Power Spectral Density	PSD-RRI	ms^2	>2400 <4600	1	567	945	5070	385	5527	38
				2	1060	330	573	257	6167	34
LF/HF Ratio	LF/HF-RRI	*	<2.0	1	0.4	2.3	9.7	0.5	4.7	0.2
				2	0.1	0.8	1.7	1.5	2.6	0.2
Sympatho-Vagal Balance	LFnu-dBP/ HFnu-RRI	*	<2.0	1	0.3	0.9	3.7	0.8	2.7	0.2
				2	0.2	0.9	1.7	1.3	2.6	0.3

Φ1: Spontaneous breathing: Φ2: 0.33 Hz breathing (Metronome "Rizene Dychani"); LF: 0.04-0.15 Hz; HF: 0.15-0.40 Hz. A2, B3 & C2 were not available on the day of the study.

Vascular rhythms (SBP, DBP, HR) monitored ambulatory around the clock on each enrolled subject revealed individual characteristics and their month-to-month fluctuations in terms of circadian amplitudes (tab.5). Average values reveal circadian hyper-amplitude (CHAT) of SBP (>100%) in B3, very high amplitudes (80–100%) in A1, B2, C1, C2, high amplitudes in A2 & A3 (60–80%), and medium amplitudes in B1 & C3 (40–60%). The trends were similar though not exactly identical and

of lower intensities in DBP; no CHAT or very high amplitudes were identified; high (60–80%) and medium (40–60%) amplitudes were observed in A1, A2, B2, B3, C1 and A3, B1, C2, C3, respectively. In terms of HR circadian variability, all subjects had medium values (40–60%), expect A3 (36%), B2 (26%) & B2 (72%).

Tab.5. Circadian Amplitudes of SBP, DBP & HR

	A1	A2	A3	B1	B2	B3	C1	C2	C3	Month
SBP	92	44	84	41/43	78/95	113	46	98	65	1
	92	71	63	49/49/51	75/113	101	105	93	44	2
	67	84	36	59/62/56	109/61	92	85	79	28	3
Aver.	84	66	61	51	88	102	79	90	46	
DBP	82	52	65	41/42	65/78	88	55	57	56	1
	75	82	50	42/48/51	56/97	45	81	60	41	2
	59	80	28	56/56/47	72/47	81	62	59	29	3
Aver.	72	71	48	48	69	71	66	59	42	
HR	76	45	45	43/27	32/14	81	43	33	47	1
	34	42	39	43/51/59	30/40	74	38	49	50	2
	51	37	24	37/37/41	18/20	62	47	47	58	3
Aver.	54	41	36	42	26	72	43	43	52	

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate; Month 1: Aug/Sep; Month 2: Sep/Oct; Month 3: Oct/Nov. Amplitudes are expressed in % and are defined as the double amplitude of the circadian rhythms in blood pressure (SBP & DBP) and heart rate (HR), respectively, relative to those of reference limits (min/max) of healthy peers (95% CI). B1 & B2 were monitored continuously during the lifespan of study as well as before and after, which explains the additional information sourced from those two subjects.

A circaseptan component was detected with statistical significance ($P<0.05$) in 20 of the 36 profiles for SBP and in 14 cases for DBP. A circasemiseptan component was detected in 15 and 17 of the SBP and DBP profiles, respectively. Overall, the circadian component was the most prominent in the spectrum ($P<0.001$), accounting for 26% (SBP) and 20% (DBP) of the variance. Several harmonic terms contributed significantly to the circadian waveform. The 12-hour component accounts for 5% (SBP) and 4% (DBP) of the overall variance ($P<0.001$) and the 6-hour component accounts for 1.5% of the variance ($P<0.001$). An about 3.4-hour component that may correspond to the REM cycle is also detected for DBP ($P=0.049$). As expected, circaseptan-to-circadian and circasemiseptan-to-circadian amplitude ratios showed a concave relation with age, with a trough in mid-adulthood. The fit of a second-order polynomial of the circasemiseptan-to-circadian amplitude ratio versus age reached borderline statistical significance in the case of SBP ($R^2=0.141$, $P=0.081$; on $\log_{10}$ amplitude ratios: $R^2=0.159$, $P=0.058$).

Endothelial function (Reactive Hyperemic Response or RHI) and arterial stiffness (Augmentation Index or AI @ 75 bpm) were assessed with the Endo-PAT 2000 (Safaric Hospital, Kosice) (tab. 6). The first endothelium-related parameter or endoscore (RHI) identified an anomaly (1.38) in A3, but this was later relieved as the adolescent admitted having wolfed on a fairly large amount of ice cream right before the test (a accompanying friend A0 did show a similar though less dramatic deviation: RHI: 1.61, HR (bpm): 65, AI (%): –10; rAI(%): 78; a minor defect in endothelium function (1.48)

was detected in the eldest person C2. The second endothelium-related parameter (rAI) was much more scattered among individuals & subgroups; it ranged from 7 to 94% in the adolescent group A.

Tab.6. Endothelial Function & Arterial Stiffness

	Norm	A1	A2	A3	B1	B2	B3	C1	C2	C3
RHI	>1.67	1.99	2.26	1.38*	2.38	2.90	3.67	2.08	1.48*	2.01
HR	-	68	71	69	69	65	67	50	81	67
AI (%)	-	–31	+3	–11	–7	+13	–19	+22	+14	+28
rAI(%)	5–95	7	94	75	33	58	26	45	23	75

(*)Out of norms; RHI: Reactive Hyperemic Response or Endoscore; AI: Augmentation Index @ 75 bpm, rAI: Patient-relative to Age & Gender Matched Distribution Augmentation Index @ 75 bpm.

The hemodynamic parameters obtained on the Task Force Monitor (St Anna Hospital, Brno) under conditions of spontaneous Φ1 and controlled Φ2 (0.33 Hz) breathing did not differ from each other and therefore only those under conditions of spontaneous Φ1 breathing are reported (tab.7). One elderly – the grandmother C1 – displayed rather low heart rate (confirmed by ABPM). More remarkably were cardiac, stroke and peripheral resistance indexes at the lower and higher limits, respectively, or outside those norms for both the adults & the elderly subgroups taken to Brno.

Tab.7. Hemodynamic Parameters Nov 4, 2010 (end of study).

Parameter	Abbr.	Unit	Norms	A1	A3	B1	B2	C1	C3
Heart Rate	HR	bpm	60–90	69.0	73.3	72.9	65.7	56.4*	72.5
Cont. Systolic Blood Pressure	sBP	mmHg	90–140	98.0	125.3	119.9	114.5	122.2	129.3
Cont. Diastolic Blood Pressure	dBP	mmHg	50–90	52.5	66.9	84.9	73.8	72.8	81.0
Sroke Index	SI	ml/m^2	30–80	48.8	49.4	31.6	32.6	43.1	28.1*
Cardiac Index	CI	$l/min*m^2$	2.5–4.5	3.4	3.6	2.3*	2.1*	2.4*	2.0*
Tot Peripheral Resistance Index	TPRI	$dyne*s*m^2/cm^5$	>1200 <2400	1536	1833	3332*	3020*	2674*	3509*
Left Ventricular Index	LFWI	$mmHg*l/min*m^2$	3.0–5.0	2.9*	4.1	2.9*	2.4*	2.7*	2.5*

(*)Out of norms.

The monthly changes in total blood fatty acid profiles over the 3-months of dietary supplementation (PUR3 & Lipistase) – from AUG 15 to NOV 15, 2010 – are reported in table 8a (adolescents), table 8b (adults) and table 8c (elderly). Saturated fatty acids (SAFA), mono-unsaturated fatty acids (MUFA), polyunsaturated fatty acids (ω6 & ω3 PUFA) and, within the latter family, highly unsaturated fatty acids (ω6 & ω3 HUFA) were individually assessed. The C20:4ω6 (AA) / C20:5ω3 (EPA) ratio and the ω6 HUFA / (ω6 + ω3 HUFA) or omega–6 status (Ω6S) were then computed. A common characteristic to all three groups and subjects was that the total blood fatty acid distributions reported here, from

36 analyses performed with no consideration of fasting and timing on nine subjects distributed over three generations (adolescents, adults, elderly) supplemented over three months with reasonably large amounts (2.7 to 5.4 g/d) of ω3 HUFA, show relatively stable patterns of saturated (SAFA: 40–45%), monounsaturated (MUFA: 20–25%), and polyunsaturated (PUFA: 30–35%) fatty acids. Common trends to adolescent (A) and elderly (C) groups (tables 8a & 8c): the 6 subjects were clearly different at baseline with AA/EPA & Ω6S ranging from 4.06 & 59.25 (A1) to 6.22 & 68.90 (C2) to 6.35 & 64.27 (A3) to 10.04 & 72.12 (C3) to 11.44 & 72.94 (c1) to 21.86 & 79.69 (A2), yet ended up the intervention program (6x PUR3/d + 2x LIPISTASE/d) with similar results, i.e. AA/EPA & Ω6S of ~ 2.70 & ~ 55.0. These results were reached after just one month intervention for A1 (best starting case scenario), no more than two months for A2 (worst starting case scenario), and three months for A3 (least compliant scenario). The elderly responded similarly though more intensively than adolescents to the treatment, with a sharp response in the first month followed by a clear trend to stabilization over the duration of the intervention. In terms of concurrent changes in fatty acids, all subjects did show an increase in ω3 HUFA (C20:5 + C22:5 + C22:6) at the main expenses of SAFA, with no influence on ω6 HUFA (C20:4 + C22:4 + C22:5). Independently of those diet-induced changes, HUFA contributed ~ 2% more to the relative composition of blood total fatty acids in the adolescents vs. the elderly. Adult group B (table 8): the adults maintained relatively constant blood fatty acid composition (AA/EPA & Ω6S) during the entire duration of the intervention, i.e. 1.35 & 42.00 (B1), 1.78 & 47.45 (B2), 7.47 & 68.50 (B3). However, B1 & B2 did so through remarkable parallel increases in ω6 and ω3 HUFA probably due to a shift towards a higher protein/carbohydrate diet and/or additional dietary supplementation (CLA) at the time of the intervention[1], whereas B3 achieved it as a result of keeping on a similar diet and level of supplementation, i.e. 0.9 g/d ω3 HUFA or 2x PUR3/d, as he had been following prior to entering the reported pilot study.

1 Between AUG and OCT 2010, B1 adjusted his daily supplementation program from previous “3.9g ω3 HUFA + 1g CLA” to “5.4g ω3 HUFA + 2g CLA” whilst B2 refined it from “2.6g ω3 HUFA + 1g CLA” to “3.6g ω3 HUFA + 2g CLA”.

Tab 8a. Adolescent group A: total blood fatty acid changes over 3-month intervention

	A1				A2				A3			
	15-Aug–10	14-Sep–10	17-Oct–10	15-Nov–10	15-Aug–10	14-Sep–10	21-Oct–10	15-Nov–10	15-Aug–10	14-Sep–10	17-Oct–10	15-Nov–10
SAFA	**45.70**	**43.49**	**42.45**	**41.84**	**44.59**	**44.08**	**40.34**	**42.36**	**46.53**	**47.33**	**41.20**	**42.49**
C16:0	26.24	25.15	25.43	24.09	26.64	25.79	24.11	24.84	26.42	25.81	23.41	24.34
C18:0	13.62	13.38	12.70	13.47	12.73	13.46	11.94	12.97	14.29	15.16	13.08	13.42
C20:0	0.64	0.53	0.48	0.44	0.55	0.54	0.47	0.51	0.52	0.56	0.41	0.42
C22:0	2.19	1.79	1.45	1.45	1.97	1.78	1.40	1.51	2.04	2.31	1.52	1.48
C24:0	3.00	2.63	2.39	2.39	2.72	2.51	2.43	2.53	3.27	3.48	2.78	2.84
MUFA	**22.18**	**20.71**	**22.92**	**21.23**	**24.16**	**23.92**	**22.76**	**23.21**	**23.92**	**21.96**	**22.47**	**23.52**
C16:1	0.78	0.62	0.91	0.70	1.22	0.95	1.09	0.89	0.97	0.63	0.68	0.68
C18:1ω7	1.55	1.34	1.54	1.43	1.56	1.54	1.57	1.74	1.63	1.48	1.48	1.63
C18:1ω9	16.11	15.26	17.33	16.20	17.43	17.91	16.32	16.68	17.62	16.09	16.96	17.75
C20:1	0.30	0.21	0.14	0.21	0.26	0.24	0.16	0.21	0.28	0.27	0.15	0.26
C22:1	0.16	0.11	0.09	0.10	0.16	0.15	0.11	0.12	0.11	0.15	0.11	0.10
C24:1	3.29	3.16	2.91	2.60	3.53	3.12	3.52	3.58	3.30	3.34	3.09	3.11
PUFA	**32.12**	**35.65**	**34.46**	**36.79**	**31.05**	**31.85**	**36.77**	**34.43**	**29.38**	**30.55**	**36.15**	**33.86**
HUFA	**14.33**	**16.00**	**16.24**	**17.02**	**13.04**	**13.30**	**19.40**	**16.14**	**13.12**	**14.23**	**17.02**	**17.21**
ω6 PUFA	25.91	28.03	27.18	28.34	28.30	27.28	27.95	27.14	24.48	24.69	28.19	25.23
ω 6 HUFA	8.49	8.70	9.17	8.90	10.39	9.10	10.84	9.25	8.43	8.72	9.40	9.23
C18:2	17.24	19.17	17.84	19.30	17.70	18.02	16.98	17.73	15.89	15.80	18.62	15.87
C18:3	0.17	0.15	0.17	0.14	0.20	0.15	0.13	0.15	0.16	0.16	0.17	0.13
C20:3	0.65	0.64	0.72	0.62	0.86	0.60	0.61	0.57	0.83	0.75	0.76	0.66
C20:4	7.07	7.33	7.89	7.71	8.09	7.35	9.16	7.81	6.68	7.09	7.76	7.73
C22:4	0.66	0.54	0.49	0.45	1.25	0.97	0.92	0.76	0.77	0.78	0.73	0.71
C22:5	0.11	0.19	0.07	0.12	0.19	0.18	0.15	0.12	0.15	0.10	0.15	0.13
ω3 PUFA	6.15	7.71	7.40	8.53	2.87	4.65	8.89	7.25	5.01	5.97	8.06	8.71
ω 3 HUFA	5.84	7.30	7.07	8.12	2.65	4.20	8.56	6.89	4.69	5.51	7.62	7.98
C18:3	0.30	0.41	0.32	0.41	0.22	0.45	0.34	0.35	0.33	0.45	0.44	0.73
C20:5	1.74	2.79	2.67	3.53	0.37	1.39	3.64	2.89	1.05	1.69	2.59	2.88
C22:5	1.07	1.34	1.26	1.33	0.80	0.94	1.56	1.31	1.08	1.17	1.55	1.54
C22:6	3.03	3.17	3.15	3.27	1.48	1.87	3.36	2.69	2.56	2.65	3.49	3.56
AA/EPA	**4.06**	**2.63**	**2.96**	**2.18**	**21.86**	**5.28**	**2.52**	**2.70**	**6.35**	**4.20**	**3.00**	**2.68**
Ω6S	**59.25**	**54.36**	**56.46**	**52.29**	**79.69**	**68.41**	**55.88**	**57.29**	**64.27**	**61.26**	**55.23**	**53.63**

Tab 8b. Adult group B: total blood fatty acid changes over 3-month intervention

	B1				B2				B3			
	15-Aug–10	14-Sep–10	19-Oct–10	15-Nov–10	15-Aug–10	14-Sep–10	19-Oct–10	15-Nov–10	17-Aug–10	15-Sep–10	19-Oct–10	16-Nov–10
SAFA	**47.33**	**41.82**	**41.42**	**42.63**	**45.90**	**43.95**	**41.36**	**43.09**	**42.02**	**42.67**	**40.09**	**42.97**
C16:0	27.61	22.65	23.67	24.88	26.50	24.33	24.40	25.01	26.62	25.77	25.00	26.72
C18:0	14.84	14.45	13.14	13.70	14.85	14.49	12.57	13.70	11.38	12.57	11.16	12.33
C20:0	0.54	0.48	0.40	0.36	0.55	0.58	0.46	0.43	0.46	0.42	0.38	0.38
C22:0	1.65	1.53	1.38	1.20	1.65	1.88	1.50	1.47	1.49	1.41	1.19	1.17
C24:0	2.69	2.71	2.82	2.50	2.35	2.68	2.43	2.48	2.07	2.51	2.36	2.37
MUFA	**23.19**	**21.85**	**20.51**	**20.91**	**23.75**	**23.47**	**20.71**	**22.09**	**25.64**	**26.81**	**26.17**	**26.58**
C16:1	0.83	0.60	0.61	0.61	1.39	0.73	0.86	0.82	1.31	1.19	1.31	1.37
C18:1ω7	1.64	1.59	1.52	1.48	1.71	1.46	1.26	1.36	1.76	1.74	1.69	1.85
C18:1ω9	17.39	16.39	14.75	15.66	17.37	18.10	15.50	16.99	19.17	20.31	19.79	19.93
C20:1	0.28	0.36	0.24	0.25	0.40	0.35	0.14	0.18	0.30	0.31	0.20	0.24
C22:1	0.10	0.11	0.08	0.10	0.16	0.13	0.09	0.07	0.22	0.11	0.08	0.10
C24:1	2.95	2.81	3.30	2.81	2.72	2.69	2.87	2.66	2.87	3.15	3.10	3.10
PUFA	**29.30**	**36.20**	**37.99**	**36.36**	**30.24**	**32.48**	**37.79**	**34.69**	**32.34**	**30.35**	**33.49**	**30.20**
HUFA	**13.41**	**15.97**	**17.90**	**16.60**	**14.57**	**14.99**	**18.04**	**17.64**	**14.46**	**14.95**	**16.28**	**14.49**
ω6 PUFA	21.43	26.03	27.11	26.56	22.27	23.62	27.89	25.05	27.66	25.02	27.89	25.56
ω 6 HUFA	5.69	6.28	7.46	7.37	6.97	6.82	8.60	8.61	10.26	9.89	10.97	10.08
C18:2	15.56	19.62	19.56	19.10	15.19	16.69	19.15	16.30	17.17	14.96	16.67	15.24
C18:3	0.19	0.13	0.08	0.10	0.11	0.10	0.14	0.14	0.23	0.17	0.25	0.25
C20:3	0.51	0.47	0.50	0.47	0.50	0.39	0.60	0.67	0.85	0.87	1.15	0.96
C20:4	4.94	5.47	6.55	6.51	5.99	6.05	7.44	7.46	7.38	7.82	8.65	8.01
C22:4	0.16	0.21	0.34	0.30	0.30	0.33	0.43	0.38	1.94	1.00	1.00	0.95
C22:5	0.08	0.13	0.08	0.09	0.18	0.05	0.13	0.09	0.09	0.20	0.17	0.16
ω3 PUFA	8.04	10.24	10.92	9.85	8.05	8.92	9.98	9.71	4.58	5.38	5.72	4.79
ω 3 HUFA	7.72	9.69	10.44	9.23	7.60	8.17	9.44	9.03	4.20	5.06	5.31	4.41
C18:3	0.32	0.55	0.48	0.61	0.45	0.75	0.54	0.68	0.38	0.32	0.41	0.38
C20:5	3.58	4.75	4.47	4.57	3.29	3.80	3.84	4.21	1.00	1.13	1.16	0.99
C22:5	1.05	1.27	1.77	1.37	1.03	1.15	1.53	1.38	0.83	1.17	1.22	1.05
C22:6	3.09	3.66	4.20	3.30	3.28	3.22	4.07	3.44	2.37	2.76	2.93	2.37
AA/EPA	**1.38**	**1.15**	**1.47**	**1.43**	**1.82**	**1.59**	**1.94**	**1.77**	**7.38**	**6.93**	**7.47**	**8.12**
Ω6S	**42.38**	**39.35**	**41.70**	**44.39**	**47.82**	**45.50**	**47.68**	**48.80**	**70.96**	**66.14**	**67.39**	**69.57**

Tab 8c. Elderly group C: total blood fatty acid changes over 3-month intervention

	C1				C2				C3			
	15-Aug–10	14-Sep–10	19-Oct–10	16-Nov–10	15-Aug–10	14-Sep–10	19-Oct–10	16-Nov–10	15-Aug–10	14-Sep–10	19-Oct–10	16-Nov–10
SAFA	**42.90**	**42.43**	**38.67**	**37.59**	**42.38**	**40.47**	**39.23**	**42.82**	**46.16**	**44.26**	**33.62**	**41.12**
C16:0	26.58	25.84	24.25	22.68	27.56	26.79	25.96	28.39	28.25	27.95	22.54	26.56
C18:0	12.22	12.65	11.05	11.22	11.17	10.83	10.21	11.14	13.16	12.67	8.87	11.42
C20:0	0.45	0.44	0.39	0.44	0.48	0.44	0.38	0.41	0.53	0.39	0.27	0.31
C22:0	1.45	1.25	1.08	1.16	1.37	0.94	1.03	1.07	1.73	1.32	0.68	0.98
C24:0	2.20	2.24	1.90	2.08	1.79	1.47	1.66	1.81	2.50	1.93	1.27	1.86
MUFA	**28.65**	**24.74**	**27.82**	**28.79**	**30.48**	**27.82**	**26.37**	**26.37**	**25.14**	**22.51**	**32.21**	**28.01**
C16:1	1.42	0.91	1.07	0.81	2.40	1.57	1.96	1.73	1.29	1.26	1.66	1.43
C18:1ω7	2.04	1.61	1.83	2.14	2.04	1.80	1.71	1.88	1.51	1.49	1.85	1.88
C18:1ω9	22.04	18.88	22.20	22.84	23.24	22.26	20.30	20.12	19.03	16.80	26.13	21.70
C20:1	0.28	0.27	0.19	0.34	0.22	0.24	0.19	0.19	0.22	0.26	0.77	0.32
C22:1	0.15	0.10	0.08	0.13	0.12	0.14	0.06	0.09	0.16	0.13	0.07	0.09
C24:1	2.71	2.97	2.45	2.54	2.45	1.81	2.14	2.37	2.93	2.57	1.73	2.60
PUFA	**28.25**	**32.72**	**33.34**	**33.49**	**26.89**	**31.53**	**34.15**	**30.57**	**28.46**	**33.24**	**33.96**	**30.68**
HUFA	**11.29**	**14.85**	**14.78**	**12.84**	**11.20**	**13.22**	**16.35**	**13.03**	**11.17**	**15.55**	**13.98**	**13.85**
ω6 PUFA	24.95	26.40	26.52	27.15	23.10	24.66	25.05	24.53	25.16	25.90	25.03	24.07
ω 6 HUFA	8.24	8.91	8.23	7.76	7.72	6.88	7.98	7.28	8.06	8.69	6.93	7.98
C18:2	16.52	17.38	18.12	19.25	15.13	17.60	16.82	17.01	16.87	17.03	17.91	15.91
C18:3	0.20	0.12	0.17	0.14	0.25	0.18	0.25	0.24	0.23	0.18	0.20	0.18
C20:3	0.95	0.67	0.80	0.68	1.05	0.87	1.01	0.95	0.89	0.88	0.79	0.83
C20:4	6.64	7.52	6.90	6.57	5.97	5.47	6.36	5.80	6.43	7.09	5.61	6.53
C22:4	0.53	0.59	0.41	0.38	0.58	0.43	0.50	0.43	0.62	0.63	0.42	0.49
C22:5	0.12	0.13	0.11	0.13	0.12	0.11	0.11	0.10	0.12	0.09	0.10	0.12
ω3 PUFA	3.43	6.36	6.93	6.42	3.95	6.98	9.29	6.24	3.47	7.27	9.06	6.71
ω 3 HUFA	3.05	5.94	6.55	5.08	3.48	6.34	8.37	5.75	3.11	6.86	7.05	5.87
C18:3	0.37	0.42	0.38	1.34	0.46	0.64	0.91	0.49	0.35	0.41	2.01	0.84
C20:5	0.58	2.16	2.58	1.93	0.96	2.84	3.41	2.18	0.64	2.82	2.99	2.51
C22:5	0.71	0.93	1.11	0.93	0.74	1.09	1.45	1.02	0.66	1.06	1.03	0.98
C22:6	1.76	2.84	2.86	2.22	1.78	2.42	3.51	2.56	1.81	2.98	3.03	2.39
AA/EPA	**11.44**	**3.48**	**2.68**	**3.41**	**6.22**	**1.93**	**1.87**	**2.66**	**10.04**	**2.52**	**1.87**	**2.61**
Ω6S	**72.94**	**60.01**	**55.67**	**60.45**	**68.90**	**52.05**	**48.80**	**55.84**	**72.12**	**55.89**	**49.55**	**57.61**

Discussion

The main purpose of this pilot study was to assess the feasibility of titrating and reaching plateaus in such titration exercises of blood fatty acids – the omega–6 status – in individuals (males & females) of a typical Western subpopulation group distributed over three generations (adolescents, adults & elderly) (fig.1). Another purpose was to assess the potential of new markers (vascular rhythms) and symptoms (sympatho-vagal balance) of the autonomic cardiovascular regulation (ACR) as probes to access and eventually assess the influence of changes in blood fatty acids on psychosomatic health. The subgroup involved was a family composed of two twin m/f children, the mother and her two parents; external references were used for the sake of controls, mainly. The heterogeneity of the subgroup was demonstrated at levels ranging from lifestyle, morphology & body mass composition, blood group, behavior and composition, personality & psychosomatic aspects (vascular rhythms & sympatho-vagal balance) of the autonomic cardiovascular regulation, endothelium function & hemodynamic parameters, and blood fatty acids. The results presented in tables 1 to 7 do characterize each individual along these aspects and as such confirm the reliability of non-invasive and non-obtrusive characterization of a wide array of information about individual's psychosomatic health status.
More specifically, the vascular rhythm of the systolic blood pressure appear to provide an interesting insight into the daily average load – mind strain – that an individual take on his / herself on a scale that represents his / her own current capacity of coping with such load. If confirmed, such probes to mind strain could tell about how much an individual stretches his / herself on an average daily basis, according to the following tentative score scale:

- 0–25% would indicate a probable need for socio-psychological advice as the subject really under-performs his/her potential and such situation if not taken care of could eventually take his/her to depressed mood and rampant vigor, fatigue and diseases;
- 25–50% would support the view that the subject has much room for improvement in his/her career and life, if he/she so wish. Clearly, he/she can do far better. Just need to do it. Little guidance from family and close friends may perhaps help his/her a long way;
- 50–75% would identify a subject that is not far from knowing him/herself, the kind of mature individual. He/she may just want to stay there or to take the next challenge with appropriate counseling and/or training in order to keep progressing;
- 75–100% would points to someone who is pushing. For him/her, the sky is the limit, which is fine as the society needs his/her, too, and provided he/she scores ok in his/her body resistance (YBR), he/she should be a long run winner;
- >100% would indicate that the subject should come down a bit for a while. He/she overdo it at the cost of his/her own health. He/she definitely burnt his/her flame.

The larger prominence of the week and half-week versus the day early and late in life is corroborated in this rather small population involving subjects in an age range (17 to 71 years) narrower than that in earlier studies. Ultradian endpoints of interest in their own right and as a gauge of a non-sinusoidal circadian waveform deserve mapping on a population basis, as do infradians, for alignment with environmental cycles in longer and larger follow-up studies.
The parameters of the autonomic cardiovascular regulation obtained on the Task Force Monitor revealed interesting aspects of the sympatho-vagal balance in the five family subjects in relation with their self-assessed personality traits put in evidence by EPQ-R. This approach may in fact well probe and compare endogenous versus behavioral personalities (fig. 4) and as such represents a potentially interesting approach to evidence-based psychology.

An endoscore cut-off value of 1.67 provides a sensitivity of 82% and a specificity of 77% to diagnosing coronary endothelial function (Bonetti PO et al., 2004, 2005). The endoscore has been found to be inversely correlated with the number of cardiovascular risk factors (Kuvin et al., 2003, 2007). In this study, it was clear that all but one elderly subjects had endoscore values well above (≥ 2.0) pathological cut-off range at the exception of one adolescent whose data must be excluded for obvious reason (see table 5). Arterial stiffness was highly variable among individuals and in no correlation with endothelium function; however a clear trend to increased stiffness with age was observed.
With regards to fatty acids, the three adolescents and three elderly reach similar omega–6 status (55 ± 5%) after two months of supplementation and this was not influenced by the original status of the individual. The "ΔΩ6S = –7.5 units/(g ω–3 HUFA)/day" response observed in these two age groups was confirmed in the adult subgroup supplemented with different daily amounts of ω–3 HUFA. In fact, blood fatty acids titration appear to respond linearly to daily intake, independently of gender, age, lifestyle, body composition and other standard medical health markers and symptoms. This observation leads to the tentative conclusion that the daily intake of ω–3 HUFA needed to reach/ maintain an Omega–6 Status (Ω6S) of 50% in the blood-tissue of a modern Western population in the presence of a "blunter" of inter-individual genotypic variance nears 3.35g. The Omega–6 status was also expressed as tissue resistance (from 0 to 100%) to chronic inflammation based on earlier reported population-based observations that the omega–6 status is a reliable predictor of %risk of CHD (http://efaeducation.nih.gov/sig/dietbalance1.html), according to the following tentative score scale:

- 0–25% would indicate the need for nutritional advice for the subject obviously feeds him/herself the wrong fats, and probably not exactly the ones he/she may think. It is time to change for there currently is no umbrella, the higher the mind stress → body strain (YMS) the higher the risk of developing a degenerative chronic disease on the long run;
- 25–50% would indicate there is room for improvement in the diet. The subject is borderline good in comparison with most of his/her peers, but still not quite on the safe side as yet;
- 50–75% would be sign of a modern well-informed dietician or lucky enough individual to dwell nearby one. Body tissues can absorb the daily load and eventually heal if hurt. Great status;
- 75–100% calls for the big fight. Body tissues are all set for keeping up with a very active lifestyle and will sustain continuous strive towards the better.

Mind and body have evolved independently in conscious species, yet they interact closely for the span of a lifetime within individuals. Whereas the mind-related memes have evolved rapidly over the past 5–10,000 years of nascent humanity, the body-related genes have barely changed. Gene-wise, modern man is very much similar to his hunter-gatherer ancestor. It is therefore no surprise that memes and genes have a difficult time cohabitating the same environment. Mind stress induces body strain, which if not taken care of at individual level, induces tissue injuries and chronic degenerative diseases, ie functional gastrointestinal disorders, cardiovascular disease, and the like. For various reasons extending from commercial availability of non-invasive/ non-obtrusive monitors to access to institutional analytical interpretation of collecting data and established international data banks, the parameters of the autonomic cardiovascular regulation (ACR), ie vascular rhythms (SBP, DBP, HRV) and sympatho-vagal balance (HRV-LF/HF) were selected as far-reaching probes to monitor mind-body interactions. The experimental group consisted of a Polish family (five members) extending on three generations, three external references (one per generation) and the promoter of the study (Chronomics). The only variable in the 3 months monitoring program was the blood omega–6 status of the subjects that was taken down from the Polish standard of ~75% to somewhere closer (~55%) to the Mediterranean standard of through the daily dietary intake of ~2.5 g omega–3 long chain (C20–

22) fatty acids associated with a epi-genetic/-genomic blunter (premix of trace elements involved in PPAR-α regulated lipid metabolism). Vascular rhythms did reveal large variations, among and within individuals, respective to their environmental exposure to stress. Blood/tissue responses to omega–3 fatty acids titration appeared to be rather uniform across the board. In conclusion, the parameters of the autonomic cardiovascular regulation (ACR) appear as promising probes to monitor mind-body interactions and to detect – perhaps assess – risk of developing chronic degenerative diseases at individual level. Given the volatile response of vascular rhythms to mind-body stress, nothing short of an urgent re-balancing of omega–6/3 fatty acids at tissue level will likely suffice to control the explosion of chronic degenerative diseases at population level.
The longitudinal study will be conducted in three different age subgroups of healthy subjects living in Southern Poland (adolescents, adults, elderly), with focus on psychosomatic markers and symptoms of development of cardiovascular and psychological diseases.

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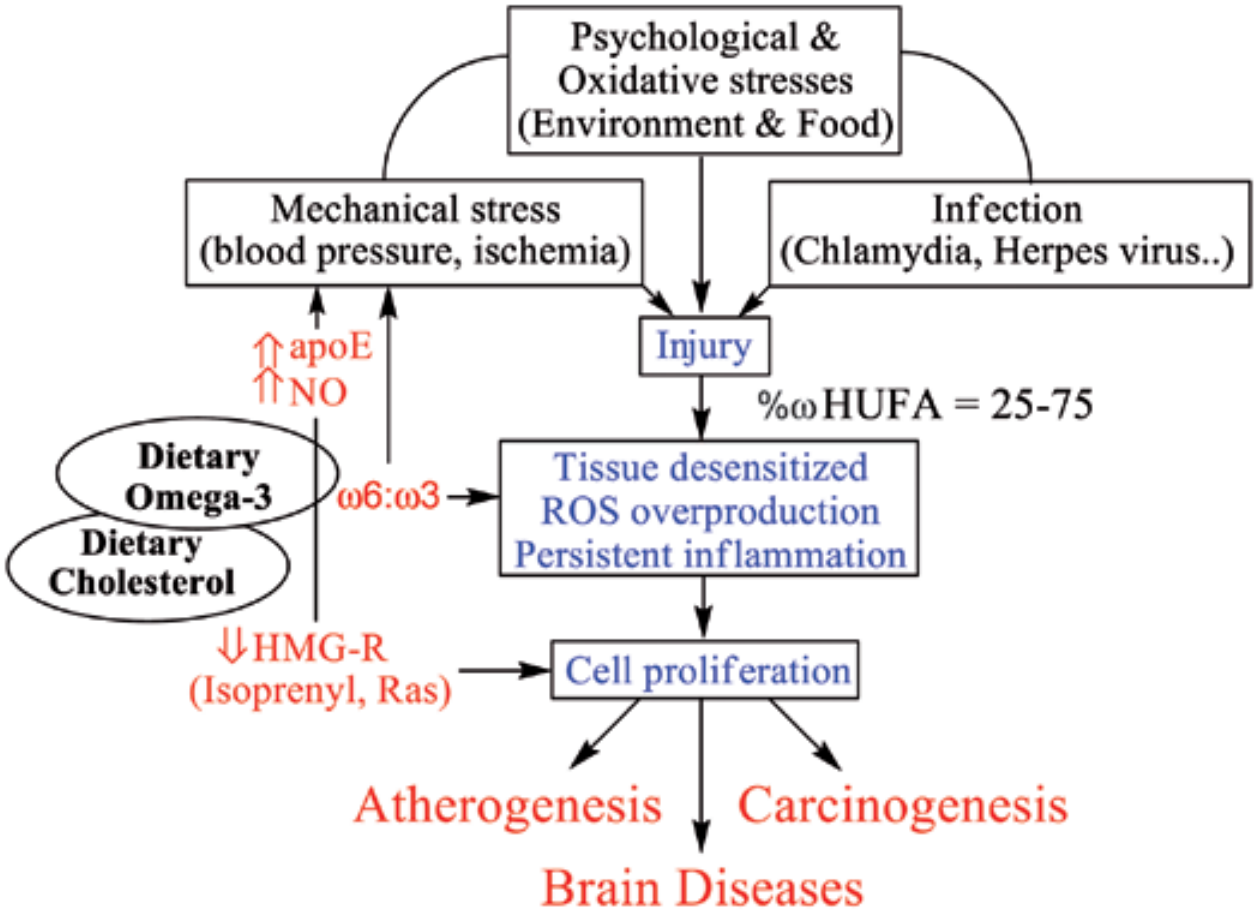

Fig.1. Modern view on chronic degenerative diseases

Chronic degenerative diseases account for some 85% of all annual death worldwide (WHO Global Health Observatory: Cause-specific mortality and morbidity http://apps.who.int/ghodata/). They also represent a major threat to modern civilizations and their societies as they appear to cause ever earlier acute morbidity which, in some cases, transmits from one generation to the next through epigenetic / genomic inheritance. Cardiovascular ill-health was first; mental ill-health appears second in a row that extends to the wide spectrum of exploding modern inflammatory diseases related to a most single cause, ie the typical 75% proportion of ω6 highly unsaturated fatty acids (HUFAs) in blood total lipids (%ω6 in HUFAs = 75).

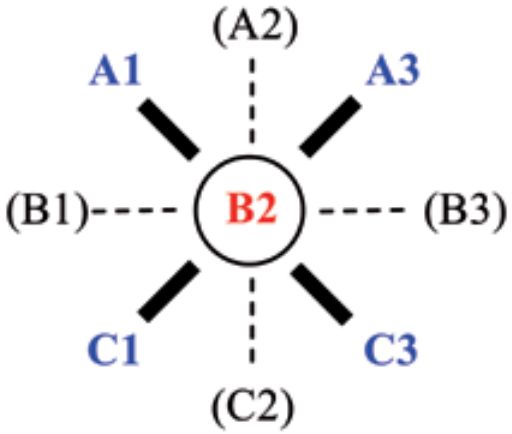

Fig.2. Social distribution of pilot subject group
{A1A3-B2-C1C3} shapes a family extending on 3 generations: A1A3 (m/f twin children); B2 (Mother); C1C3 (Grand Parents). {A2-B1B3-C2} are external references with no family connection.

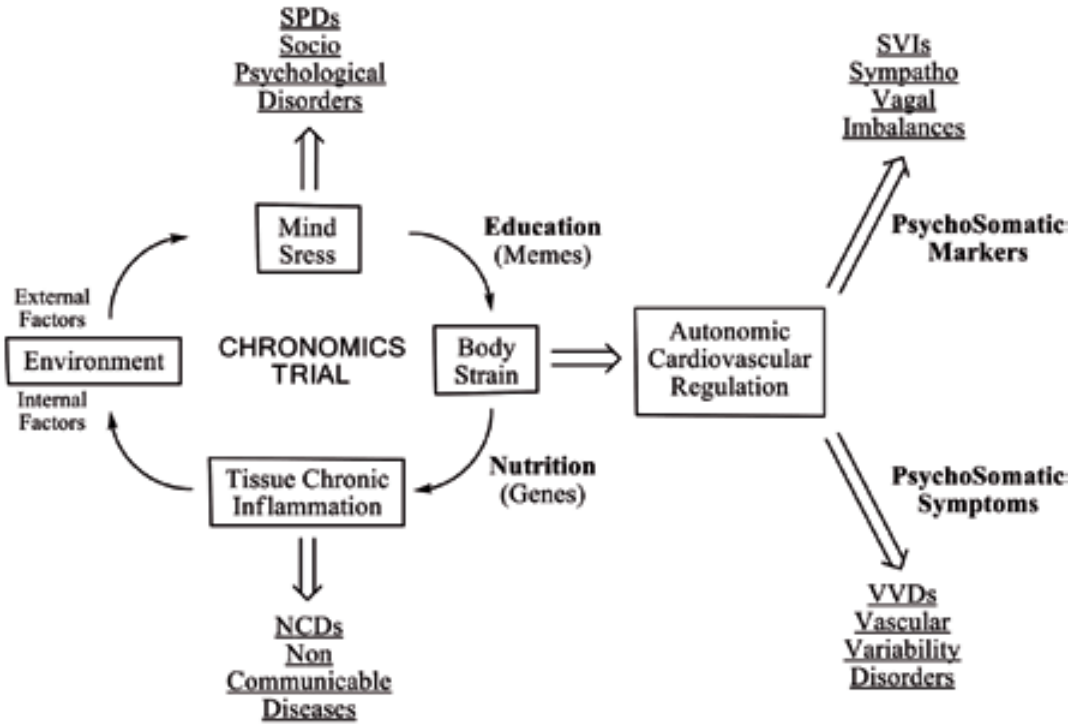

Fig.3. The Chronomics Trial
The Chronomics Trial will test-validate (1) the sympatho-vagal balance of the autonomic cardiovascular regulation, on the one hand, the circadian & infradian vascular rhythms of blood pressure & heart rate, on the other hand, for accessing/assessing markers and symptoms, respectively, of the mind stress/resilience (education) → body strain/resilience (nutrition) response, and (2) the reliability of such probes for predicting socio-psychological disorders otherwise assessed by conventional tests (MSV[2], EPQ-R, PANAS, GHQ–28) and non-communicable diseases otherwise confirmed by standard biomedical examinations (morphological & blood/urine parameters).

2 MSV: Self-perceived and assessed mood (M), stress (S) & vigor (V).

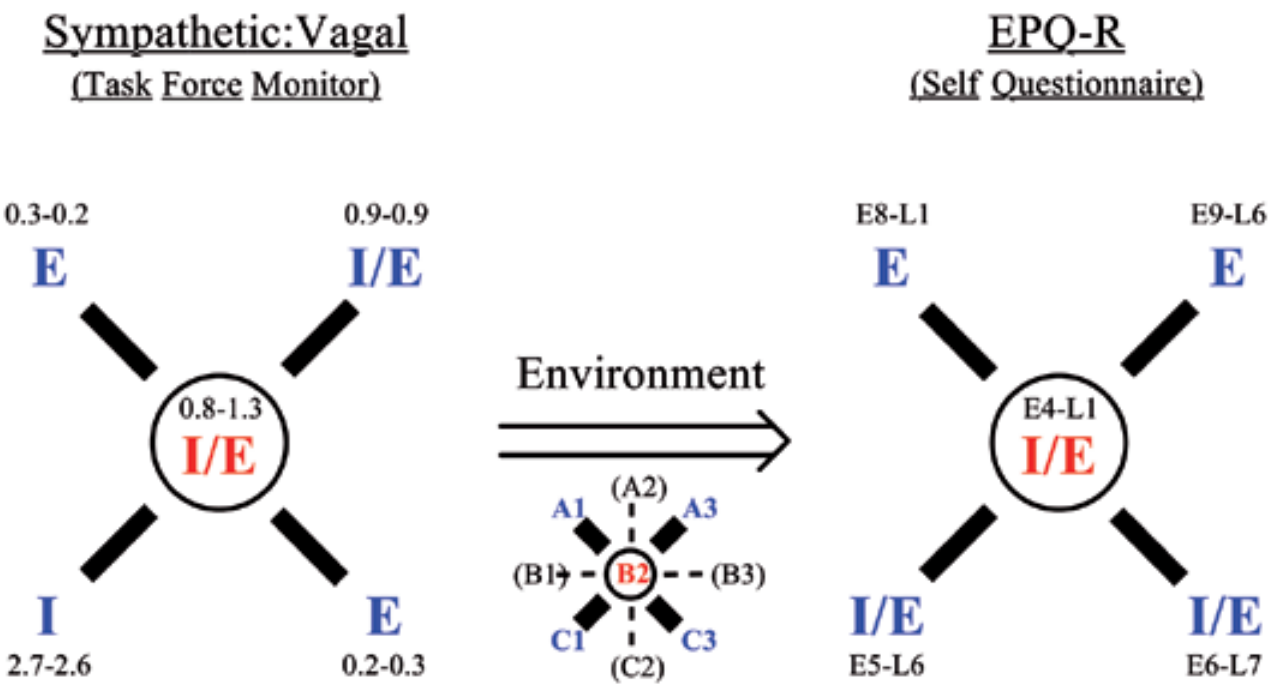

Fig.4. Endogenous vs Behavioral Personalities

Endogenous personalities assessed by beat-to-beat heart rate variabilities reveal hidden aspects of behavioral personalities self-assessed by psychological questionnaires: whereas the mother B2 clearly is a true balanced personality as per TSF & EPQ-R, her parents C1 & C3 have achieved this state with experience/age only, in fact from two original opposite traits (the grand mother C1 is an introvert whereas the grand father C3 is an extrovert to start with). Her two twins behave as extroverts, but only her daughter A1 is a true one, whereas her son A3 is more educationally so.

Left-hand side diagram shows sympatho:vagal balance (LFnu-dBP:HFnu-RRI) under spontaneous (F1) and controlled (F2:0.33 Hz) breathing conditions. Right-hand side diagram shows scores in EPQ-R self-assessment questionnaires (E: Extrovert; L: Lie) normalized to 1–10 sten scales.

TFM: Task Force Monitor; EPQ-R: Eysenck Personality Questionnaire – Revised.

SEVEN DAY AMBULATORY BLOOD PRESSURE MONITORING: AMBULATORY ARTERIAL STIFFNESS INDEX IN PATIENTS AFTER INFARCTUS OF MYOCARDIUM

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Introduction

Noninvasive methods for arterial stiffness evaluation are current requirements in clinical practice. Stiffening of large arteries predicts adverse cardiovascular outcomes (Benetos et al. 1997, Hayashi et al. 2002, Weber et al. 2004). Direct measurements of arterial stiffness require ultrasound equipment to measure peripheral arteries in the subject in the supine or sitting position (Van Bortel et al. 2002). The ambulatory arterial stiffness index (AASI) is defined as one minus the regression slope of diastolic on systolic pressure during 24 h ambulatory blood pressure monitoring and might be a measure of arterial stiffness (Li et al. 2006, Dolan et al. 2006). The stiffer arterial tree, the closer the regression slope and AASI are ranging from 0 to 1, respectively (Meaume et al. 2001, Schillaci et al. 2008).
When studying the infradian rhythms in chronobiology of blood pressure we performed ambulatory blood pressure monitoring for 7 consecutive days (Siegelova et al. 2006, Halberg et al. 2006, Halberg et al. 2007). The preliminary results from our laboratory were published (Siegelova et al. 2008) and showed the variability of AASI in 6 full consecutive days.
In the present study we attempted to estimate the reliability of AASI determination in individual patients after infarctus of myocardium in the days after cardiovascular exercise training and in the days without exercise training.

Methods

The set being monitored consisted of 41 patients after myocardial infarction in the past history more than 3 months before, of mean age 63 ± 6.5 years and mean ejection fraction of the left ventricle 43 ± 12.3 %.
The patients underwent phase II of cardiovascular rehabilitation (controlled ambulatory rehabilitation program) lasting two to three months with the frequency of three times in a week at the Department of Functional Diagnostics and Rehabilitation of St. Anna Teaching Hospital.
In the course of rehabilitation they went through 7-day ambulatory monitoring of blood pressure. During blood pressure recording they did not interrupt their pharmacotherapy.
The seven-day blood pressure monitoring was made by using the instrument TM – 2421 of the Japanese firm AD on the principle of oscillometric methods of blood pressure measurement. The regime of measurement of blood pressure was performed for 7 days repeatedly every 30 minutes from 5 to 22 h during the day time and once in an hour from 22 to 5 h at night (Siegelová et al. 2006).
The measured blood pressure values for every patient from the monitored set were statistically processed in the form of arithmetic means for systolic and diastolic blood pressure value during each hour for every day of the measurement. The average SBP and DBP and their standard deviations

(SD) in the given days were determined by the calculation of arithmetic mean of these values. We evaluated AASI in individual patients after infarctus of myocardium in the days after cardiovascular exercise training and in the days without exercise training separately.
These data were used for every consecutive day of seven-day monitoring to calculate the slope of diastolic on systolic pressure and to calculate the ambulatory arterial stiffness index (AASI) as one minus regression slope of diastolic on systolic blood pressure.
The study was approved by local ethic committee and the patients signed the informed consent.

Results

The results of AASI values in individual patients after infarctus of myocardium in the days after cardiovascular exercise training were presented in Table 1 and Table 2, in the days without exercise training in Table 3 and Table 4 together with 24-hour mean values of systolic (SBP) and diastolic blood pressure (DBP), pulse pressure (PP) and correlation coefficient R of 20 patients. Table 5 summarizes the mean data of AASI, SBP, DBP, PP, and R.

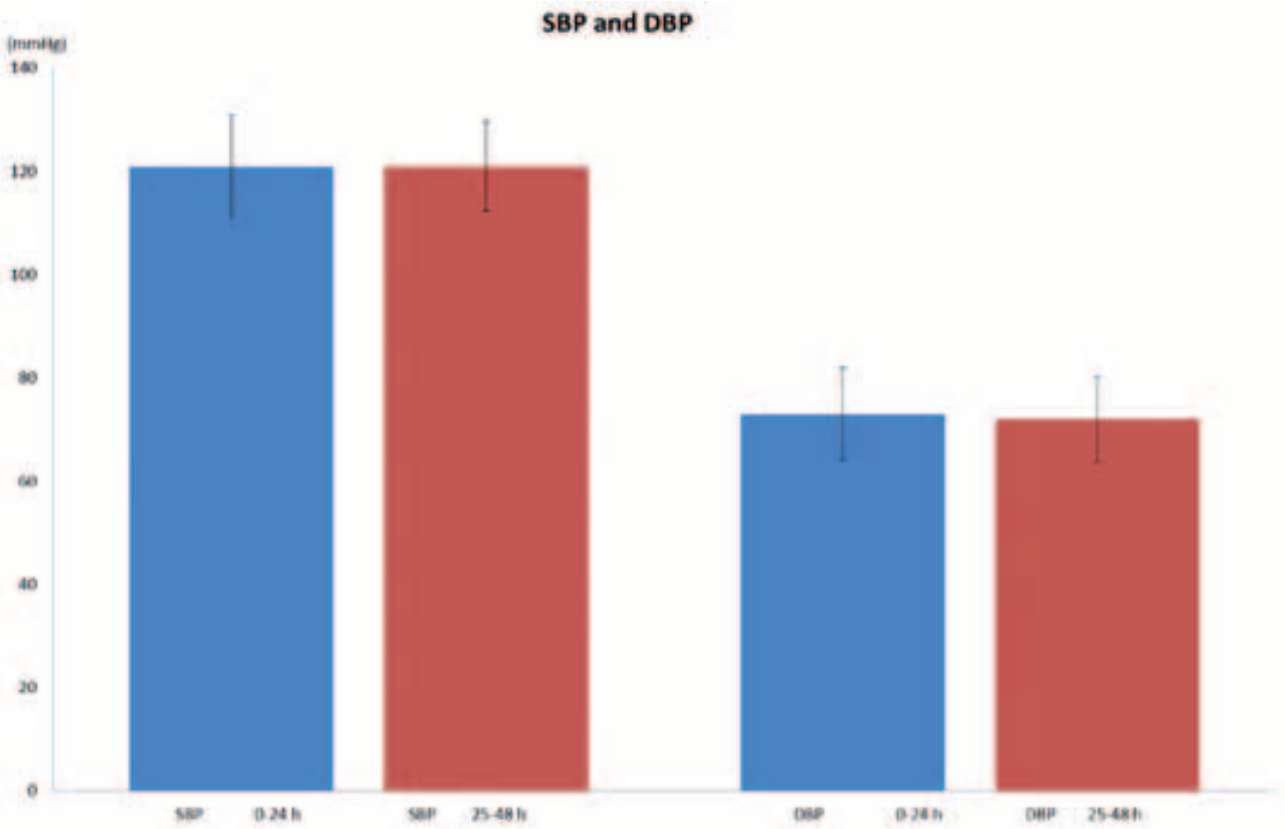

Fig. 1 Systolic and diastolic blood pressure in the day with cardiac exercise training (0 – 24) and in the day without exercise training (25 – 48) in patients after infarctus of myocardium

Tab. 1 *Ambulatory arterial stiffness index* in the day of physical activity

pat.	age [years]	EF [%]		SBP [mm Hg]	± SD	DBP [mm Hg]	± SD	PP [mm Hg]	AASI	R
1	53	65	1. cycle	144	10,8	96	9,8	49	0,17	0,92
			2. cycle	146	10,2	94	10,0	52	0,26	0,76
2	68	69	1. cycle	122	13,8	72	10,8	50	0,40	0,76
			2. cycle	118	13,6	66	8,5	52	0,50	0,81
3	67	60	1. cycle	122	12,7	81	8,7	42	0,49	0,75
			2. cycle	115	12,8	77	10,6	38	0,37	0,76
4	64	46	1. cycle	107	10,7	63	9,3	44	0,43	0,66
			2. cycle	106	12,7	64	7,6	42	0,49	0,86
5	44	73	1. cycle	125	13,5	78	9,7	47	0,44	0,77
			2. cycle	125	12,3	77	9,7	48	0,47	0,67
6	48	63	1. cycle	110	10,6	69	7,5	41	0,49	0,72
			2. cycle	108	14,3	65	12,0	42	0,37	0,75
			3. cycle	110	16,9	63	10,4	48	0,52	0,79
7	73	61	1. cycle	114	13,6	58	5,8	57	0,68	0,74
			2. cycle	116	7,7	58	6,4	58	0,58	0,51
8	41	56	1. cycle	118	11,2	77	9,1	41	0,55	0,55
			2. cycle	124	9,7	77	9,0	48	0,55	0,49
9	65	63	1. cycle	125	16,0	81	12,6	45	0,37	0,80
			2. cycle	127	12,6	83	10,1	45	0,39	0,76
10	63	52	1. cycle	118	13,1	68	8,9	50	0,42	0,86
			2. cycle	112	16,2	61	10,4	51	0,42	0,90
11	56	61	1. cycle	127	10,8	79	8,7	48	0,36	0,79
			2. cycle	124	16,1	78	10,7	46	0,49	0,77
12	78	59	1. cycle	108	12,9	54	10,1	54	0,72	0,36
			2. cycle	129	22,7	61	12,9	68	0,68	0,56
13	57	67	1. cycle	132	9,8	78	8,3	54	0,63	0,44
			2. cycle	131	7,8	79	7,2	53	0,42	0,63
14	49	26	1. cycle	112	15,3	76	11,4	37	0,58	0,57
			2. cycle	112	10,5	79	8,8	32	0,25	0,90
			3. cycle	104	11,3	68	9,1	37	0,67	0,41
15	69	66	1. cycle	126	11,4	73	6,3	53	0,69	0,56
16	64	72	1. cycle	115	8,4	70	8,1	45	0,63	0,38
			2. cycle	116	16,7	66	6,8	49	0,77	0,57
17	56	57	1. cycle	127	15,2	86	13,0	42	0,24	0,88
			2. cycle	124	9,5	83	6,8	41	0,62	0,53
18	55	33	1. cycle	139	11,8	70	6,0	69	0,79	0,41
			2. cycle	127	12,1	68	8,4	59	0,77	0,34
			3. cycle	124	11,2	68	8,4	57	0,50	0,67
19	66	40	1. cycle	146	14,9	91	10,4	55	0,49	0,73
			2. cycle	127	10,7	82	9,2	45	0,30	0,81
20	56	51	1. cycle	118	14,7	74	13,4	45	0,15	0,93
			2. cycle	112	17,1	70	11,1	42	0,41	0,90

Note: EF ejection fraction, PP – pulse pressure; AASI – *ambulatory arterial stiffness index*; R – correlation coefficient

Tab. 2 *Ambulatory arterial stiffness index* in the day of physical activity

pat.	age [years]	EF [%]		SBP [mm Hg]	± SD	DBP [mm Hg]	± SD	PP [mm Hg]	AASI	R
21	68	60	1. cycle	131	11,6	84	10,2	47	0,29	0,80
			2. cycle	136	14,3	88	8,4	48	0,62	0,65
			3. cycle	132	13,4	85	11,8	47	0,44	0,65
22	66	52	1. cycle	128	16,3	74	12,3	54	0,97	0,04
			2. cycle	120	16,1	70	11,7	50	0,61	0,53
23	56	37	1. cycle	109	13,5	73	10,0	36	0,41	0,80
			2. cycle	101	16,1	64	9,2	37	0,63	0,65
24	60		1. cycle	110	17,4	61	10,3	49	0,67	0,56
			2. cycle	125	26,9	61	10,3	64	0,91	0,22
			3. cycle	113	18,1	63	11,1	50	0,64	0,59
25	58	53	1. cycle	128	22,0	72	13,0	56	0,77	0,38
			2. cycle	131	21,4	70	12,0	61	0,69	0,55
26	58	40	1. cycle	146	25,3	73	15,8	73	0,64	0,58
			2. cycle	120	31,1	66	15,5	54	0,61	0,78
27	60	47	1. cycle	110	13,8	70	9,9	40	0,57	0,60
			2. cycle	108	13,5	66	7,7	42	0,68	0,57
28	74	54	1. cycle	112	8,0	59	7,0	53	0,71	0,34
			2. cycle	113	16,2	57	9,0	56	0,68	0,57
29	61		1. cycle	109	17,7	72	11,9	37	0,68	0,47
30	66	64	1. cycle	126	15,3	84	12,0	42	0,29	0,91
			2. cycle	134	13,3	88	8,7	46	0,47	0,81
			3. cycle	123	9,7	83	6,0	40	0,50	0,82
31	54	68	1. cycle	136	23,3	83	15,3	53	0,43	0,87
			2. cycle	136	22,9	79	14,8	57	0,46	0,84
32	62	53	1. cycle	122	17,0	69	10,6	53	0,57	0,70
			2. cycle	118	19,9	63	8,9	55	0,66	0,77
33	77	54	1. cycle	124	11,2	58	7,3	66	0,75	0,39
			2. cycle	120	11,1	57	9,6	63	0,60	0,46
34	84	48	1. cycle	126	9,3	77	5,0	49	0,60	0,75
35	62	70	1. cycle	124	7,4	73	7,7	51	0,24	0,73
			2. cycle	122	9,2	74	8,0	48	0,33	0,77
36	75	59	1. cycle	119	17,3	72	13,3	47	0,53	0,61
			2. cycle	121	18,5	73	16,4	48	0,22	0,88
37	64	65	1. cycle	114	10,9	78	7,3	36	0,57	0,64
38	64	46	1. cycle	114	9,3	67	7,4	47	0,55	0,56
39	64	64	1. cycle	120	7,7	74	601	46	0,56	0,56
			2. cycle	129	12,3	79	6,0	50	0,67	0,63
40	55	58	1. cycle	123	11,4	77	9,1	46	0,51	0,61
			2. cycle	114	15,4	71	9,9	43	0,55	0,69
			3. cycle	117	13,5	68	8,4	49	0,79	0,34
41	64	70	1. cycle	113	10,3	70	9,0	43	0,54	0,53
			2. cycle	121	12,1	77	11,6	44	0,37	0,65

Note: EF- ejection fraction, PP – pulse pressure; AASI – *ambulatory arterial stiffness index*; R – correlation coefficient

Tab. 3 *Ambulatory arterial stiffness index* in the day without physical activity

pat.	age [years]	EF [%]		SBP [mm Hg]	± SD	DBP [mm Hg]	± SD	PP [mm Hg]	AASI	R
1	53	65	1. cycle	145	11,8	91	11,3	54	0,14	0,90
			2. cycle	136	10,6	85	10,0	51	0,21	0,83
2	68	69	1. cycle	127	12,7	74	8,1	53	0,65	0,56
			2. cycle	122	15,9	71	9,9	51	0,59	0,66
3	67	60	1. cycle	116	15,4	79	15,1	38	0,09	0,92
			2. cycle	115	8,2	78	9,4	38	0,46	0,47
4	64	46	1. cycle	105	13,3	62	9,5	43	0,53	0,66
			2. cycle	106	5,9	68	7,8	39	0,43	0,43
5	44	73	1. cycle	120	10,4	76	9,0	44	0,34	0,76
			2. cycle	116	10,6	71	8,1	45	0,39	0,80
6	48	63	1. cycle	115	12,9	71	8,7	44	0,82	0,27
			2. cycle	106	10,7	59	8,9	47	0,52	0,58
			3. cycle	115	11,7	69	8,8	46	0,50	0,67
7	73	61	1. cycle	115	13,8	57	8,4	59	0,51	0,81
			2. cycle	118	8,8	58	5,9	60	0,59	0,62
8	41	56	1. cycle	116	8,4	75	10,7	41	0,49	0,40
			2. cycle	118	6,9	74	6,1	43	0,44	0,63
9	65	63	1. cycle	119	9,0	78	6,0	41	0,66	0,51
			2. cycle	121	21,4	77	10,4	44	0,74	0,53
10	63	52	1. cycle	115	12,2	65	7,8	50	0,53	0,74
			2. cycle	117	15,3	66	9,9	52	0,42	0,89
11	56	61	1. cycle	124	12,1	77	9,1	47	0,50	0,66
			2. cycle	127	19,0	76	13,1	52	0,49	0,75
12	78	59	1. cycle	112	11,4	55	11,0	57	0,83	0,18
			2. cycle	117	7,7	60	13,6	57	0,44	0,32
13	57	67	1. cycle	134	7,9	79	9,0	55	0,47	0,46
			2. cycle	137	11,1	78	8,7	59	0,49	0,65
14	49	26	1. cycle	111	11,0	78	8,8	33	0,34	0,82
			2. cycle	110	12,5	77	8,5	32	0,53	0,69
			3. cycle	109	15,8	75	11,3	33	0,39	0,86
15	69	66	1. cycle	119	14,2	77	4,6	42	0,92	0,25
16	64	72	1. cycle	113	11,4	67	11,1	46	0,72	0,29
			2. cycle	112	14,9	64	7,9	48	0,93	0,13
17	56	57	1. cycle	126	11,2	83	7,9	43	0,51	0,69
			2. cycle	114	10,5	78	8,5	36	0,42	0,71
18	55	33	1. cycle	121	13,4	68	7,2	53	0,71	0,53
			2. cycle	129	10,5	67	9,8	61	0,49	0,55
			3. cycle	125	11,7	68	8,9	57	0,43	0,75
19	66	40	1. cycle	129	12,9	82	9,6	47	0,48	0,70
			2. cycle	130	16,4	85	13,8	45	0,20	0,95
20	56	51	1. cycle	126	20,0	78	12,9	49	0,53	0,73
			2. cycle	108	12,3	65	10,3	43	0,41	0,71

Note: EF ejection fraction, PP – pulse pressure; AASI – *ambulatory arterial stiffness index*; R – correlation coefficient

Tab. 4 *Ambulatory arterial stiffness index* in the day without physical activity

pat.	age [years]	EF [%]		SBP [mm Hg]	± SD	DBP [mm Hg]	± SD	PP [mm Hg]	AASI	R
21	68	60	1. cycle	133	11,0	84	9,6	49	0,65	0,40
			2. cycle	136	13,7	88	13,8	48	0,73	0,44
			3. cycle	129	9,6	84	9,5	45	0,30	0,71
22	66	52	1. cycle	127	17,9	74	11,1	53	0,78	0,35
			2. cycle	128	16,5	78	8,5	50	0,70	0,58
23	56	37	1. cycle	99	10,7	63	8,4	36	0,77	0,29
			2. cycle	108	6,6	74	7,4	34	0,14	0,77
24	60		1. cycle	120	16,8	65	13,0	55	0,64	0,46
			2. cycle	117	17,3	64	8,9	53	0,96	0,07
			3. cycle	121	21,0	66	9,4	55	0,81	0,42
25	58	53	1. cycle	132	18,3	65	16,7	67	0,59	0,45
			2. cycle	130	23,3	63	12,4	67	0,80	0,37
26	58	40	1. cycle	121	23,0	67	15,8	54	0,53	0,68
			2. cycle	122	25,5	72	17,2	50	0,55	0,67
27	60	47	1. cycle	117	13,4	72	9,9	45	0,52	0,70
			2. cycle	106	11,5	60	6,9	46	0,76	0,39
28	74	54	1. cycle	112	13,9	56	8,4	56	0,93	0,11
			2. cycle	112	14,0	56	6,4	56	0,84	0,35
29	61		1. cycle	119	18,5	72	9,2	47	0,75	0,50
30	66	64	1. cycle	133	16,5	86	13,0	47	0,42	0,74
			2. cycle	129	12,8	84	11,7	45	0,35	0,72
			3. cycle	123	14,5	81	11,9	42	0,30	0,85
31	54	68	1. cycle	134	21,4	77	13,1	57	0,49	0,83
			2. cycle	133	25,7	75	13,6	58	0,62	0,73
32	62	53	1. cycle	122	13,3	69	9,4	53	0,46	0,77
			2. cycle	117	18,1	66	9,1	51	0,65	0,68
33	77	54	1. cycle	122	15,4	61	11,6	61	0,54	0,61
			2. cycle	118	11,6	56	8,6	62	0,58	0,56
34	84	48	1. cycle	131	16,2	76	11,8	55	0,47	0,73
35	62	70	1. cycle	124	15,1	76	9,6	48	0,58	0,66
			2. cycle	124	12,3	73	9,5	51	0,33	0,87
36	75	59	1. cycle	131	15,6	74	13,3	57	0,61	0,46
			2. cycle	119	17,6	74	14,8	45	0,45	0,65
37	64	65	1. cycle	108	12,1	72	10,6	36	0,28	0,82
38	64	46	1. cycle	113	8,8	67	8,1	46	0,43	0,62
39	64	64	1. cycle	125	11,3	78	9,0	47	0,37	0,80
			2. cycle	131	13,5	81	8,1	50	0,57	0,71
40	55	58	1. cycle	118	10,5	75	6,9	43	0,65	0,53
			2. cycle	119	11,1	72	8,3	47	0,55	0,61
			3. cycle	115	10,9	73	9,5	42	0,29	0,82
41	64	70	1. cycle	117	10,1	74	4,0	43	0,91	0,22
			2. cycle	123	26,0	72	12,9	51	0,75	0,50

Note: EF ejection fraction, PP – pulse pressure; AASI – *ambulatory arterial stiffness index*; R – correlation coefficient

Tab. 5 *Ambulatory arterial stiffness index*

n=41	cycle	SBP [mm Hg]	± SD	DBP [mm Hg]	± SD	PP [mm Hg]	± SD	AASI	±SD	R	±SD
	0–24h	121	9,9	73	9,0	49	7,9	0,53	0,17	0,65	0,18
	25–48h	121	8,8	72	8,2	49	7,6	0,54	0,19	0,60	0,20

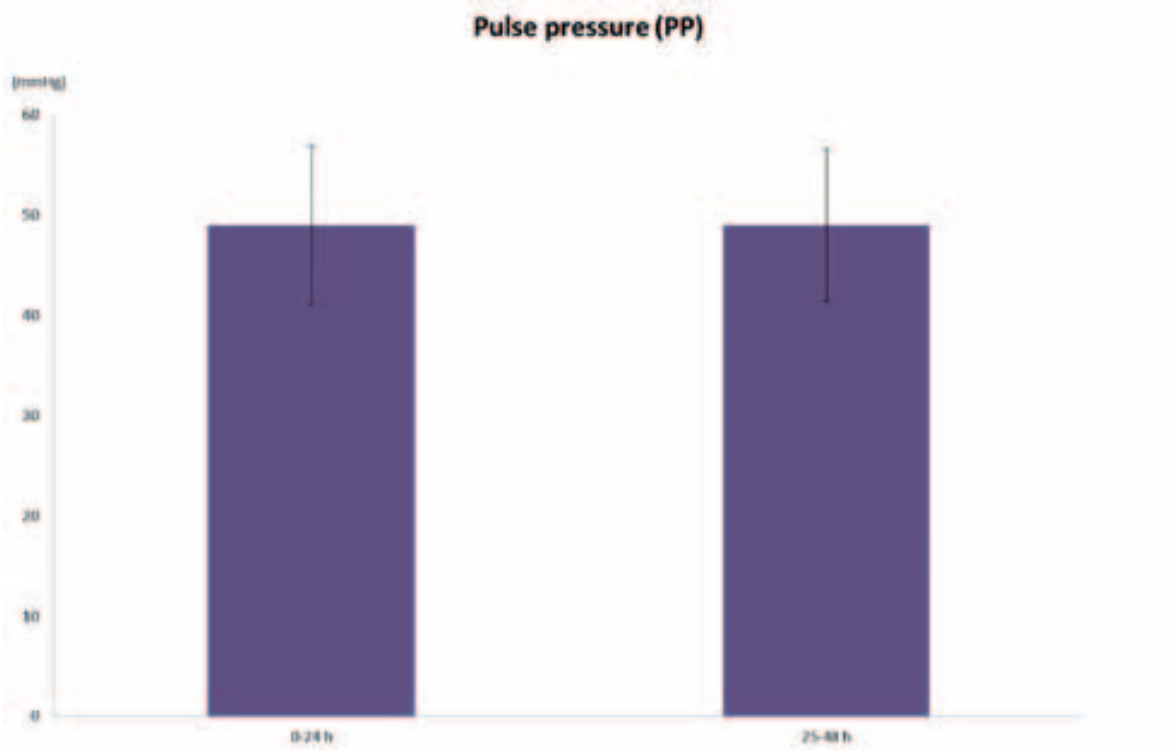

Fig. 2 Pulse pressure in the day with cardiac exercise training (0 – 24) and in the day without exercise training (25 – 48) in patients after infarctus of myocardium

Note: EF ejection fraction, PP – pulse pressure; AASI – *ambulatory arterial stiffness index*; R – correlation coefficient

Every patient had in the seven-day record one, two or three cycles of days with physical activity and without physical activity. The systolic and diastolic blood pressure variations, AASI variations, PP variations can be seen in Tables 1, 2, 3, 4 and the inter-individual variations of AASI are large.

Table 5 and fig. 1, 2, 3, 4 summarize the mean values ± SD of AASI, SBP, DBP, PP and R in the days with exercise and in the days without exercise. There are not significant differences in the mean values. These results summarize the data of patients after infarctus of myocardium, who are under therapy with ACE inhibitors, beta-blockers, Calcium antagonists and statins.

DISCUSSION

Arterial stiffness is increased when elastic properties of the arterial wall are reduced (Kotsis et al. 2011). Aging is a process that causes structural and functional modifications in the vasculature, resulting in decreased arterial compliance and ability of arteries to strain and accommodate changes in blood pressure.

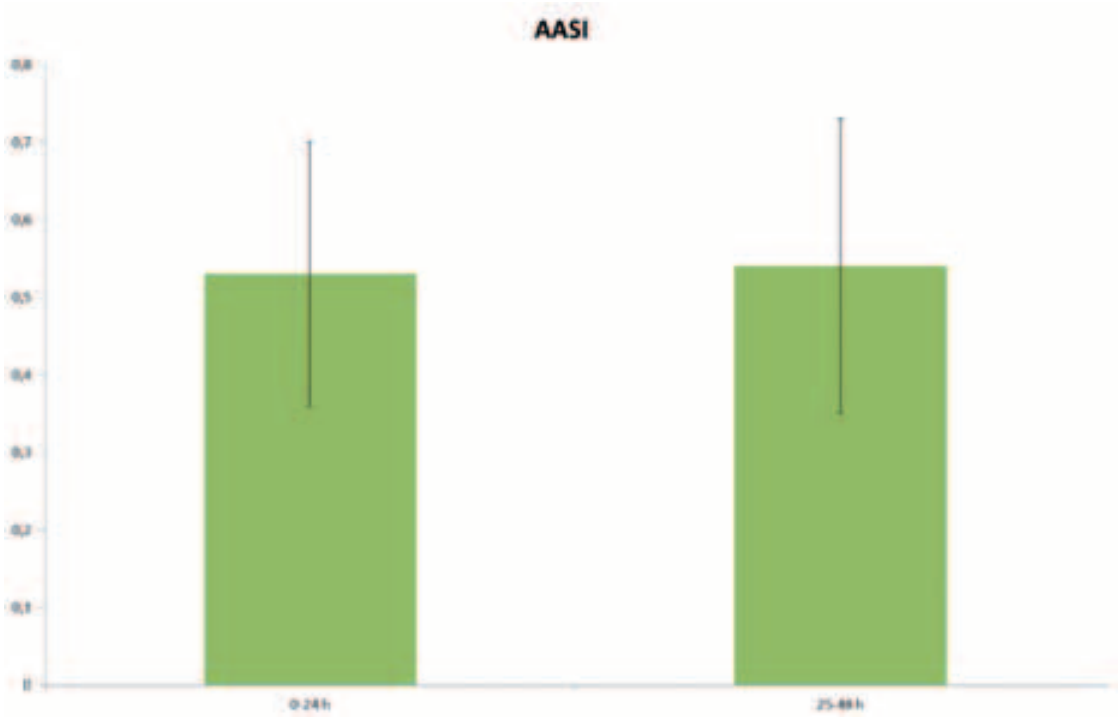

Fig. 3 Ambulatory arterial stiffness index in the day with cardiac exercise training (0 – 24) and in the day without exercise training (25 – 48) in patients after infarctus of myocardium

It has been observed that vascular alterations that occur in otherwise healthy senior people, including an increase in stiffness and thickness of large arteries as well as endothelial dysfunction, seem to be more extensive in patients with hypertension or atherosclerosis at an earlier age (Lakatta et al. 2003). This status of subclinical vascular disease may not reflect an early stage of hypertension or atherosclerosis but rather an interaction between vascular aging and vascular disease manifestation. Therefore a new pathophysiological model was introduced for deeper understanding of cardiovascular risk. The idea of early vascular aging, that is the acceleration of vascular aging, seems to be a promising tool for clinical guidance in individuals at increased cardiovascular risk or a strong family history of early cardiovascular manifestation (Nilsson et al. 2009).

The simplest explanation for the variation in AASI is that it reflects spontaneous variability in arterial stiffness from one session to another. However, it should be considered that AASI is under the influence of other sources of variability, which are necessarily related to arterial functional properties (Schillaci et al. 2008). We have not found differences between the days with exercise training and the days without exercise training.

Due to mathematical reasons AASI obtained form standard regression analysis depends on day-night blood pressure change (Schillaci et al. 2007), and hence variation in the latter may be expected to induce variation in the former. The reproducibility of day-night blood pressure changes and of the dipper or non-dipper classification is far from being optimal. In a recent study (Henskens et al. 2008) in which 150 hypertensive patients underwent 24-hour blood pressure monitoring twice, between section measurement for the dipping or non-dipping classification was found to vary from fair-to-moderate and the coefficient of repeatability of day-night blood pressure change was as high as 42–49 %. Such a large variation can be expected to influence variability of AASI as well.

The strong relation between AASI and day-night blood pressure changes is further confirmed by the paradoxical finding that daytime and night-time AASI are both much higher (0.48 ±0.26 and 0.40 ±

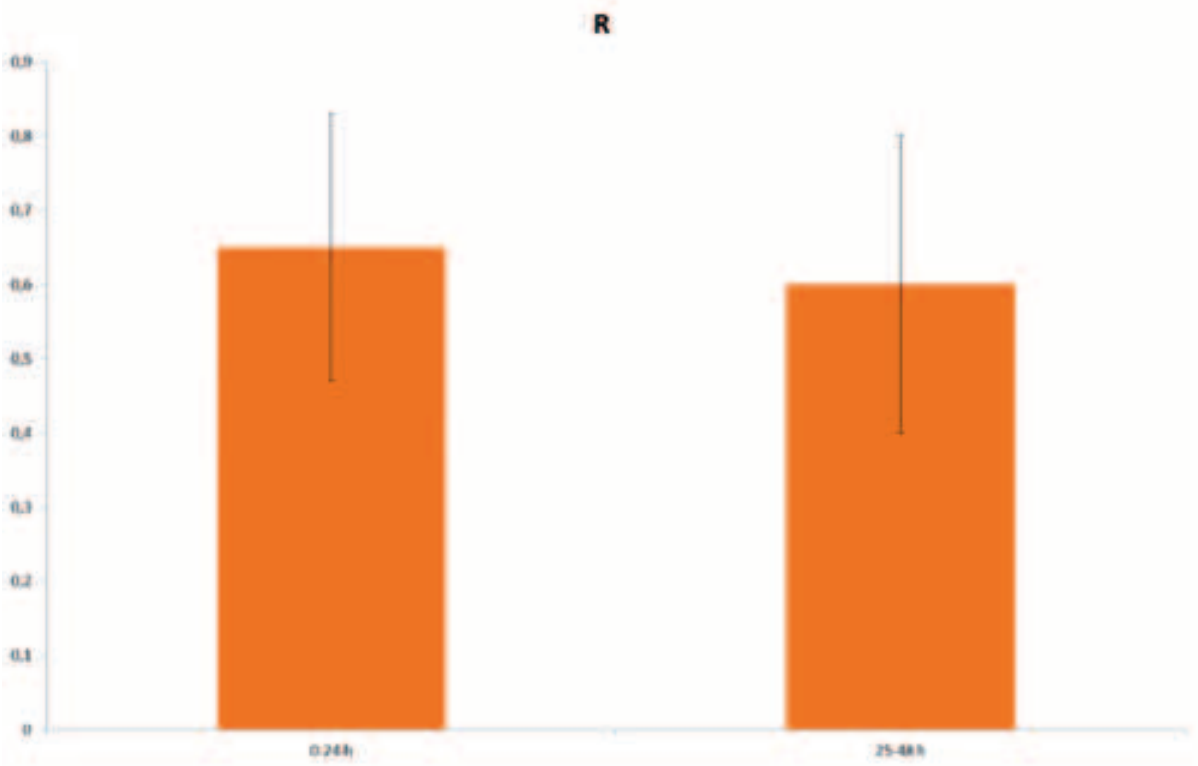

Fig. 4 Correlation coefficient between systolic and diastolic blood pressure, measured 24 h in the day with cardiac exercise training (0 – 24) and in the day without exercise training (25 – 48) in patients after infarctus of myocardium

0.21) than the corresponding 24-h values (0.31 ± 0.17), emphasizing its limited ability to specifically reflect arterial wall properties (Schilaci et al. 2007).

A further source of variation in AASI values is represented by the night/day ratio of blood pressure measurements number. In our study we calculated AASI from the blood pressure values, given in the regime one per hour. In the literature it was demonstrated that the dependence of AASI on the number of daytime and nocturnal readings is a phenomenon related to the above relationship between day-night blood pressure reduction and AASI (Schillaci et al. 2007).

There is a need for more substantial data on AASI repeatability in larger cohorts of hypertensive patients and in the normal individuals in any case, due attention should be paid to the influence of day-night blood pressure changes and to that of daytime and night-time between-reading time intervals on AASI and its variability (Detechering et al. 2007).

Our results show also variability of pulse pressure on the days with and without physical activity. Pulse pressure is considered to be an important cardiovascular risk (Halberg et al. 2007). Another number of studies revealed that brachial pulse pressure predicts the risk of cardiovascular events, especially in the elderly, and that its prognostic value is closely related to systolic blood pressure (Darné et al. 1989, Franklin et al. 2001, Staesen et al. 2000, Benetos et al. 2000, Kotsis et al. 2011, London et al. 2001, Safar et al. 2002).

The inter-individual variation of AASI is large. It doesn't mean that the determination of AASI as a risk factor of individual patient is useless, but that the determination of AASI from 24-hour blood pressure monitoring should be supplemented by blood pressure self-monitoring lasting several days irrespective of the method of AASI calculation.

CONCLUSION

The results showed no differences between systolic and diastolic blood pressure, ambulatory arterial stiffness index, pulse pressure and correlation coefficient in 24 values measured in the day with exercise and in the day without exercise in patients after infarctus of myocardium. There are not significant differences in the mean values. These results summarize the data of patients after infarctus of myocardium, who are under therapy with ACE inhibitors, beta-blockers, Calcium antagonists and statins.

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MEASUREMENT OF VASCULAR FUNCTION BY CARDIO ANKLE VASCULAR INDEX – THEORY, REPRODUCIBILITY AND AGING –

Arno Schmidt-Trucksäss

Increased cyclic stress on the arterial system causes fragmentation of the elastin lamellae and concomitant increase of collagen in the arterial wall which results untreated in a stiffening of the artery[1]. The stiffening process is mainly associated with arterial aging but may be accelerated by increased atherosclerotic risk factor burden as present in hypertension, diabetes, dyslipoproteinemia, smoking or physical inactivity. Thus, there is a clinical reason to measure arterial stiffness in order to detect increased risk for cardiovascular events like myocardial infarction or stroke[2].
Several methods are available for the measurement of the arterial stiffness. Central and peripheral pulse wave velocity (PWV), augmentation index, stiffness index beta, pulse pressure, elastic modulus and cardio ankle vascular stiffness index (CAVI)[3]. The latest is derived from stiffness index beta with application of Bramwell-Hill equation[4].

Bramwell-Hill equation

$$\beta = \left(ln\frac{P_s}{P_D}\right)\left(\frac{D}{\Delta D}\right)$$

Stiffness Index β (local stiffness)

$$PWV^2 = \frac{\Delta P}{\rho} * \frac{V}{\Delta V} = \frac{\Delta P}{2\rho} * \frac{D}{\Delta D}$$

$$\frac{D}{\Delta D} = \frac{2\rho}{\Delta P} * PWV^2$$

CAVI

$$CAVI = a\left(2\rho * ln\frac{P_s}{P_D} * \frac{PWV^2}{\Delta P}\right) + b$$

PWV in CAVI is measured from the beginning of the aorta to the tibial artery right above the ankle, thus covering central elastic type artery (aorta) and muscular type arteries (femoral and tibial artery) (Fig. 1 from [4]).

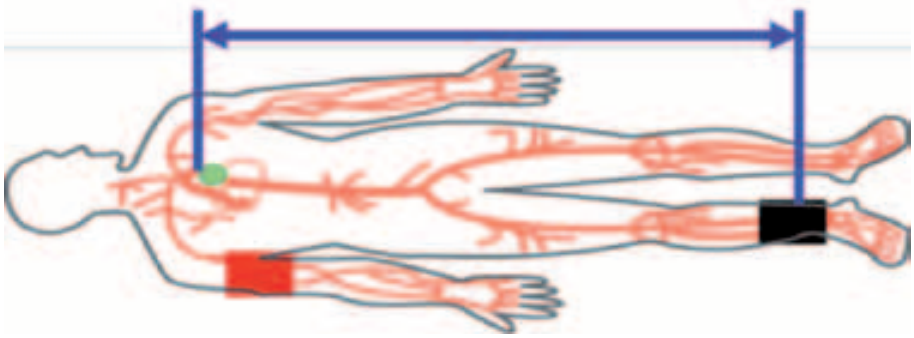
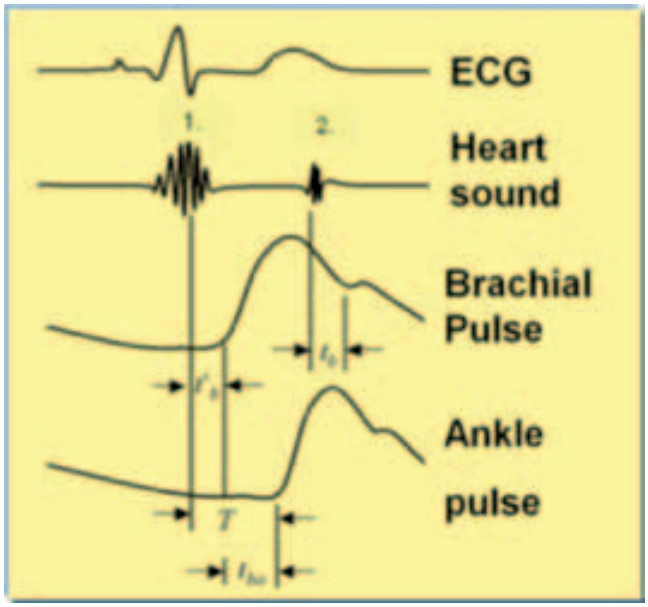


Fig. 1



The time intervals are determined by calculating distances between heart sound (microphone in 2nd to 3rd intercostal notch) and the ascent of brachial and ankle pulse pressure curve, respectively (Fig. 2 from [4]).

In order to prove the validity of the application of stiffness index beta to Bramwell-Hill equation, the correlation of local aortic stiffness measured by transoesophagal echocardiography and CAVI was determined. A correlation
Fig. 2
coefficient of r= 0.67 ($p < 0.01$) showed a reasonable association indicating that the application is valid[5]. CAVI is more independent of blood pressure than other measures of arterial stiffness like central PWV. This has been shown by the comparison of brachial ankle PWV and CAVI due to the effect of blood pressure lowering substances metoprolol (beta blocker) and doxazosin (alpha blocker). While both drugs reduced blood pressure and brachial ankle PWV, CAVI was exclusively lowered by doxazosin. Doxazosin – but not metoprolol – causes a relaxation of vascular smooth muscle cells, which indicates that CAVI reflects a change of vascular smooth muscle cell tone[4].

Reproducibility of parameters of arterial stiffness is a prerequisite for usage in clinical practice. CAVI was measured at five consecutive days in 22 subjects with an average of 41 years. The coefficient of variation was 3.8% which gives a good reproducibility[6]. It is common in daily practice that patients are examined at different time points over the day. Therefor we measured CAVI at 9–10, 13–14 and 17–18 hours across the day. Preliminary data shows that the reproducibility is even better.

In the beginning the effect of age on arterial stiffness was mentioned. To discriminate healthy aging from risk factors, the age-associated increase of CAVI was measured in men and women with a low risk factor burden and no manifest cardiovascular disease. The biggest data base is derived from a Japanese Health screening program showing an increase of approximately 0.5 units with ten years[4]. Women had lower values at 0.2 at every age from 20 – 70 years, which seems to reflect the later incidence of myocardial infarction and stroke in female subjects. Ongoing research in Europe now aims to establish age tables for Caucasian subjects.

The potential value of arterial stiffness for prevention will be strengthened in the future when the association of CAVI with hard endpoints (cardiovascular events and death) will be published. This is already existent for central PWV[2] and is an aim of present CAVI research.

In summary, CAVI has the potential to be established as a novel parameter of arterial stiffness in research and practice.

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EFFECTS OF OROFACIAL REHABILITATION AFTER STROKE

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INTRODUCTION:

Facial (n. VII) paresis is one of the most common disorders in patients after stroke, which is reflected by the change in facial movement. Stroke is defined as the rapidly developing focal or global symptoms of brain function disorder which last more than 24 hours or might result in the death of the patient, all without an apparent cause other than vascular origin (1). Stroke is an acute condition resulting from disorders of blood circulation (ischemia) or bleeding (haemorrhage) into the brain tissue. Common consequences of stroke are mobility and sensitivity disorders in the legs, arms and face; there can also be disturbances in speech and vision, impaired cognition, or it can even cause the death of the patient (2).

Facial movement is one of the functions of the human nonverbal communication system. It serves not only to maintain the facial expression, but also has an important role in speech, singing, social communication interaction, food intake and eye protection.

Facial muscles can alter the facial surface and in various ways impeding execution of their functions. In addition to opening and closing the eyes and mouth they also have a reporting function. Highly differentiated and complex facial musculature can express a large number of sensations and can reflect the state of mind and the mood of an individual.

Paresis of the facial nerve after stroke causes a functional and aesthetic defect in a patient manifested by facial asymmetry with the muscle disability of the lower half of the face, falling of the corner of the mouth, saliva leakage from the corner of the mouth, asymmetrical smile and a speech explicitness disorder with atonia of the lips, tongue and throat (1, 2).

In the present study this disability of facial movement and symmetry was evaluated qualitatively and quantitatively. Neurological facial examination was conducted on the basis of an examination of the function of the facial nerve. On the basis of a clinical examination, a diagnosis of central or peripheral paresis of the facial nerve was performed. We used standard international clinical scales in the quantitative n. VII paresis (paresis of nervus facialis) evaluation. The most commonly used test battery is testing by means of the House-Brackmann Grading System (HBGS) (3–5).

Changes in facial movement were also the result of other symptoms, including the psychological state of the patient, and vice versa. Therefore, most cases of facial movement failure might be due to psychological consequences. Many patients suffered from anxiety and depression after stroke. Depression has many causes. One of the causes of depression can be changes of the face after facial paresis. After stroke, 50–60 % of patients suffer from depression within three months (6–9). Patients with depression after stroke have a worse prognosis. Deterioration in the quality of life is demonstrated with increasing motor movement disability in normal daily activities. Patients have worse rehabilitative care effect, a longer period of hospitalization and are less often able to return to the

home environment (6, 8, 10). The Beck Depression Inventory (BDI-II) test was used to quantitatively evaluate the burden of depression (10–12).
The aim of this study was to evaluate the impact of central n. VII paresis in patients after stroke on functions of facial movement and mental functions using international clinical scales and the objective measurement of facial movement changes using two-dimensional video analysis (13–15).

METHODOLOGY:
The study included 99 patients in the subacute stage of stroke (1–2 weeks after onset). Patients began rehabilitation on the second day after the stroke. Initially they were in the "stroke unit" / ICU/ – Neurology Clinic, Hospital in Olomouc – and after the transfer rehabilitation continued at the Department of Rehabilitation and Exercise Medicine, University Hospital in Olomouc. The inclusion criterion for the study was central n. VII paresis after stroke. The exclusion criterion was lack of cooperation.
At the beginning of rehabilitation, patients were randomly divided into two comparable groups, i.e. experimental and control groups. The experimental group consisted of 50 subjects, 26 of which were males with the average age of 57 years and 24 females with the average age of 62 years; the type of stroke: 38 (76%) ischemia and 12 (24%) haemorrhage, lesion side: 32 (64%) right-sided hemiparesis and 18 (36%) left-sided hemiparesis, level of severity: average value was 12 (SD 2) according to NIHSS. The control group consisted of 49 subjects – 27 males with the average age of 60 years and 22 females with the average age of 61.5 years; the type of stroke: 39 (79%) ischemia and 10 (31%) haemorrhage, lesion side: 29 (59%) right-sided hemiparesis and 20 (41%) left-sided hemiparesis, level of severity: average value was 13 (SD 1) according to NIHSS. In both groups the speech therapy scheduled once a day focused on the treatment of communication disorders; rehabilitation exercises scheduled twice a day aimed at the reconstruction of damaged physical functions of the trunk, arms and legs.
In addition, targeted physiotherapy orofacial treatment was given in the experimental group once a day, including rehabilitation of myofascial structures of the face, breathing rehabilitation and targeted facilitation of facial functions using the elements of orofacial regulation therapy, which seeks the creation of physiological function in the orofacial areas by applying pressure, touch, vibration and traction in specific points on the face activating the orofacial muscles (16).
A clinical evaluation was performed at the beginning of therapy and after 4 weeks of therapy. Facial movement was assessed using the HBGS standardized clinical questionnaire (3) and by device measurement – two-dimensional (2D) video analysis, which measured changes in the distance of control points on the paretic corner of the mouth and earlobe (13, 15), mental functioning was evaluated according to the BDI-II (11). This blind study was conducted to measure the distribution of data from experimental and control groups.
Basic statistics (arithmetic mean, standard deviation - SD) were calculated for individual parameters. The data were statistically verified using single-factor analysis of variance for repeated measures with statistical significance set at $p < 0.05$; as a subsequent post-hoc test the Fischer LSD test was used to compare individual groups in repeated measurements. Furthermore, the correlation of facial movement changes with mental function was tested using the Spearman correlation coefficient at $p < 0.001$.

RESULTS:
Our results showed a substantial improvement in functions of facial movement in both groups. Statistically significant improvement of facial movement was observed in the experimental group. The evaluation of results by HBGS (Table I) and 2D video analysis showed changes in length

measurement between the corner of the mouth and earlobe after the 4-week treatment (Table I). A significant difference in the mean values HBGS before and after rehabilitation in the experimental group was 1.66 (SD 0.55), in the control group it was 0.59 (SD 0.57). A significant difference in the mean input and output values of changes in distances between corner of the mouth and earlobe in experimental group was 11.5 (SD 3.50) mm and 2.0 (SD 2.30) mm in the control group.
Statistically significant improvement of the condition in the experimental group can be seen again in the evaluation of mental functions according to BDI-II (Table I). A significant difference in the mean values BDI-II before and after rehabilitation in the experimental group was 14.3 (SD 5.1) and in the control group 6.9 (SD 5.1).
A very close relationship with a positive Spearman correlation coefficient value of 0.69 ($p < 0.001$) was found in the correlation of changes in facial movement and psychological functions.

DISCUSSION:
Our study demonstrated significant positive results in patients treated with targeted orofacial rehabilitation. Significant facial movement improvement of two and more degrees according to HBGS was observed after 4 weeks in 31 cases (62%); a facial movement improvement by one degree according to HBGS was found in 18 cases (36%). The condition remained unaltered in 1 case (2%), and there was no upset in the experimental group. Unlike the control group, in experimental group there was spontaneous improvement by two degrees or more in 2 cases (4%), a slight improvement in one grade occurred in 20 cases (40.8%), an unaltered state remained in 28 cases or 55.2%.
Similar results were obtained by Svensson et al. in their study comparing the effect of mimic EMG biofeedback in 23 patients after stroke with a control group of 12 patients without EMG mimic therapy (17). In their study they observed the recovery of facial functions after 1 month in both groups, and there were normal facial functions or only mild dysfunctions after 6 months in two-thirds of patients. Patients with right-sided facial disability had significantly better results than patients with left-sided facial disability.
Furthermore, in their study, Svensson et al. provide the same functional state of facial movement (according to HBGS), sensitivity and awareness of facial asymmetry in both experimental and control groups 6 months after the inception of stroke. Based on this finding the authors in conclusion did not recommend mimic EMG biofeedback therapy in patients after stroke with n. VII paresis. They predicted spontaneous remission of central n. VII paresis. It should be noted that this study was conducted on a relatively small group of patients and the results did not reach statistical significance. In comparison with Svensson et al., our study involved a sufficiently large group of patients with statistically significant results confirming the positive effects of orofacial physiotherapy with central paresis after stroke.
In assessing depression after stroke using the BDI-II we again find significant improvement in mental functions in the experimental group, with 45 cases (90%) showing significantly improved mental state; 5 cases (10%) remained unaltered and no cases showed an impaired condition. In the control group we observed improvement in 29 cases or 60%; in 20 cases (40%) the condition remained unaltered and no cases showed an impaired condition.
In both groups all patients used SSRI class antidepressants (citalopram 10 or 20 mg / day) in the effective prophylactic or therapeutic dose recommended by the psychiatrist.
Depression after stroke (post-stroke depression – PSD) occurs in 40–60% of patients (6–9). Patients with depression after stroke have a significantly poorer self-sufficiency prognosis, worse rehabilitation effect, worse quality of life, longer hospitalization period, and impaired ability to return to the home environment (6, 7, 10). Women have greater difficulty accepting the facial change and orofacial rehabilitation, which plays an important role (9, 10). Mikulik and Svensson et al. suggested that in

a small number of patients there is spontaneous alteration in facial movement and PSD remission, without treatment (9, 17). In contrast, studies by Roth et al. and Rim et al. are associated with better modification of cognitive function and neurological deficit including central paresis of the facial nerve in patients with PSD treated with antidepressants and psychotherapy (6, 7).
The most significant negative prognostic factors influencing the mental function and quality of life of patients after stroke were repeated stroke attacks, old age of patients, immobility, urine and stool incontinence, cognitive dysfunction, and impaired ability to communicate (18–23).
In the "central type" of n. VII paresis the aim of orofacial therapy is to relax spastic muscles, restore selective functions of orofacial muscles and re-educate fundamental facial movement and communication (verbal and non-verbal) features, and functions during food intake.
In conclusion, orofacial rehabilitation as a part of complex rehabilitation care contributes considerably to improving the quality of life after stroke with orofacial function disorder. After complete stabilization of basic life functions and after improving the overall functional state, orofacial rehabilitation is one of the most important aspects of rehabilitation for the patient.
Our study confirmed the positive effect in orofacial function improvement after 4 weeks – improvement of facial movement and alleviation of depression in patients after stroke with the central n. VII paresis who had – in addition to physiotherapy and speech therapy – targeted orofacial therapy.

APPENDICES:

Table I.

	Before		After		Difference	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
HBGS	3.74 (0.63)	3.69 (0.65)	2.08 (0.63)	3.10 (0.71)	1.66 (0.55)	0.55 (0.57)
SP	66.0 (4.0)	64.0 (4.0)	55.0 (4.0)	62.0 (3.7)	11.5 (3.5)	2.00 (2.3)
BDI-II	35.7 (5.7)	34.9 (6.3)	21.4 (4.2)	28.0 (6.3)	14.3 (4.5)	6.90 (5.1)

Table I - legend:
Before …mean value before rehabilitation, After … mean value of HBGS score after rehabilitation, Difference … difference in the mean values before and after rehabilitation.
Group 1 …experimental group, Group 2 … control group
HBGS …score values according to HBGS, SP … distance between corner of the mouth and earlobe in mm assessed by 2D video analysis at maximal voluntary mouth pouting, BDI-II …score values of depression according to BDI-II

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DEVELOPMENT OF BLOOD PRESSURE CONTROL IN MULTIPLE SCLEROSIS PATIENTS

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INTRODUCTION

Multiple sclerosis (MS) is an autoimmune, progressive, degenerative, chronic, diffuse, inflammatory and demyelinating disease that affects the central nervous system (Edwards, 2002; Havrdová, 2009). Central myelin damage and subsequent damage of the exposed axons, their collapse and loss, are primarily caused as a result of autoimmune mechanisms. The volume of damage and loss of axons is proportional to the disability affected by MS (Havrdová, 2009). MS has a number of clinical manifestations. The most visible of them is motor dysfunction. Patients themselves, however, consider fatigue, incontinence and sensory dysfunction, such as paresthesia and dysestesia, to be more unpleasant. Other functions of the autonomic nervous system (ANS), such as sexual functions and sudomotoric functions, are also affected. Impaired autonomic regulation of cardiovascular functions is often overlooked (Březinová et al., 2004). Autonomic cardiovascular regulation can be evaluated by means of baroreflex sensitivity (BRS). Examination of baroreflex sensitivity is a method which determines the baroreflex function, and thus the level of regulation of cardiovascular autonomic control (Tank et al., 2000). Baroreflex arc ensures short-term stabilization of blood pressure (Závodná, 2007), especially when changing body position (Fráňa, 2007). Previous investigations of BRS showed that a higher degree of clinical disability can be influenced by an impairment of baroreceptors in the cardiovascular regulation of blood pressure (Konečný et al., 2008; Konečný 2010; Kocourková 2011).

AIM OF STUDY

Assessment of the state of autonomic control of blood circulation in a group of patients with multiple sclerosis (MS) in the 3-year period of the disease, measured by sequencing method of baroreflex sensitivity of heart rate (BRS).

SET OF PATIENTS

There was examined a group of 8 patients with clinically confirmed MS disease in remission (n = 8, mean age 41.8 ± 8.1 years, height 1.7 ± 0.1 m, weight 65.3 ± 12.5 kg, length of illness 7.1 ± 7.1 years; degree of clinical disability EDSS 2.3 ± 1.1; 7 patients with a relabs-remitting form of MS) in the year 2007. The observed group of patients had a consistent set of pharmacotherapy in the form of corticosteroids and immune-modulating drugs. No internal or metabolic disorder and manifest disease of the autonomic nervous system was shown, which could affect results of baroreflex sensitivity. The monitored group of patients was repeatedly examined in the year 2010 (n = 8, mean age 45.5 ± 7.9 years, height 1.7 ± 0.1 m, weight 68.4 ± 8.3 kg, length of illness 8.8 ± 5.9 years; degree of clinical disability EDSS 2.3 ± 1.4; 5 patients with a relabs-remitting form of MS and 3 patients with a secondary progressive form of MS).

METHODS

The clinical examination was performed to determine the degree of clinical disability. The level of disability was measured by Expanded Disability Status Scale (EDSS). EDSS (Kurtzke's Expanded Disability Status Scale) is a standard scale for evaluation of disability of MS patients. It is a neurological examination with evaluation by 0.5 point, in the interval from 0 (no functional disorder or impairment) to 10 (death because of MS), impact of MS disease being on 8 basic functional systems. Status of cardiovascular autonomic regulation was examined by sequential method of BRS as follows. Non-invasive continuous recording of heart rate and blood pressure was made by beat-to-beat method of TASK FORCE MONITOR (CNS System, Graz, Austria). 5-minute recording was made in a supine position with spontaneous and controlled breathing. Metronome-controlled frequency of breathing was 0.33 Hz. Obtained record of heart rate and blood pressure was further processed by software-sequential analysis. The aim of sequential analysis is to find a sequence up or down with at least three consecutive monotonous increases or decreases of systolic blood pressure (SBP) with a deflection of at least 1 mm Hg during one beat of R-R intervals of QRS complex. Software processing of continuous recording of heart rate and blood pressure by sequential analysis of BRS was analyzed: R-R interval [ms], heart rate [beat/min], systolic and diastolic blood pressure [mm Hg], number of sequences (BRS events) and the absolute value of baroreflex sesitivity [ms/mm Hg] (BRS slope mean). Monitored indicators obtained from the examination years 2007 and 2010 were compared statistically.

RESULTS

Comparison of monitored indicators from 2007 and 2010 has not detected objective anamnestic or clinical worsening in the observed group of patients (EDSS 2.3 ± 1.1 vs. 2.3 ± 1.4). No significant changes in pharmacotherapy were found in the three-year period. The absolute value of baroreflex sensitivity examined in 2007 was 12.3 ± 7.4 ms/mm Hg and in 2010 it was 11.0 ± 8.4 ms/mm Hg. Summary of BRS results (f 0,33 Hz) are shown in Table 1.

Table 1

Monitored values		Examination in 2007	Examination in 2010	p
RRI [ms]		818,09 ± 105,18	863,09 ± 107,85	NS
HR [beat × min^{-1}]		75,08 ± 9,32	71,98 ± 8,25	NS
SBP [mm Hg]		111,55 ± 12,80	110,80 ± 8,17	NS
DBP [mm Hg]		74,73 ± 10,13	75,59 ± 4,73	NS
BRS events	**Up events**	9,00 ± 7,09	8,13 ± 6,94	NS
	Down events	11,63 ± 9,97	11,13 ± 7,72	NS
	Total number of events	20,63 ± 16,61	19,25 ± 13,92	NS
BRS slope mean	**Up events [ms/mm Hg]**	13,03 ± 8,44	15,04 ± 8,44	NS
	Down events [ms/mm Hg]	11,65 ± 6,53	10,19 ± 6,73	NS
	Total number of events [ms/mm Hg]	12,33 ± 7,42	11,02 ± 8,35	NS

Notes: values are given as means and standard deviations; BRS events - number of sequences, mean BRS slope - the value of BRS, p - statistical significance of 0.05; NS - statistically non-significant change; RRI - RR interval; HR - heart rate, SBP - systolic blood pressure, DBP - diastolic blood pressure.

DISCUSSION

The total number of measured sequences and the absolute value of BRS in both spontaneous and metronome-controlled breathing were decreased between 2007 and 2010, but the difference was not significant. The absolute values correspond to BRS reference range for the average age of the studied cohort (41.8 ± 8.1 years vs. 45.5 ± 7.9 years; Tank et al., 2000). Studies of McDougall and McLeod (2003) indicate that abnormalities in autonomic control of cardiovascular system are closely associated with a more severe multiple sclerosis disease course and with the secondary progressive form of the disease. The clinical form of MS and EDSS of disability were not changed, as well as BRS in the study. Baroreflex acts as a short-term regulator of blood pressure. Sources of information are baroreceptors located in the wall of the aorta. The elasticity of blood vessels is therefore very important for their functionality. Semrád et al. (1998) and Tank et al. (2000) presented that elasticity decreases with age and physiological reference values for BRS decrease with age too. Due to the average age of our studied set of patients (41.8 ± 8.1 years vs. 45.5 ± 7.9 years) mean BRS should be in the range 9 ± 4 ms/mm Hg. The reduced level of BRS is a risk factor of cardiovascular morbidity and mortality. In essential hypertension (Honzíková and Fišer, 2009, Siegelová et al. 2004) the BRS is decreased. It could be the changed function at the level of baroreceptors, which are not optimally stimulated because of wall rigidity of arterial vesels. The above mentioned two works point to the coincidence of increased blood pressure and reduced BRS, Fleming et al. (1994) presents a study which compared the diagnoses for which the patients were hospitalized. They compared the group of patients with MS with the group of persons of the same average age and gender. The results of this study showed that the patients with MS were clinically stable during three years. Vita et al. (1993) and Acevedo et al. (2000) argue that in multiple sclerosis patients the cause of this impairment could be demyelination in the brainstem and in the descending pathways of ANS. Symptoms of cardiovascular dysfunction occur less frequently than cardiovascular dysfunction itself. Therefore Acevedo et al. (2000) points to the fact that just the presence of cardiovascular dysfunction may be a prognostic factor in the development of MS.

CONCLUSION

Sequential analysis of BRS has not detected significant changes in parametres of baroreflex sensitivity in the monitored set of patients after three years of control testing. Clinical stabilization of MS disease in this set of patients does not suggest the development of any negative changes in autonomic control of baroreflex function during a three-year period of the MS disease.

Key words: multiple sclerosis, baroreflex sensitivity

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ASSESSMENT OF ARTERIAL STIFFNESS IN PATIENTS WITH CARDIOVASCULAR DISEASES: EFFECTS OF EXERCISE TRAINING AND ELECTROMYOSTIMULATION

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ABSTRACT

Transcutaneous electromyostimulation (EMS) has been established as alternative to conventional exercise training (ET) in patients with chronic heart failure (CHF); however, the role of ET or EMS on the reduction of arterial stiffness in patients with CHF or with coronary artery disease (/CAD) has not been studied yet. ***Methods.*** Patients with stable CHF (mean age 58.9 (2.1) years; mean EF 31 (4.2) %, NYHA II-III) were randomly assigned into 2 groups: a) group EXE (n = 37) underwent 12 weeks of bicycle ET (3x40min a week); b) group EMS (n = 35) performed 12 weeks of EMS of leg extensors (frequency 10Hz, mode "20s on - 20s off"), 2x60min/day. VO_{2peak}, heart rate variability (HRV) parameters and cardio-ankle vascular index (CAVI) were evaluated before and after RHB program. Another part of this study focused on the effect of ET on arterial stiffness in patients with CAD (n=16; mean EF 55.0 ± 10.2%; mean age 61.5 ± 10.6 years) ***Results.*** Both types of RHB reduced significantly the CAVI value [group EXE from 9.6 (0.2) to 8.9 (0.2), $p<0.012$; group EMS from 9.3(0.2) to 8.7(0.2), $p<0.013$]. In the group with CAD the CAVI value decreased after 12 weeks of ET from 9.1 ± 1.4 to 8.8 ± 1.6, however, without statistical significance. ***Conclusion*** ET or EMS has been shown to improve significantly arterial stiffness in patients with moderate and stable CHF. A clear tendency to improvement was also present in patients with CAD. This study highlighted also the importance of exercise training on risk reduction in patients with cardiovascular diseases.

KEY WORDS

heart failure - electrical muscle stimulation - heart rate variability - big-endothelin - arterial stiffness

INTRODUCTION

The incidence of chronic heart failure (CHF) in populations of European countries is 0.4–2%. The disease has overall bad prognosis and its diagnostics and therapy are demanding, from medical as well as economical point of view. Neurohumoral hyperactivation is a typical symptom of failing heart

[1]. Resulting endothelial dysfunction is a concurrence of hypercoagulation, vasoconstriction, oxidative and pro-inflammatory processes which potentiate one other [2]. These pathological changes in patients with CHF have immense impact especially on skeletal muscles where devastating structural and metabolic changes and extensive atrophies take place [3]. The exact reasons for global damage of skeletal muscles in patients with CHF have not been fully elucidated yet, however, most probably combined effect of anti-inflammatory cytokines and increased sympathetic activity are responsible [4]. Demonstrable relationship between increased tonus of sympathetic nervous system, decreased fitness and bad prognosis has been proved [5]. Therefore a careful evaluation of autonomic nervous system (ANS) balance is of great importance for assessment of heart failure stage [6]. The care of patients with CHF is very complex and rehabilitation (RHB) plays an important role in it [7]. Supervised physical training could reverse the pathologic changes in patients with CHF and there have been many reports from past two decades clearly demonstrating the benefits of exercise on functional capacity, skeletal muscle performance and ANS regulation [8,9]. Although there is well working network of local facilities ensuring controlled cardiovascular rehabilitation program in most European countries, it is not possible to guarantee full RHB for all patients with less advanced form of CHF at present, despite the fact that these are patients who might mostly profit from it. The reasons are mainly socio-economical, e.g. distance from home address, financial situation or transportation expenses, but also insufficient motivation and age. Therefore it is important to lay standing emphasis on search of alternative forms of RHB. Recently, noteworthy new data about successful application of a rehabilitation alternative, the transcutaneous low-frequency electromyostimulation (EMS), in patients with CHF have been published [10,11]. Using direct electromyostimulation of big muscle groups, almost the same effective changes in CHF patients can be reached as with classical fitness exercising. EMS causes significant increase of aerometabolic capacity, total fitness and muscle force as well as quality of life [12]. Existing objective proofs of EMS effectiveness in patients with CHF are base of hypothesis that this method may beneficially affect not only functional parameters but also defective vegetative functions which are accompanying sign of congestive heart failure. Recently, a new parameter of arterial stiffness has been introduced into clinical practice, s.-c. cardio-ankle vascular index or CAVI [13,14]. CAVI reflects stiffness of the wall of aorta, femoral and tibial arteries as a whole in direction heart – ankles. Very valuable fact is that CAVI is blood pressure independent parameter. The values of CAVI were studied in healthy humans as well as in various so-called life-related diseases in past. It has been conclusively proved that CAVI value increases with age and that increased values are typical mainly for patients with increased coronary risk, such as coronary artery disease (CAD), hypertension, diabetes mellitus, chronic renal insufficiency or metabolic syndrome [15]. However, systematic evaluation of CAVI changes in patients with chronic heart failure or CAD in European population has not been done yet.

AIM

This study was undertaken to assess and to compare the effects of 12-weeks exercise training and electromyostimulation on arterial stiffness and selected biochemical parameters in patients with stabilized form of CHF.

PATIENTS & METHODS

Patients with CHF

Seventy-two patients (58 men, 14 women) with stable form of CHF (NYHA II/III – 49/23) with standard pharmacological treatment (ACEI, β-blockers, diuretics and statins) were randomly divided into 2 groups. Pharmacotherapy was not changed during rehabilitation program. The CHF etiology was ischemic heart disease (57 cases) and dilatation cardiomyopathy (15 cases).

Protocol of exercise training (group EXE)

Patients (n = 37) underwent supervised combined exercise training at the clinic. Combined training consisted of two phases – aerobic and resistance training. Aerobic training of interval type (1min of work - 2min of relaxation) was performed for 40 minutes on electromagnetically braked bicycle ergometers (REHA E900, Ergoline®, Bitz, Germany) with the intensity at the level of individual anaerobic threshold. This type of training was performed only for the first 2 weeks. During next 10 weeks the time of aerobic training was shortened to 20min and resistance training (20min) was added. The resistance training contained three standard exercises: pulley lifting, kicking-off and bench-press. The load for resistance training was always assessed individually using entrance test 1-RM (one repetition maximum). Before the start with power lifting training, all patients were instructed how to manipulate with powerlifting machines and all of them underwent practice how to prevent Valsalva manoeuvre during exercising. Initially, the intensity of exercise was set to 30% 1-RM and then it was increased up to 60% 1-RM (this intensity was kept during the rest of training period). Each of three powerlifting elements was always repeated in three series 10 exercises each (one minute rest was inserted between the series). Each training session lasted always 60min (warming introductory phase lasting 10min, physical training - 40min and final 10min phase of relaxation in supine position). The realization of the exercise training was done under supervision of medical staff (doctor, physiotherapist and nurse). The training sessions were performed 3 times a week (Monday – Wednesday – Friday, at the same time period 10:00 AM), for the total period of 12 weeks.

Protocol of EMS application

First testing application of EMS was done in all 35 patients of this group in hospital under medical supervision; 12-lead resting ECG and basic hemodynamic parameters (BP and HR) were monitored. Effective and clinically successfully tested stimulation protocol described previously has been used in this study [16]. The quadriceps and calf muscles of both legs were stimulated using self-adhesive surface electrodes 80x130mm (PALS® Platinum, Axelgaard Manufacturing, Denmark) and the battery-powered stimulator (Rehab X-2, Cefar®, Sweden). EMS was performed 2 x 60 min/day, 7 days a week and for 12 consecutive weeks. Stimulation parameters were set up as follows: biphasic current of 10Hz frequency, "on-off" mode stimulus (20s stimulation, 20s rest) and maximal stimulation amplitude 60mA. All patients underwent two 60-minutes applications of EMS at the clinic under medical supervision. Blood pressure and heart rate values were monitored during these periods in order to evaluate reaction of hemodynamic parameters to EMS. Next, during the period of home stimulation, patients visited the clinic once a week to check the stimulators and to measure resting values of blood pressure and heart rate. At baseline and after 12 weeks of the given type of rehabilitation, all patients underwent spiroergometric test for the evaluation of exercise performance. Spiroergometry was performed by all patients according to a standardized protocol by Wasserman et al. (2005 - 17). The test was done at progressively increasing working rate (10W/min) to the maximal tolerance level on an electromagnetically braked bicycle ergometer (Ergoselect, Ergoline®, Bitz, Germany). Heart rate was monitored continuously using 12-lead electrocardiograph (AT-104 PC, Schiller®, Baar, Switzerland), and blood pressure was measured manually every 2min. The peak workload was recorded; oxygen uptake and carbon dioxide production were calculated breath-by-breath (Power Cube, Ganshorn® Medizin Electronic, Niederlauer, Germany), interpolated, and averaged over 10-s periods. Blood gases were analyzed during the whole exercise and the recovery period (5min). Peak oxygen uptake (VO_{2peak}) and oxygen uptake at anaerobic threshold (VO_{2AT}) were determined according to the method by Wasserman *et al.* [17]. $VO_{2peak\ represents}$ maximal minute volume which may be given by myocardium and at the same time also maximal amount of oxygen which can be extracted by tissues. Decreased aerometabolic capacity of organism may be classified according to identification of functional damage based on s.-c. Weber scale [18].

CAVI assessment

CAVI was measured by VaSera® 1500 device (Fukuda Denshi Co, Tokyo, Japan) using standard protocol [19]. 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:

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

(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 a.brachialis. Patients with ankle-brachial index (ABI) lower than 0.9 were excluded from this study.

Biochemistry

In order to evaluate possible influence of the given type of rehabilitation on the homeostasis, the plasmatic level of big-endothelin (big ET-1) and other selected biochemical parameters (serum lipids and CRP), was assessed. Plasma big-endothelin measurement was done using an immunometric (i.e., sandwich) method ELISA (Biomedica® Group, Vienna, Austria).

Patients with CAD

In a separate trial performed in patients with coronary artery disease (CAD) we evaluated the effect of supervised exercise training on the arterial stiffness. Arterial stiffness was assessed by the parameter CAVI according to the protocol which was described previously. Sixteen patients (8 men/8 women; mean EF 55.0 ± 10.2%; mean age 61.5 ± 10.6 years) attended the study. Supervised exercise training took place 3 times a week for consecutive 12 weeks. The exercise protocol was identical to the protocol used in patients with CHF and 1 training session lasted 60 min.

Statistical data analysis [20].

Estimates of arithmetic mean and standard error were used as standard summary statistics describing obtained primary data. Prior to any parametric data processing, we verified normality of sample distribution (Shapiro-Wilk's test) and homogeneity of variance (Levene's test). Pearson's correlation coefficient was used as a measure of mutual correlation between parameters as well as between the differences in values due to experimental exercise. Repeated measure ANOVA model was applied as principal method evaluating outcomes of experiments with model design including both experimental groups (EXE, EMS as independent, effect components) and sampling in different time points (as dependent, pair-wise component). Greenhouse-Geisser correction was applied to correct violation of sphericity assumption in case of testing repeated measures effect. For detailed mutual comparison of experimental variants with control group, Dunnet's post hoc test (independent comparisons) and pair-wise t-test (pair-wise comparisons) were used. Statistical analyses were computed using SPSS 19.0.1 (IBM Corporation, 2010). A value $p < 0.05$ was accepted as boundary of statistical significance in all applied tests.

Ethics

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 and to the GCP guidelines of the European Community.

RESULTS

Patients with CHF

There was no significant difference in any parameter at baseline in both studied groups. This indicates baseline comparability of the experimental groups. Initial characteristics of patients in the two experimental groups (EXE, EMS) are outlined in Table 1.

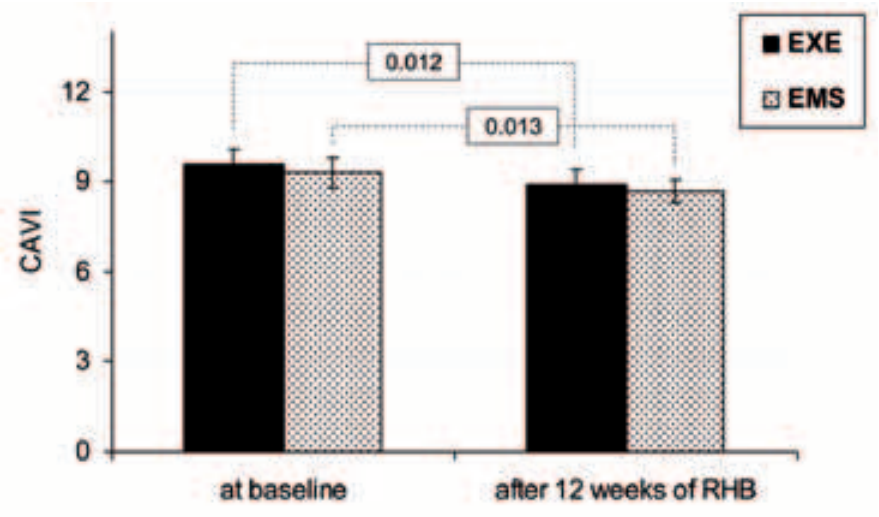
Table 1
Initial characteristics of patients in both experimental groups of patients with CHF

Parameter [1]	**Exercise group** (N = 30)	**EMS group** (N = 31)	**P value** [2]
Age (years)	60.7 (1.5)	58.1 (2.1)	0.112
Men/women	24/6	24/7	0.718
LVEF (%)	32.5 (2.3)	29.2 (3.1)	0.358
NYHA	24/6	25/6	0.413
CAVI	9.6 (0.2)	9.3 (0.2)	0.061
BMI	29.3 (0.7)	28.0 (0.7)	0.184
HR_{rest} (beats/min)	80.1 (4)	78.6 (5) 0.305	
Systolic BP_{rest} (mmHg)	112.0 (6.1)	115.3 (4.8)	0.243
Diastolic BP_{rest} (mmHg)	73.2 (5.3)	75.5 (4.3)	0.187
Pharmacotherapy			
ACE inhibitors	26	27	-
ACE inhibitors	18	21	-
diuretics	27	27	-
digoxin 4 5 -	4	5	-
statins	25	24	-

[1] Categorical data are described by absolute number and percentage of patients in given category; continuous variables are described by mean (S.E.)
[2] Statistical significance of differences between groups is tested by ML-c^2 test for categorical data and by t-test for continuous parameters.

A statistically significant improvement of initial values of CAVI was detected in both experimental groups (in group EXE from 9.6 (0.2) to 8.9 (0.2); $P < 0.012$; in group EMS from 9.3 (0.2) to 8.7 (0.2); $P < 0.013$. This represents a decrease of –6.8% in group EXE and –5.7% in group EMS. The obtained results may be interpreted as improvement (decrease) of vascular wall stiffness due to long-lasting (12-weeks) regular physical loading of skeletal muscles (Fig.1).

Fig.1
CAVI at baseline and after 12 weeks of given type of exercise training in 2 experimental group



Twelve weeks of exercise training or electrical stimulation decreased significantly the plasmatic levels of big-endothelin and CRP, while the serum lipids values remained without significant change but within physiological values (this finding is very probably related to the effect of chronic treatment by statins). The results of the evaluation of selected biochemical parameters are summarized in Table 3.

Table 3
Biochemical parameters at baseline and after 12 weeks of given type of exercise training in 2 experimental groups of patients with CHF

		Experimental results [1]		Differences [2]		
parameter [1]	**group**	**baseline**	**12th week**	**value**	**% of values at baseline**	**p value [4]**
big-endotelin[5]	EXE	1.1 (0.05)	0.9 (0.05)	-0.1 (0.05)	-12.8%	**0.014**
(pmol/l)	EMS	1.2 (0.10)	0.9 (0.05)	-0.3 (0.10)	-23.0%	**0.001**
	p value [3]	0.962				
CRP[5]	EXE	8.5 (3.2)	3.4 (2.1)	-5.1 (2.5)	-60%	**0.039**
(mg/l)	EMS	7.2 (3.4)	2.5 (1.9)	-4.7 (2.7)	-65.3%	**0.043**
	p value [3]	0.567				
LDL[5]	EXE	2.62 (0.7)	2.16 (0.4)	-0.46 (0.2)	-17.6%	0.065
(mmol/l)	EMS	2.93 (1.3)	2.67 (1.0)	-0.26 (0.7)	-8.9%	0.088
	p value [3]	0.771				
HDL[5]	EXE	1.22 (0.3)	1.24 (0.3)	0.02 (0.01)	1.6%	0.665
(mmol/l)	EMS	1.30 (0,4)	1.28 (0.5)	-0.02 (0.01)	-1.5%	0.421
	p value [3] 0.634					
TAG[5]	EXE	1.72 (0.9)	1.58 (0.8)	-0.14 (0.2)	-8.1%	0.198
(mmol/l)	EMS	2.00 (0.8)	1.82 (0.9)	-0.18 (0.3)	-9.0%	0.113
	p value [3] 0.584					

[1] Arithmetic mean and standard error (SE)
[2] Pair-wise differences expressed as difference arithmetic mean (standard error) and as % of initial value
[3] Significance level of independent component in rm ANOVA model
[4] Significance level of pair-wise (time-related) component in rm ANOVA model
[5]rm ANOVA model computed using log-transformed data; trimmed mean used for parametric data description in these variables

Patients with CAD

At the end of rehabilitation program a slight decrease of CAVI (from 9.1 ± 1.4 to 8.8 ± 1.6) was present, however, without statistical significance (Fig.2 and 3). Nevertheless, the tendency to improvement of the arterial stiffness could be considered as a positive influence of regular physical activity on an important cardiovascular risk factor (a decrease of CAVI value below 9.0 is considered as a reduced risk).

Fig. 2
CAVI at baseline and after 12 weeks of aerobic exercise training in patients with CAD

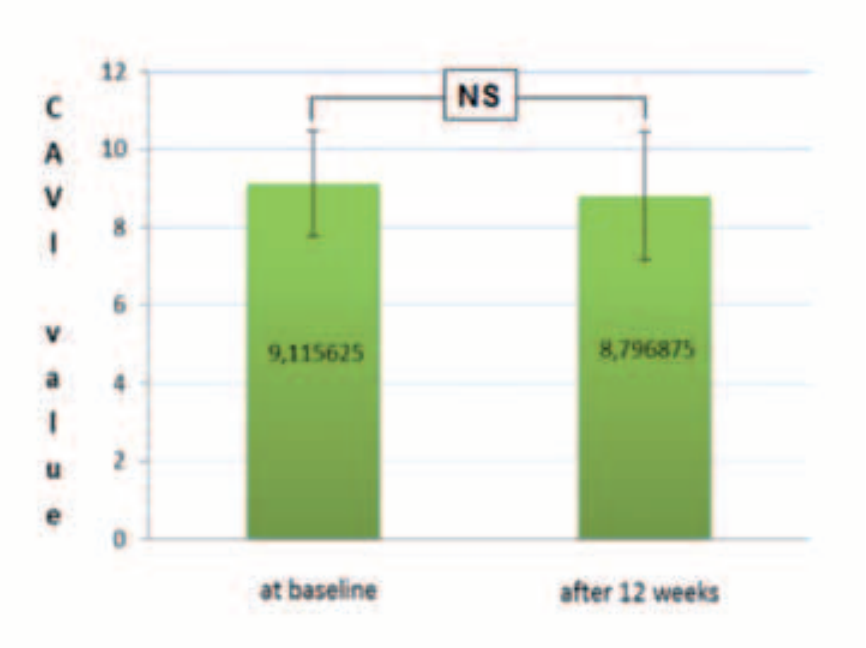
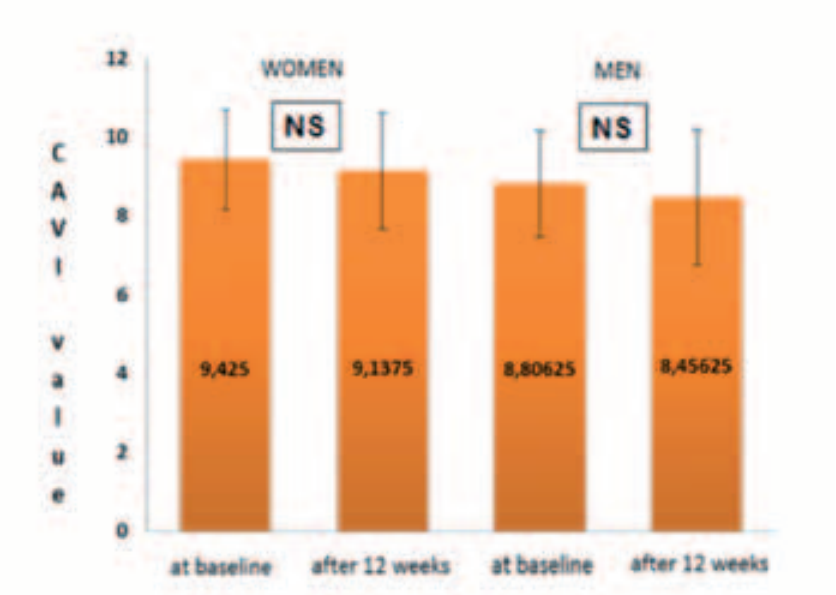


Fig. 3
CAVI at baseline and after 12 weeks of exercise training in patients with CAD (women vs. men)



DISCUSSION

This study compared effects of supervised fitness training and EMS in home conditions in patients with stabilized form of CHF (NYHA II-III) and in group of patients with CAD. The main and in actual scientific literature still sporadic topic of this study was the evaluation of the effect of physical exercise or EMS on changes in arterial wall stiffness expressed as CAVI parameter. This study is apparently the first one which deals with this problematic and brings unique results. The observed significant improvement of CAVI confirms very probably the positive effect of 12 weeks of exercise training or EMS on arterial stiffness in patients with moderate CHF. Arterial wall stiffness is a significant factor determining the prognosis of cardiovascular diseases. It is well know that decreased elasticity results from dramatic structural changes which precede formation of atherosclerotic plaque or thrombus in arteries. The crucial fact is that CAVI reflects the condition not only of elastic, but also of muscular arteries [21]. It means that CAVI value is affected by smooth muscle cells activity in arterial wall, where a number of vasoconstriction (angiotensin II, tromboxan A2, endothelin, etc.) as well as vasorelaxation factors (NO, prostacyclin, natriuretic peptide, etc.) acts. It has been proven that arterial stiffness is closely related to diastolic function of left ventricle in patients with cardiovascular risk factors [22,23]; both these studies showed that CAVI is positively correlated to peak early diastolic trans-mitral flow velocity, E/A, and deceleration time of the early diastolic trans-mitral flow velocity (E-DT). Another study brought the finding that CAVI significantly increases in patients with decreased diastolic function of left ventricle (LV) and increased value of CAVI is independently connected to diastolic dysfunction of left ventricle [24]. It means that if diastolic function of left ventricle correlates to vascular elasticity (reflected by CAVI), then high CAVI may signalize worsened diastolic function of left ventricle. The existence of these relationships will have to be studied and proven. We believe that there is large number of reasons for diagnostic as well as prognostic use of CAVI in patients with CHF. Pathophysiologic processes of chronic heart failure are sufficiently known at present. One of the characteristic symptoms is massive production of inflammatory and vasoactive substances which can trigger smooth muscle cells contractions or initiate remodelation of vessel wall. Therefore it is probable that these biosignals generated by endothelium may increase CAVI also in patients with CHF. According to some recently published studies CAVI may reflect occurrence of global inflammatory reaction of vessels in whole organism. Wakabayashi *et al.* [25] reported that CAVI increases with plasmatic level of C-reactive protein, amyloid A, sialic acid, fibrinogen and number of leukocytes in diabetes mellitus type 2. However, the mechanisms which cause increase of CAVI under these conditions are not fully elucidated yet. Nevertheless, CAVI may be applicable complementary tool for monitoring of CHF development and for monitoring of potential changes of vascular system caused by therapy.

Due to regular physical activity vasoconstrictory substances as well as anti-inflammatory cytokines are reduced; detailed review by Gademan *et al.* [26] gives evidence that exercise training not only increases baroreflex sensitivity and HRV, but also decreases plasmatic level of catecholamines, angiotensin II, vasopressin and brain natriuretic peptide. Vasoconstrictory substance endothelin is considered an important factor of defect vasodilatatory reaction in microcirculation of skeletal muscles in chronic heart failure. Its pathological effects on muscles stability have been proven [27]. Increased plasmatic activity of endothelin is one of the causes of low tolerance of workload and worsening of prognosis in patients with heart failure [28]. Precursor of endothelin is big-endothelin which expresses overproduction of this substance better than circulating endothelin itself because it is quickly degraded [29,30]. It is clear that it is very important to reduce increased activity of vasoactive and pro-inflammatory substances in patients with CHF. Also it is necessary to emphasize enormous importance of regular fitness training which can significantly reduce the level of neurohumoral substances [31,32]. Physical load represents therefore very strong anti-inflammatory impulse reducing catabolic

wasting processes connected to CHF progression [33]. Only limited number of studies is focused on the effect of EMS on markers of anti-inflammatory activation or vasoconstrictory substances. E.g. Karavidas *et al.* [34] reported decrease of representative markers of anti-inflammatory activation (TNF-alpha, interleukins IL-6 and IL-10, adhesive molecules sICAM-1 and sVCAM-1) after 6 weeks of EMS in 42 patients with CHF. No reports are available on analysis of EMS effects on the level of endothelin or big-endothelin in patients with CHF. Only a few papers are available at present focusing exclusively on the effect of fitness training on levels of endothelin in patients with CHF. Kobayashi *et al.* [35] observed insignificant decrease of endothelin level as a result of exercising as compared to control group. Callaerts-Végh *et al.* [36] found improvement of peak oxygen intake due to 8-weeks fitness training in patients with CHF; however without significant effect on endothelin level. Similar results brought also the study by Spinarova *et al.* [37] where the trend to decrease of big-endothelin was observed in group of exercising patients with CHF in comparison to group of non-exercising after two months of fitness training.

In past 20 years, several authors reported that electromyostimulation induces profound structural and metabolic changes in the stimulated muscles and increases the number of fatigue resistant (slow-oxidative) fibers [38]. Direct electromyostimulation promotes higher work intensity than any type of exercise because the electrical stimulus bypasses the hierarchic physiological recruitment and activates all motor units simultaneously [39]. Muscle contractions triggered by electrical impulses activate the sequence of metabolic and vascular processes very similar to those which accompany normal muscle activity. Resulting reactive hyperemia and increased NO production promote vasodilatatory signaling and may counterbalance the sympathetic overactivity and cytokine production [40]. These conclusions are supported by two recent clinical studies which describe significant improvement of endothelial functions by EMS in patients with CHF [41,42]. Regarding the fact that similar benefits as by standard exercise were achieved by electromyostimulation, we supposed that EMS (as a form of exercise training) could positively affect the neuro-humoral overactivity and decrease the arterial stiffness. Our postulate proved true and it was also clearly visible in the results of this study. It is fully justified in believing that EMS is dynamic developing up-to-date method in rehabilitation of chronic diseases. According to recent literature, EMS effectively prevents the development of protein catabolism in the course of post-operation period [43] and significantly increases effectiveness of clearance during hemodialysis in patients with chronic renal insufficiency [44].

CONCLUSION

It is necessary to emphasize two essential facts which were brought in this study:

1) both methods may affect health conditions of patients with CHF comparably and EMS may be applied safely and effectively at home (without professional medical supervision),
2) based on obtained experience CAVI assessment may be recommended as fast and noninvasive way of monitoring of changes in cardiovascular system in patients with CHF or CAD.

For these reasons the presented results are largely unique and bring a lot of new findings. However, future intensive clinical research is absolutely necessary for their confirmation.

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