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NONINVASIVE METHODS IN CARDIOLOGY 2009

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OF PROFESSOR FRANZ HALBERG

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Prof. Dr. Franz Halberg

90 years of age

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

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

His chronobiological studies represent a new original Minnesotan branch of science based upon resolving the chronome and its mapping from womb to tomb. Womb -to- tomb chronome initiative consists in extension of a unique existing data archive and reference standard bank on variables of biomedical interests: heart rate, blood pressure, body temperature, a host of chemical determinations on blood, saliva and urine.

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

Needless to say, not only those researchers who are deeply interested in this field, but also others who are less interested, have all been strongly impressed by such incomparable records of work achieved by Prof. Halberg. In recent years he has been strenuously promoting chronobiological research further in the field of clinical medicine on the worldwide scale. We feel honored to have had the possibility of cooperation with Prof. Halberg since 1980s. In the year 2000, Prof. Franz Halberg from University of Minnnesota, USA, received the degree of honorary doctor of Masaryk University and thus have the honor also to be members of Masaryk University Brno. In the last 25 years, the cooperation between Masaryk University and University of Minnesota was intensive and was enlaged also to the international project BIOCOS.

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

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

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

Prof Halberg suffers by the fact, that his ideas overrun the development of science for tens of years. He suggested the ambulatory 24 hours blood monitoring in 1948. The first scientific study using this method in Czech Republic was published in 1994. Also the treatment of oncology diseases on the chronobiological basis started many years after Halberg suggestion. The last Halberg proposal for diagnosis of vascular variability disorders on the basis of several day ambulatory blood pressure and heart rate monitoring or on the basis of several days lasted self-monitoring is nowadays not broadly accepted; despite it enables the risk stratification of hypertensive patients. The risk-stratification guided treatment is more effective than the treatment based on diagnosis only.

I wish professor Halberg good health necessary to continue his scientific work for many years. I also wish scientific community to accept all Franz Halberg ideas as quickly as possible, because it is an interest of patients all over the world.

Ad multos annos!

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Masaryk University
90^{th} ANNIVERSARY

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

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

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

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

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

A. FOLLOW-UP TO THE CORNELISSEN-SERIES

INHERITANCE OF FORM IN SPACE FROM PARENTS AND OF FORM IN TIME FROM THE COSMOS: FROM BRNO'S MENDEL AND SIEGELOVA, RESPECTIVELY

Cosmic inheritance rules: congruence and selective assortment; implications for health care and science[1]

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Abstract. Countering the trend in specialization, we advocate the transdisciplinary monitoring of blood pressure (BP) and heart rate (HR) for signatures of environmental cyclic and other variabilities in space as well as terrestrial weather on the one hand, and for surveillance of personal and societal health on the other hand. New rules (if confirmed novel laws) emerge as we recognize our inheritance from the cosmos of cycles that constitute and characterize life and align them with inheritance from parents. In so doing, we happen to follow the endeavors of Gregor Mendel, who recognized the segregation and independent assortment of what became known as genes. Circadians, rhythms with periods, τ, between 20 and 28 hours, and cycles with frequencies that are higher (ultradian) or lower (infradian) than circadian, are genetically anchored. An accumulating long list of very important but aeolian (nonstationary) infradian cycles, characterizing the incidence patterns of sudden cardiac death, suicide and terrorism, with drastically different τs, constitutes the non-photic Cornélissen-series (1).

Laws and rules. Between 1856 and 1863, Gregor Mendel cultivated and tested some 29,000 pea plants. Between 2000 and 2008, Jarmila Siegelova's team collected some 73,888 sets of systolic (S) and diastolic (D) BP and HR measurements. With his 29,000 peas, Mendel collected evidence for the laws of heredity: segregation and independent assortment. Siegelova's some 73,888 cardiovascular sets, and these and her earlier proceedings, led to the rules of cosmic

[1] Dedicated to the senior author's daughter Francine Halberg on her 57th birthday, June 28, 2009.

inheritance, which document the congruence and selective assortment of cycles around and in us. In monitoring the solar wind's signatures, we follow the aging Mendel: about (~) 13.5 months before his death Mendel considered an association of solar activity with worldwide auroras, searching for what is now recognized as the solar wind, i.e., particle radiation from the sun.

Mendel did this 124 years before we learned on a 16-year series of SBP from an elderly man (FH) that the same solar wind's far-transyear (1.2 years ≤ [τ - CI {95% confidence interval}] < [τ + CI] < 1.9 years) and cis-half-year (of ~5 months length) are built into us as wobbly cycles amplified in the presence of a counterpart in the solar wind, dampened in the absence of this counterpart but not lost in us when the corresponding τ is no longer detected in the solar wind (2). Thus, the Brnoese, Minnesotan and other BIOCOS monitoring is the aging meteorologist and epidemiologist Mendel's legacy. It has led to a complement to the two laws of genetics. When we align Mendel's inheritance from our immediate parents (i.e., the segregation and independent assortment of genes) with the manifold cycles one inherits from the sun and the broader cosmos, that is when we turn to cosmic inheritance, the two new rules are, first a wide transdisciplinary spectrum of congruent τs around and in us, with their congruence defined and documented by overlapping or overlying CIs of their τ, and second (if not quite independent assortment), then selective congruence, among different environmental and biospheric variables at various frequencies characterizing both.

Thus, we find that the HR of an adult (RBS) between 20 and 60 years of age is congruent with the ~33-year BEL cycle in Wolf's relative sunspot numbers, while his BP is congruent with an ~didecadal Hale cycle in the polarity change of the same Wolf numbers (3). Two variables of the same circulation are locked into different environmental cycles. Selective congruence is again documented by overlapping or overlying CIs of the τs of heliomagnetics gauged by solar wind speed, geomagnetics gauged by the antipodal index aa and the estimation of 1 minute, a mental function, among others, in the transyear region of the spectrum of RBS. It is selective in that at some frequencies all three variables are congruent, or only two variables out of three at other frequencies, or at still other frequencies there is a statistically significant spectral peak in a biospheric or other variable with no congruent counterpart in other time series of the same variable, of other related variables (no intradisciplinary congruence) or in variables of other disciplines (no transdisciplinary congruence).

By the same token in the circaseptan spectral region, BP and HR are locked into different helio- and geomagnetic variables of an elderly man (GSK) (2). An assortment of the congruence of different physiological variables with the same environmental cycle is also encountered in another elderly man (WRB) (4). In the parasemiannual spectral region of RBS, different variables of his circulation can again show a different spectral behavior, as they do in a young man (DG) (5). When congruence involves non-photic invisible cycles in the environment and conditions such as human individuals' and populations' illnesses such as sudden cardiac death and terrorism, respectively (1, 6, 7), it gains in interest and justifies in itself the monitoring of the congruences of solar activity in the human circulation. But the justification also stems from what the given person can learn immediately for his/her health care.

In these proceedings, a physician-scientist (YW) (8) and his son, starting as a child and ending as an adolescent (FW) (9), set an example of family monitoring of BP and HR, the father providing for more than two decades, mostly half-hourly around the clock measurements, the son surveilled half-hourly for the first 40 days of his life (10) and self-measuring in childhood and during adolescence once a day for 8 years (9). Thus YW gathered evidence for a chronobiologically and longitudinally examined development (in well over two decades of his half-hourly around-the-clock measurements) of his high BP, MESOR-hypertension, MH, which is reversible, absent on Sundays and during a vacation spent at home (8). The MESOR, M, is a Midline-Estimating Statistic Of Rhythm assessed parametrically by the fit of a 24-hour cosine curve. YW's M detects abnormality, MH, when the complementary non-parametric approach by stacking data does not (yet) find it in the prediction interval for single values, the "normal range" of peers of the same gender and age.

YW documents that MH can persist in his systolic (S) BP when it is cleared from the diastolic (D) BP. On the average, he shows no abnormality on Sundays and during a vacation. By intervention, with timed dietary measures or exercise, and by continuing monitoring he may provide more longitudinal data to reverse the workday elevation of the SBP MESOR as well, rather than to find an eventual excessive elevation of the SBP and/or DBP also on Sundays and on other days away from work. In the manipulation of sodium intake, it seems important to realize great inter-individual differences, and further the importance of circadian stage, that can both lead to decreases, rather than increases in BP in response to sodium. Alternatively, if progression cannot be stopped and the BP-M is not normalized by the absence of work, it will be of interest to see whether the parametric and the nonparametric approach reveal a concomitant DBP and SBP failure to reverse to normality on weekends or do so in a sequence, and if the latter is the case, which of the BP remains abnormal on Sundays first. Clearly, the over two decades of monitoring by YW do not suffice to draw full inferences concerning the development of a human MH on weekends as well as on workdays. In these proceedings, YW's contribution to the development of workday MH is accompanied by the contribution of three elderly men (WPB, GSK and FH) who are all treated for MH and whose data on the one hand indicate the need for continued surveillance to avoid CHAT, Figures 1 and 2 (11), and two of them also allow the as-yet basic demonstration of a transtridecadal spectral component in their circulation and in one case in body weight. FH's follow-up record shows the need for continued surveillance to detect and, if so, to attempt to eliminate CHAT and further to validate the extent of success -- e.g., by the use of coenzyme Q10 (Q-Gel) with the evening meal (12) in eliminating 7-day CHAT -- and to recognize any failure, e.g., to eliminate 24-hour CHAT (data not shown).

The approach demonstrated in Figures 1 and 2 is practiced as yet by a minuscule minority in noninvasive automatic cardiology in the spirit of Theodore C. Janeway (13) and Frederic C. Bartter (14), who had to rely on self-measurement. Let us call this school chronomic, when it now aligns make-ups in time -- chronomes -- of an organism with those of the sun's variability, the original time structures or chronomes. Not only ~daily, ~half-weekly and ~weekly but many much longer τs have been found to characterize human physiology and pathology at the levels of individuals and societies, including ~5-month as well as ~6-month cycles, the former helio-, the latter geomagnetic in origin, with signatures in BP, HR, cardiac arrhythmia and sudden cardiac death, facts that must not allow their neglect. Yet practicable restrictions of focus at this time, primarily on ~24-hour rhythmic behavior during a week and on the relation of these circadian characteristics to half-weekly ones could provide novel information bringing millions of people into the loop of self-help for preventive care. The chronomic approach can be implemented by self-measurements and more readily and more densely, by self-help with automatic recording thanks to modern technology. It has accumulated, with gaps, half-hourly data for up to well over two decades yet as a minimum for seven days on sets of hundreds of individuals.

The data document day to day and other presumably normal variability in human BP and HR around the clock and lead to the construction of reference ranges and, in their light, to the finding of Vascular Variability Disorders (VVDs). These VVDs could be detected in current practice, as could be the fact that a good drug combination for BP-lowering, such as 12.5 mg of hydrochlorothiazide and 50 mg of losartan (Hyzaar), can exacerbate a SBP VVD (a circadian overswing, CHAT) and induce this DBP abnormality with one timing of its administration and eliminate CHAT with another timing, each particular timing tested for a month in the same patient (15). The inferences drawn on the basis of long records comparing the same drug in the same dose, taken by the same person with a different timing in relation to awakening, revealing drastically different effects, constitute evidence that, sooner rather than later could be considered by those who currently rely on their platinum standard of a single day's profile. A 24-hour record simply does not suffice for a prognosis when in the same young neurosurgeon during office hours (09:00-17:00), 77% acceptable measurements on one day alternate with 100% unacceptable (too high) ones on another day (16; cf. 17-21).

If in turn current health care remains homeostatic, still assuming, rightly or (we believe wrongly) that there is indeed a "true" BP and that this can be assessed, if not by single measurements than by single 24-hour profiles, some recent suggestions sound reasonable. In 2009, some advocate "... lowering BP in everyone over a certain age, rather than measuring it in everyone and treating it in some" (22). A polypill containing three BP-lowering drugs, each at half the standard dose -- a statin, folic acid and aspirin -- would serve the purpose of primary and secondary prevention (23). Others (24) also "support the use of a 'polypill' to lower the risk of cardiovascular disease in people likely to be at risk (such as all people over the age of 55) without first checking their BP." This approach is logical and justified from the viewpoint of a health care based on pseudo-evidence that is based upon a few spotchecks including at best a single chronobiologically uninterpreted 24-hour profile, which checks a small fraction of a half-weekly or weekly cycle, as if the pulse were taken for just a small fraction of one cycle, i.e, a fraction of a second. When all VVDs requiring long-term surveillance are ignored, as is, for instance, the risk of a stroke in 6 years which can be elevated by an undiagnosed VVD from ~5% to 100% in one study (21), a polypill is an attractive and economical answer. But as we monitor with self-help, cost-free to start with at half-hourly intervals for 7 days and continuously monitor when abnormality is found, the merits of self-surveillance become obvious, also for checking on the demerits of the polypill or any other treatment, such as the induction and exacerbation of CHAT, on a substantial number of patients (15, 21).

The arguments that such monitoring is costly, complex and hence futuristic can be met with modern computer-aided technology by the demonstration that self-surveillance is possible and is now ongoing on a limited scale, and the complexity can be eliminated by the computer charged with all complex calculations and providing free and clear interpretations.

Following Mendel's interest in the aurora. Human population and broader biospheric monitoring has a long way to go in the biosphere to match the information gathered on the aurora, where the record covers nearly a millennium, as analyzed in Figure 3 (25), which reveals a transtridecadal cycle also found in environmental temperature (26) in the sediments of an African lake (27) and in many other variables (3, 28-34).

According to Battersby (35), Galileo described the auroras as sunlight reflected in vapors rising from the earth. Battersby also writes: "In the late 1600s, Edmond Halley [1656-1742] was the first to correctly link the aurora to the Earth's magnetic field." According to Egeland (36), a close connection between the aurora and the geomagnetic field was found around 1730 by Hierter and Celsius. It is the more interesting to read in De Mairan's book (37) on that topic that he ruled out magnetism as underlying the aurora because "magnetic matter is constant". Had he pursued his earlier botanical observation (38) that the sensitive plant continued its sleep movements in continuous darkness, and had he measured geomagnetism concurrently, he could have found an ~24-hour cycle in both and would perhaps not have ruled out constant magnetism in the genesis of the aurora. It is the more interesting that in 1882 Mendel associated solar activity with the aurora. A transtridecadal cycle in this phenomenon was first reported for the past 500 years without specific comment by Sam Silverman (39).

In the case of yearly data on northern lights from a catalogue by Krivsky and Pejml (40), between the years 1001 and 1500 our meta-analysis (illustrated in Figure 3) shows a BEL. The linear-nonlinear extended cosinor (41-43) reveals a τ of 32.8 years, with the CI of this τ extending from 31.8 to 33.8 years and an amplitude with a CI that does not overlap zero (Figure 3, row 3). Also by linear-nonlinear extended cosinor, during the entire span from 1001 to 1900, a transtridecadal BEL τ is ~29.6 years long with a CI extending from 29.0 to 30.3 years and an amplitude with a CI only slightly overlapping zero, Figure 3C (bottom row).

While the quality of the data analyzed (40) has been questioned, there is the fact that the greater the noise in a time series, the more convincing is the validation of an anticipated result. This is indeed the case in Figure 3, which also shows our analysis of data deemed more reliable by Schröder and Treder (44). When the analysis of the data of Krivsky and Pejml is restricted to the span of the data published by Schroeder and Treder, the results are in excellent agreement in Figure 3.

For the interval 1500 to 1948, as noted, a scholarly analysis and review by Silverman (39) supports the hypothesis that a nonrandom albeit greatly variable transtridecadal pattern in solar activity includes a spectral component of 33.3 years in the power spectrum of monthly auroral occurrence, in keeping with the prior report of a climatic ~33-year cycle by Eduard Brückner (45), who fully realized the transdisciplinary importance of his wet/cold-dry/hot cycle and offered public lectures on that topic.

"[In any event, the aurora can be] more than a pretty display. These storms are caused by violent outbursts from the sun and can play havoc with satellites, scramble GPS signals, endanger astronauts and even blow power lines on Earth" (35). This is as far as scientific journalism ventures, not yet to human physiology. The effect of storms in the biosphere is rarely considered by the public, but is of particular interest to neuroendocrinologists. It will be up to scholars of melatonin (46, 47), to further map the infradian challenges found in the record-holding test pilot, Dr. Robert B. Sothern (RBS), author of a comprehensive scholarly book in the field of rhythms (48). RBS yielded a model for motivation and consistency and demonstrated in a record of ~5 HR measurements around the clock now covering over 40 years, a transtridecadal cycle also found in Zürich (Wolf) sunspot numbers during the span covered by his data.

The BEL (3, 28-34) is one of the windows for non-photic mostly invisible effects of the cosmos upon the biosphere. It also characterizes the aurora as the "greatest show on earth" for most of the past millennium, with associations in the biosphere. NASA's flotilla of satellites, named THEMIS, sent into space to analyze magnetic substorms as they happen and to understand the sequence of events that bring about the northern lights, promises to tell us more about the physical mechanisms involved, but should be checked for biospheric associations. Battersby writes: "During a geomagnetic storm there are typically several substorms, but how the two are connected is unclear. So far during the mission, solar activity has been low, but it should increase over the coming year or so, giving THEMIS a chance to watch a much larger storm unfold" (35). We should concomitantly watch what happens in the biosphere as well. Long-term monitoring, such as that ongoing for years or decades is needed to learn about infradians in a number of frequency windows that also include a transyear (2, 49-52) and cis-half-years (2, 53), the latter involving steroids and melatonin (54) in mediating effects of our cosmos, perhaps via the eyes (55).

Cycles with a τ of over 3 decades' length now documented in an individual's, RBS', physiology and psychology are reminiscent of the documentation by W.J.S. Lockyer (33) that these rather long cycles may stem from changes in the length of the sunspot cycle generated by the cosmos and reflected in the interplanetary magnetic field. We can look with hindsight at what could have been done in dealing, for instance, with sunspots by individuals who could not observe too many ~35-year cycles. They, like ourselves, could probably measure not much more than part of a single adult or part of an elderly 35-year cycle. If Carl Friedrich Gauss' least-squares had been available in Horrebow's time, i.e., in the 18th century, he did have enough data to objectively document, with the cosinor method by least-squares, a cycle of ~9 years in his observation span (54).

In either case, for the variable sunspot cycle at the times in history when it happened to be studied in the 18th and 19th centuries, the necessary length of the time span needed for rejecting the zero-mplitude assumption and to get reliable estimates of parameters was not longer than a single cycle's length (54). Without extrapolating beyond the scope of the specific data analyzed, we find the same success for the transtridecadal BEL (3, 28-34). These precedents should encourage neuroendocrinologists, among many others, to sample systematically for very long spans, since some if not many of the novel infradian rhythms, such as cis-half-years and transyears, may well be modulated by transtridecadal cycles. The latter have implications as an aspect of the climate for global temperature, that as Brückner lectured have contributed to population dynamics and many other human affairs (30, 45).

Discussion. The challenge of circadians is complemented by the greater challenge of infradians that require lifetime monitoring, preferably by unobtrusive and generally affordable methods yet to be developed in nanotechnology. Before this goal is achieved, data collection by available automatic instrumentation, as used by FH, YW, DG and FW, or manually by RBS, FW and WRB, has to be relied upon so that infradian focus can be directed at major problems of society such as those documented elsewhere (6). Data for this critical monitoring of solar activity could be contributed by humans, rendering their health care cost-effective for stroke and other severe vascular disease prevention by self-monitoring and obtaining data analyses automatically and cost-free from a website, as BIOCOS did since 1991 (56; cf. 57), analyzing physiological data, Figure 4, as well as those accumulating in archives, Figure 5. This website could thus serve for service and research, both medical and transdisciplinary, and is being constructed by the Phoenix Study Group, composed of volunteering members of the Twin Cities chapter of the Institute of Electrical and Electronics Engineers (http://www.phoenix.tc-ieee.org). In the interim, analyses are available from the international project on The BIOsphere and the COSmos, BIOCOS (corne001@umn.edu).

Conclusion. All known τs in solar activity up to ~500 years length that may seem to be negligible peaklets in the aurora, Figure 6, characterize human individuals' and populations' variables including, as far as an individual's lifespan allows, HR, BP, body weight and mental performance in health, and have signatures in societal variables including morbidity and mortality, as had long been suggested, mostly without any inferential statistical documentation of the uncertainties involved. These uncertainties (CIs) can now be mapped with their well-known τs, such as the Horrebow-Schwabe decadal cycle, the Makarov and Sivaraman global solar cycle of ~17 years, Hale's ~didecadal bipolarity cycle, and for what we rediscovered as the Brückner-Egeson-Lockyer (BEL) cycle which is reflected in the total solar flare index, in solar wind parameters of the interplanetary magnetic field and in many human physiological and societal variables including 2,556 years of international battles, thousands of years of tree rings, and cave temperatures, and in the emergence on different continents of outstanding physicians, poets and historians (the emergence of outstanding individuals a contribution by Prof. Miroslav Mikulecky) (58; cf. 59). A major transdisciplinary point is that the presence of a biospheric counterpart may support if not validate the corresponding environmental counterpart and vice versa. The eons of evolution have likely contributed to the biospheric finding, whereas, e.g., any peaklets found in Figure 6 by the cosinor analysis of a 900-year series of the aurora poses legitimate doubts about possible artifacts. Such doubts are always part of science and the limitations of the kind of data available are ever present; but when a peaklet found in the aurora at a trial τ of ~500 years has biospheric counterparts, as indeed it does, it gains greatly in transdisciplinary interest.

The immediate now inferentially statistically documented health effect of new ~5- or ~16-months cycles relate to sudden cardiac death, suicide, crime and terrorism (6), in which non-photic cycles characterizing the solar wind can altogether replace photic cycles such as the yearly (circannual) change. While we develop unobtrusive, affordable monitoring tools for stroke and other hard disease prevention, and these tools are already available as prototypes for general use, let us also analyze the same data of our physiology and health departments' archives about our pathology for monitoring space weather. While we contribute greenhouse gases, it is necessary to know climatic changes as a result not only of human activity but of the external influences as well. The most powerful such influence is solar variability, predictable only insofar as it is cyclic. What is new is that we can gauge that variability by that of BP and HR. Let us not fly blind with respect to both solar and human variability as these affect individual and societal health. A polypill will neither explore the risk of societal disease nor will it lower this risk. If, perhaps, it has merit in clinical trials, like any other antihypertensive treatment, it will represent increased risks that require self-surveillance, which is the essential recommendation of the accompanying set of 19 presentations.

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pressure determined each day at 6 in the afternoon provides especially convincing evidence that this patient is a hypertensive. ... My plea today is that information contained in such curves [cosinor fits] become a *routine minimal amount* of information accepted for the description of a patient's blood pressure. *The analysis of this information by cosinor should become a routine.* It is essential that enough information be collected to allow objective characterization of a periodic phenomenon, to wit, an estimate of M [the time structure or chronome-adjusted mean, or MESOR] … an estimate of [the amplitude] A itself, and finally an estimate of acrophase, ϕ [a measure of timing]. In this way, a patient can be compared with himself at another time, or under another treatment, and the patient can be compared with a normal or with another patient."

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Legends

Figure 1. A difficult-to-eliminate circadian overswing (CHAT) (C) of a 24-hour synchronized rhythm (A) of systolic (S) (I) and diastolic (D) (II) blood pressure (BP) (and heart rate [III]) can be the unwelcome trade-off for a successful BP MESOR-lowering (B). Continuous monitoring is required once a vascular variability disorder, such as a high blood pressure (BP), and/or a circadian overswing, CHAT (short for **C**ircadian **H**yper-**A**mplitude-**T**ension), is diagnosed. A circadian rhythm of systolic BP and heart rate of a physician-scientist, GSK, is assessed by the fit of 24-hour cosine curves to data sections of 7 (left) and 28 (right) days, the latter smoothing more than the former, in that transient episodes of abnormality such as an overswing, shown in black, that last only for one or a few 24-hour spans, are likely eliminated. The elimination of CHAT in GSK, based on surveillance by half-hourly measurements analyzed weekly, was nonetheless a very long process, taking years, with only transient success and frequent recurrences over many years. © Halberg.

Figure 2. Need for continued (systolic) blood pressure monitoring: CHAT recurs after year(s) of absence, even in smoothed 28-day records analyzed. Continuous monitoring is required once a vascular variability disorder, such as a high blood pressure (BP), and/or a circadian overswing, CHAT (short for Circadian Hyper-Amplitude-Tension), is diagnosed. A circadian rhythm of systolic (S) (I) and diastolic (D) (II) BP of an elderly man, FH, is assessed by the fit of 24-hour cosine curves to data sections of 7 and 28 days. Note the large black spot at the very end of row C, showing the recurrence of a BP overswing, CHAT. Subsequently, for 3 consecutive weeks, the 7-day (but not the occasional 1-day) CHAT was eliminated by 100 mg of coenzyme Q10 (Q-Gel) taken with the evening meal. © Halberg.

Figure 3. In a series of northern lights covering 900 years, a transtridecadal cycle is seen insofar as the CI, but not the point estimate of the period, τ, extends beyond 30 years. Data analyzed were questioned with the implication that their analyses may be invalid, even though they had yielded a result close to the anticipated finding. In view of that outcome and the observation that a statistically significant result in noisy data in our opinion constitutes a stronger evidence

than the corresponding result in data with little or no noise, it seemed worthwhile to pursue the problem further. For part of the span analyzed, another set of data, regarded as more reliable (44), happened to be available. This afforded the opportunity for comparative analyses of that part of the 900-year span, 1545-1724, for which data deemed reliable were also available. It turned out that the extended cosinor yielded for the span of Schröder and Treder (1545-1724), in the latter's data, a component with a τ of 29.1 years and in the corresponding span from data of Krivsky and Pejml a τ of 29.4 years, as seen from this figure, which also shows that the CI of Schröder and Treder extending from 26.3 to 31.8 years overlies that of Krivsky and Pejml extending from 27.1 to 31.7 years. © Halberg.

Figure 4. Global cross-spectral association of a man's circulation with the planetary geomagnetic disturbance index Kp. © Halberg.

Figure 5. Global cross-spectral association of the incidence of myocardial infarctions in Moscow (1979-1981) and the Bz-GSK component of the interplanetary magnetic field. © Halberg.

Figure 6. Data from J. Strestik (1001-1900). Results to be interpreted with caution since the average number of yearly observations increased as a function of time, likely in relation to technological observational progress. Data inspection finds about 3 different spans: the earliest with fewer observations, the middle one with more observations, and the more recent with considerably more observations. Trial periods: 500, 300, 200, 120, 70. Nonlinear results (each fitted separately): 477 [430, 524], 305 [282, 327], 227 [210, 245], 125.6 [118.4, 132.8], 67.2 [65.9, 68.6]. Composite model failed completely prompting removal of 300-year trial period. Results from concomitant fit with conservative limits are in years:

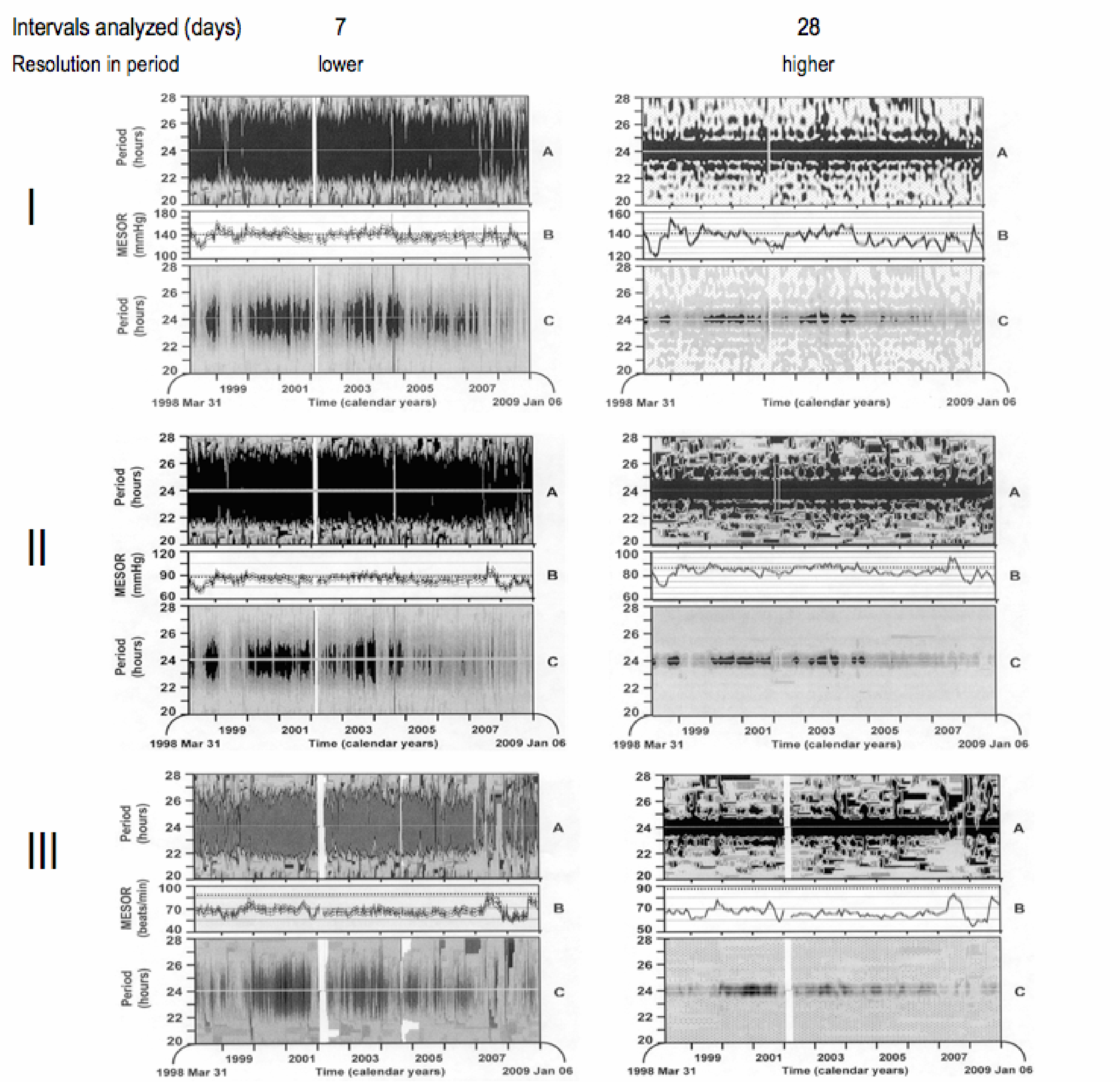
503.5 [418.1, 588.9] A=8.21 [4.58, 11.83]

243.1 [216.2, 270.1] A=5.10 [1.19, 9.01]

117.4 [107.2, 127.6] A=3.06 [-.73, 6.86] $[1.49, 4.64]_{1P}$

69.6 [67.4, 71.7] A=5.27 [1.55, 8.99].

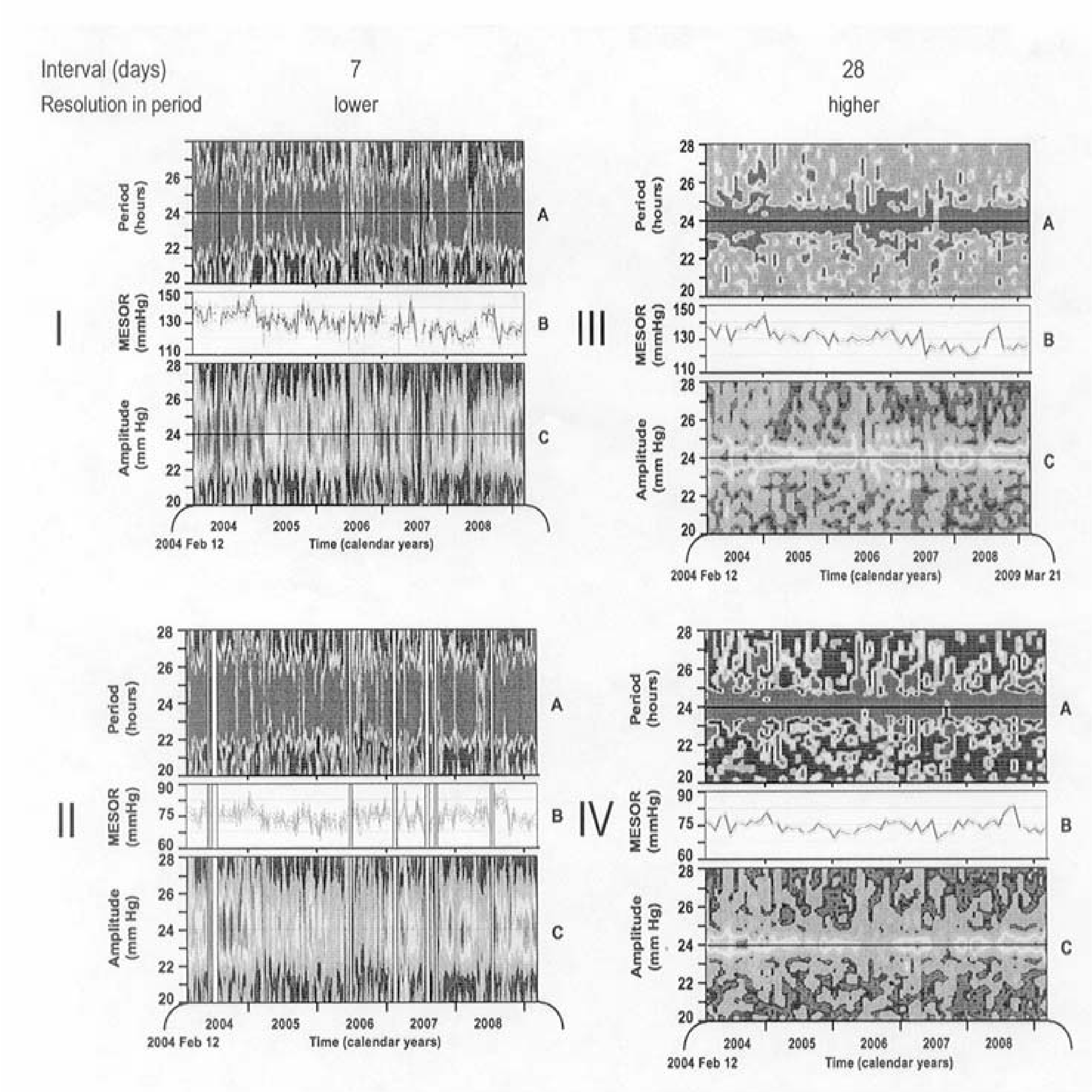
Since the conservative 95% confidence limits of the 117.4-year period overlap zero, 1-parameter limits (1P) are also given in this case. Periods of 243.1 and 117.4 are possibly 2nd and 4th harmonics of 503.5, describing waveform. © Halberg.



*In GSK, treated MESOR-hypertensive man 72 years of age at start of automatic measurements; original data analyzed, N=175,171.
Gliding interval and increment = 7 (left) or 28 (right) days, longest trial period (τ) = 28 hours (h), shortest τ = 20.
A: Probability of rhythm, without account for any pink spectrum; shading density corresponds to: >0.05 (dots), 0.05-0.01 (light), 0.01-0.001 (middle), <0.001 (dark). B: MESOR: thin sidelines: 99.9% confidence corridor; dotted line: upper 95% prediction limit from gender- and age-matched peers. C: amplitudes: darker shading corresponds to larger amplitude. Strongest spectral components have double amplitudes: in SBP ~60 (7 days) or ~58 (28 days) mm Hg, in DBP ~19.2 (7 days) or ~17 (28 days) mm Hg (black = CHAT), in HR ~14.8 (7 days) or ~12 (28 days) beats/min.

CHAT = **c**ircadian **h**yper-**a**mplitude-**t**ension. © Halberg.

Figure 1



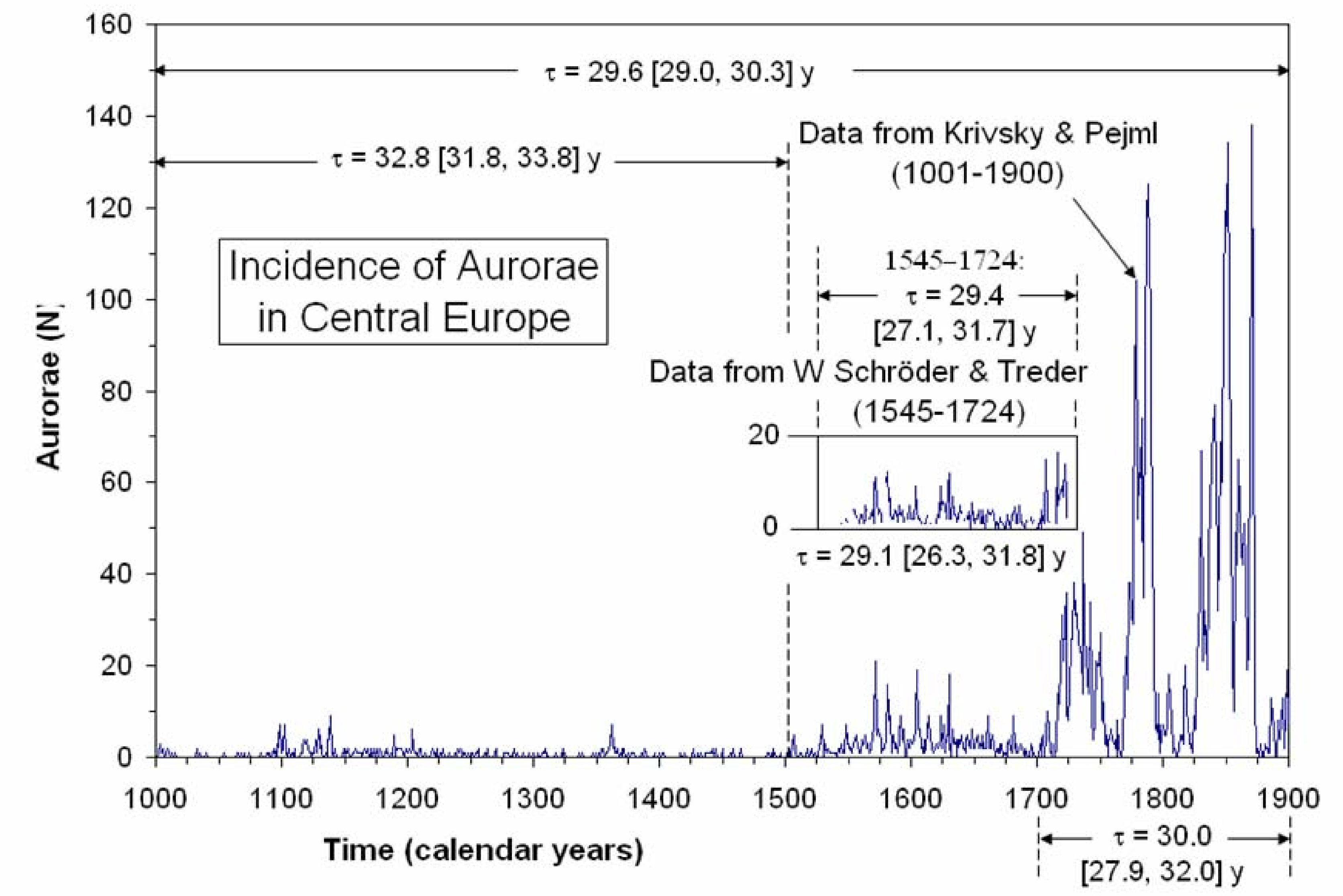
*In FH, treated MESOR-hypertensive man 84 years of age at start of observation, monitored every ~30 minutes with few gaps (original data analyzed, N=67,598). Gliding interval and increment = 7 (left) or 28 (right) days, longest trial period (τ) = 28 hours (h), shortest τ = 20.

A: Probability of rhythm, without account for any pink spectrum; colors correspond to: blue >0.05, green 0.05-0.01, yellow 0.01-0.001, red 0.001-0.0001, violet <0.0001.

B: MESOR: red sidelines: 99.9% confidence corridor; dotted line: upper 95% prediction limit.

C: amplitudes: darker shading corresponds to larger amplitude. Mostly strong spectral components have amplitudes ~12 mm Hg. © Halberg.

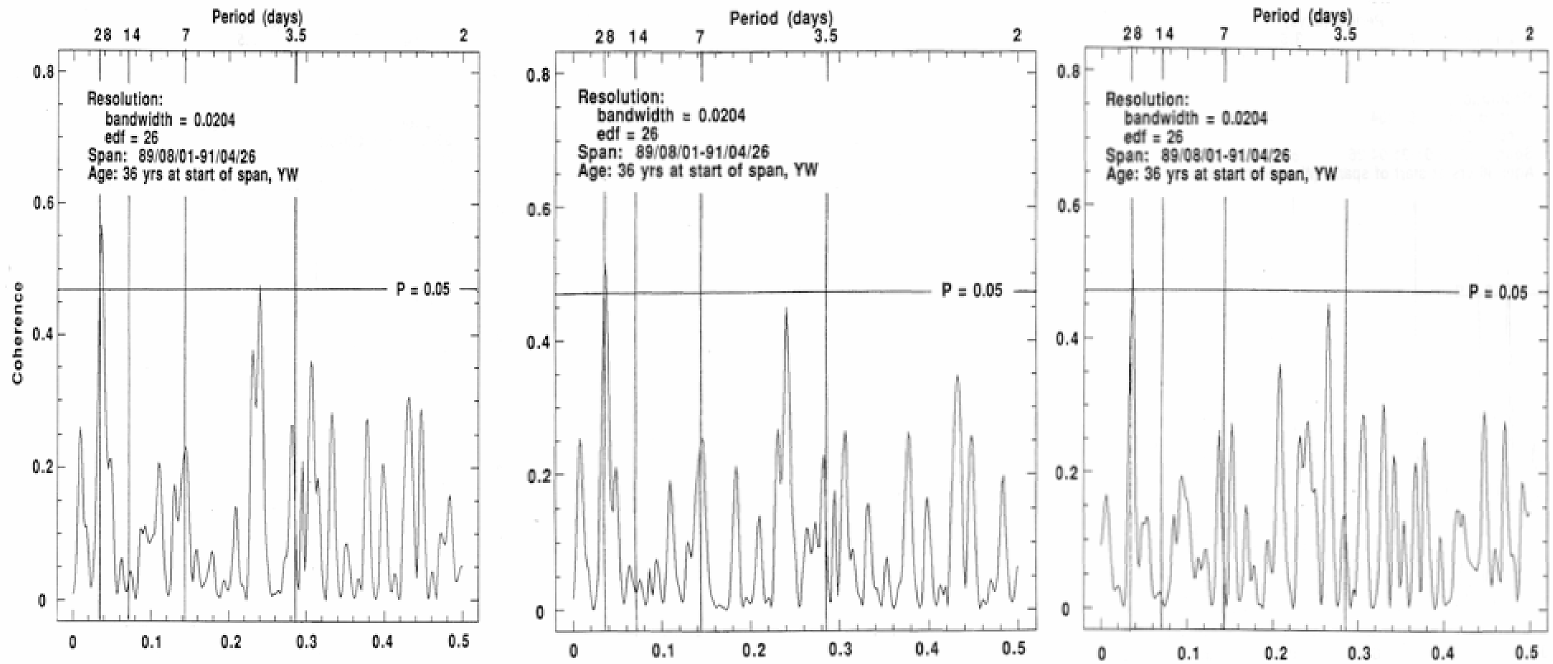
Figure 2



τ = 29.6 [29.0, 30.3] y
τ = 32.8 [31.8, 33.8] y
Data from Krivsky & Pejml
(1001-1900)
Incidence of Aurorae
in Central Europe
1545–1724:
τ = 29.4
[27.1, 31.7] y
Data from W Schröder & Treder
(1545-1724)
τ = 29.1 [26.3, 31.8] y
Aurorae (N)
Time (calendar years)
τ = 30.0
[27.9, 32.0] y

Figure 3

CROSS-SPECTRAL COHERENCE BETWEEN THE GEOMAGNETIC INDEX (Kp) AND A CLINICALLY HEALTHY MAN'S (YW) SYSTOLIC (left) AND DIASTOLIC (middle) BLOOD PRESSURE AND HEART RATE (right)



Frequency (cycles per day)

Figure 4

CROSS-SPECTRAL COHERENCE BETWEEN DAILY INCIDENCE OF MYOCARDIAL INFARCTIONS (MI)* AND THE Bz-GSE COMPONENT OF THE INTERPLANETARY MAGNETIC FIELD (1979-1981) (left) AND DURING 3 CONSECUTIVE YEARS BETWEEN MI AND A GEOMAGNETIC INDEX (K) (right)

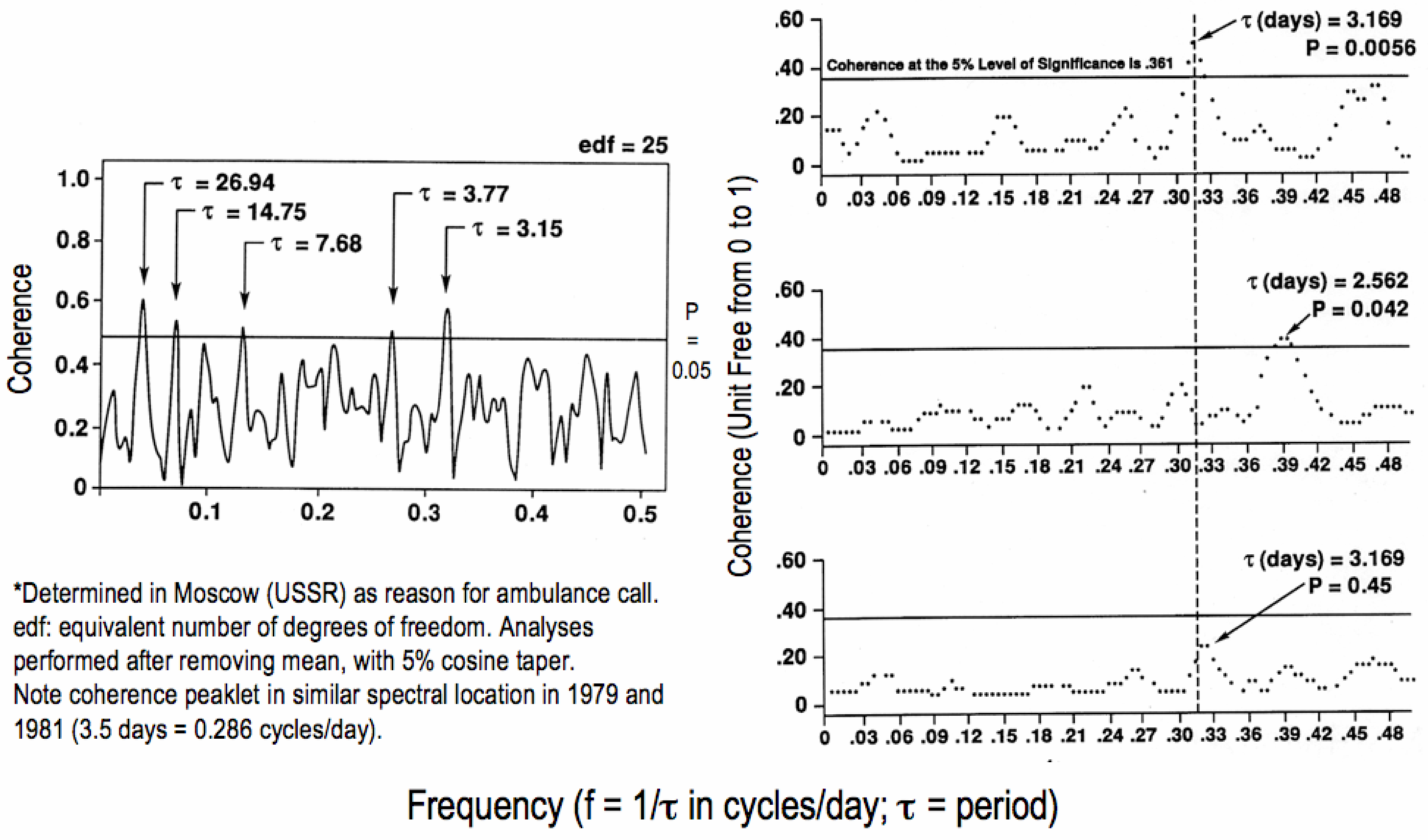


Figure 5

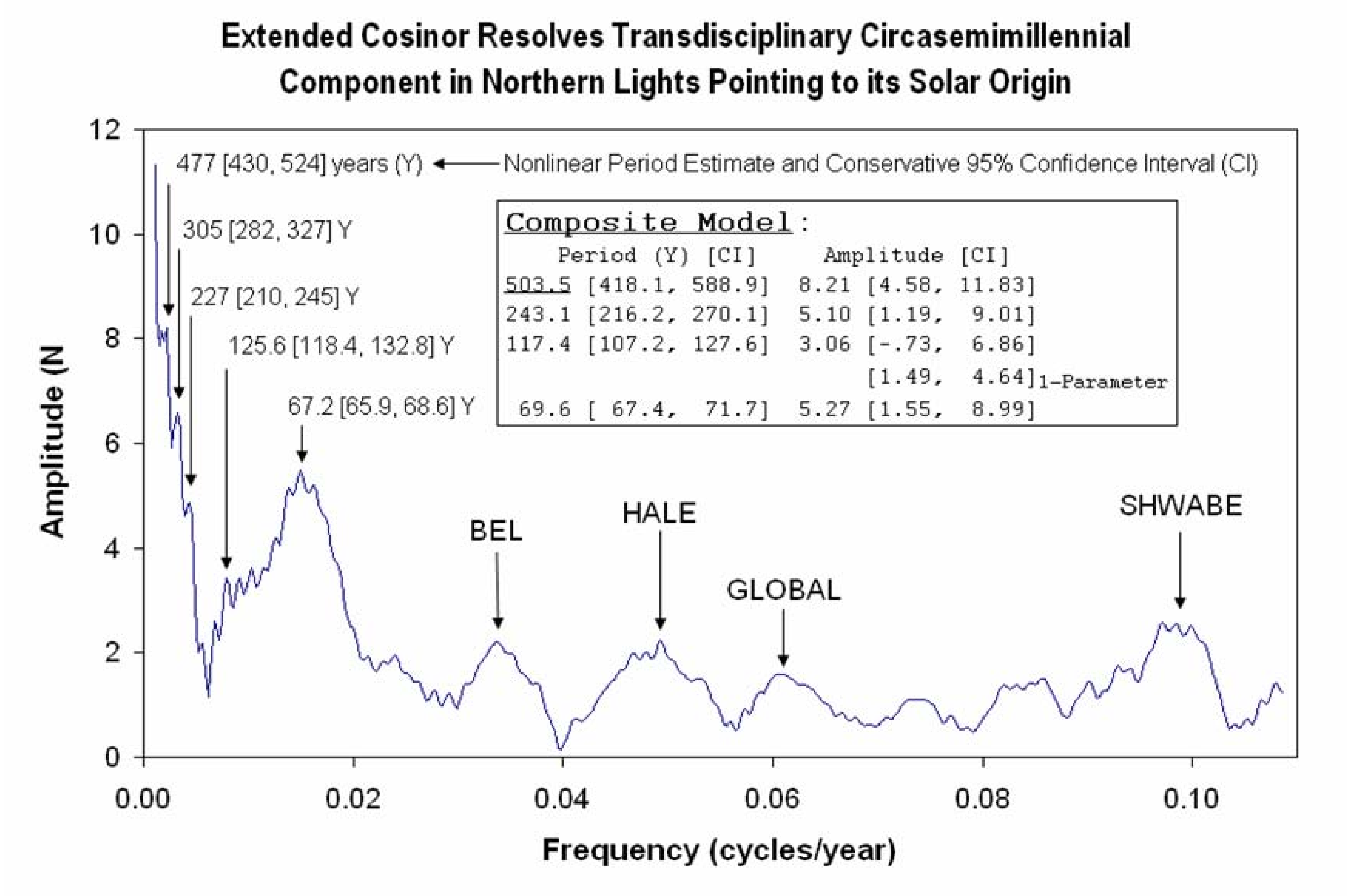

Extended Cosinor Resolves Transdisciplinary Circasemimillennial Component in Northern Lights Pointing to its Solar Origin
477 [430, 524] years (Y)
Nonlinear Period Estimate and Conservative 95% Confidence Interval (CI)
305 [282, 327] Y
227 [210, 245] Y
125.6 [118.4, 132.8] Y
67.2 [65.9, 68.6] Y
Composite Model:
Period (Y) [CI] Amplitude [CI]
503.5 [418.1, 588.9] 8.21 [4.58, 11.83]
243.1 [216.2, 270.1] 5.10 [1.19, 9.01]
117.4 [107.2, 127.6] 3.06 [-.73, 6.86]
[1.49, 4.64] 1-Parameter
69.6 [67.4, 71.7] 5.27 [1.55, 8.99]
BEL
HALE
GLOBAL
SHWABE
Amplitude (N
Frequency (cycles/year)
0
2
4
6
8
10
12
0.00
0.02
0.04
0.06
0.08
0.10

Figure 6

B. DEDICATIONS

Achievements near 60 years of age of Academician Germaine Cornélissen: the Cornélissen-series revisited[1,2]

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Abstract

Nearly 15 years ago, on November 22, 1994, in Ekaterinburg (formerly Sverdlovsk), Russia, a conference of chronobiologists endorsed the name "Cornélissen-series" for broadening the mapping of biological circadian systems, first by focus upon the half-week and week and eventually by study of the broader and broader spectrum of biospheric multifrequency rhythms, with as dense and long data series as possible. In the interim, in the context of her project on The BIOsphere and the COSmos, BIOCOS, this task of building a novel transdisciplinary spectrum was pursued, and further periods of decades, centuries, and thousands and millions of years were documented. Much of the evidence was provided with unique success by Germaine Cornélissen, PhD, Professor of Integrative Biology and Physiology at the University of Minnesota.

The Cornélissen-series extends the range of periods, τ, in and around us, to the spectral region of millions of years in the diversity of genera on the ocean floor, to thousands of years in the temperature record of caves, to about 500-year cycles in tree rings and cave temperatures and to the 35-year BEL cycle in climate on earth, economics and political and military affairs as well as in psychophysiology, to cite but a few examples.

Germaine's scientific ancestor in her discovery of (novel cyclic) signatures in the biosphere of heliogeomagnetics was William Gilbert (1544-1603), the court physician to Queen Elizabeth I and King James I of England, who crossed disciplinary barriers by writing a treatise on magnetism (4), considered by Sydney Chapman and Julius Bartels (5), leaders in this field, as the first truly scientific treatise, now updated transdisciplinarily (6). Germaine crossed from physics to biomedicine and added transdisciplinary information, pertinent for everybody. While she excelled in Gilbert's steps, she learned from the blunder of another distinguished scientist, the physicist Jean-Jacques d'Ortous de Mairan (1678-1771), who in 1729 wrote a book on the aurora borealis (7). He discussed in great detail whether magnetism underlies the aurora borealis, notably since Edmond Halley (1656-1742) had speculated that magnetism was involved (8). De Mairan ultimately explicitly ruled out magnetism as underlying the aurora because "magnetic matter is constant". De Mairan, however, made a major contribution remembered primarily in biology (9): he not only noted the sleep movements of a plant, a phenomenon known already to Androsthenes in the fourth century BC; he also recorded the persistence of periodicity in the dark and suggested in a broad extrapolation that these rhythms may be of interest in dealing with patients.

But de Mairan refrained from pursuing the problem further. As a physicist he felt that the problem was beyond the scope of his discipline. He did not seize the opportunity to explore the putative (exogenous and/or endogenous) features underlying the sensitive plant's sleep movements that may only be the two sides of the same coin: one side may be light, the usually dominant circadian and circannual synchronizer when present, the other may be the time structure of terrestrial magnetism, either or both acting, if not continuously then intermittently, concomitantly and/or in alternation. Geomagnetic disturbance may be an influencer and/or an interacting circasemiannual synchronizer during the night at middle latitudes (10), becoming dominant with its half-yearly signature at noon near the pole (11). Along the evolutionary scale, the actions of both light and geomagnetism may well be coded in the genome, albeit the temporal location of the (synchronizing) cycles is determined by the environment (12). Had De Mairan pursued the problem of mechanism for the case of the sensitive plant's "sleep movements", irrespective of whether he may have ruled magnetism out as a mechanism associated with sleep movements or ruled it in, he would have found at least that magnetic disturbance, as he put it, is not constant, and hence not incompatible with the aurora.

The erstwhile physicist Germaine Cornélissen, to whom this paper is dedicated near her 60th birthday (November 22, 2009), did not adhere to any barriers after her training, which started with masters in physics and education in 1971 and a PhD in physics in 1976. Her thesis (for which she was supported by a fellowship) "Signal Analysis and its Application to the Problem of Frequency Stability Definition", at the Laboratory of Frequency Standards, was directed by the late Prof. Jean De Prins, University of Brussels (who could enjoy many of Germaine's presentations at international meetings to which she invited him). A secondary project, "A proposal for a procedure for the analysis of rapid eye movements", was carried out under the direction of Dr. Olga Petre-Quadens, Neurophysiology Laboratory, University of Antwerp, Belgium; again the advisor could enjoy Germaine's invitations and presentations at international meetings. From 1976 on, Germaine went through the ranks at the University of Minnesota as a Visiting Research Fellow, Research Fellow, Assistant Professor, Senior Research Associate in the Departments of Laboratory Medicine and Pathology and of Pediatrics (1994-2008) and Director of Biometry of the Chronobiology Laboratories.

Germaine is currently the de facto director of the Halberg Chronobiology Center and is Professor of Integrative Biology and Physiology at the University of Minnesota. She coordinates the International Project on The Biosphere and the Cosmos (BIOCOS) (formerly the International Womb-to-Tomb Chronome Initiative Group), and is a member of the Phoenix Group (http://www.phoenix.tc-ieee.org/), comprised of members of the Twin Cities chapter of the Institute of Electrical and Electronics Engineers (IEEE), the Société Francophone de Chronobiologie, the International Society for Chronobiology, the American Association for the Advancement of Science, the American Physical Society, the Biometric Society, the American Statistical Association, the New York Academy of Science, the Academy of Integrative Anthropology, the American Physiological Society, and the Book Committee of the National Chapters of Phi Beta Kappa. She was secretary of the North American branch of the International Society for Research on Civilization Diseases and the Environment (SIRMCE), and is a member of the Scientific Council of SIRMCE.

Among her many honors, she is a recipient of the Hoechst Foundation Chronobiologia Award, a member of the Sigma Xi Society, an honorary member of the Cardiff Scientific Society, and was a foreign member of the Problem Commission on Chronobiology and Chronomedicine of the Russian Academy of Medical Sciences. She has been profiled in "The Achievements of Chronobiology and Chronomedicine" by the late N.I. Aslanyan and S.Kh. Madoyan, and was just elected to membership in the Leibniz Society for the Sciences of Berlin, one of the oldest scientific academies, functioning without interruption since its founding by Gottfried Wilhelm Leibniz in 1700.

Germaine has consistently followed the crossing of disciplinary barriers between physics and health care, from which De Mairan had refrained. She had other predecessors: The give-and-take between biology and physics continued when the erstwhile pharmacist and amateur astronomer and botanist Samuel Heinrich Schwabe in 1844 (3) reported on the circadecadal sunspot cycle explicitly as a periodicity. Schwabe's data by 1838 (2) sufficed to validate periodicity by cosinor with the rejection of the zero-amplitude assumption as shown by Germaine. Furthermore, by 1776 Christian Horrebow (1718-1776) had accumulated a sufficient number of observations of sunspots (1) for Germaine to further document a circadecadal cycle. The epochs of maximum and minimum had been known since Galileo Galilei, Christopher Scheinert, Johannes Fabricius and Thomas Harriot discovered the sunspots almost simultaneously (1610-1611).

The opinion leaders in astronomy of Schwabe's and earlier times (and perhaps in physics and biology more generally today) had concluded that the study of cycles in sunspots was "not profitable". Likewise, the opinion leaders of a contemporary homeostatic physiology share the opinion of their predecessors in astronomy. The study of cycles in biology quite generally, as compared to the reductionist fashions of the 1990s, continuing into the current millennium, does not appear to be "profitable", potential monetary profit being the historically recurrent yardstick misapplied to gauge the quality of research. In 1997, the physicists Douglas Hoyt and Kenneth Schatten, in their book "The Role of the Sun in Climate Change" (13), while thoroughly discussing A.V. Clough's research, felt that Clough overemphasized the search for cycles. Moreover, they refer to "cyclomania" while using a citation from Sir Norman Lockyer: "Surely in Meteorology, as in Astronomy, *the thing to hunt down is a cycle* [emphasis ours], and if that is not to be found in the temperate zone, then go to the frigid zones or to the torrid zone to look for it, and if found, then above all things, and in whatever manner, lay hold of, study it, record it and see what it means" (14).

Germaine's scholarship in turn uses the foregoing Norman Lockyer citation without any double entendre by proximity to cyclomania. She follows Sir Norman's admonition into the Arctic with Kuniaki Otsuka's ECGs (15) and Andi Weydahl's salivary melatonin (16), and into the Antarctic with data from Mark Engebretson's magnetometer (17) and with blood pressures from Yoshihiko Watanabe (18). With Miroslav Mikulecky, she analyzed natality data in the tropical, if not "torrid", Philippines (19). Germaine has thus explored Sir Norman's frigid and torrid zones, and many other areas in between these sites. But one of her most important challenges remains, in all zones on earth and beyond, the exploitation of vascular variability disorders for a universal preventive health care delivery based on cyber-implemented self-help in collecting time series for the multiple purposes the time series may serve -- stroke and other hard event prevention for individuals first and foremost.

Dividends of her many analyses of data from all over the world relate both to medical and transdisciplinary research. Medically, by her analyses of data, she compares the relative merits of harbingers of risk elevation. In addition, she seeks an understanding of the effects of the sun in dealing with aggression and other diseases of society. The effects of the sun, that could not be gauged by Zürich sunspot numbers by Brückner, are now shown by Germaine to be expressed in a transtridecadal cycle in the aurora (20), economics (21) and most importantly in the solar wind, in plasma speed, proton temperature, sigma, Bz (22) and terrestrial weather, notably temperature, as the newest member of the Cornélissen-series dubbed the BEL (22-26; cf. 27).

Just as Mendel was forgotten for a time as founder of genetics, Brückner, with a notable exception, has been mostly forgotten, and when he is remembered his name may be written incorrectly, i.e., "Bruckner" (without the umlaut) or "Brikner". When we find apparently new cycles, we must take care not to overlook forgotten pioneers. Germaine's scholarship did not forget Gilbert, Horrebow, Schwabe or Brückner. Most important, when we honor Germaine and Jiri

Dusek as we did Jarmila Siegelova and Bohumil Fiser, we must remember that Brno has produced more than the father of genetics and a well-known meteorologist. In 1882, a year of high solar activity, as documented by sunspots, the notes of Mendel (who in his last years also occupied himself with observations of sunspots; 28, 29) associated difficulties in telephonic communications and the aurora borealis in different geographic locations with solar activity, notes that identify him as one of the earliest space scientists.

Footnotes

1. The joint published titles rest on analyses carried out or checked by Germaine and cover a very wide range, whether we consider the length of cycles or the scope of the analyses and involve a very long list of cooperating scientists from many disciplines and geographic locations. Thanks are due to all of them, without whom the results could not have been obtained. Particular gratitude is due to Prof. Jarmila Siegelova's team in Brno, Czech Republic, notably to Prof. Jiri Dusek, whom we also honor today.

2. The authors are indebted to Ilya G. Usoskin (University of Oulu, Finland) for prompting the analysis of Christian Horrebow's original observations (1). Germaine validated his data as sufficient to establish the cyclicity of sunspots in inferential statistical terms by the 18th century. Germaine thereafter further detected in Samuel Heinrich Schwabe's records the minimal number of cycles required to establish a sunspot periodicity, thereby indicating that by 1838 (2) there was enough evidence to refer to a periodicity (2), which Schwabe did only in 1844 (3).

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MUDr. Jiří DUŠEK, CSc: A fruitful cooperation

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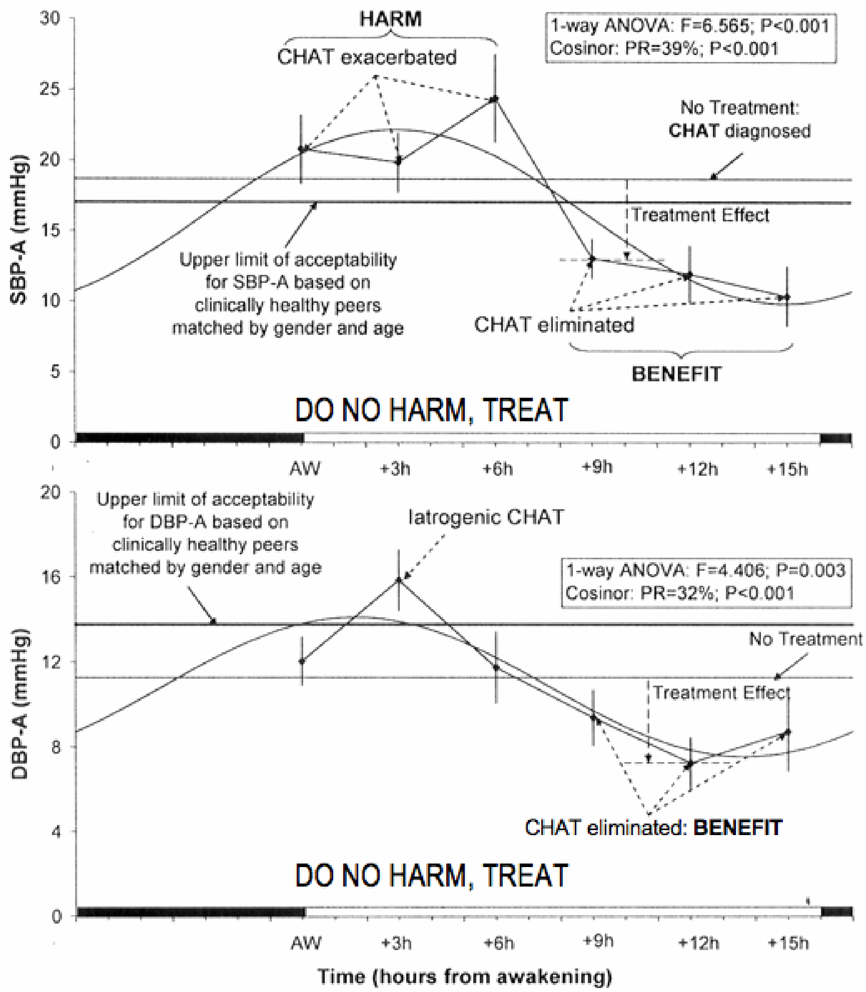
Earlier in these annual conference reports, we honored Profs. Jarmila Siegelova and Bohumil Fiser, whose investigations on the chronomics of blood pressure have now placed Brno on the map of international transdisciplinary science. The honor roll would not be complete without dedicating an issue to MUDr. Jiří Dušek,CSc, the third member of Europe's leading chronomics team, born on 19 December 1946 in Vítkov, Czech Republic.

After finishing secondary school in 1963, Jiří attended the Faculty of Medicine at Hradec Kralové and graduated in 1969 from Charles University Prague. In 1973 he took the postgraduate examination in Internal Medicine (of a first degree); in 1978 he passed the postgraduate examination for General Medicine (of a first degree); in 1980 he took the postgraduate examination for Internal Medicine (of a second degree); and in 1990 he graduated and received his Ph.D degree. After finishing his medical studies, he worked in the Department of Medicine at the Military Hospital in Brno, Czech Republic. Later he became head of the outpatient medical department in Brno. Since 2002 he has been a department head at the National Centre of Nursing and Other Health Professions (part of the Ministry of Health) in Brno. His scientific interests are occlusion plethysmography and essential hypertension.

Twenty years ago he started to cooperate with Prof. MUDr. Jarmila Siegelova, DrSc. and Prof. MUDr. Bohumil Fišer, CSc, and, the first three authors are happy to add, with the University of Minnesota in Minneapolis. Jiri has published many articles in Czech and foreign journals. His publications include the appended record of cooperation with the University of Minnesota. The broad range of topics apparent from the titles of his papers and their content attest better to his accomplishments than this laudatio.

In summary, Jiří, with Profs. Siegelova and Fišer, has been a pillar of a cooperation that began in 1990 between the Universities of Brno and of Minnesota, and thus between the birthplaces of both genetics and chronobiology and chronomics. It was a problem to assess the value of Gregor Johann Mendel's studies in his time; by the same token, it will be up to others to weigh the importance of a chronobiologic interpretation of blood pressure monitoring as the start of a universal educated self-help in health care. As a minimum, patients with a reliably diagnosed high blood pressure can ascertain that they do not pay a high price for lowering their blood pressure. As seen in Figure 1, discussed in last year's conference volume by Prof. Yoshihiko Watanabe, the antihypertensive treatment at different circadian times can have opposite effects in the same patient investigated (Su): desired ones in the afternoon and undesired ones in the morning. It would be nice if Dušek, Fiser and Siegelova could get the credit for avoiding such a circumstance in Brno. We are at the dawn of a health care switching to focus on variability as a fact, replacing the fiction of time-unqualified normal ranges and equally imaginary baselines. If this is accomplished, Jiří Dušek, as well as Bohumil and certainly the dynamo Jarmilka, following in Pavel Prikryl's steps and with Pavel Homolka's contribution, will get the deserved credit.

Treatment Beneficial at Certain Other Times (9, 12 or 15 hours after awakening) can EXACERBATE a Pre-existing CHAT in Systolic Blood Pressure (SBP) and INDUCE CHAT in Diastolic Blood Pressure (DBP) when Given at the Wrong Time in Patient Su *



*Su, M, 66y, treated with Losartan (50 mg) and hydrochlorothiazide (12.5 mg). Each point represents 1 week of half-hourly around-the-clock monitoring after ~1 month on a given treatment time.

Legend

Figure 1. Monitoring of blood pressure for treatment validation and optimization is not a luxury when, as shown on top and in the middle of this figure, the same currently popular drug Hyzaar (a combination of 12.5 mg of hydrochlorothiazide and 50 mg of Losartan) can do harm in a patient (Su) in the morning, but is beneficial when taken in the same dose by the same person in the evening some months later. Medication was changed systematically, on a usual routine of living with diurnal activity and nocturnal rest. On each treatment timing in relation to awakening, Su was studied for ~1 month with the blood pressure monitored for the last week, as described in detail by one of us (YW). In the morning the medication raised the circadian amplitude of blood pressure to an extent of exacerbating or inducing a circadian overswing (or CHAT), a risk greater than a high blood pressure, whereas at another time the same dose lowered both the circadian amplitude and MESOR, eliminating all abnormality, and thus offered benefit. The painting at the bottom by Pieter Brueghel, "The Parable of the Blind Leading the Blind", is reproduced by kind permission of the Fototeca della Soprintendenza of the BAS PSAE and of the Polo Museale of the City of Naples, in order to emphasize that CHAT is silent to both the caregiver acting on the basis of a conventionally interpreted (chronobiologically uninterpreted) 24-hour blood pressure profile as well as to the majority of providers treating on the basis of single measurements in their office. © Halberg.

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Steps toward Mikulecky's semimillennials in the emergence of outstanding individuals

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On his 82nd birthday, June 22, 2009, this paper is dedicated to Prof. Miroslav MIKULECKY, the first professor of medicine and department head to write a textbook on inferential statistical methodology and to engage in a documentation of the role of the cosmos in clinical practice. About 500-year cycles in the emergence of outstanding physicians, historians and poets are to his credit, and we dub these cycles Mikulecky's circasemimillennians.

Perspective. For as long as the human lifespan cannot be substantially prolonged, cycles of about 500 years are a challenge for scholars of population dynamics; their underlying physiological mechanisms must be studied with serial independence as to individuals over several generations. This goal requires the monitoring of successive human generations from womb to tomb. This aim may be reached more readily if human lifelong monitoring can be achieved by the development of preferably affordable, unobtrusive automatic recorders of blood pressure and heart rate for use by everybody interested. Good enough reasons must suffice for a prompt general implementation in each generation in its own right. Such aims are to assess infradian rhythm abnormalities that may complement the already-known circadian ones. Infradians include transtridecadals when each cycle covers nearly half a lifetime. The discovery of circadian **v**ascular **v**ariability **d**isorders, VVDs, and of their combination transforming them into **v**ascular **v**ariability **s**yndromes, VVSs, revealed that VVSs constitute a high increase in risk of hard events (from 5% to 100% in one study). If recognized, these risks, much greater than those of hypertension, can be reversed. This is one reason for monitoring by the individual. The further finding of 35-year cycles in climate, economics and international battles as well as in one's heart rate (HR) constitute reasons revolving around clarifying the roots of societal (as well as the individual's) disease, such as crime and terrorism.

Background. Vindicating Brückner, Egeson and the Lockyers (BEL) (1-4), an about 35-year periodicity was validated in inferential statistical terms (5-7). This cycle persists in climate to this day in environmental temperature (8) as an intermittently statistically significant phenomenon in some of Brückner's original data; we extend by far the scope of this spectral component in various human affairs; and its submittal for publication by invitation (8) happened to coincide with other reports on the same BEL cycle (9, 10) and its detection in the total solar flare index available from 1966 to 2007 (42 years) (this issue). With other papers in these proceedings (11, 12), we extend to three persons the documentation of the physiological BEL as an approach to monitoring the sun by human blood pressure and heart rate series, actually collected for a personalized health care. The demonstration of the same transtridecadal cycle on two elderly men (11, 12) complements the finding of the same BEL in a man aging from 20 to 60 years (7).

Papers on a 35-year climate cycle in heliogeophysics, psychophysiology, military politics, and economics (8) and on global tropospheric temperature variations (9) both deal separately directly with cycles in terrestrial climate and indirectly with the dynamics of the cosmos. A meta-analysis of the latter paper (9; cf. 10) reveals a BEL, or Brückner-Egeson-Lockyer component (1-4; cf. 5-8), further supporting the essence of the original papers on the 35-year climate cycle (1-4), showing important influences of non-photics in various human affairs. Pertinent is that global tropospheric temperature also reveals the BEL cycle. Still more convincing is a further recent paper, in the April 17, 2009 issue of Science: Shanahan et al. (10) show, without comment or citation, a 33-year BEL peak. It stands out and is marked by the number 33 in Figure 4A of their paper on the history of climate in Africa, computed with modern methods, reproduced with permission in Figure 1 (8).

The paper in Science on droughts in West Africa reflected in Lake Bosumtwi in Ghana complements Eduard Brückner's studies (1) prompted by changing water levels of Russian lakes in the 19th century. Shanahan et al. (10) confirm Brückner's alternating wet and dry periods (1) and indirectly render timely the demonstration of an about 35-year period in the length of the circadecadal Horrebow-Schwabe cycle in sunspot numbers reported by the son (3) of Sir Norman Lockyer (4), the founder of the journal Nature and discoverer of helium. Brückner and the Lockyers are not cited in pertinent contemporary papers (10, 13-15). Standards for citation are a matter of discussion (16, 17). Two reasons for omission may be the lack of an inferential statistical validation and lack of a putative underlying mechanism. Hence, two of us (GC and DH), with different methods, happened to look at 42 years (1966-2007) of the solar flare index (the total from both solar hemispheres), only to encounter again a prominent transtridecadal component, with nearly identical point estimates but a relatively broad 95% confidence interval, shown elsewhere (18).

A transtridecadal periodicity is just one component among other cycles in climate that can also be gauged by several biospheric variables, including an about 500-year periodicity (19). Section B of Figure 2 in the recent paper in Science (10) also shows a Morlet wavelet with an about 500-year periodicity that was reported earlier to characterize 3,200 years of stalagmite coloring, 2,790 years of tree rings width and 2,556 years of international battles (19), Figure 2A (see bottom section below dashed horizontal line). We do not have long enough series on solar flares to examine whether the same periodicity prevails in them, as in Figures 2A-D, which also focus upon the emergence of distinguished physicians, historians and poets on different continents, including times prior to the Silk Road (19) when there was little intercontinental communication. The latter figures confirm the scholarship of Prof. Miroslav Mikulecky and Dr. Emil Pales (20, 21), who originally documented the circasemimillennial cycles in the appearance of outstanding individuals in seemingly unrelated cultures on different continents. Circaseptennian cycles had been reported for outstanding quantum physicists, among others (22-25; cf. 26, 27).

The varied interwoven facts, along windows of about 35 and about 500 years, among many other resonant solar-terrestrial biospheric frequency bands, await scrutiny of the underlying non-photic as well as photic mechanisms, notwithstanding the claim "... that over the past 20 years all the trends in the Sun that could have had an influence on the Earth's climate have been in the opposite direction to that required to explain the observed rise in global mean temperatures" (28). We better investigate the dynamics of climate with Gauss' least-squares, if not with the methods of Joseph Fourier, the discoverer of the fact that gases in the atmosphere might increase the surface temperature of the earth, what would later be called the greenhouse effect. Multifactorial situations require multifactorial analyses. In this context, a prominent BEL cycle, which we find very prominently in solar flares during the last 42 years, must not be ignored. These same solar flares relate to human physiology (29-31) and pathology (32), including sudden human cardiac death characterized by a cis-half-year of about 0.42 year and at a far-transyear of about 1.72 years, deserving scrutiny for further biospheric counterparts, all features of the Cornélissen-series (33).

Acknowledgement. The authors are indebted to Dr. Taeil Bai, Senior Research Scientist, Center for Space Science and Astrophysics, Wilcox Solar Observatory, Stanford University, Stanford, California, USA, for a list of important flares since 1976, of interest in further analyses by superposed epochs. Data analyzed herein (see Figure 2) are the total solar flare index available daily over 42 years.

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Legends

Figure 1. (A) Multi-taper method (MTM) spectral analysis of the Bosumtwi X-ray fluoroscopy data (10). Significant power is apparent on inter-annual (3.6- to 4.6-year), decadal (7.1-, 7.8-, 10.6-, and 13.8-year), multidecadal (33- to 42-year), and century (90-, 175-, 225-. and 302-

year) time scales. For clarity, only the portion of the power spectra >3.57 years (F = 0.28) is shown. The oblique lines denote the 99 to 95% confidence interval. MTM analyses were performed with the program k-spectra. Parameters p = 3, K = 5, and a null hypothesis of red noise were used in the analysis. Labeled are periods (in years) for peaks that are significant at 95%. Note the prominent spectral peak protruding above the 1% level of statistical significance with a period of 33 years (arrow) corresponding to a BEL.

(B) Cross-spectral coherence computed for Lake Bosumtwi (600-year detrended first principal component [PC1] of the full suite of elemental data [aluminum, Al; silicon, Si; potassium, K; titanium, Ti; manganese, Mn; and iron, Fe]) and the Atlantic multidecadal oscillation reconstruction. The horizontal line indicates the 90% confidence interval. The records are in phase and highly coherent at a period of 30 to 50 years (indicated by gray shading). Reproduced from (10) with kind permission.

Figure 2A. Mikulecky's circasemimillennial period in the emergence of outstanding individuals (above dashed lines) and in international battles and in two series likely related to climatic changes, namely tree ring widths and stalagmite coloring. © Halberg.

Figure 2B. Acrophase chart estimated at average period for Mikulecky's circasemimillennials. © Halberg.

Figure 2C. Mikulecky's circasemimillennial synchronized cycles in the emergence in three different geographical regions of famous physicians. © Halberg.

Figure 2D. Mikulecky's circasemimillennial synchronized cycles in the emergence in three different geographical regions of famous historians and poets. © Halberg.

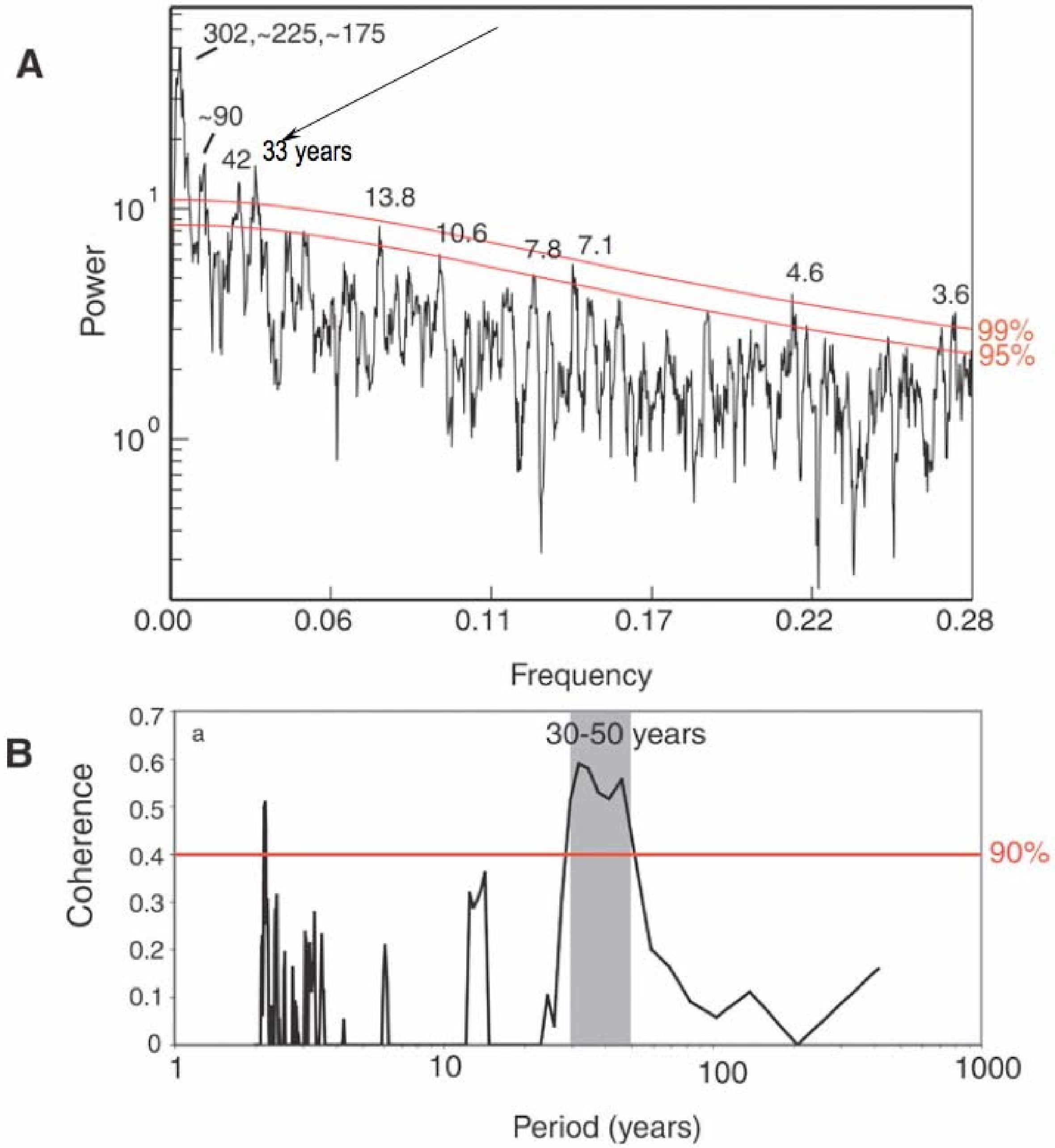

A
302,~225,~175
~90
42
33 years
13.8
10.6
7.8
7.1
4.6
3.6
99%
95%
Power
Frequency
0.00
0.06
0.11
0.17
0.22
0.28
B
a
30-50 years
90%
Coherence
Period (years)
1
10
100
1000

Figure 1

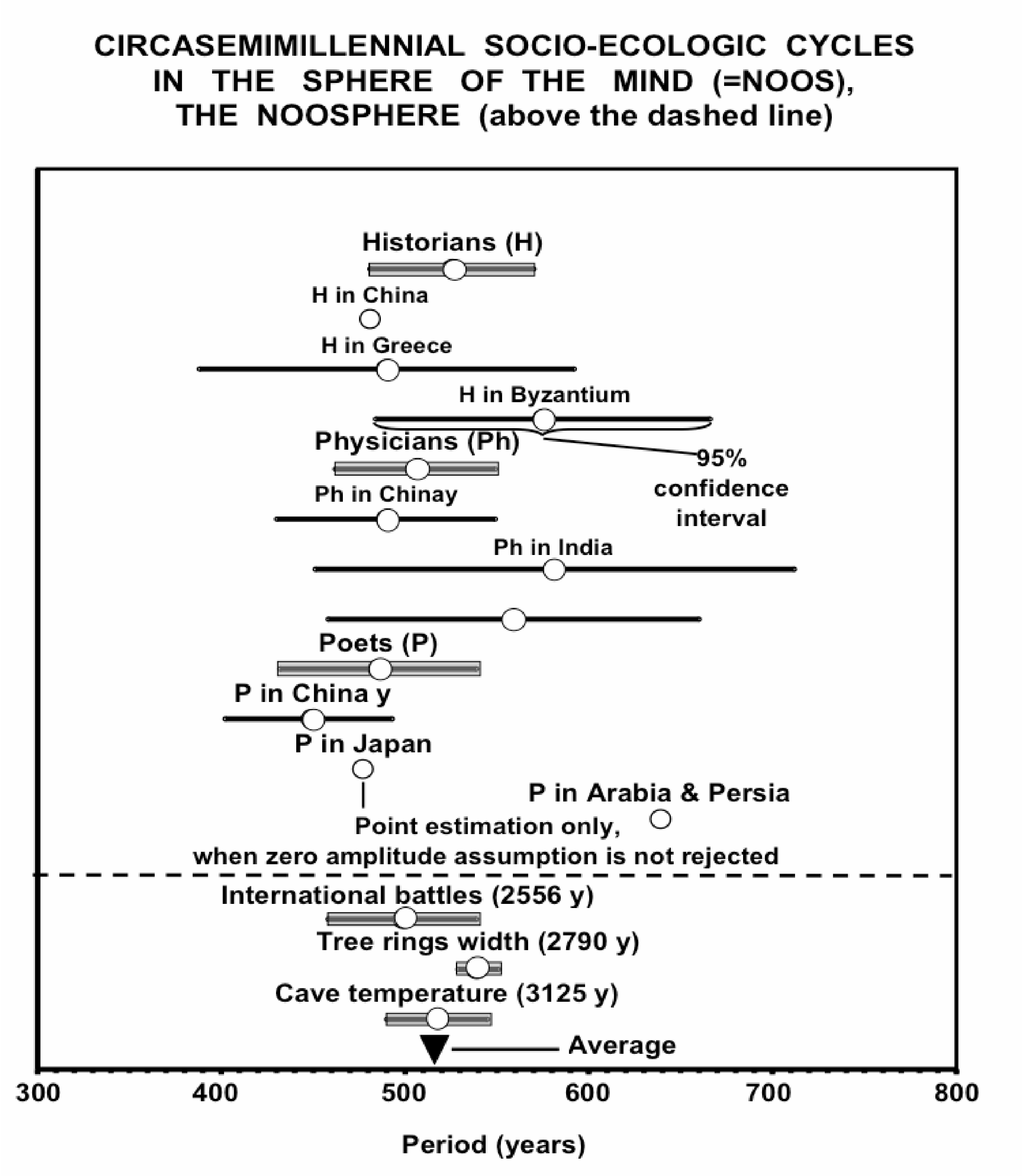
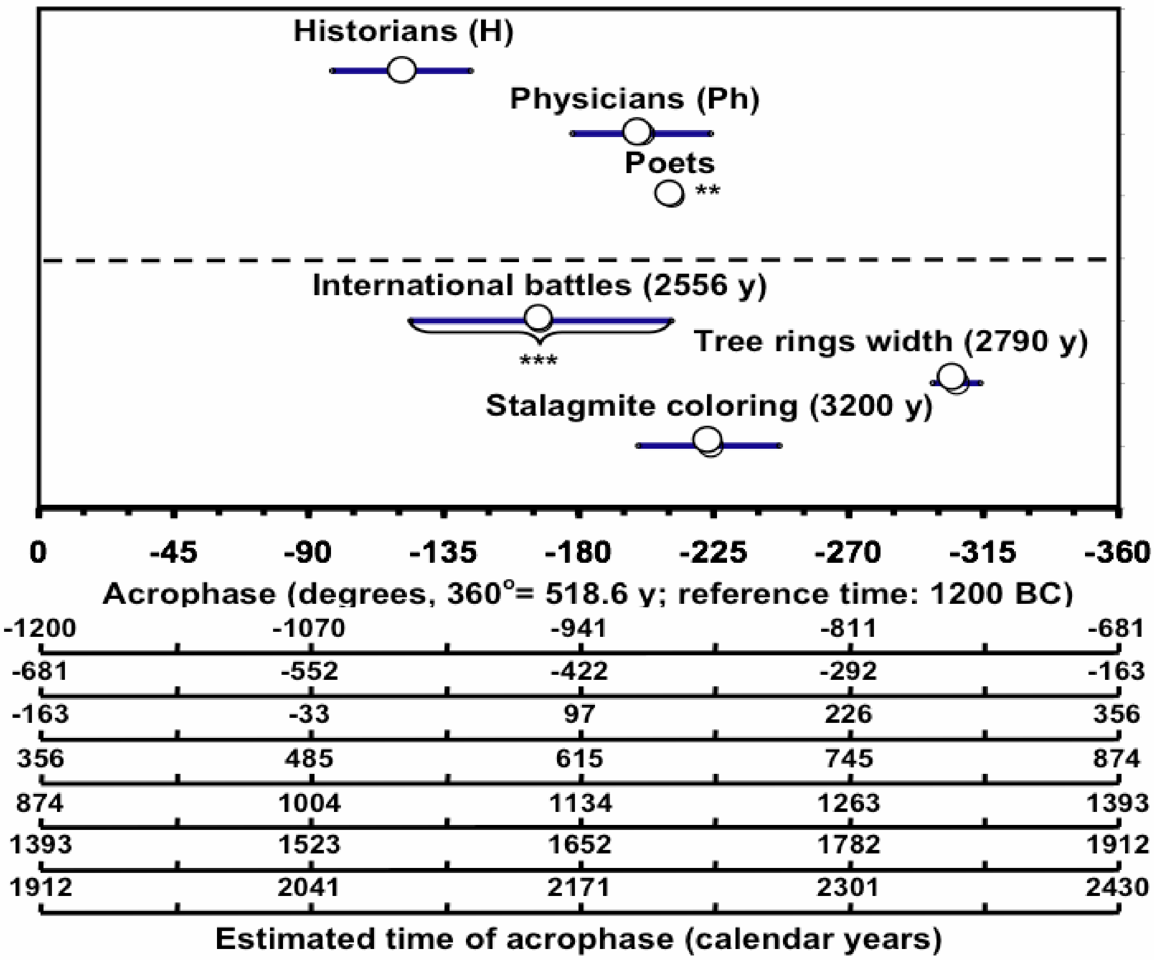

CIRCASEMIMILLENNIAL SOCIO-ECOLOGIC CYCLES
IN THE SPHERE OF THE MIND (=NOOS),
THE NOOSPHERE (above the dashed line)
Historians (H)
H in China
H in Greece
H in Byzantium
Physicians (Ph)
95%
confidence
interval
Ph in Chinay
Ph in India
Poets (P)
P in China y
P in Japan
P in Arabia & Persia
Point estimation only,
when zero amplitude assumption is not rejected
International battles (2556 y)
Tree rings width (2790 y)
Cave temperature (3125 y)
Average
300
400
500
600
700
800
Period (years)

Figure 2A

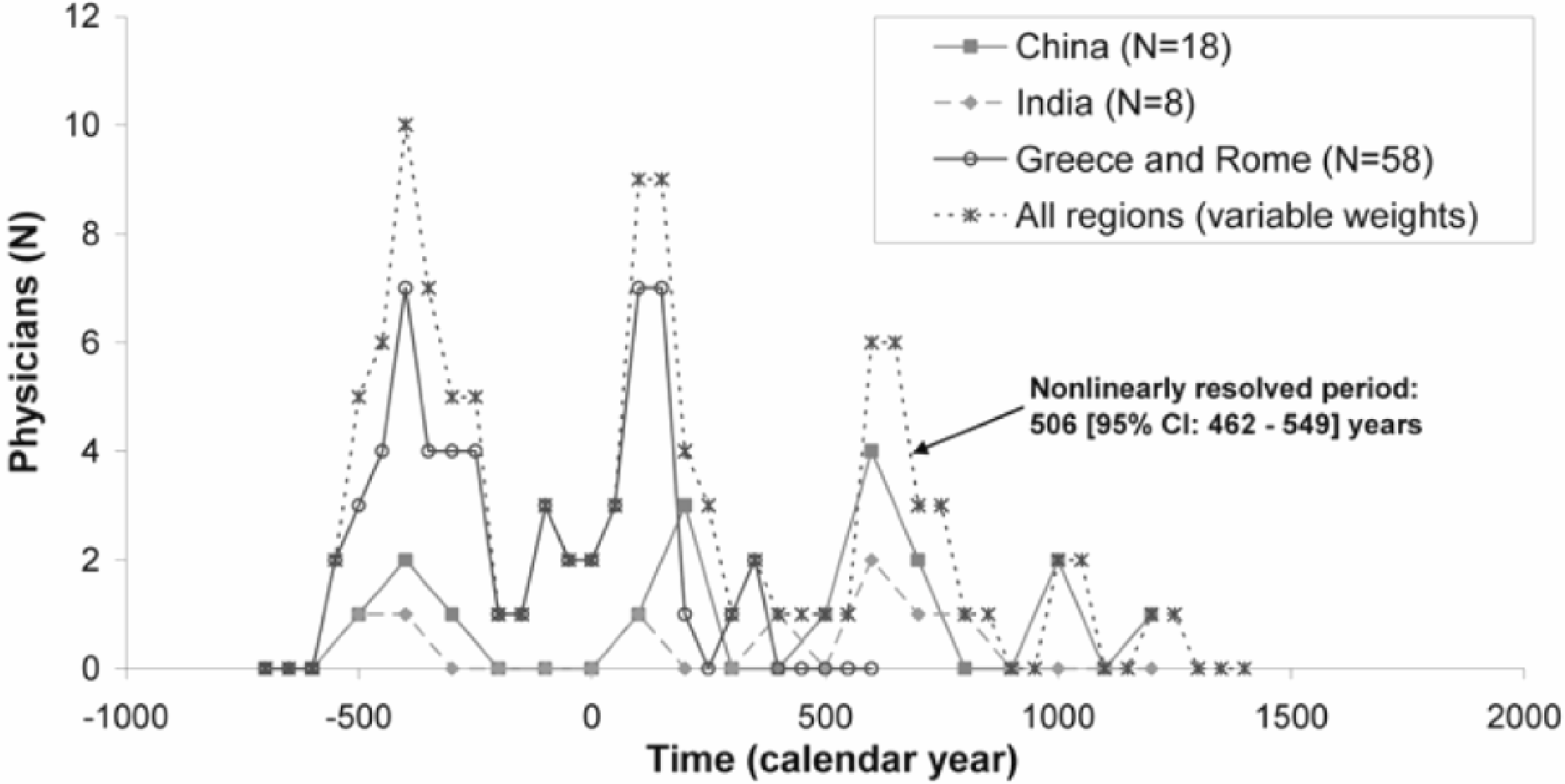
CIRCASEMIMILLENNIAL CYCLES
IN THE EMERGENCE OF PROMINENT PERSONALITIES
AND IN THEIR ENVIRONMENT
REVEALING LIMITATIONS OF FOCUS UPON A FIXED CYCLE*



* Estimates ignore other documented components of variation characterizing the same time series and show the fallacies of focusing upon a cycle with a single frequency in a multifrequency-cyclic world.
** Point estimation only, when zero-amplitude assumption is not rejected.
*** 95% confidence interval.

Figure 2B

CIRCASEMIMILLENNIALLY CYCLING EMERGENCE OF PROMINENT PHYSICIANS*

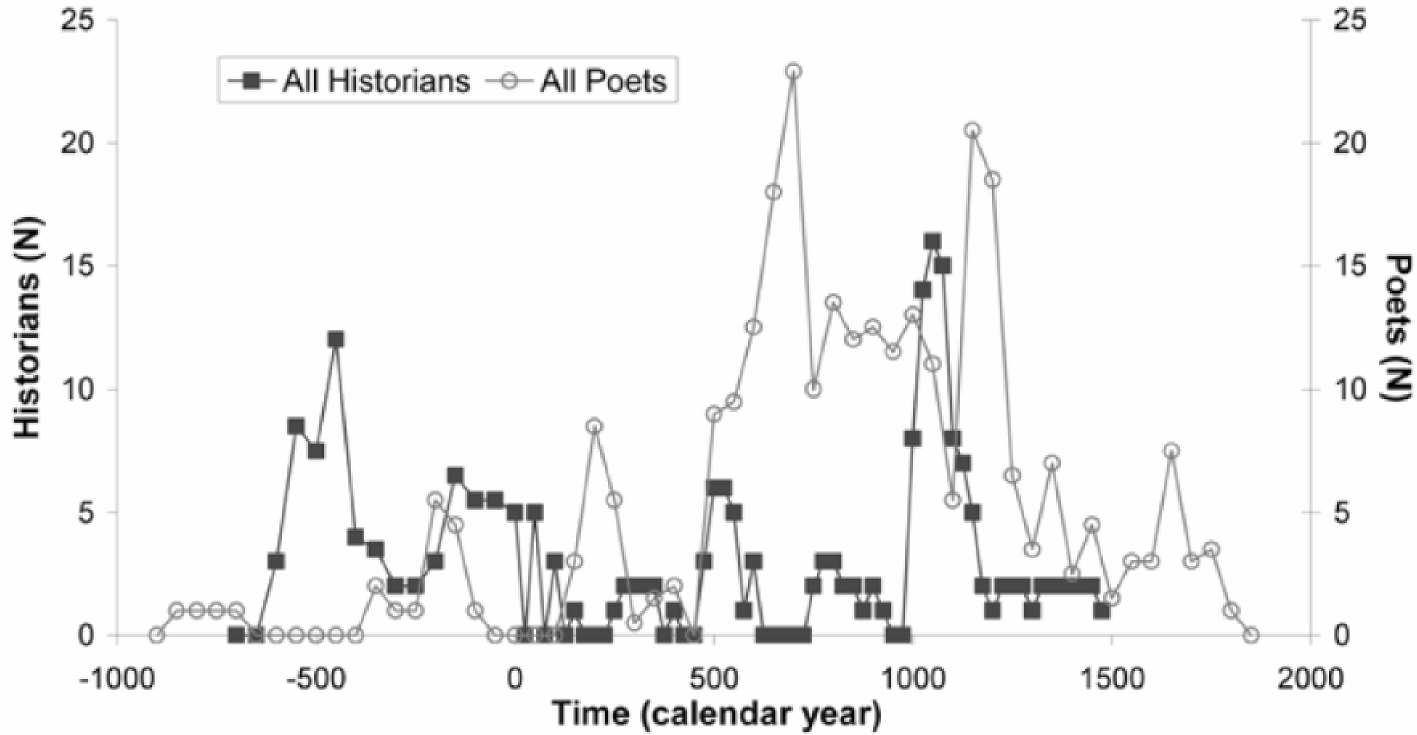


*In different, seemingly separate settings between 700 BC and 1400 AD, extracted from A.L. Kroeber: Configurations of culture growth. U. of California Press, Berkeley and Los Angeles, 1963, 882 pp. Results of Emil Pales and Miroslav Mikulecky, in keeping with similar circasemimillennial cycles in series of tree rings and international battles covering 2198 and 2558 years, respectively.

Pales E, Mikulecky M. Periodic emergence of great physicians in the history of ancient Greece, India and China. Abstract, 23rd Seminar, Man and his terrestrial and cosmic environment, Upice, Czech Republic, May 21-23, 2002.

Figure 2C

CIRCASEMIMILLENNIALLY CYCLING EMERGENCE OF PROMINENT HISTORIANS AND POETS*



*In different, seemingly separate settings between 700 BC and 1400 AD, extracted from A.L. Kroeber: Configurations of culture growth. U. of California Press, Berkeley and Los Angeles, 1963, 882 pp. Results of Emil Pales and Miroslav Mikulecky, in keeping with similar circasemimillennial cycles in series of tree rings and international battles covering 2198 and 2558 years, respectively.

Figure 2D

C. MENDEL's LEGACY

Omnis cyclus e cosmo: Mendel's chronoastrobiological legacy for transdisciplinary science in personalized health care

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Dedication and Preamble

This presentation, a follow-up on an earlier paper by the senior author (1), is dedicated with infinite gratitude to the memory of his father, Dr. Julius Halberg, who had guided his poetically inclined son to science, medical school, and life in the USA. In the USA, his path led to research into cyclicities in biological and other temporal variability. Chronomes -- time structures -- complement genetic and cosmo-spatial diversity near and far, a first major link to genomics and then to Johann Gregor Mendel, recognized earlier as a geneticist, meteorologist and epidemiologist, all in one person, who pursued these superficially diverse activities during a productive if relatively short lifetime. From the relation of the fields of spatial and temporal variability, the senior author's lifetime concerns, common reciprocal structures emerged in and around us, in whatever was measured. A self-sustaining multifrequency rhythmic pattern of variability was mapped. It organized chaos and underwent trends, while intermodulating, self-reproducing and evolving. Rhythms turned out to be much more than the signature of the cycles in our cosmos, which they are. They also constitute the mechanism of living matter and eventually led to the spirituality of life. As we learn more and more about our chronomes, Figure 1, we recognize them as a product of our cosmoi: chronomes are interwoven but resolvable as somewhat wobbly recurrent patterns. Thus, we gained a perspective of an open system from the perspectives of a chronomedicine, chronoecology and, eventually, a yet broader chronoastrobiology, all transdisciplinarily dependent upon chronomics, the aligned study of biospheric and cosmic time structures, that, while of interest in their own right, complement genomics.

Whatever one measures or renders measurable, repeatedly, densely and/or along longer and longer time scales characterizing individuals, populations and eventually species, genera and their habitats, gains from a resolution of cycles, defined as an inferentially statistically documented recurrent phenomenon in a spectrum consisting of photic and other constituents. For each component cycle, 1. the no-cycle (zero-amplitude) assumption is to be rejected and 2. point-and-interval estimates of parameters are to be provided. Photic variations, notably about (~) 24-hour cycles, are usually environmentally well synchronized, more than the non-stationary, aeolian non-photics. Based on the foregoing criteria, non-photics and photics both qualify as cycles, until they become rhythms, once they are replicated over many cycles and documented as to intermodulations and their mechanisms. We are dealing with exophased endocycling: many built-in periods in the biosphere can be exogenously synchronized and phase-shifted (whereby we account for the "exophasing") while they persist in the absence of the external cycles, being partly endogenous, the point we are trying to make by "endocycling".

Endeavors in science dealing more broadly with civilization and in particular with a hard-to-define culture are best referred to their temporal as well as to spatial coordinates, and are thus rendered more meaningful in the context of chronomes in us and around us, as Mendel put it, in the context of "terrestrial and cosmic factors". The systematic mapping of the spatial environment has been done by physicists for centuries on earth and for decades via satellites in space: it awaits complementary systematic temporal mapping, in physics and in the biosphere. Mendel, the meteorologist at heart, concomitantly mapped physical conditions and diseases, first with the head of a hospital in Brno, and continued recording them after the latter's death, implementing meteorology in relation to the epidemiology of disease. Mendel the meteorologist practicing chronomics was the topic of a lecture delivered at a symposium held at the Mendelianum in Brno, Czech Republic, here summarized with an update, and was also the topic of a keynote opening a symposium given in Nagoya, Japan, published in 1991, with 70 figures (2). Many more figures mapped in the interim are mostly available at least as bibliographic references, on our website (http://www.msi.umn.edu/-halberg/). The present paper continues to summarize chronomics in the framework of a long-standing cooperation between Brnoese and Minnesotan co-investigators.

Abstract

This paper reviews the development of chronobiology, the science (logos) of life (bios) in time (chronos), and of chronomics, against the background of Mendel's contributions far beyond genetics. In keeping with Mendel the meteorologist, we document for rhythms that light and food are not the only external switches. The "master switch", light, can be overridden more often and more critically than we visualize by feeding (3) or by a magnetic storm (4). Very important

hypothalamic "oscillators" (5) are not the only internal mechanism of rhythms. Time structures, chronomes, reside in every biological unit, pro- or eukaryote, Figure 2 (6; cf. 5, 7). Chronomes in us have a strong genetic component which, in turn, entered the genome in response to environmental chronomes, explored meteorologically by Mendel. The more remote environmental origin of rhythms and their less remote genetic aspect both qualify biological chronomes as the legacy of Mendel the meteorologist as well as the geneticist.

Our continued resonance with the environment renders an exophased endocycling even more interesting. The need for coordinated physical and biological monitoring, the topic of a project on The BIOsphere and the COSmos, briefly BIOCOS, to complement genomics, can also be viewed as the legacy of Mendel the meteorologist/cartographer. Some of Mendel's meteorological data were meta-chrono-analyzed. Mendel himself published more often on meteorology than on what became genetics. His legacies of paraphernalia are those of a meteorologist. Despite failing his examination for certification as a regular teacher in 1850 -- his lowest marks were in biology and geology (!) -- and although he reportedly never passed his teacher's license examination, Mendel started the science that distinguished the rules of dominant vs. recessive behavior and eventually led to the cloning of organisms and the debate about stem cells, again raising the question "What is life?" (1, 8, 9). Mendel is the de facto teacher par excellence of this generation of genomics, proteomics and nanochemistry by virtue of what became not only genetics but also chronomics in Brno. Our advocacy of education in instrumented self-help for chronobiologic literacy includes genetics and ecology, and qualifies as Mendelian. Chronobiologic literacy in everyday health care serves for the quantification of normalcy. By resolving chronomes in the normal range, we act positively rather than defining health negatively and only qualitatively (as the absence of disease, i.e., of deviations outside that range) summarized as % morbidity and % mortality only for a population, not for the individual.

From these several viewpoints that have as a common denominator focus upon the usual, we view Johann Gregor Mendel as a chronobiologist. We view chronobiology in a broad perspective of its now thoroughly documented roots in our genes and via our genome in the cosmoi, as they were when and where life began and as they changed from then to now. Evolution, ecology, genetics and chemistry, the legacies of Darwin, Haeckel, Mendel and Lavoisier respectively, and their transdisciplinary fusion by Brückner, Egeson, Norman Lockyer, W.J.S. Lockyer, Chizhevsky and Vernadsky in the spirit of Dokuchaev, like everything else, occur in time. They are part and parcel of chronobiology and of a much broader temporal perspective from chronomics, an overdue transdisciplinary cartography of the as-yet unknown.

Omnia metire quaecumque licet, et immensa ad mensuram tempestive et ergo significative redige: Measure what is measurable and render measurable, *meaningfully in time,* what as yet is not

A concern for measurement, revealing variability, led to basic and applied lessons in a broad science, chronobiology, which explores our origins in the cosmoi and offers applications in preventive as well as curative aspects of health and environmental care (10). Chronobiologic concerns, basic or applied, require a dynamic perspective of life and the cosmoi. The need for such a concern about the changes around us as well as in us was fully envisioned by Mendel's activities. His signature impacts far beyond the pea patch of the monastery in Brno, where genetics was born. There, Mendel read Darwin and made notes in the latter's book. He eventually added genetics to natural selection and was concerned, in the struggle for survival, about the "dawn of empathy", about going beyond life as a food chain to lay the basis for fields in which genetically coded life could evolve toward spirituality, which as yet may have escaped classification by otherwise meritorious approaches of physicists and biologists alike (11).

Mendel, the chronobiologist, recorded physical cycles in nature, some of them now shown to be anchored in our genes. In his pre-satellite era, changes in solar wind speed escaped him, but he collected original data on wind speed, meta-analyzed by us to emphasize Mendel's concern about environmental effects, rather than merely to quantify another circannual pattern. Unfortunately, this to-us available series of measurements is not long enough to examine the putative presence of a transyear of ~1.3-years length, non-photic and unseen, and its possible beating with a calendar-yearly component. Transyears characterize our physiology from human babies and the elderly in particular. The ~yearly and ~daily patterns in us and around us, and their importance have become obvious (12, 13). Much less conspicuous are about half-weekly (circasemiseptan) and about-weekly (circaseptan) changes, unseen, non-photic, in our environment, well known in human pathology since antiquity and now found to have counterparts in helio- and geomagnetic phenomena, as well as in rainfall, where a physical near-match was reported (14). Heliogeomagnetics also exhibit ~half-yearly (circasemiannual), ~10-yearly (circadecadal or circadecennian), ~21-yearly (circadidecadal or circavigintunennian), and other natural, e.g., transtridecadal (15-17; cf. 18) physical cycles and even broader time structures, chronomes, Figure 1, that have biological counterparts and enlarge the scope of biological time measurement, leading us to the essence and origins of life, the feedsidewards, at various levels of organization, Figure 3.

From dense and long time series and inferential statistical procedures applied thereto, we learn that most if not all of the above mentioned and other bioperiodicities resonate with terrestrial and more remote magnetic and/or other solar or galactic activity, a broad field in its own right explored largely without concern for time structures (19). Solar and, perhaps, more remote astral dynamics (recorded by space-borne vehicles, traceably gauged by velocity, proton density and temperature changes in the solar wind) and some of their consequences, include associations with biota. Modern technology complements the tools available in Mendel's time, to build on his legacy and to examine the relative importance of factors in us vs. those around us in determining our "behavior" in the broadest possible sense, including the spheres of the mind (= noos) -- the noosphere -- and of spirituality, the soul, that some researches based on spirituality, located in the pineal, and others in the gut, insofar as melatonin's circadian rise in the intestine, can precede those in plasma, the hypothalamus and the pineal (20).

It took the last quarter-century to explore molecularly the genetics of the ~daily rhythms. Their built-in nature was one reason for coining the various circa-rhythms, "about" (= circa) referring to a frequency characteristic of the biological system approximating an environmental periodicity, yet deviating from precisely that length. Other important considerations for "circa" are being accepted more slowly. One of them is the fact that we are dealing with uncertainties, i.e., with statistical rather than purely deterministic entities. To determine their variability and, once this is done, to quantify their characteristics, we need inferential statistical procedures for both the testing of a cycle's occurrence and for determining the interval as well as point estimates of its parameters, e.g., as 95% confidence intervals.

Some of the uncertainties encountered reflect the operation of unknown distant as well as of proximal measurable drummers. Cases in point are subtle geophysical associations with myocardial infarctions (21) relating, in their turn, to events from interplanetary space and to Horrebow-Schwabe's ~0.5-year, Hale's ~21-year and Brückner, Egeson and Lockyer's ~35-year cycles (15-18) in solar activity that in turn may be subject to galactic influences. There may also be effects on biota from outside our galaxy, within our cosmos and/or other cosmoi (19). These as yet must be documented.

A hint of possible extra-solar system effects could be provided by any finding in physiology consistently preceding events in solar or interplanetary physics, such as a southward turn of the north-south component, B_z, of the interplanetary magnetic field (IMF). Thereby, the question is raised whether an extra-solar-system factor influences both the IMF and human physiology. Furthermore, an explanation for ~10-year cycles in microbial sectoring, i.e., as probable genetic changes of air bacteria, that are in near-antiphase with the solar activity cycle of similar length, is the possibility that the effect upon the human heart, whether it occurs during a magnetic storm in the laboratory (4) or on the neonatal intensive care unit along the scale of a day or with an ~10-year solar cycle (22) may be an effect of the displacement by geomagnetic storms of the flux of galactic cosmic rays and thus the mutagenic effect of a driver from our own galaxy or from another.

Chronomes and Mendel

By objectively and consistently measuring meteorological as well as biological variation patterns with time and by seeking reproducible patterns in what others may have regarded as random variation, and in particular by interpreting them contrary to the dogma of his era, Gregor Mendel was a scholar not only in chronobiology but also in chronomics: he recorded samples as well as publishing terrestrial weather reports. Meteorological observations from 1856 on were incorporated by 1862 into publications of the observations of all meteorological stations in Moravia. From 1878 to 1883, Mendel ran a weather station in Brno. In the spirit of Mendel, we are led beyond the molecular genetics of a time-invariant genome to its expression in chronomes. We here draw and test generalizing inferences concerning structures in time. In the chronomes of organisms, the major element, the circa-rhythms, are integrated from within on the one hand, while they are also adapted to external chronomes, including cyclic among other (environmental) patterns, with the perspective broadening from an impenetrable normal range, over clocks and calendars to chronomes, Figure 4.

In its turn, the spectrum of rhythms renders chaotic-appearing changes predictable and diagnostically useful (23, 24) while on the basic side it may point to sites of life's origins by the behavior of rhythms in our ontogeny and phylogeny (25). An example is the prominent biological week found early in human life (26, 27) and again in the human elderly (28). These patterns during aging may "recapitulate" phylogeny and perhaps also those temporal features of cosmogeny, including some prevailing in times long past, when life started on earth and/or beyond in our cosmos and/or in other cosmoi. Data on hundreds of human babies from different geographical areas are pertinent as to ontogeny, as is evidence on dozens of unicells and more limited data obtained early in the ontogeny of the crayfish (29), rats (30) and piglet (31).

The value of chronomes of blood pressure and heart rate variability, apart from their basic interest, relates to self-help for health care, based on a chronobiologic literacy. Too much blood pressure and too little heart rate variability serve in diagnosing an elevation of disease risk, prior to overt illness. The task of detecting Vascular Variability Disorders (VVDs) and their combinations in disease risk syndromes prompts the need for every-man, -woman and -child to benefit from general education in chronobiology. This bioscience complements, by rendering more interesting and more useful, the learning of other sciences such as mathematics, physics and chemistry. Topics in hard science can all be taught by chronomedical examples for self-help in health care, in the spirit of Mendel the teacher who was recognized as such only after his death; Mendel the researcher, who was recognized as the father of genetics only decades after his death; and Mendel the chronobiologist, whom we recognize as such well over a century after his death. Unlike single sample-based time-unqualified homeostatic biology, which can be misleading, chronobiology renders the teaching of the hard sciences interesting and useful in health and environmental care (32). To be specific, the teaching of the blood pressure measurement certainly is of homeostatic interest, but as such misleading if decisions are based on single measurements or single 24-hour profiles. It is critical to learn in middle or preferably in elementary school that taking a single time-unqualified measurement, from a biomedical viewpoint, can be equivalent in some patients to flipping a coin (33).

Since his focus includes the chronomes of the environment, with which those of life are intricately interwoven, Mendel, the chronobiologist, set yet another example by providing systematic data that allow the resolution of 1-year synchronized circannual and of other meteorological rhythms, once his data in meticulous handwriting are transformed into an electronic format. His legacy prompts findings discussed herein in their historical context. The multifrequency components of the chronomes in us are interwoven among themselves, with other chronome elements, and with chronomes around us, as feedsidewards par excellence, for the resolution of what can be regarded as a transdisciplinary "biggest problem".

Sequence within a circadian cycle: RNA before DNA

There is the chronobiologic question of what comes first in a single circadian (or other) cycle. Toward this goal, it seemed reasonable by the fifties to fill in the Gs (that stand for Gaps in knowledge) in the cell cycle of that time. These gaps remain exactly what the word means: it had to be realized that the cell cycle is a sequence of more than two events, such as DNA labelling and mitosis, and that referring to the rest as one of the Gs can be equivalent to building on quicksand (as if the gaps were more than lack of specific knowledge of what happens during a gap). For instance, the effects of agents such as pituitary growth hormone, GH (34), an ACTH analogue (35), or an immunomodulator (36), as already demonstrated, depend critically on a circadian, circaseptan or circannual cell cycle time and probably on many other as-yet not tested, e.g., circatrigintan, transannual rhythm stages, some of which are already mapped.

For replacing the Gs, in the 1950s we used a battery of techniques. For locating intracellular sites, we combined differential centrifugation and histology with wet chemistry and radioactive tracers. Physiological markers were the circulating blood eosinophils (gauging the adrenal cortex and medulla) and core temperature (as a marker of hypothalamic mechanisms underlying a mammalian circadian system). We determined the relative specific activities, i.e., the specific activity of chemically isolated phospholipid-, RNA- or DNA-phosphorus in relation to the specific activity of pool (acid soluble or inorganic) phosphorus. This approach yielded a biochemical sequence of events, starting with phospholipid labeling at the membrane, which preceded RNA formation in the cytoplasm. There was no need to obscure these features by reference to a gap, as G1. We dissected events in time further to find that RNA formation preceded the formation of DNA, rather than the reverse, with RNA preparing perhaps the cell for DNA synthesis and for the subsequent (again clearly following rather than coincident) division of the cell with an intermediate peak in glycogen content.

Thus, by the 1950s, what was to become chronobiology revealed that a circadian cell cycle in immature growing mouse liver starts at the membrane with phospholipid labeling. RNA-, not DNA-synthesis follows. With cosinor methodology for time series analysis, we could demonstrate a statistically significant lead in phase of phospholipid labelling over RNA formation. In mammalian liver, there is a lag of ~9 hours between RNA formation and DNA synthesis, with non-overlapping 95% confidence intervals, when the results are analyzed by cosinor. The results of the 1950s found extension by the 1960s. We learned from Leland Edmunds that the sequence of a peak in murine RNA formation (a result of synthesis) has a counterpart in RNA content, which leads that in DNA, in the unicell Euglena, within a single cell, not complicated by the presence of metabolizing cells that are not yet dividing (37). From there, it is just one further step to analyzing the sequence of gene expression in the mammalian heart (38).

The spectrum of ultradian rhythms broadens

The ultradian courtship song of the fruit fly is associated with circadian genetics (39), as may be developmental changes in the roundworm *Caenorhabditis elegans* (40). Ultradians and infradians can replace circadians in the case of circulating endothelin (41-44) and in the numbers of endotheliocytes (45). Ultradians can also characterize gut hormones (46) and have been detected in molecular biology (47). Among non-photic infradian cycles in the environment, some long known counterparts of the ~10.5-year Schwabe and the ~21-year Hale cycles are now marked by signatures of the solar wind in the form of near-transyears (1.00 year < [τ {period} - CI {95% confidence interval}] < [τ + CI] < 1.20 years), far-transyears (1.2 years ≤ [τ - CI] < [τ + CI] < 1.9 years) and a cis-half-year found by Rieger (48), or an ~0.42-year cycle. Counterparts in physiology (49) must be aligned with those in pathology (50).

Circaseptans

An ~weekly or circaseptan pattern critically interacts with the outcome of an attempt to optimize, by timing, the effect of an immunomodulator in a mammal (36). In manipulating a unicell, the increasing interval in numbers of days between consecutive changes of an LD12:12 lighting regimen reveals an ~7-day pattern in the intact organism that changes to a half-weekly or circasemiseptan pattern after enucleation of the unicell (51). For the electrical potential of *Acetabularia* standardized in LD12:12 and released into continuous light, the circaseptan component is more prominent than the circadian. Both a circaseptan and a semicircaseptan pattern fit the declining vitality (gauged by the glutathione content) of the anucleate human platelet (52). Both these patterns fit data on growth or colony advance of E. coli (53).

A circaseptan pattern is apparent for cell settling in another unicell, *Euglena gracilis* Klebs; in the same unicell, *Euglena,* cell division also shows a circaseptan pattern (54). A mutation is associated with a change of this circaseptan pattern into a circasemiseptan one, in keeping with extremely limited yet further pertinent data (55). The multiseptans are just one set of harmonics of the sun's (solar latitude-dependent) rotation periods (56; cf. 57) and must be separated from periodicities associated with the moon. Among others, ~10- and ~5-day periods, described by G. Hildebrandt may also have been favored by an internal integrative evolution, complementing Darwinian adaptations.

The multiseptans may be linked to the circadian component, if, as seems to be the case in a hamster, a mutation involving a shortening of the circadian is associated with a circaseptan-to-circasemiseptan change of retinal melatonin production (insofar as curve-fitting to extremely short time series can allow speculation) (58).

The original documentation of the endogenicity of circaseptans was based originally on the monographic description of a case of human desynchronization from the societal week for ~3 years (59). It was strengthened by the observation that it related to only one variable -- 17-ketosteroid excretion, the breakdown product of some hormones -- and not to another variable, the urine volume, 7-day synchronized by a bottle of beer and an extra cup of tea each Sunday (59). The 17-ketosteroid also free-ran from the planetary geomagnetic index Kp and in records from hundreds of human newborns, showing a prominence of circaseptans, with amplitudes larger than those of the circadians in Brno, Moscow and Minneapolis.

There is a need for broader-than-circadian focus and the technology is available to implement it. Until this is done, however, short time series are valuable, as long as it has been made clear that inferences from data covering only one or a few putative cycles serve for hypothesis formulation and need added longitudinal or transverse validation in the same individual or across similar individuals, respectively. In the case of unicells, further experimental validation is required, with data inspection by the naked eye complemented with inferential curve-fitting. With these caveats, the chronobiology of unicells, just like that of arabidopsis, if not peas, and of mammals all add new dimensions to Mendel's legacy. One of these is the possible linkage of a built-in week and half-week in our chronomes to circadian and faster rhythms. The other related chronobiologic dimension is our resonance with events in the cosmos, which almost certainly has molded our genetic time structure. New components are being uncovered with periods of ~half a year, as in epileptic attacks (60) or in circulating melatonin of people living at high latitudes (61); of ~7 years, e.g., in marine invertebrates or in atmospheric pollution, or of ~10.5 and ~21 years, in neonatal morphology and adult physiology (62-64). These rhythms, found in biology, all have prominent counterparts in geomagnetic disturbance, responding to magnetic storms and other events within and beyond the solar system, that need to be made amenable to concerted contemporaneous biomedical and purely physical measurement. Cis-half-years, transyears, decadals and multidecadals continue to be documented in this year's proceedings. Segregation and independent assortment are now known as laws of inheritance originating in Mendel's pea patch. In Siegelova's non-invasive cardiology "patch", the congruence of novel solar-terrestrial-biospheric periods and their independent assortment (selective congruence) await further study by chronomics.

Mendeliana

Against the foregoing chronobiologic background, we look back to the time some decades ago in Brno, when the centenary of the publication of Gregor Mendel's research with Pisum was marked by an international memorial symposium, and again to the time when under the ambitious title "The past, present and future of genetics" in Kuparovice, then Czechoslovakia, Mendel's role in the foundation and early development of genetics was reconsidered (65). To the wealth of memorabilia in these volumes and others, we add chrono-meta-analyses of some of Mendel's data in meteorology, Table 1.

Mendel measured wind speed in 16 directions in 1862 and summarized his data on a monthly basis. In 50% of the cases, a circannual component was the most prominent in the least squares spectrum spanning frequencies of 1 to 5 cycles per year. The circannual component is statistically significant in four cases ($P<0.05$) and is of borderline statistical significance in another two cases. As seen in Table 1, there seems to be a gradual change in the circannual acrophase of maximal wind speed as a function of the direction from which the wind blew: three clusters can be recognized, one from south to west-northwest with circannual acrophases occurring around September; one from northwest to east-northeast with acrophases occurring around May; and one from east to south-southeast, with acrophases occurring around December-January.

Hardly surprisingly, a circannual rhythm also characterizes environmental temperature ($P<0.001$). Mendel's data further allow the demonstration of an ~yearly rhythm in cloudiness ($P<0.001$) and rainfall ($P=0.004$), but not in atmospheric pressure ($P=0.411$). The largest positive deviation in temperature is found in mid-July (acrophase = -205° from December 22, 1861, the latter date chosen as zero phase) in keeping with some rather high temperatures experienced whenever the senior author had the privilege of visiting Brno in mid-summer. The temperature acrophase corresponds to that of maximal rainfall (acrophase = -203°), whereas maximal cloudiness occurs in early January (acrophase = -15°). The predictable yearly changes in these variables can be quite large, those in temperature averaging 17.7° Reaumur.

Whether applied to data from physics or biology, computer methodology isolates and quantifies predictable features in serial data, that need not be regarded as "too complex". For chronobiologists, Mendel's finest legacy is his function as a role model for perseverance against the greatest of odds. In this context, Mendel provides solid advice, found in his handwriting, in a verse he took from Johann Wolfgang von Goethe, constituting Insert I (66; cf. 67).

One of us (AM) emphasizes Goethe's and Mendel's verse as her motto when describing Mendel's personality. We also owe her the reference to the painting that symbolizes Mendel's interests: a setting of a telescope, globe, compass needle, scrolls of maps, thermometer and pocket sundials. Some of the objects (telescope, thermometer, pocket sundials) were found among Mendel's relics. These artifacts symbolize Mendel's interest in meteorology. Perhaps, in view of his telescope, we may read into this legacy an interest by Mendel in a budding chrono-astrobiology far beyond earthly meteorology.

We owe Ivo Cetl the chronology of Mendel's scientific activities (65). Mendel published his studies on plant hybridization later than his findings in meteorology. His interest in the weather continued for much longer than any other of his concerns. Historians may indicate rightly that to establish a new science one needs no more than a good publication or two. The chronobiologic perspective we convey here is that Mendel's concerns in plant hybridization are interrelated with those in meteorology and apiculture. They should lead to more than local or terrestrial weather forecasting. We have an opportunity to benefit from space weather forecasting (68), perhaps to reduce traffic accidents, myocardial infarctions or strokes and epilepsy. On the basic side, we may also find in the cosmoi the origin for some of the now-genetically-anchored, heretofore neglected components in the spectrum of biological rhythms, such as the ~5 and ~16-month and ~7-, ~10-, ~21-, ~35- and ~500-year cycles in nature, inanimate and animate (69-73), including those in ourselves (10, 49).

If the genetics of structure in time as well as in space have their origin in the resonance of organisms with the dynamics of the cosmoi, the "theological" week, regarded by too many as all culture and not nature (74), may have a physico-chemical basis (75). A computation of the oscillating frequency during the diffusion of ions in a magnetic field such as that of an organism shows values for a period of ~1 week (75). Accordingly, this presentation takes us from Mendel's interest in the weather over space weather forecasting to the origin of Mendel's "hard" genetics in the light of Darwin's "soft" genetics. At its start, life may have been a mere resonance with the chronomes in cosmoi near and far. Eventually, the environmental frequencies became anchored as chronomes in RNA and then in DNA-based systems, with some features of integration with our environs, "recapitulated" perhaps whenever a cell is born, in a cyclic fashion with choices among several time scales. The biological week and the ~5-month cycles as well as those of ~6 months, now built into us, still resonate with distant drummers, whether they originated as a response to the solar wind, to the moon and/or to even more remote stimuli. As we undertake the journey from rhythms to a budding chrono-astrobiology, we learn about new health effects that are both mirrored by our genetically anchored chronomes and still influenced by the environment.

Solar monitoring: where Gregor Mendel and Jarmila Siegelova meet

In his letter III to Carl Naegeli (76), dated November 6, 1867, Mendel wrote: "... I am no longer fit for botanical excursions, since the heavens have blessed me with an overweight which, in further parties on foot, notably in climbing hills, becomes too readily sensed as a consequence of general gravity" ("... auch tauge ich nicht mehr recht für botanische Excursionen, da mich der Himmel mit einem Uebergewichte gesegnet hat, welches sich bei weiteren Fusspartien, namentlich aber beim Bergsteigen, in Folge der allgemeinen Gravitation, sehr fühlbar macht.") Refraining from hiking, Mendel late in life made observations on sunspots. Iltis (77) reports the following notes that are the more noteworthy since the time of the observations, albeit a solar maximum was not remarkable, Figures 5 and 6: "17 [November 17, 1882] vesp. aurora in Geneva and Pola; 18th, a.m., disturbance in telephone communications; 17th, 18th, aurora in San Francisco extending to Boston (very imposing!)." Iltis comments: "In [Mendel's] drawings of sunspots we find for the 18th and 19th of the same month a large group of spots near the central meridian of the sun's disk" (77). Thus, about 8 decades before Mariner 2 documented the solar wind, the scholar of heredity and of earthly weather looked for the link between solar activity and terrestrial affairs, Figures 5 and 6.

Herein lies the challenge of noninvasive cardiology, notably in Brno: to monitor both personal and societal health, the latter by solar surveillance via BP and HR across generations, to map the spectral region between BEL cycles of ~35 years and Mikulecky's circasemimillennials. We may become able to do so with modern instrumentation developed by the Phoenix Study Group, composed of volunteering members of the Twin Cities chapter of the Institute of Electrical and Electronics Engineers (http://www.phoenix.tc-ieee.org). An unobtrusive and affordable software and hardware combination with modern computer technology is an important step toward universal preventive cardiac health care, so that as long as health prevails, all is being done by cost-free self-help, as practiced now in BIOCOS, and we contribute concomitantly to what is today basic science, but tomorrow may lead to countermeasures against ills of society, influenced unfavorably by solar activity.

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Legends

Figure 1. Measurable time structure (chronome) of a variable. More and more components in the spectrum of physiological variation are found to have numerical physical environmental counterparts and, vice versa, environmental counterparts have been found for some unusual physiological cycles, believed to be purely societal, such as the week, and for new cycles shorter than 6 months and longer than 12 months, signatures of the solar wind. Physical or biological spectra, organizing irregular chaotic and complex variations and trends in endpoints of rhythms, chaos, and complexity constitute time structures, or chronomes. The mapping of physical and biological chronomes proceeds as yet opportunistically in a project on The BIOsphere and the COSmos (BIOCOS). A data base of reference values thus accumulates with a target length of at least 7 days beat-to-beat for the electrocardiogram and again for at least 7 days at intervals from 15-60 minutes, in the case of human blood pressure. Such mapping is critical for a quantification of health in the range of otherwise neglected physiological variation. Chronome maps are the invaluable and indispensable reference values for the detection of disease risk syndromes. "Measure what is measurable and render meaningfully measurable in time what as yet is not" is what chronomes are all about. © Halberg.

Figure 2. Sketch of factors and pathways known to participate in frequency synchronization *among* circadian rhythms themselves, as well as in synchronization between rhythm(s) and environmental synchronizer(s). Note intracellular mechanisms documented by 1960 (5-7). © Halberg.

Figure 3. **Left**: Chronomodulation at different levels: in the **left** half, interplanetary solar and galactic factors (**top right**) are conceived as modulating socioecological conditions in the habitat (**top left**), acting upon the healthy or sick organism as a whole. **Right**: Results on lack of effect, attenuation, or amplification by aqueous pineal homogenate of corticosterone production by bisected adrenals are summarized on top. Those in the second diagram from the top refer to the effect of the bilateral ablation of the suprachiasmatic nuclei (SCN) on circadian amplitude and acrophase. Loss of circadian rhythm (documented by a zero amplitude) is the result of SCN

removal in the case of locomotor activity and water drinking but not in a vast majority of other rhythms sampled at 4-hour or shorter intervals for 24 hours or longer spans and analyzed by inferential statistical means. The third diagram from the top refers to chronomodulation by feedsidewards observed for the effect of ACTH 1-17 upon metaphysical DNA labeling in the rat. Intermodulations in the case of an invading microorganism of sufficient virulence to elicit a host response are sketched at the bottom. Feedsideward: Multiple interactions among several rhythmic entities resulting in a predictable rhythmic sequence of attenuation, no effect, and amplification, implemented by a modulator acting on the interaction between the actor and reactor. As shown in the diagrams, the role played by the modulator, the actor, and the reactor can vary among the interacting entities, and these systems can be exposed to different influences and an integrator.

■ actor ↔ reactor;
■ modulator ↔ actor;
■ modulator ↔ reactor;
□ feedsideward;
□ integrator;
→ influencers.

© Halberg.

Figure 4. The chronomes in us, that came about as a function of chronomes around us, to be eventually coded genetically, await further exploration in health care, notably for stroke prevention. © Halberg.

Figure 5. On November 17, 1882, Mendel made the connection between sunspots and the aurora during a solar maximum that was not unusual whether it is viewed in the context of centuries (top), that of years (second row), of months (third row) or of days (bottom row). © Halberg.

Figure 6. Mendel's drawings of sunspots show almost-daily changes in their appearance; sometimes the sun's disk is free of spots. These observations led him to postulate a connection between sunspots and the aurora. From (60).

Insert I: Mendel's citation (from Goethe's "Lila" [66]) is pertinent to the switch (from the fictions of homeostasis, secularity, baselines and other current dogmas) to chronobiology

Feiger Gedanken,	(Cowardly thoughts,
Bängliches Schwanken,	anxious vacillation,
Weibisches Zagen,	spineless* hesitation,
Ängstliches Klagen,	anguished complaint,
Wendet kein Elend,	does not alleviate misery,
Mach dich nicht frei.	does not set you free.
Allen Gewalten	Opposing all force
Zum Trutz sich erhalten,	while maintaining one's course,
Nimmer sich beugen,	never to bend,
Kräftig sich zeigen ...	to show oneself strong ...)

*Goethe's "weibisches" literally translates as "woman-like", connoting "effeminate". We here change this reference into a gender-neutral one on the assumption that hesitation is not specific to a supposedly "weaker sex", as documented by women warriors (67).

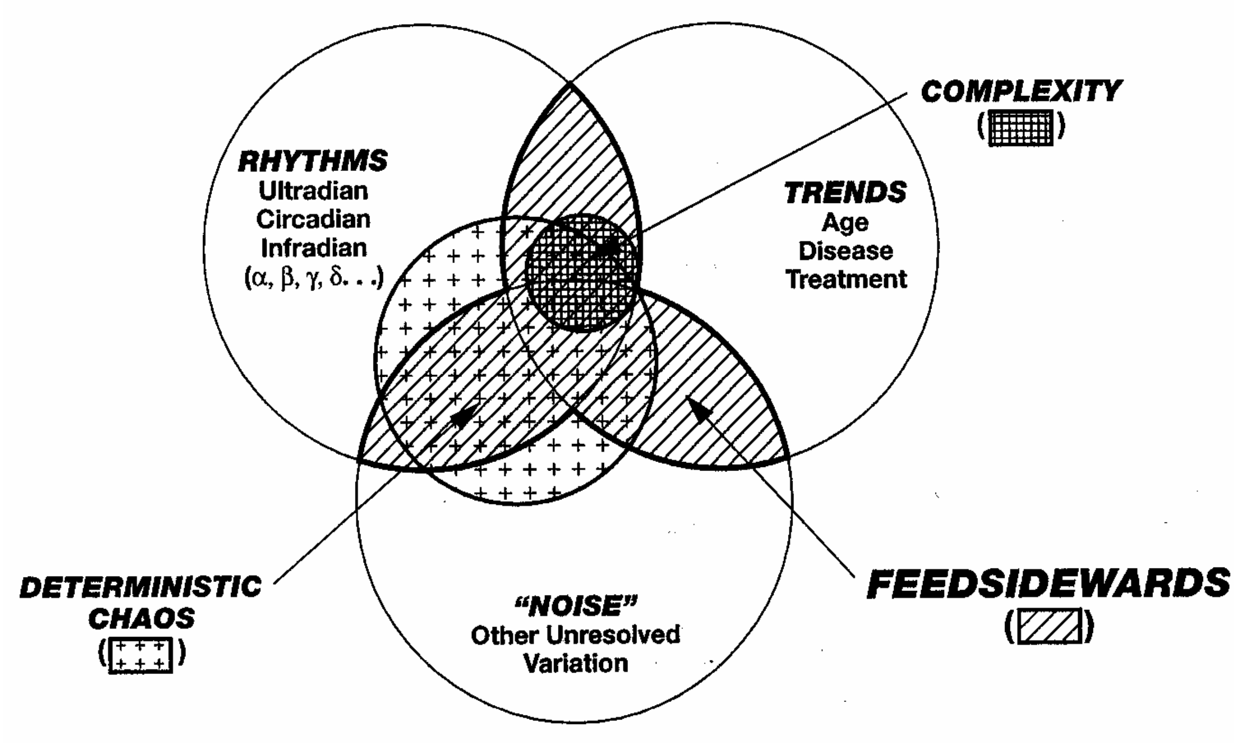

COMPLEXITY
RHYTHMS
Ultradian
Circadian
Infradian
(α, β, γ, δ. . .)
TRENDS
Age
Disease
Treatment
DETERMINISTIC
CHAOS
"NOISE"
Other Unresolved
Variation
FEEDSIDEWARDS

Figure 1

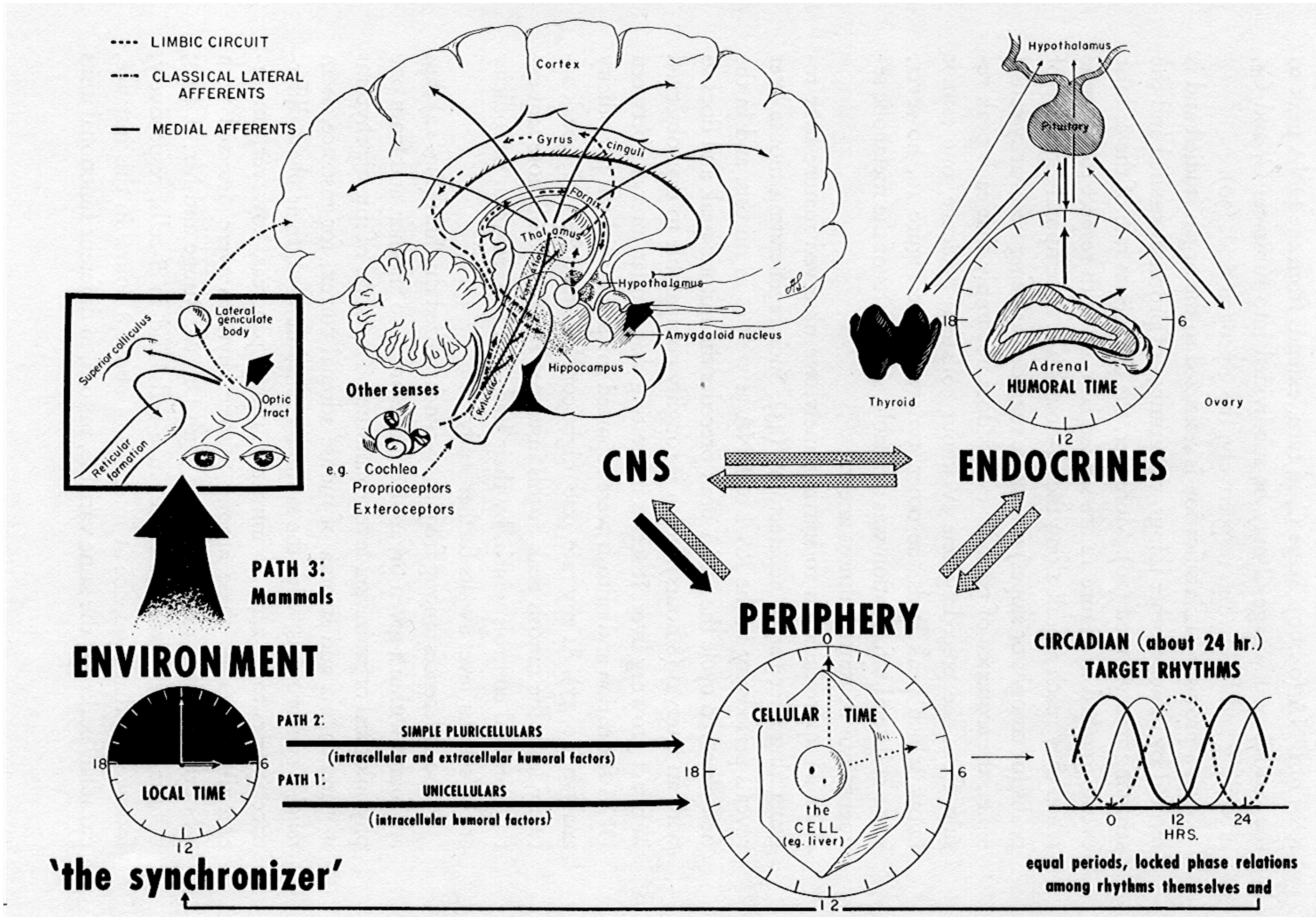

LIMBIC CIRCUIT
CLASSICAL LATERAL AFFERENTS
MEDIAL AFFERENTS
Cortex
Gyrus
cinguli
Fornix
Thalamus
Hypothalamus
Amygdaloid nucleus
Hippocampus
Lateral geniculate body
Superior colliculus
Optic tract
Reticular formation
Other senses
e.g. Cochlea
Proprioceptors
Exteroceptors
Hypothalamus
Pituitary
Thyroid
Adrenal
HUMORAL TIME
Ovary
CNS
ENDOCRINES
PATH 3:
Mammals
PERIPHERY
ENVIRONMENT
LOCAL TIME
PATH 2:
SIMPLE PLURICELLULARS
(intracellular and extracellular humoral factors)
PATH 1:
UNICELLULARS
(intracellular humoral factors)
CELLULAR TIME
the CELL (eg. liver)
CIRCADIAN (about 24 hr.)
TARGET RHYTHMS
HRS.
equal periods, locked phase relations
among rhythms themselves and
'the synchronizer'

Figure 2

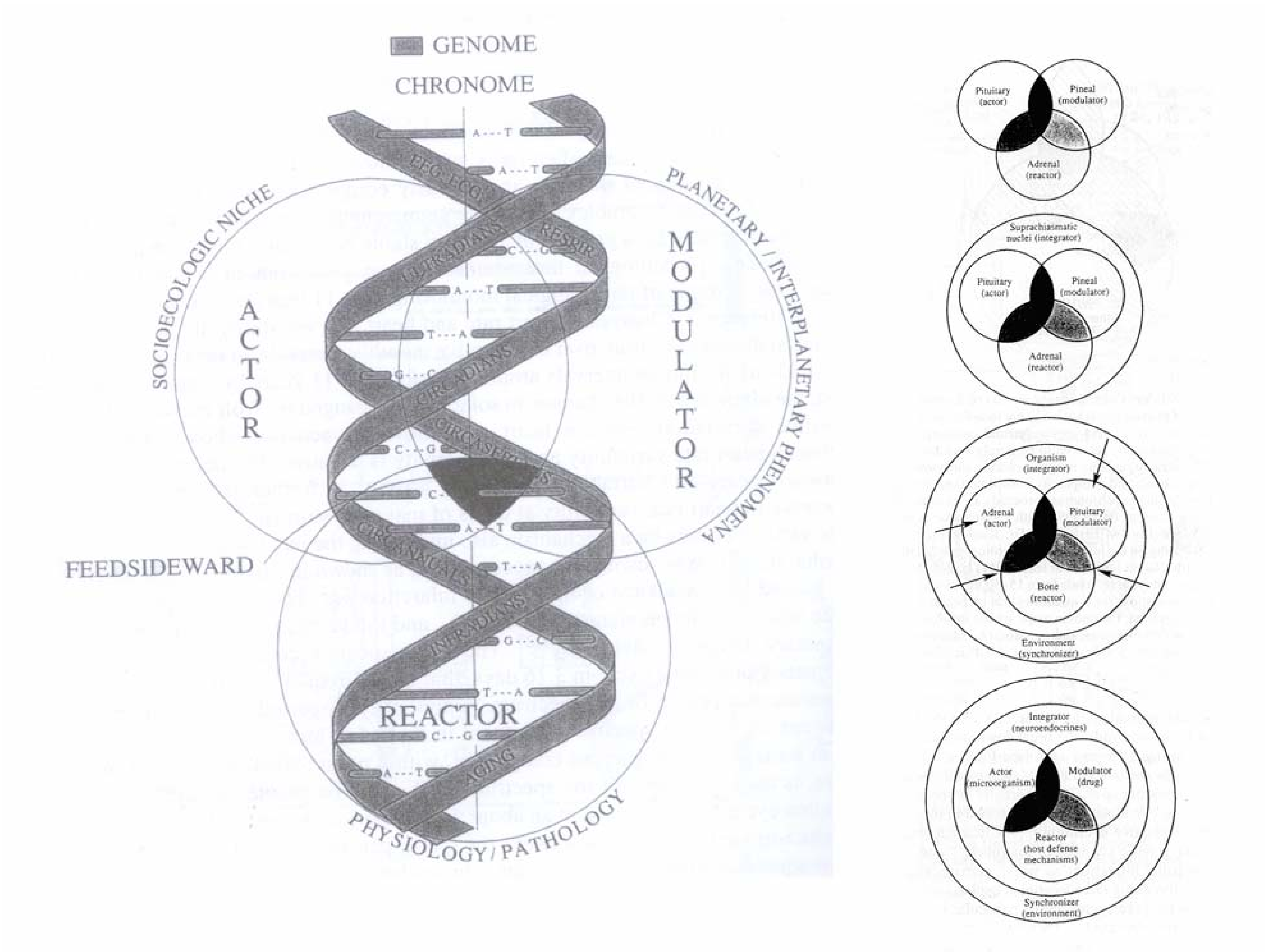

GENOME
CHRONOME
SOCIOECOLOGIC NICHE
ACTOR
MODULATOR
PLANETARY / INTERPLANETARY PHENOMENA
FEEDSIDEWARD
REACTOR
PHYSIOLOGY / PATHOLOGY
ULTRADIANS
RESPIR
CIRCADIANS
CIRCANNUALS
INFRADIANS
AGING
Pituitary (actor)
Pineal (modulator)
Adrenal (reactor)
Suprachiasmatic nuclei (integrator)
Pituitary (actor)
Pineal (modulator)
Adrenal (reactor)
Organism (integrator)
Adrenal (actor)
Pituitary (modulator)
Bone (reactor)
Environment (synchronizer)
Integrator (neuroendocrines)
Actor (microorganism)
Modulator (drug)
Reactor (host defense mechanisms)
Synchronizer (environment)

Figure 3

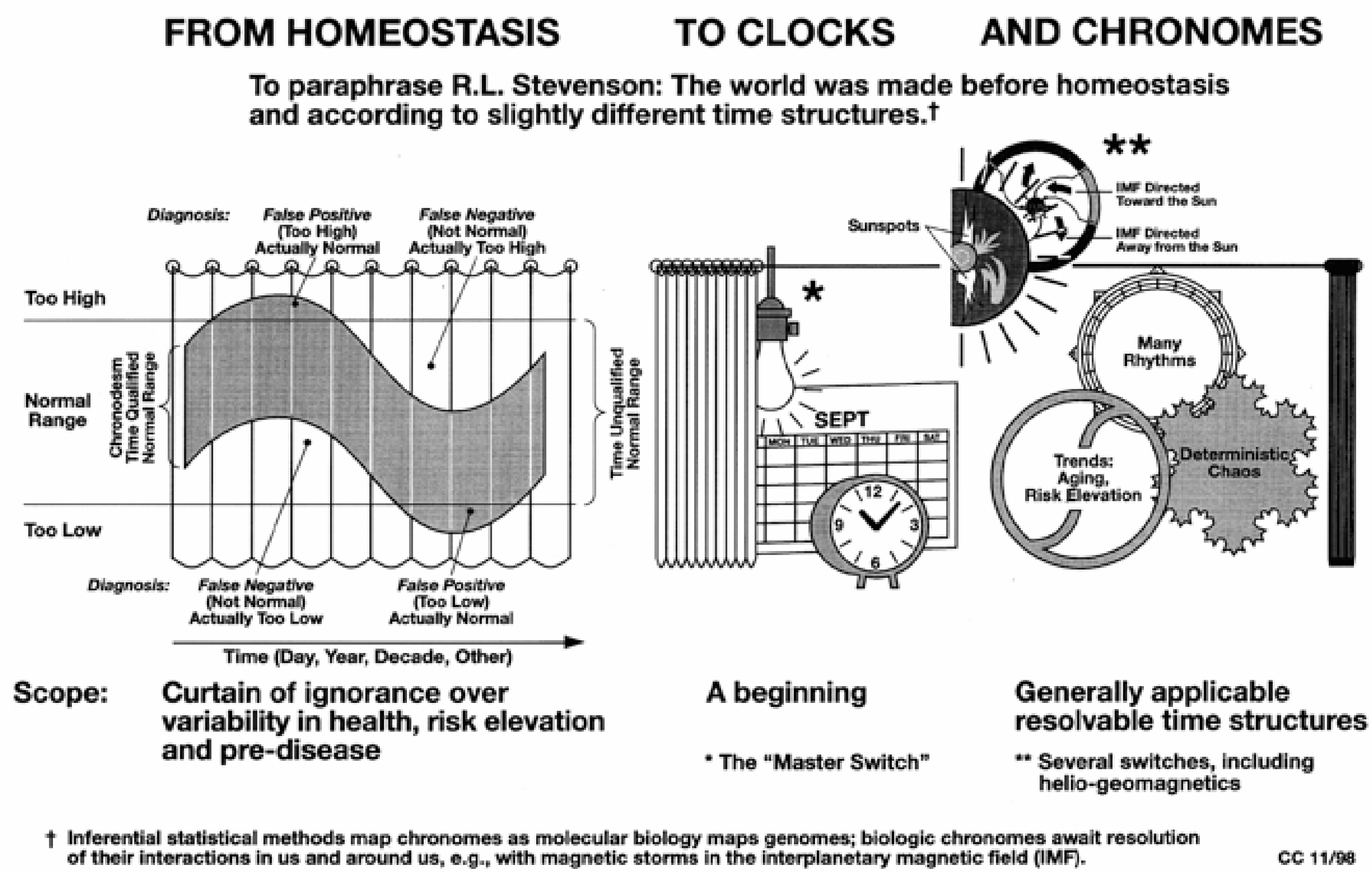

FROM HOMEOSTASIS TO CLOCKS AND CHRONOMES
To paraphrase R.L. Stevenson: The world was made before homeostasis and according to slightly different time structures.†
Diagnosis: False Positive (Too High) Actually Normal
False Negative (Not Normal) Actually Too High
Too High
Normal Range
Too Low
Chronodesm Time Qualified Normal Range
Time Unqualified Normal Range
Diagnosis: False Negative (Not Normal) Actually Too Low
False Positive (Too Low) Actually Normal
Time (Day, Year, Decade, Other)
*
SEPT
MON TUE WED THU FRI SAT
12
3
6
9
**
Sunspots
IMF Directed Toward the Sun
IMF Directed Away from the Sun
Many Rhythms
Trends: Aging, Risk Elevation
Deterministic Chaos
Scope:
Curtain of ignorance over variability in health, risk elevation and pre-disease
A beginning
* The "Master Switch"
Generally applicable resolvable time structures
** Several switches, including helio-geomagnetics
† Inferential statistical methods map chronomes as molecular biology maps genomes; biologic chronomes await resolution of their interactions in us and around us, e.g., with magnetic storms in the interplanetary magnetic field (IMF).
CC 11/98

Figure 4

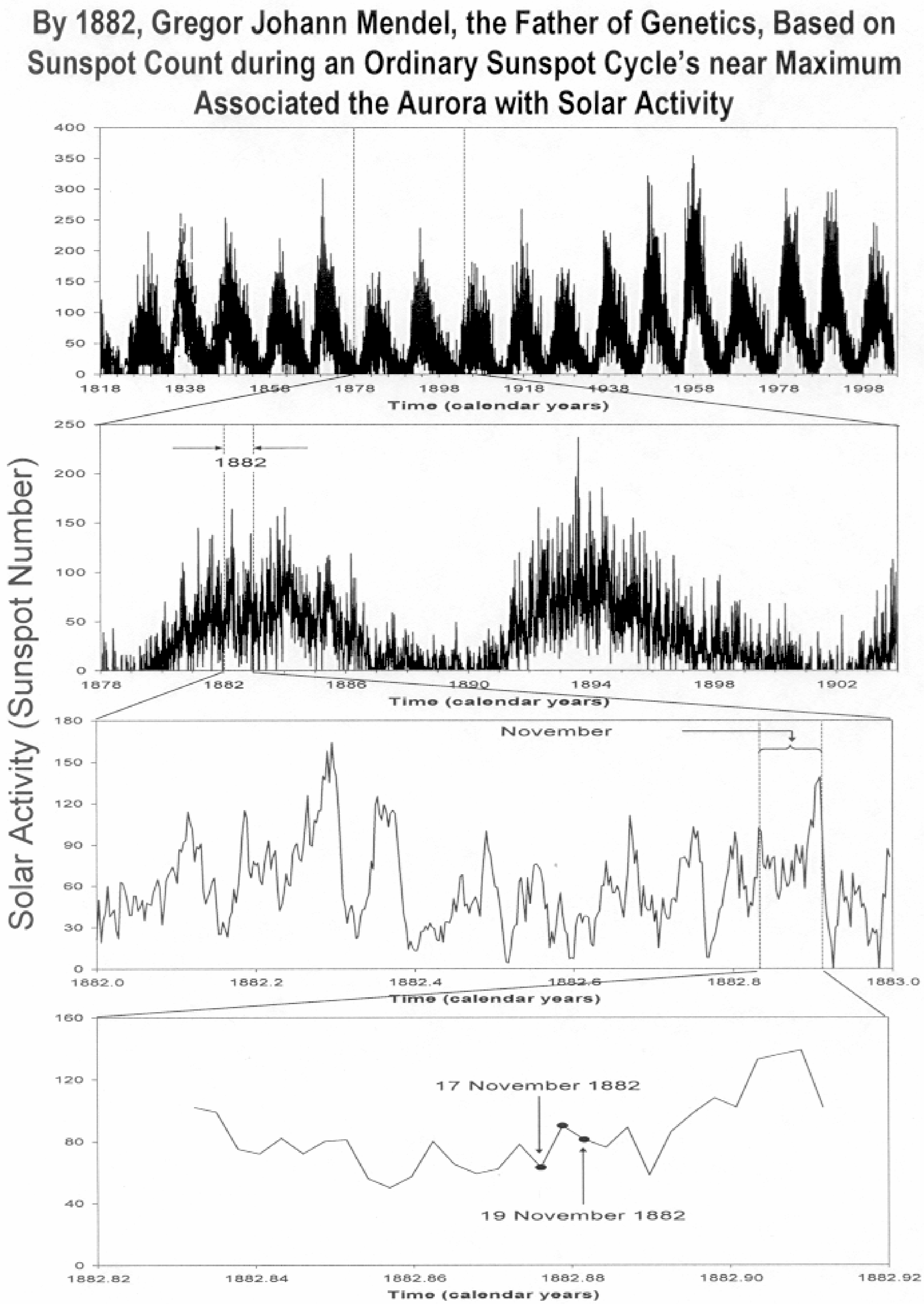
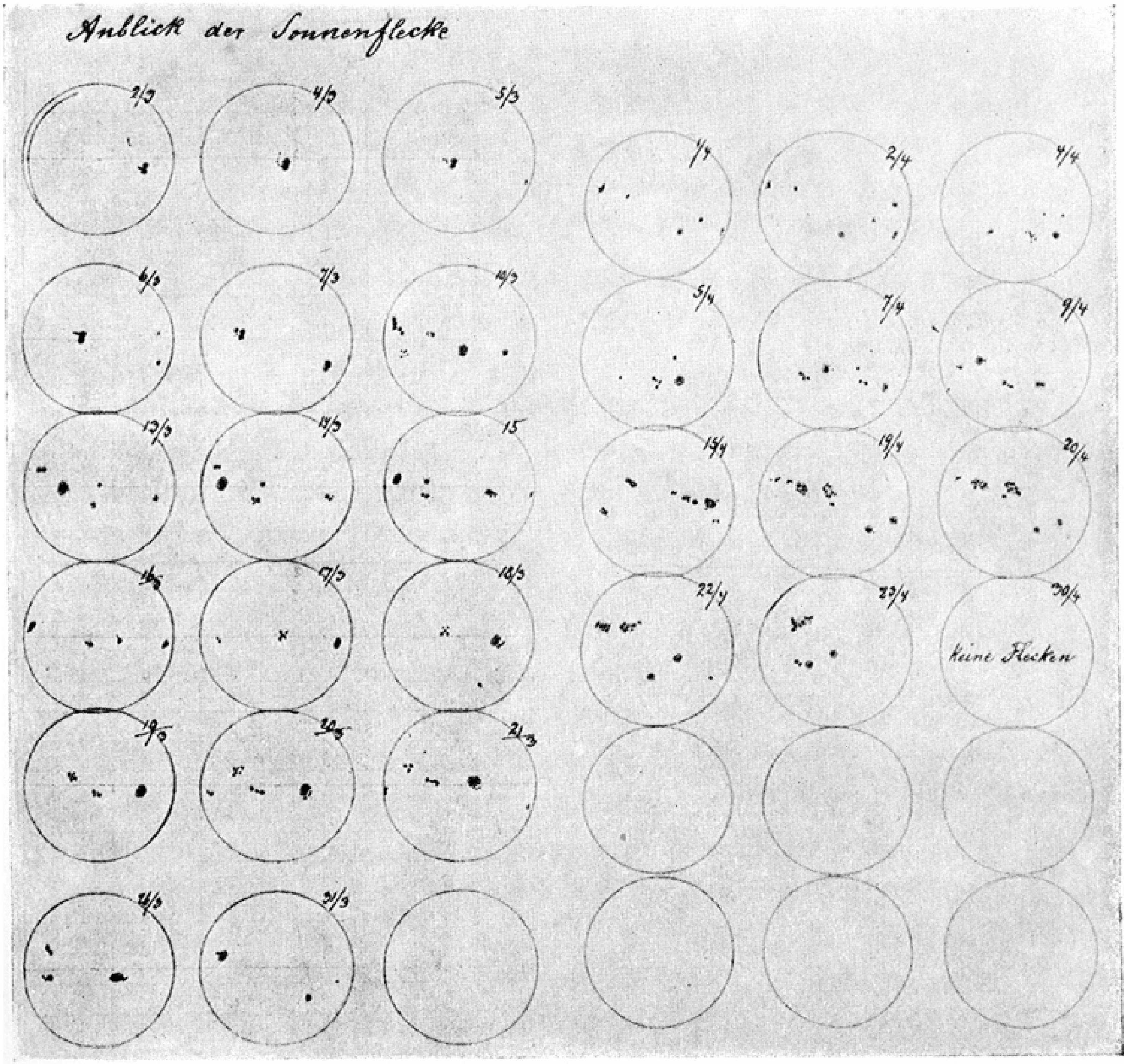

By 1882, Gregor Johann Mendel, the Father of Genetics, Based on Sunspot Count during an Ordinary Sunspot Cycle's near Maximum Associated the Aurora with Solar Activity
Solar Activity (Sunspot Number)
Time (calendar years)
1882
November
17 November 1882
19 November 1882

Figure 5

Mendel's notebook records date, number and location of sunspots, if any*



*View of sunspots *(Anblick der Sonnenflecke)* or of their lack (empty circles; *Keine Flecken)* in two pages with Mendel's sketches (from Iltis H. Life of Mendel. New York: Hafner, 1966 [originally published in English in 1932]. 336 p.)

Figure 6

Table 1: **BOLD** WHEN STATISTICALLY SIGNIFICANT CIRCANNUAL VARIATION OF WIND SPEED IN GREGOR MENDEL's HANDWRITTEN RECORDS (1862)*

Results from single cosinor

Direction	PR	P	MESOR±SE	Double Amplitude	Acrophase±SE
Cluster 1					
s	2	0.899	8.5±0.7	0.90±1.92	-292±124
ssw	46	0.063	1.7±0.2	1.62±0.58	-299±21
sw	12	0.550	1.5±0.2	0.64±0.58	-248±51
wsw	25	0.270	1.3±0.2	0.88±0.50	-252±33
w	10	**0.004**	6.9±0.3	3.28±0.70	-295±12
wnw	52	**0.038**	5.2±0.2	2.16±0.70	-257±18
Cluster 2					
nw	36	0.137	15.4±0.9	5.42±2.42	-174±26
nnw	45	0.067	8.0±0.5	4.18±1.54	-142±21
n	30	0.206	12.5±0.7	3.80±1.96	-167±29
nne	34	0.156	2.3±0.2	1.36±0.64	-148±27
ne	7	0.735	2.5±0.4	0.82±1.02	-170±72
ene	18	0.408	2.1±0.1	0.34±0.24	-113±41
Cluster 3					
e	10	0.627	6.3±0.4	1.22±1.24	-36±58
ese	20	0.367	2.4±0.2	0.96±0.64	-28±38
se	65	**0.009**	8.3±0.5	5.62±1.38	-17±14
sse	71	**0.004**	6.3±0.4	4.80±1.02	-348±12

Results from population-mean cosinor

Cluster	PR	P	MESOR±SE	Amplitude (% MESOR) (95% CI)	Acrophase (95% CI)
1	34.5	**0.030**	4.2±1.5	23.55 (9.72, 37.39)	-275˚ (-232, -302)
2	28.3	**0.023**	7.1±3.0	18.12 (9.12, 27.12)	-154˚ (-137, -175)
3	41.5	0.116	5.8±1.9	24.04 ( )	-10˚ ( )

*s: south; w: west; n:north; e: east. PR=percent rhythm; P=P-value from test of zero-amplitude (no-rhythm) hypothesis; SE=standard error; 95% CI=95% confidence interval. Units in original handwritten record not readily legible. When all amplitudes are set equal to 1 to summarize acrophases only, a circannual component is statistically significant in all 3 clusters (P≤0.001). Biological significance of record is historical, showing the environmental concern of the founder of genetics.

D. METHODS

SELECTIVELY ENVIRONMENTALLY CONGRUENT BIOTIC CIS-HALF-YEAR UNMASKED WITH NEIGHBORING SPECTRAL COMPONENTS

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**This paper is dedicated to the memory of Jean De Prins,
a great teacher, an inspiring mentor, and above all, a dear friend**

Support: U.S. National Institutes of Health (GM-13981) (FH),
University of Minnesota Supercomputing Institute (GC, FH)

Abstract

Three spectral components with periods of about (~) 0.41, ~0.5 and ~1.0 year had been found with serially independent sampling in human circulating melatonin. The time series consisted of around-the-clock samples collected for 24 hours at 4-hour intervals from different patients over several years. Some of these components had been found to be circadian stage-dependent, the daytime measurements following mostly a circannual variation, whereas a half-year characterized the nighttime samples. The latter were incorporated into a circasemiannual map. The relative brevity of the series prevented a check for the coexistence of all three spectral components, even if each component seemed to have a *raison d'être.* In time series of transdisciplinary data, a 1.00-year synchronized component is interpreted as representing the seasons. The half-year may qualify the circannual waveform, but it is also a signature of geomagnetics. An ~0.41-year (~5-month) component is the signature of solar flares. It has been called a cis-half-year (cis = on this side of a half-year) and may be detected only intermittently. Charles L. Wolff predicted the existence, among others, of ~0.42- and ~0.56-year components as beat periods of rotations at different solar latitudes.

The multiple components characterizing circulating melatonin could also be found in a (to our knowledge unique) data set of a clinically healthy scientist (RBS). Herein, we focus on vascular data self-measured by RBS as he aged from ~20 to ~60 years. A multi-component model consisting of cosine curves with periods of 0.41, 0.50 and 1.00 year was fitted to weekly means of systolic (S) and diastolic (D) blood pressure (BP) and heart rate (HR) collected ~5 times a day over 39 years by RBS. All three components can coexist for a while, although all of them are Aeolian, in the sense that they are nonstationary in their characteristics and come and go by the criterion of statistical significance. Intermittently, BP and HR are synchronized selectively with one or the other aspect of RBS' physical environment, namely the seasons (at ~1.0 year), earth magnetism (at ~0.5 year) and/or solar flares (at ~0.42 year). Cosmic-biotic transfer of information, albeit hardly of energy (the biospheric amplitudes are very small) may be mediated in this set of frequency windows. As found earlier, RBS' circulation is also frequency-trapped environmentally in multidecadal windows, HR being locked into the transtridecadal Brückner, or rather Brückner-Egeson-Lockyer, BEL cycle, while his BP follows Hale's didecadal cycle in the changing polarity of sunspots.

The ~0.41-year HR cycle may be associated with changes in solar flares, the cis-half-year amplitude of HR showing a cross-correlation coefficient of 0.79 with the total solar flare index (from both solar hemispheres) at a lag of ~3.2 years. The superposed time courses of these two variables indicate the presence of a shared Horrebow-Arago-Schwabe sunspot cycle of ~11 years, the cis-half-year in HR being more prominent after the total solar flare index reaches its ~11-year peak. Differences in the time-varying behavior of BP vs. HR are also described.

An analogy between external scrubbing and self-surveillance of internal rhythms

Paul J. Rosch reminds us that:

> Alexander Gordon, a [Scottish] physician, suggested in 1795, that [puerperal] fevers were contagious processes, that physicians were the carrier, and that "I myself was the means of carrying the infection to a great number of women." Thomas Watson, Professor of Medicine at King's College Hospital, London, wrote in 1842 [one year before Oliver Wendell Holmes published 'The Contagiousness of Puerperal Fever']: "Wherever puerperal fever is rife, or when a practitioner has attended any one instance of it, he should use most diligent ablution." (1)

Nonetheless, with all the evidence backing such claims, Ignaz Semmelweis ended up in a mental institution, where he died in 1865 probably from septicemia. Sutcliffe and Duin (2) cite Oliver Wendell Holmes as indicating that (Pasteur's) "little army of microbes [had not yet been] moved up" to support Semmelweis' and eventually Lister's position for indispensable antisepsis.

With respect to preventive measures for maintaining cardiac and mental health and preventing morbid events such as strokes and criminality in individuals and terrorism in society, we are in the same situation today as Semmelweis was with respect to antisepsis. In our case, a broad spectrum of rhythms in us and around us, albeit already mapped, has not yet been recognized in terms of pertinence to everyday life. Like circadians (3-5), now a fashion in molecular biology, the many different more or less periodic extra-circadians (6) evolved and were adaptively built into human physiology under the influence of the non-photic cycles of our cosmos. Infradians are apparent in military-political affairs, including aggression, notably crime, international battles and terrorism, in economics, in opinion polls, in education and, most important, in health and disease, including infection (7-10). Like circadians, infradians also tip the scale between life and death.

Double purpose of physiological surveillance: self-help in healthcare and photic-nonphotic environmental monitoring

Chronobiologically-interpreted BP and HR monitoring detects pre-hypertension, pre-diabetes and a pre-metabolic syndrome in Vascular Variability Disorders (VVDs), as conditions of increased vascular disease risk (11-14) and as complications of a (reliably-diagnosed) MESOR-hypertension, a VVD in its own right. Another VVD is an excessive circadian amplitude of BP (CHAT, short for Circadian Hyper-Amplitude-Tension). This condition carries a risk of cerebral ischemic event greater than a high BP. It can coexist with other VVDs to form Vascular Variability Syndromes (VVSs). VVDs are not being screened for in our current conventional health care system. Once diagnosed, some VVDs can be treated.

It is not yet generally known that in the human newborn, variables such as BP and HR have infradians such as an about-weekly component, which is usually more prominent than the 24-hour variation, awaiting testing as a gauge of risk. It is also not generally known that the incidence patterns of sudden cardiac death (ICD10, code I46.1) is characterized by ~5-month (cis-half-year) and ~17-month (far-trans-year) components, cyclic signatures of space weather, in the absence of yearly changes, notwithstanding the large difference between Minnesota's mid-continental winters and summers. A host of spectral components is shared between natural physical environmental variables, such as the solar wind and other aspects of space weather, and biological variables, such as those of the human circulation, electrical accidents of the heart (15) and suicides (16). They are said to be congruent when the 95% confidence intervals (CIs) of their (shared) periods are overlying or overlapping.

When cardiovascular and mental health and their relation to the cosmos are viewed in 40 years of self-measurements by RBS, there is selective congruence of the ~5-month component between RBS' HR and the total solar flare index (SFI). An ~0.41-year cis-half-year component in HR is modulated by solar flares, and both solar flares and the cis-half-year amplitudes of RBS' HR show the Horrebow-Arago-Schwabe pattern of sunspot numbers (Figure 1, left). Their cross-correlation function (Figure 1, section D) reaches a maximum of r=0.79 at a 3.16-year lag, raising the question whether the effect of solar flares is direct or indirect, perhaps mediated by terrestrial magnetism.

Congruence of an ~33-year cycle between RBS’ HR and Wolf's sunspot numbers (Figure 2) was reported earlier (17), as were other congruences of RBS’ HR and BP with space weather (Figure 3).

Horrebow-Arago-Schwabe modulation of cis-half-year in and around us

Both solar flares (Figure 1, left, top and bottom) and Wolf sunspot numbers (Figure 1, left, middle) are characterized by a prominent ~11-year cycle. The prominence of the cis-half-year in RBS’ HR, gauged by the 0.41-year amplitude estimated over a 4-year interval displaced in 2.5-month increments, also follows a similar ~11-year cycle (Figure 1, left, bottom). It is detected with statistical significance (filled rectangles) only part of the time, usually following a peak in solar flares and sunspot numbers. The cross-correlation function between the cis-half-year amplitude of HR versus the total solar flare index reaches a maximum of 0.79 at a 3.16-year lag (Figure 1, right, top). Whether the effect is direct or indirect should be examined further, beyond the congruence of periods and phases, as they change with time, against the background of already demonstrated prior global congruences at a trial period of ~33 years, Figures 2 and 3. Congruences can be selective, as noted in Figure 3: RBS’ HR displays a transtridecadal congruence with Wolf numbers, while RBS’ BP responds to Hale's sunspot bipolarity cycle.

Can biospheric behavior teach physical lessons?

The original task was to examine the degree of ubiquity and, in this sense, the consistency in different variables, if any, of an ~0.42-year cis-half-year component. It had been found to characterize sudden cardiac death (ICD10, code I46.1) in Minnesota and in a number of other geographic locations (15; cf. 18-20), Figure 4. It was also detected in the SBP of an elderly subject (FH) during nearly 16 years of monitoring, at 70-86 years of age (15), Figure 5, and in a 10-year DBP record (analyzed by gliding spectrum) of another elderly man (GSK) (21). The 39-year BP and HR record of RBS, at 20-59 years of age, lent itself well to the examination of the cis-half-year as it may change as a function of time.

Looking for intermittently coexisting cycles

Linear least-squares spectra of weekly means of SBP, DBP and HR of RBS showed only a small peak at a period of ~0.42 year that was not statistically significant, contrasting with its detection in the BP of two elderly men (FH and GSK). The task was to determine whether the cis-half-year was definitively absent in RBS during his 39 years of self-measurements or whether its detection was obscured by the presence of other larger neighboring spectral peaks and/or by its non-stationary Aeolian nature. Prominent yearly and half-yearly variations indeed characterized the BP and HR of RBS. The half-year may be an expression of the non-sinusoidality of the circannual component, but it may also represent the expression of a geomagnetic signature of its own right. The ~0.42-year cis-half-year was anticipated from its detection in two other long-term series, being congruent with solar flares, where this component was documented by Rieger et al. (22) and others, Table 1. An ~0.56-year component in solar activity, also of interest as another beat period of the solar rotation according to Charles L. Wolff (23, cf. 16), remains beyond the scope of this analysis. In order to answer the above question, multiple-component serial sections were carried out, including with the 0.42-year cis-half-year the other two major neighboring components with periods of 0.5 and 1.0 year. Specifically, a 3-component model was fitted by cosinor, consisting of cosine curves with periods of 1.0, 0.5, and 0.41 year (or 8766, 4383, and 3615 hours), to data in a 209-week (~4-year) interval displaced throughout the time series by increments of 11 weeks (~0.21 year or a half cis-half-year cycle).

Like many other non-photic components, the cis-half-year in the BP and HR of RBS was found to be present only intermittently and with characteristics that varied as a function of time. Specifically, based on this moving 3-component model, the following results were obtained. For SBP, the 1.0-year component reached statistical significance ($P<0.05$) in 157 of 167 (partly overlapping) intervals (94.0%). The 0.5-year and 0.41-year components were statistically significant in 110 (65.9%) and 39 (23.4%) intervals, respectively. In the case of DBP, the 1.0-year, 0.5-year, and 0.41-year components reached statistical significance in 152 (91.0%), 61 (36.5%), and 38 (22.8%) intervals, respectively, and in the case of HR, statistical significance was reached in 112 (67.1%), 61 (36.5%), and 37 (22.2%) intervals, respectively. Whereas in RBS (but not in FH and GSK), the yearly component and its second harmonic are undoubtedly the most consistent and the most prominent, the cis-halfyear is also detected with statistical significance at a rate higher than would be expected by chance alone and according to a non-random pattern in time that prompts the search for a similar clustering in environmental variables (Figure 1, left, bottom). All three components could be detected concomitantly in 33 (19.8%), 18 (10.8%), and 10 (6.0%) intervals for SBP, DBP, and HR, respectively.

Results are illustrated in Figures 6-8, where statistical significance (P<0.05) is represented as dark-filled symbols, borderline statistical significance (0.05<P<0.10) as lightly-filled symbols, and non-significance (P>0.10) as open symbols. It can readily be seen that instances when the cis-half-year reaches statistical significance do not occur at random but mostly as clusters in time. Large changes in the amplitude of all three components are also observed for all three variables.

The occasional (intermittent) presence of all three components coexisting concomitantly in the BP and HR data of RBS was of interest in relation to another study in Florence, Italy, on circulating melatonin, offering a fresh interpretation to results obtained earlier. In the course of ~4 years, blood samples had been obtained at 4-hour intervals for 24 hours from each of 172 subjects for the determination of melatonin (24). Original analyses of the serially-independent data pooled from all subjects stacked over an idealized year had reported the presence of a circannual variation characterizing daytime samples, contrasting with the detection of a half-yearly component in nighttime samples (24). A recent reanalysis of these data without stacking revealed the presence of a cis-half-year instead of the originally reported half-year, Figure 9 (25).

Phase behavior of the year, half-year, and cis-half-year components in BP and HR

Figures 10-12 illustrate the time course of the acrophases of the three components with periods of 1.0, 0.5, and 0.41 year, fitted concomitantly in ~4-year intervals displaced in ~0.21-year increments. The acrophases are shown only when the zero-amplitude test could be rejected at P<0.10. The yearly component is detected most of the time for SBP and DBP, but less often for HR. There are large changes in the circannual acrophases as a function of time, with a range larger than 4 and 5.5 months for SBP and DBP, respectively, and exceeding 7.5 months for HR, indicating that this component is much less stable than could be anticipated from the strong seasonal changes in the environmental temperature of Minnesota. The 1.0-year component may be modulated by lower-frequency components. The 0.5-year and 0.41-year components are only sporadically detected and their time course shows an intermittency contrasting with the relative consistency of the yearly component.

Global analyses assess additional components characterizing BP and HR

Apart from the cis-half-year, other non-photic components characterize RBS's data. One of these components has an anticipated period of ~0.55 year, too close to 0.5 and 0.41 year to be reliably resolved in ~4-year intervals. Additional global analyses were hence performed on the entire 39-year series (1968-2006). Because some low-frequency components account for a much larger portion of the overall variance, analyses were processed in two steps. In the first step, components with periods longer than ~4 years were assessed nonlinearly together with a fixed yearly component and its second harmonic of 6 months. The model was then subtracted from the weekly means. In the second step, residuals were nonlinearly analyzed (allowing the period to vary as a parameter to be estimated) to try to resolve the remaining components of interest and to determine their (period) length. A composite model using the nonlinearly estimated periods was then fitted linearly to determine the extent of their statistical significance.

Low-frequency components considered had trial periods of 25, 11.1, 6.5, and 4 years. They were fitted concomitantly with fixed 1.0- and 0.5-year harmonically-related components. Nonlinear results indicated that all components could be resolved for SBP, the periods and their CIs being estimated as 22.56 [21.20, 23.92], 11.44 [10.92, 11.96], 6.66 [6.44, 6.88], and 4.03 [3.91, 4.15] years. In the case of DBP, all infra-annual components were also validated nonlinearly conservatively, whereas the half-year could only be assessed on the basis of a (more "liberal") 1-parameter CI of the amplitude that did not overlap zero. The period estimates for DBP were 20.55 [19.00, 22.10], 10.75 [10.14, 11.37], 6.70 [6.38, 7.03], and 3.96 [3.82, 4.10] years. In the case of HR as well, only the half-year had only a 1-parameter CI of the amplitude that did not overlap zero. The period estimates for HR were 32.68, 13.59 [13.03, 14.15], 5.82 [5.71, 5.93], and 3.99 [3.91, 4.08] years. The selective multidecadal congruence is visualized in Figure 3.

Residuals from the above models indicated the presence of components with trial periods of 1.65, 1.38, 1.25, 0.55, and 0.41 year(s), corresponding to spectral peaklets in the global spectra of the weekly means. Nonlinearly, the three trans-yearly components were validated for SBP. Albeit the conservative approach yielded CIs of the amplitude that overlapped zero, the 1-parameter CI of the ~0.55-year and 0.41-year amplitudes did not overlap zero. With this qualification, period estimates and their CIs were 1.682 [1.646, 1.718], 1.400 [1.371, 1.428], 1.245 [1.226, 1.263], 0.548 [0.542, 0.555], and 0.413 [0.408, 0.417] year(s). In the case of DBP, the ~1.25-year component could not be validated and the other four components all had (if not conservative) 1-parameter CIs of the amplitude that did not overlap zero. With this qualification, the period estimates and their CIs were 1.695 [1.653, 1.738], 1.393 [1.339, 1.448], 1.235 [1.159, 1.310], 0.548 [0.537, 0.559], and 0.412 [0.407, 0.418] year(s). In the case of HR, a slightly different trial period had to be used for the first transyear: instead of a trial period of 1.65 years, one of 1.86 years was used. This component and the ~1.38-year component were both validated conservatively. The other three all had a 1-parameter (but not a conservative) CI of the amplitude that did not overlap zero. With this qualification, period estimates and their CIs were 1.806 [1.760, 1.851], 1.394 [1.371, 1.417], 1.247 [1.223, 1.271], 0.550 [0.541, 0.559], and 0.411 [0.408, 0.415] year(s).

A 5-component model using the periods estimated nonlinearly was then fitted, the periods differing slightly for each variable. This model and each of its constituent components was statistically significant for SBP and for HR, but in the case of DBP, only the ~1.69-year and ~1.39-year components reached statistical significance, whereas the 0.41-year component only reached borderline statistical significance (P=0.054). The other two components with periods of ~1.24 and ~0.55 year(s) were not statistically significant and had to be removed from the model.

Infra-annual modulations of the 1.0-year, 0.5-year, and 0.41-year amplitudes of BP and HR

In order to explore possible environmental influences underlying the changes in amplitude of the 1.0-year, 0.5-year, and 0.41-year components of SBP, DBP, and HR, the amplitude estimates from the 3-component serial sections were further analyzed by least squares spectra, with the understanding that P-values obtained in the following analyses cannot be taken at their face value since the serial sections were pergressive with an increment 1/19 the length of the interval. With this qualification, Figure 13 summarizes the results, rough estimates of the periods corresponding to spectral peaks marked in each case. Apart from some low-frequency components that may contribute sidelobes in global spectra of the weekly means, the following two observations may deserve further investigation. First, perhaps because of the relatively large changes in amplitude and acrophase of the yearly component as a function of time, the 1.0-year amplitudes are characterized by an ~1.1-year component for SBP and DBP and by an ~1.2-year component for HR. Second, the cis-half-year amplitudes of HR are characterized by a prominent ~11-year component.

Figure 14 (see also Figure 1) illustrates the ~11-year modulation of the cis-half-year amplitude of HR. Figure 15 shows that the cis-half-year amplitudes of DBP similarly lag after solar flares. RBS' HR and DBP as well as the total solar flare index are in synchrony with a decadal Horrebow-Schwabe cycle. As shown in Figure 2 (and discussed elsewhere), HR and Wolf numbers are also modulated by the transtridecadal **B**rückner-**E**geson-**L**ockyer (BEL) cycle (17, 26, 27).

Methodologically and basically revealing is that the search for another biotic cis-half-year has not only validated the latter in the longest available series of BP and HR, but has found near-transyears in SBP and DBP, whose presence had also been documented in physics (prompted by their presence in the elderly's BP). Whether the near-transyear is a nonlinear modulation by a lower frequency in physics, e.g., in solar magnetism or a component in its own right, it has a biological counterpart. Further, as to reciprocal periods of the beats of the rotations at different solar latitudes, Charles Wolff's predicted periods have been found not only as a cis-half-year but also as a trans-half-year of 0.55 year. At one end of the CI, its period is within one decimal of Wolff's 0.56-year prediction (23). Moreover, both these periods have been validated along with a very likely geomagnetic component of 0.50 year.

Conclusion

Multiple spectral component signatures of time-varying solar activity are likely to characterize any time series covering years. When an anticipated component is not detected by the fit of a single component, a concomitant fit of several components is indicated. Apart from this methodologic truism that bears emphasis as the control information for any and all studies, we here demonstrate the intermittency of cis-half-years in the adult human circulation and their temporal association with an about 11-year cycle in solar flares, with a lag somewhat longer than 3 years.

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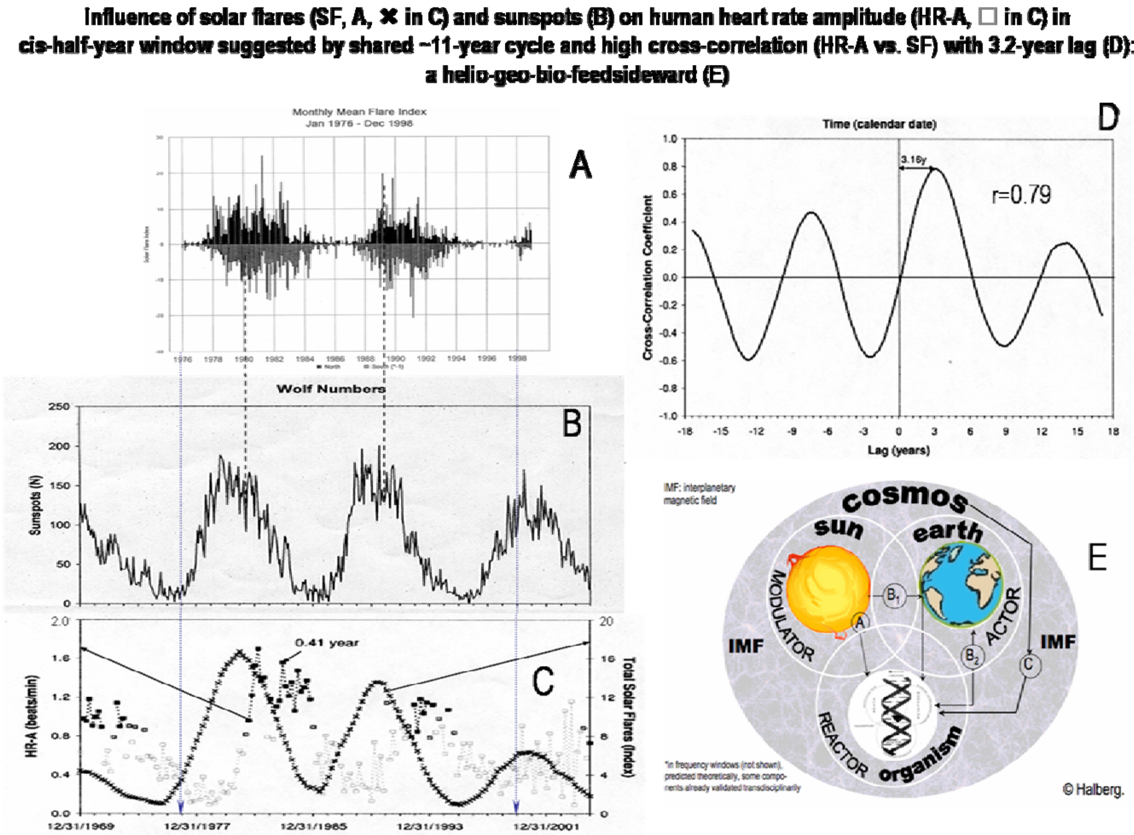
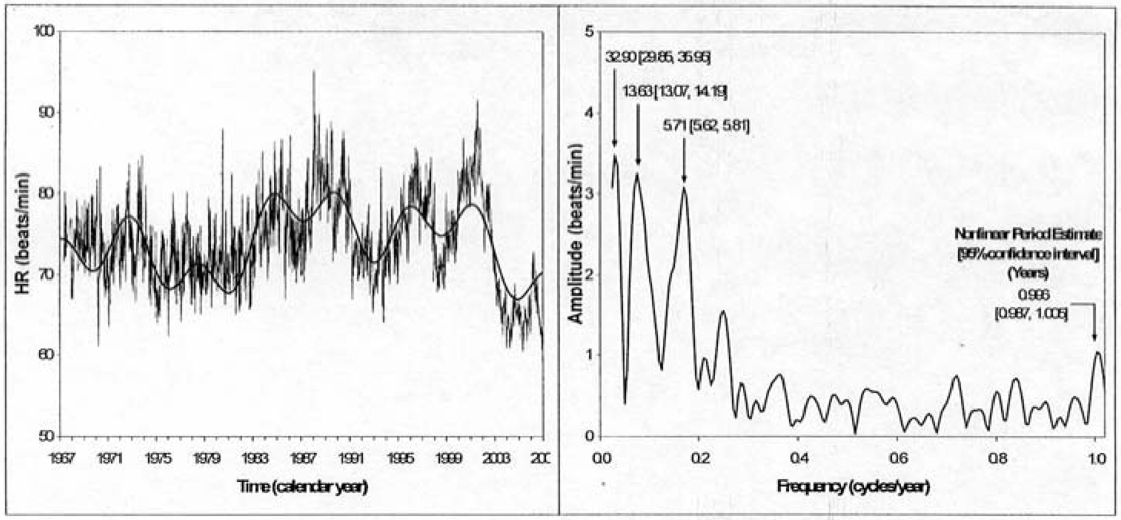


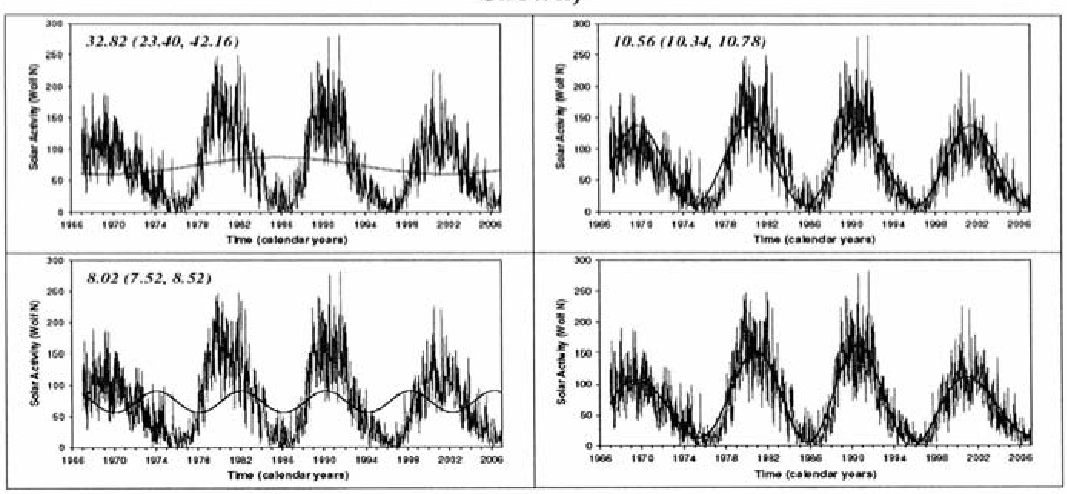
Figure 1. Horrebow-Arago-Schwabe pattern of solar flares (top and bottom, left) and of Wolf numbers (middle, left) is shared with changes in cis-half-year amplitude of RBS' HR (bottom, left). The cross-correlation function of the latter with the total solar flare index reaches a maximum of 0.79 at a 3.16-year lag (top, right). © *Halberg*.

BEL Cycle in Human Heart Rate during 40 Years *



*Weekly averages of data from RBS, clinically healthy man, 21 years of age at start of self-measurements 5-7 times per day during 1967-2006 (N=1978). Transtridecadal Brückner-Egeson-Lockyer cycle (BEL) of 32.9 years in human heart rate of RBS given with its 95% confidence interval in the spectral window (right), derived from original data shown on the left with the fitted model. Note that numerically the BEL cycle has the largest amplitude in the window examined, while it is the smallest in Figure 4 in Zürich numbers. BEL cycle is dominant while Zürich sunspot numbers below show only a week statistically significant counterpart. © Halberg.

Wolf Numbers During a 40-Year Span of Physiological Monitoring Show an About 33-Year Cycle (top left), Also Seen in Heart Rate Data (Latter Not Shown)*



Composite 3-component model fitted to data (bottom right), with contribution by each separate component also shown (top and bottom left) with nonlinearly resolved period (in years) and 95% confidence interval in person. Minor transtridecadal BEL aspect of Zürich sunspot numbers, top left, as compared to other components with much larger amplitude (top right and bottom left) and by contrast to the prominent BEL in heart rate in *RBS (clinically healthy man, about 20.5-years of age at start of monitoring) shown in Figure 3. Entire model shown at the bottom on the right. © Halberg.

Figure 2. Congruences were reported earlier (17) at a period of ~33 years between RBS' HR and Wolf's sunspot numbers. Whereas this component is rather weak in the physical variable, it is much more prominent in HR, as apparent from the least squares spectra. © *Halberg*.

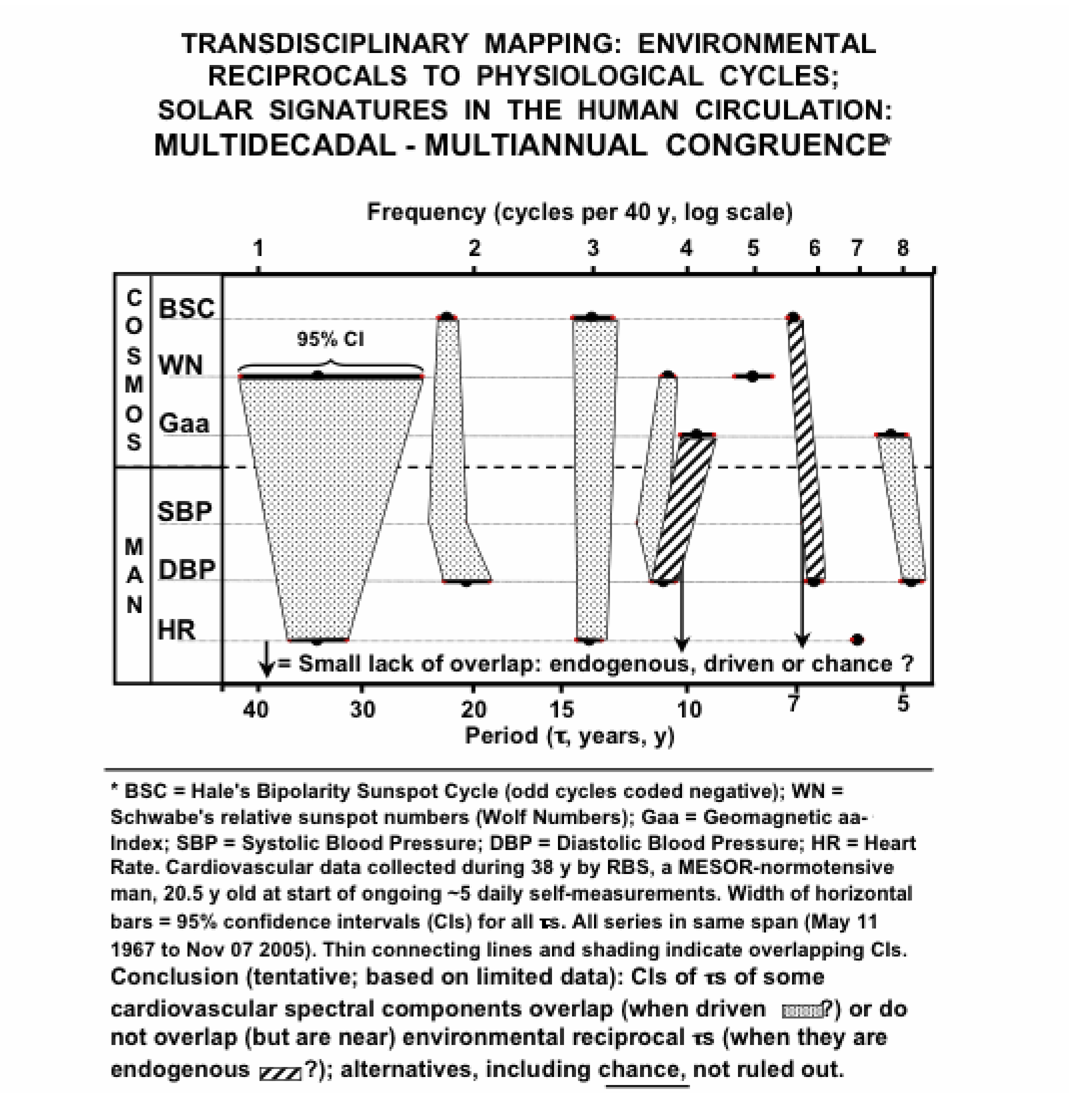


Figure 3. Summary of relative congruences between RBS' HR and BP and non-photic environmental variables, including the one shown in Figure 2 (top left). Note a didecadal congruence between RBS' BP and Hale's bipolarity cycle of sunspots. © *Halberg*.

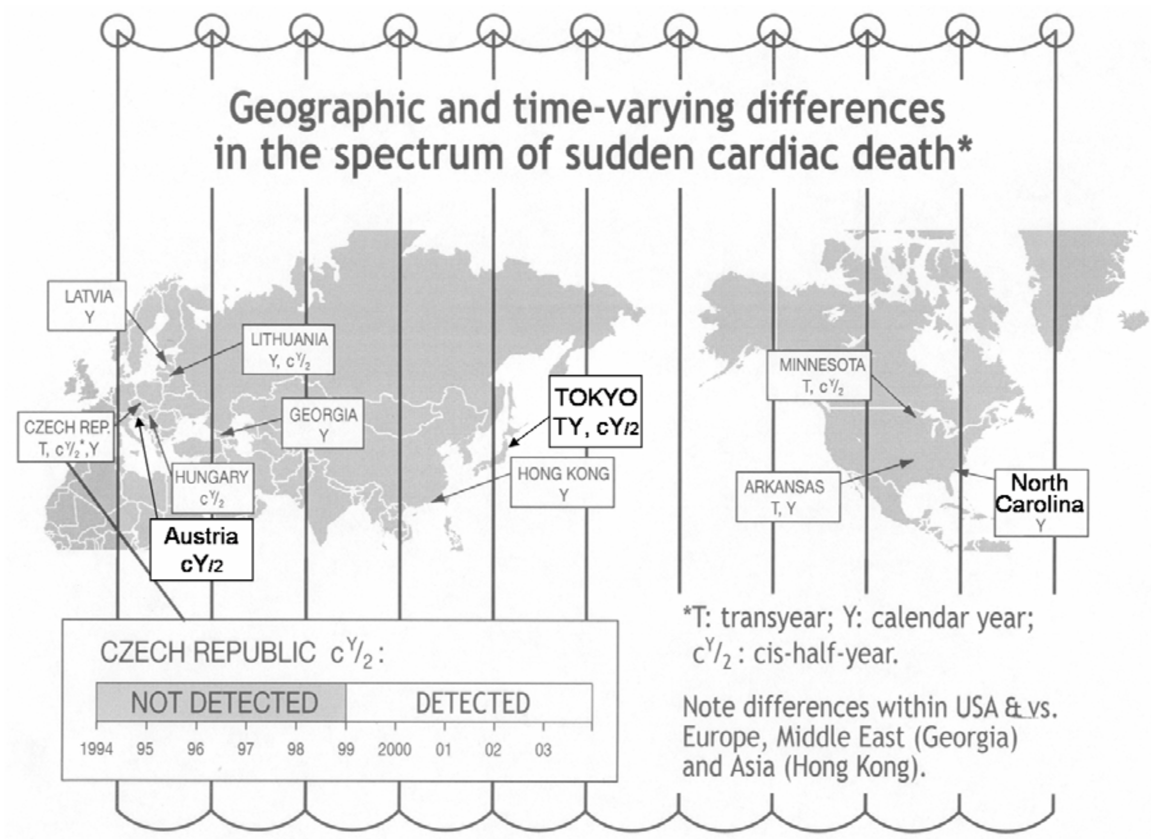


Figure 4. A cis-half-year (cY/2) had been found in the incidence patterns of sudden cardiac death in Minnesota (15) and in some other geographic locations, as summarized in this map. © *Halberg*.

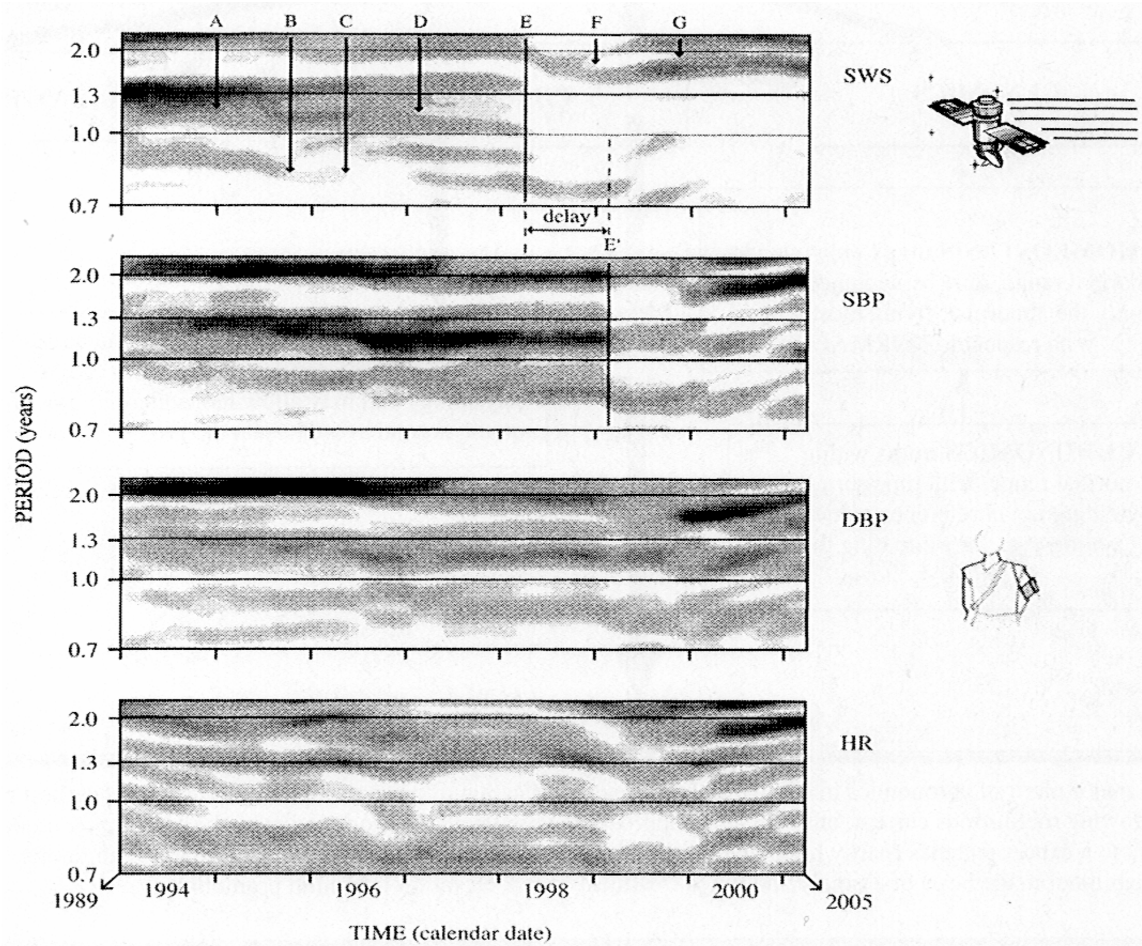


Figure 5. A cis-half-year had been found in the SBP of an elderly subject (FH) during nearly 16 years of around-the-clock monitoring (with interruptions), at 70-86 years of age (15). © *Halberg*.

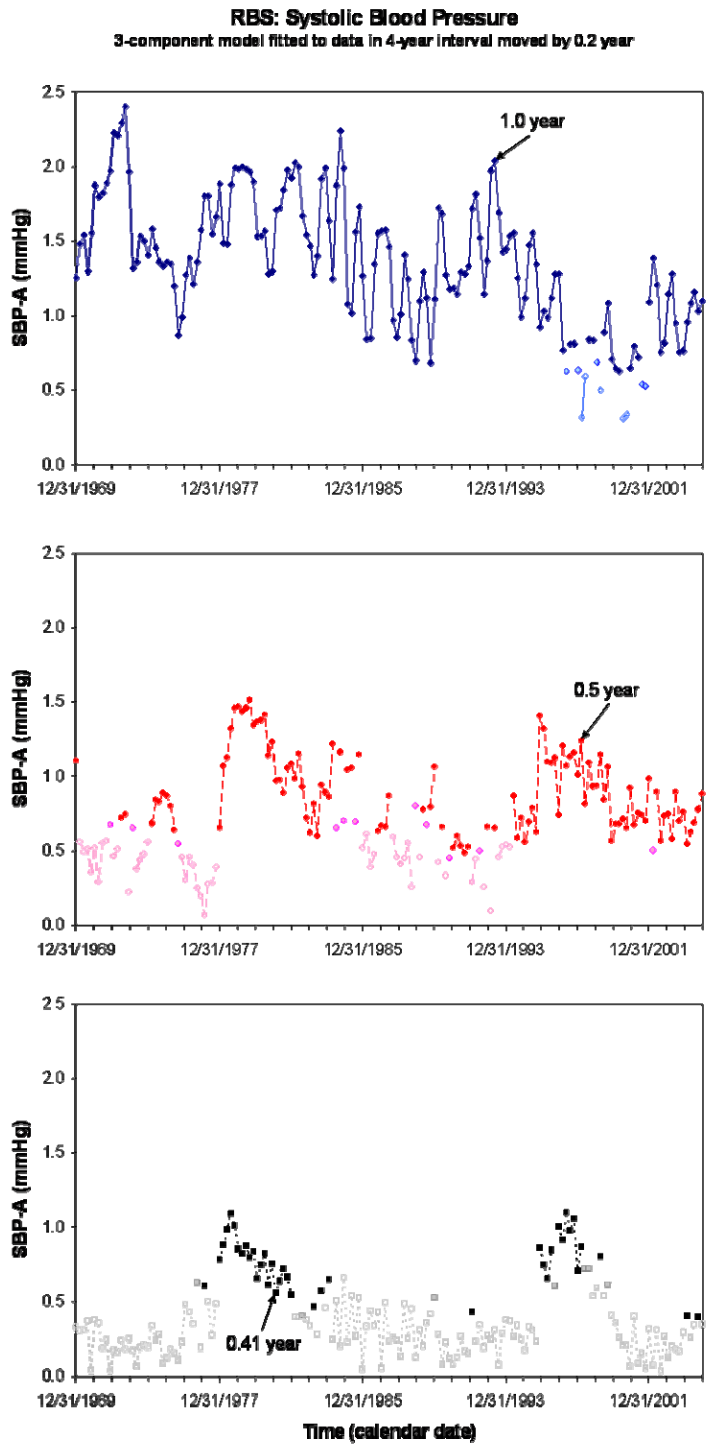


Figure 6. Statistical significance (P<0.05) of 1.0-year (top), 0.5-year (middle), and 0.41-year (cis-half-year, bottom) components fitted concomitantly to the SBP data of RBS is represented as dark-filled symbols, borderline statistical significance (0.05<P<0.10) as lightly-filled symbols, and non-significance (P>0.10) as open symbols. It can readily be seen that instances when the cis-half-year reaches statistical significance do not occur at random but mostly as clusters in time. Large changes in the amplitude of all three components are also observed for all three variables. © *Halberg*.

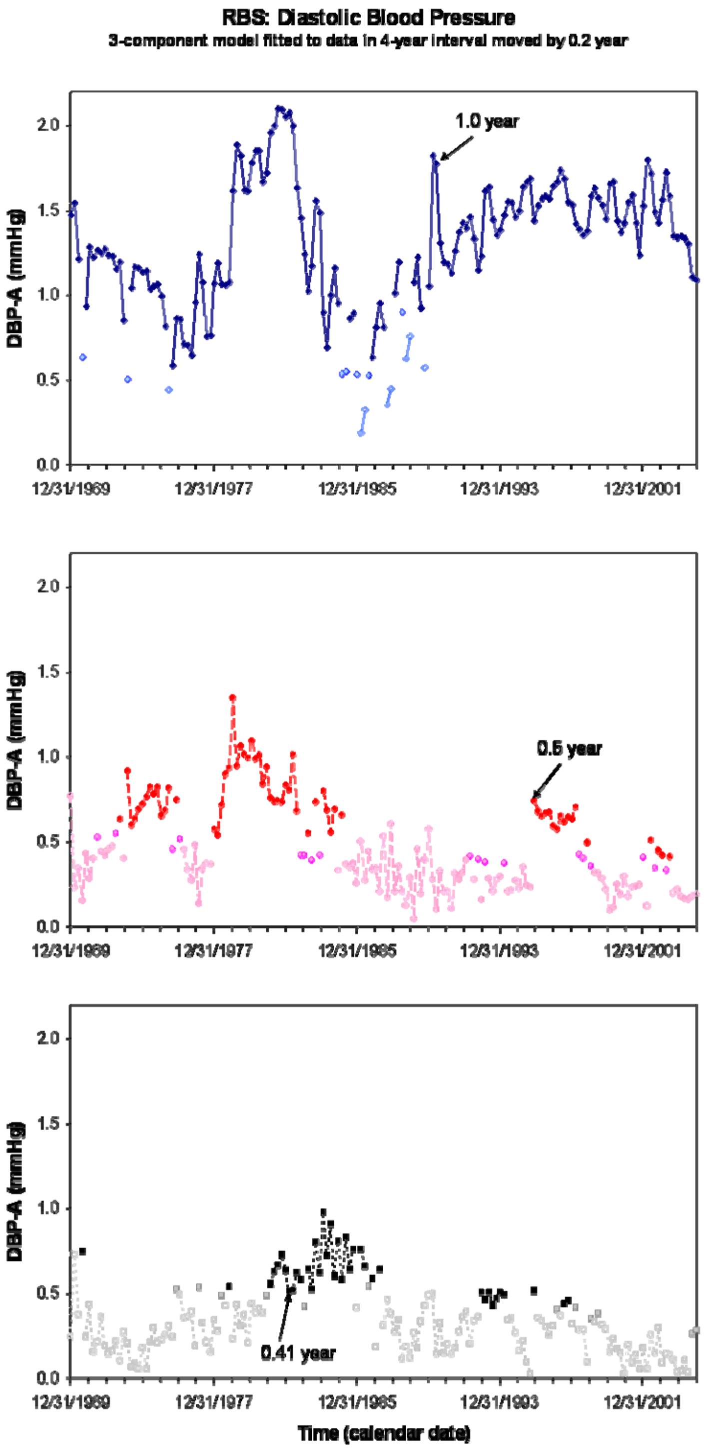


Figure 7. Statistical significance ($P<0.05$) of 1.0-year (top), 0.5-year (middle), and 0.41-year (cis-half-year, bottom) components fitted concomitantly to the DBP data of RBS is represented as dark-filled symbols, borderline statistical significance ($0.05<P<0.10$) as lightly-filled symbols, and non-significance ($P>0.10$) as open symbols. It can readily be seen that instances when the cis-half-year reaches statistical significance do not occur at random but mostly as clusters in time. Large changes in the amplitude of all three components are also observed for all three variables. © *Halberg*.

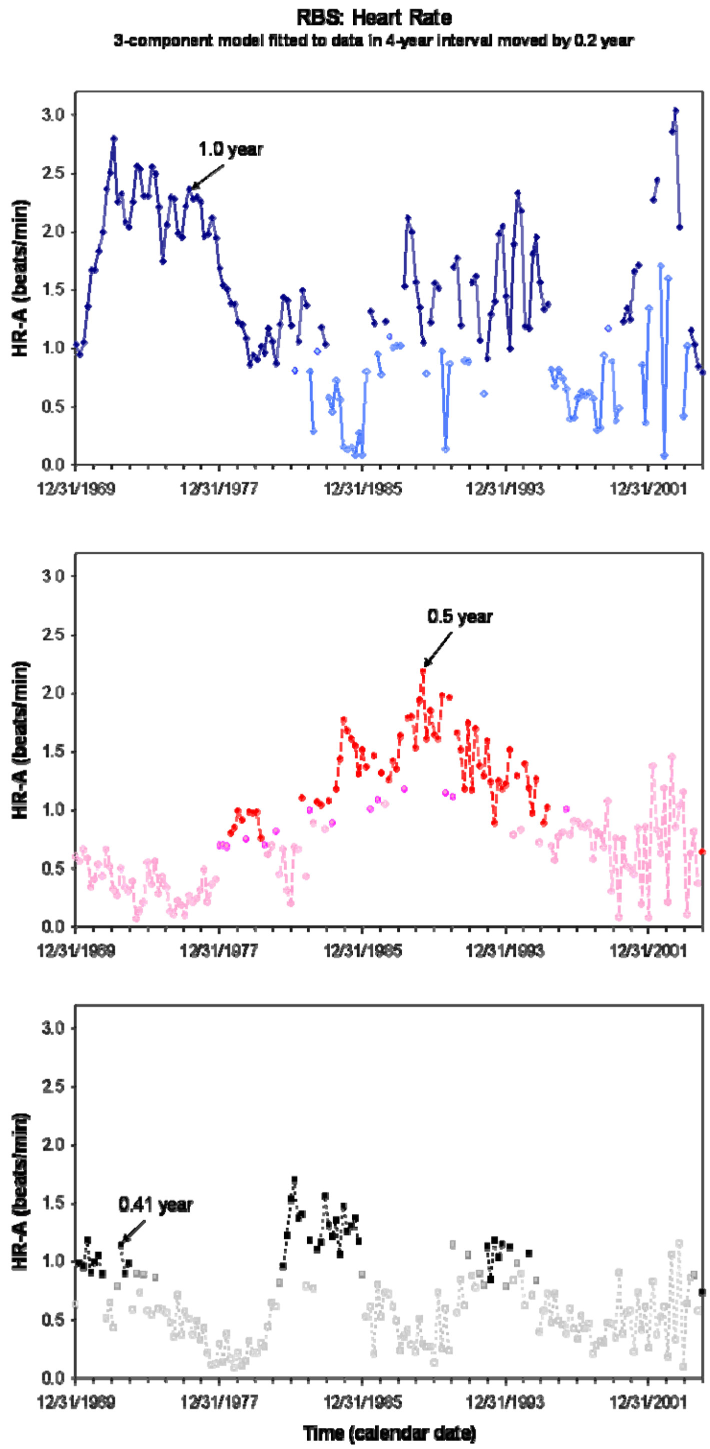
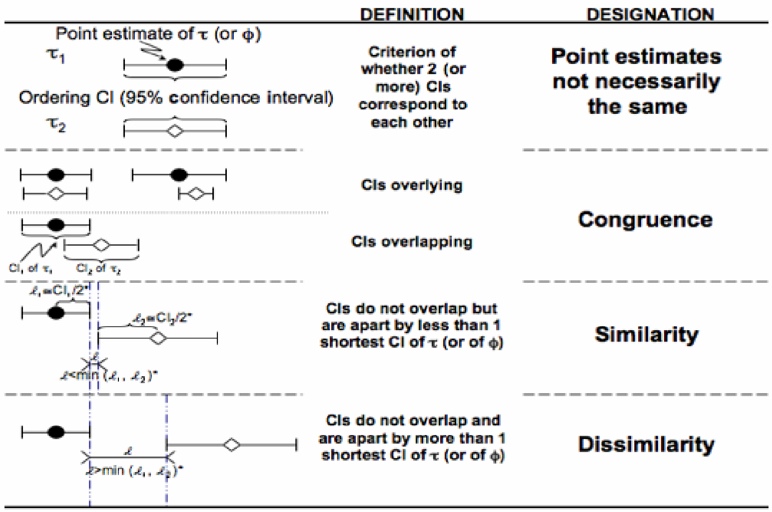


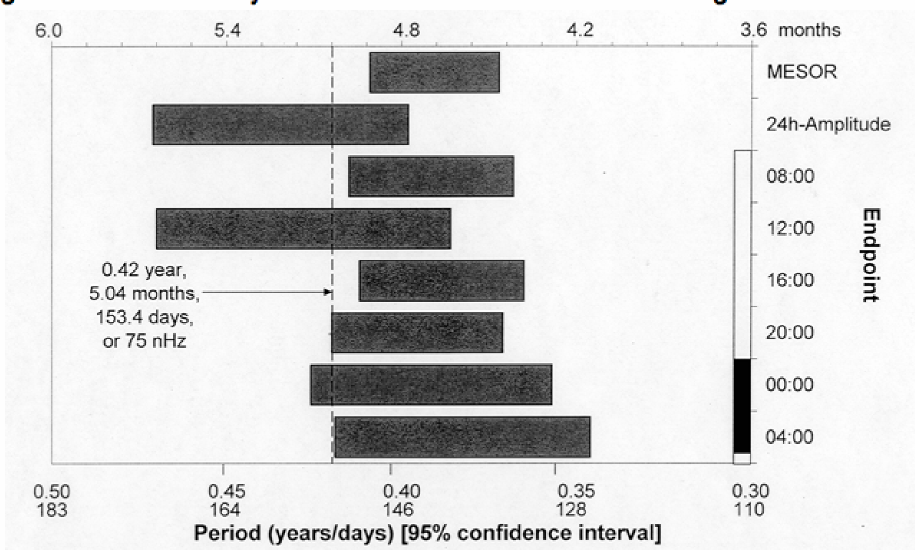
Figure 8. Statistical significance ($P<0.05$) of 1.0-year (top), 0.5-year (middle), and 0.41-year (cis-half-year, bottom) components fitted concomitantly to the HR data of RBS is represented as dark-filled symbols, borderline statistical significance ($0.05<P<0.10$) as lightly-filled symbols, and non-significance ($P>0.10$) as open symbols. It can readily be seen that instances when the cis-half-year reaches statistical significance do not occur at random but mostly as clusters in time. Large changes in the amplitude of all three components are also observed for all three variables. © *Halberg*.

Abstract scheme of **congruence** as a first step toward the test of equality of two or more periods, τ, or phases, φ*



*ℓ_1 and ℓ_2 are one-sided CI length; ℓ is distance between proximal limits of non-overlapping CIs of τs (or φs).

Congruence of cis-half-year characterizes human circulating melatonin**



**172 patients (Oct 1992-Dec 1995), each providing 4-hourly blood samples for 24 hours in Florence, Italy.

Figure 9. In melatonin data that were serially-dependent along the 24-hour scale, each person providing blood at 4-hour intervals for 24 hours, but serially-independent after pooling across 172 subjects examined in the course of ~4 years, a cis-half-year rather than half-year is invariably detected observed, characterizing the individual MESORs and circadian amplitudes as well as both daytime and nighttime samples considered separately. A map of the nonlinear estimates of cis-half-year periods and their CIs (bottom) is provided with an abstract definition of congruence (top). © *Halberg*.

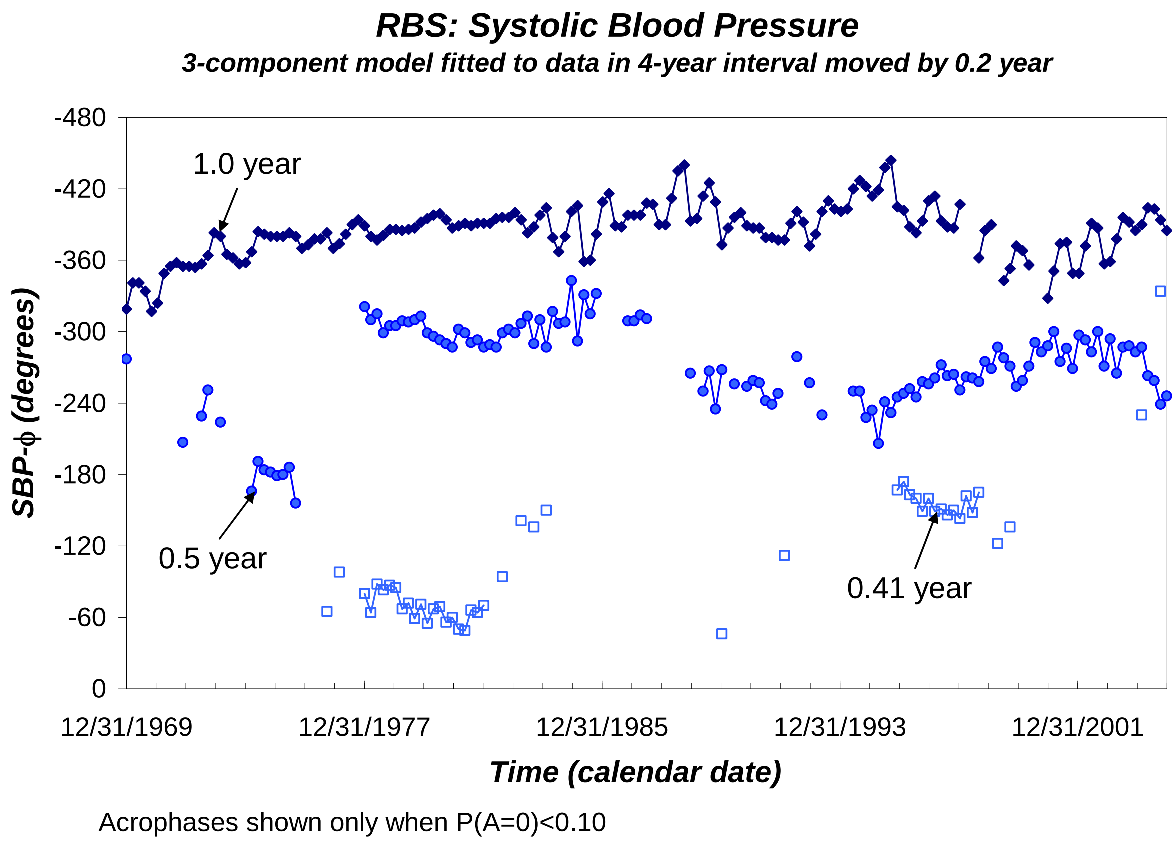


Figure 10. Time course of the acrophases of the three components (with periods of 1.0, 0.5, and 0.41 year) fitted concomitantly to the SBP data of RBS. Acrophases are shown only when the zero-amplitude test could be rejected at P<0.10. The 1.0-year component is detected most of the time, and all three components are occasionally detected concomitantly, albeit only intermittently. © *Halberg*.

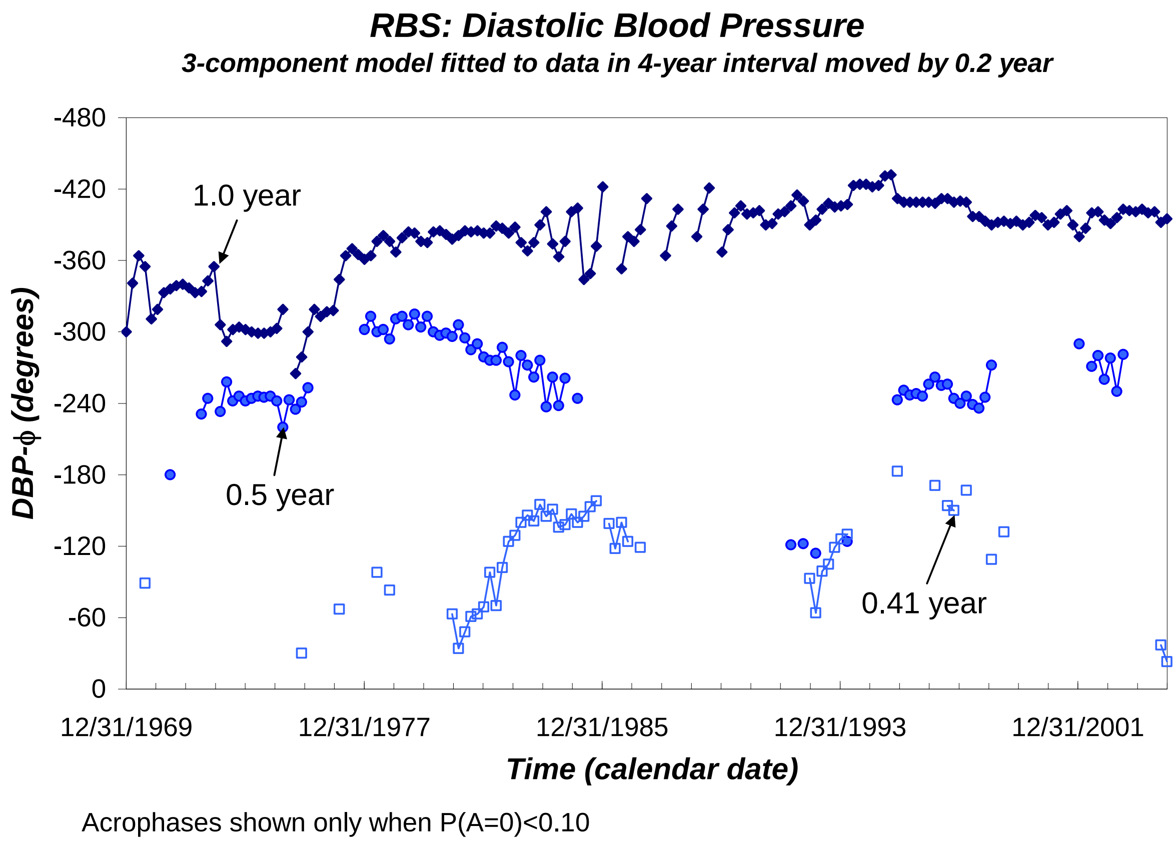


Figure 11. Time course of the acrophases of the three components (with periods of 1.0, 0.5, and 0.41 year) fitted concomitantly to the DBP data of RBS. Acrophases are shown only when the zero-amplitude test could be rejected at P<0.10. The 1.0-year component is detected most of the time, and all three components are occasionally detected concomitantly, albeit only intermittently. © *Halberg*.

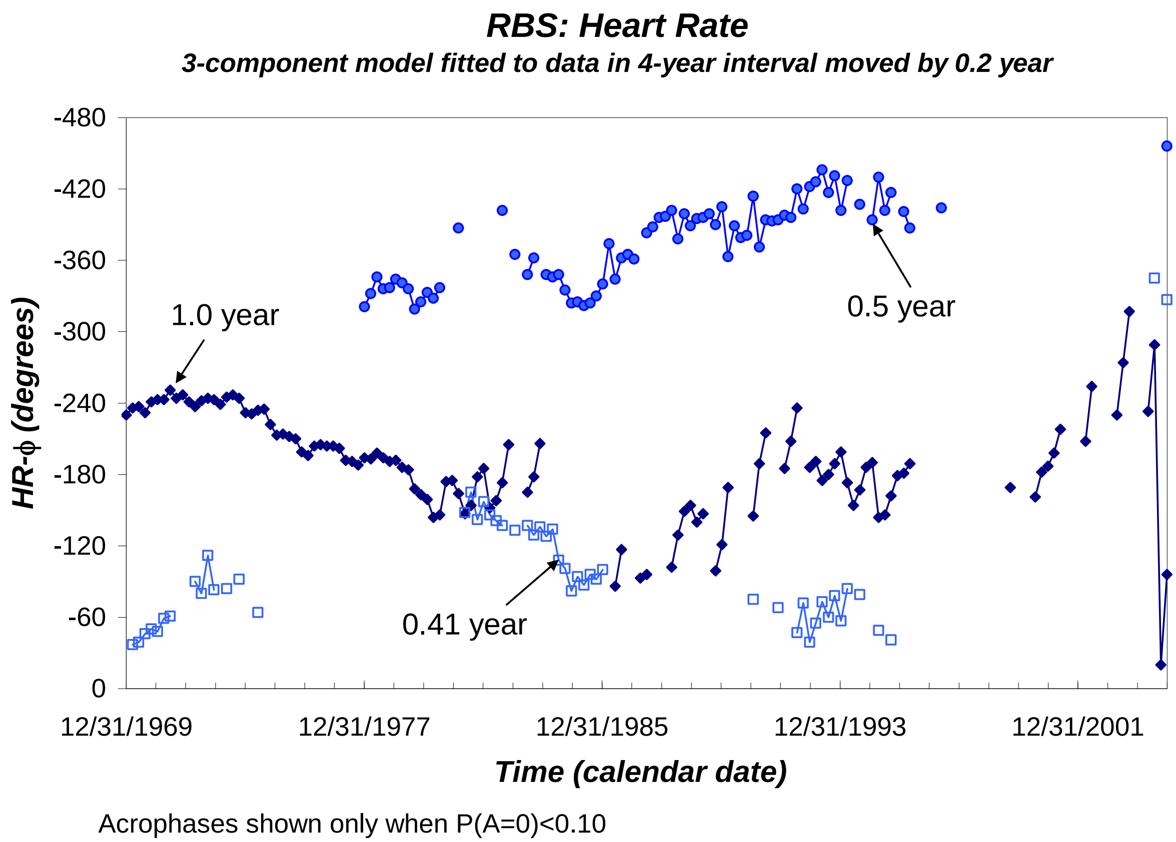


Figure 12. Time course of the acrophases of the three components (with periods of 1.0, 0.5, and 0.41 year) fitted concomitantly to the HR data of RBS. Acrophases are shown only when the zero-amplitude test could be rejected at P<0.10. The 1.0-year component detected most of the time in the case of SBP and DBP is less consistent for HR. All three components are occasionally detected concomitantly, albeit only intermittently. © *Halberg*.

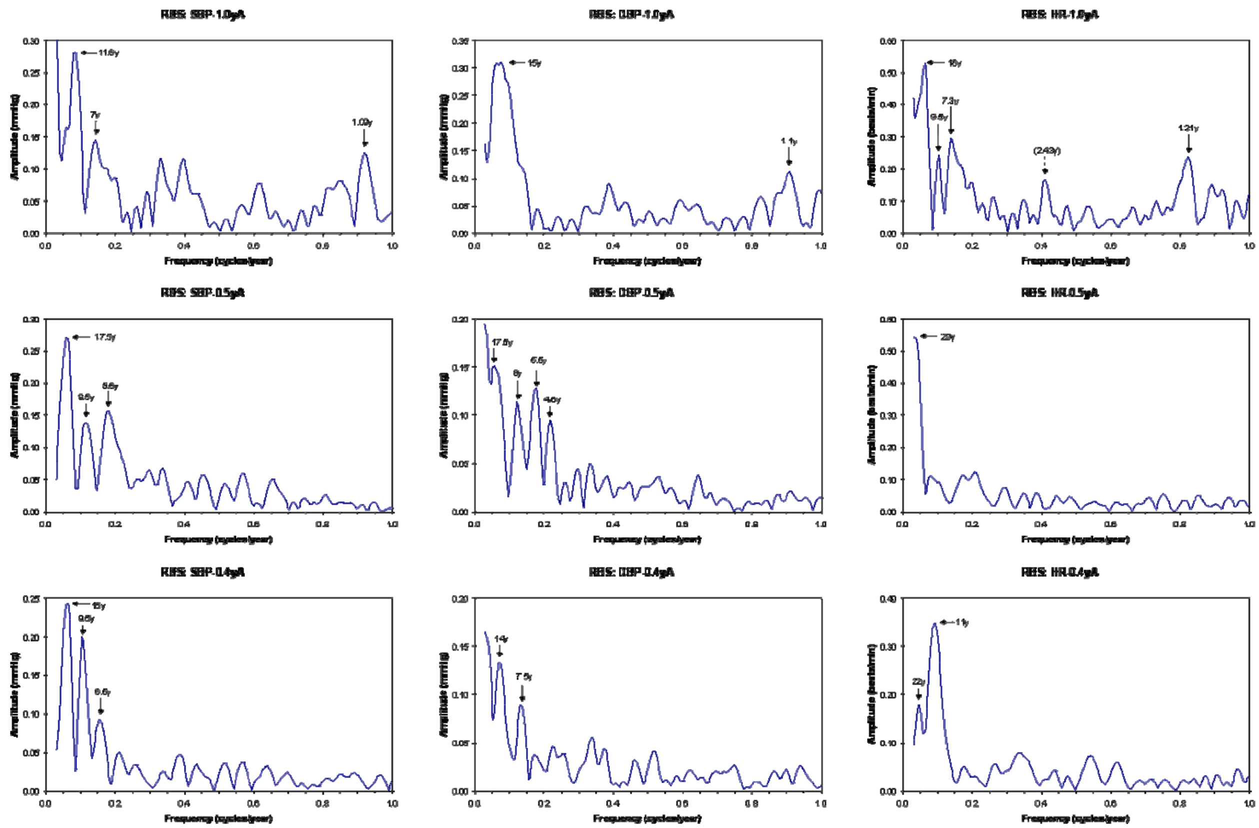
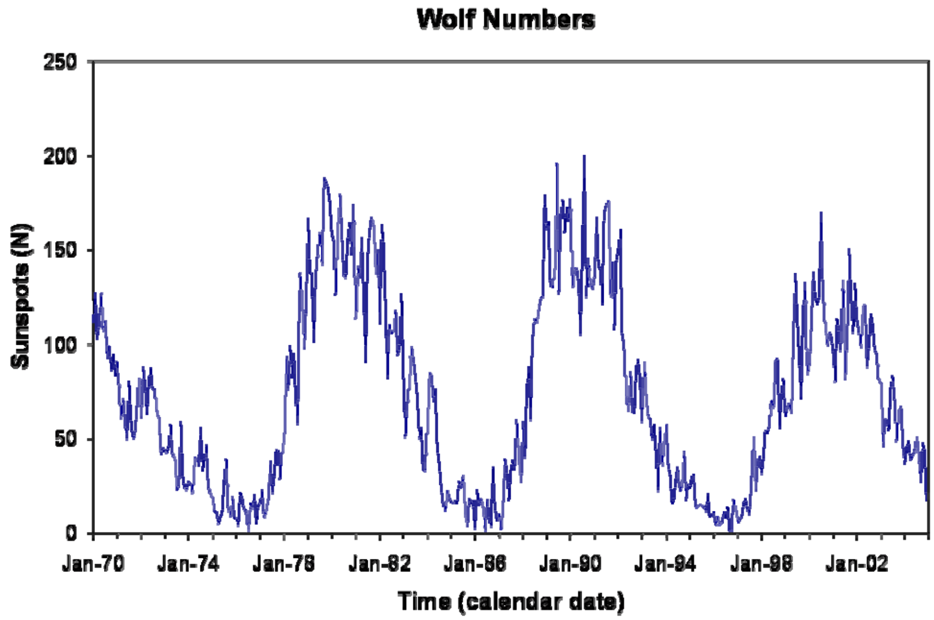


Figure 13. Least squares spectra of the amplitude estimates from the 3-component serial sections, with periods of 1.0-year (top), 0.5-year (middle), and 0.41-year (bottom) of SBP (left), DBP (middle), and HR (right) of RBS. P-values obtained in these analyses cannot be taken at their face value since the serial sections were pergressive with an increment 1/19 the length of the interval. Perhaps because of the relatively large changes in amplitude and acrophase of the yearly component as a function of time, the 1.0-year amplitudes have an ~1.1-year spectral peak for SBP and DBP and by an ~1.2-year spectral peak for HR. The cis-half-year amplitudes of HR are characterized by a prominent ~11-year component. © *Halberg*.



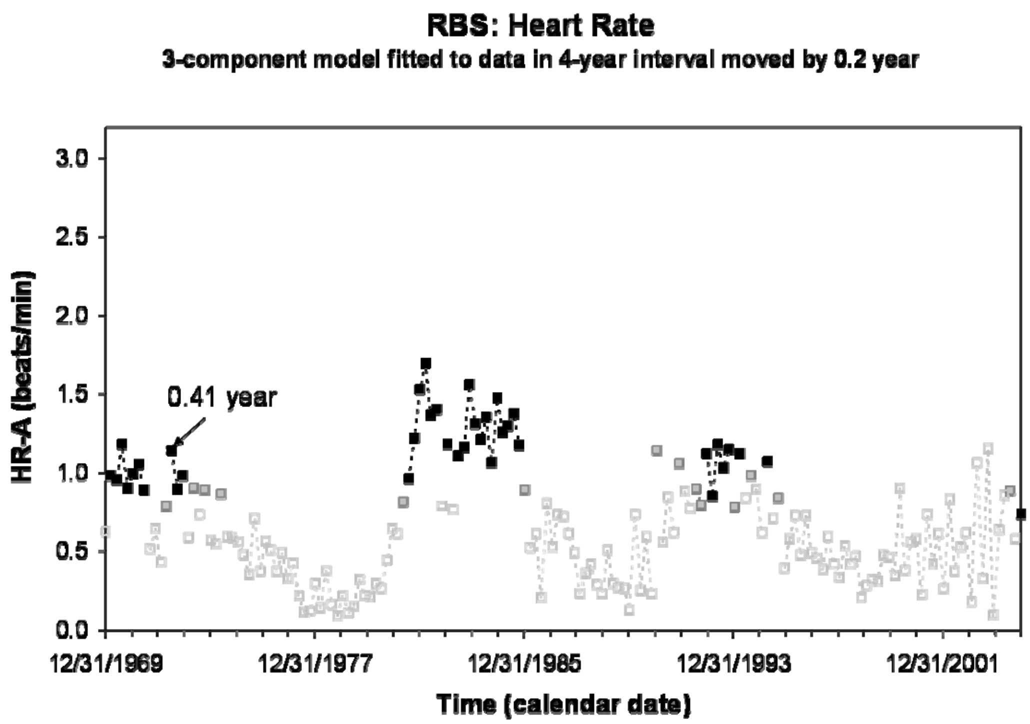
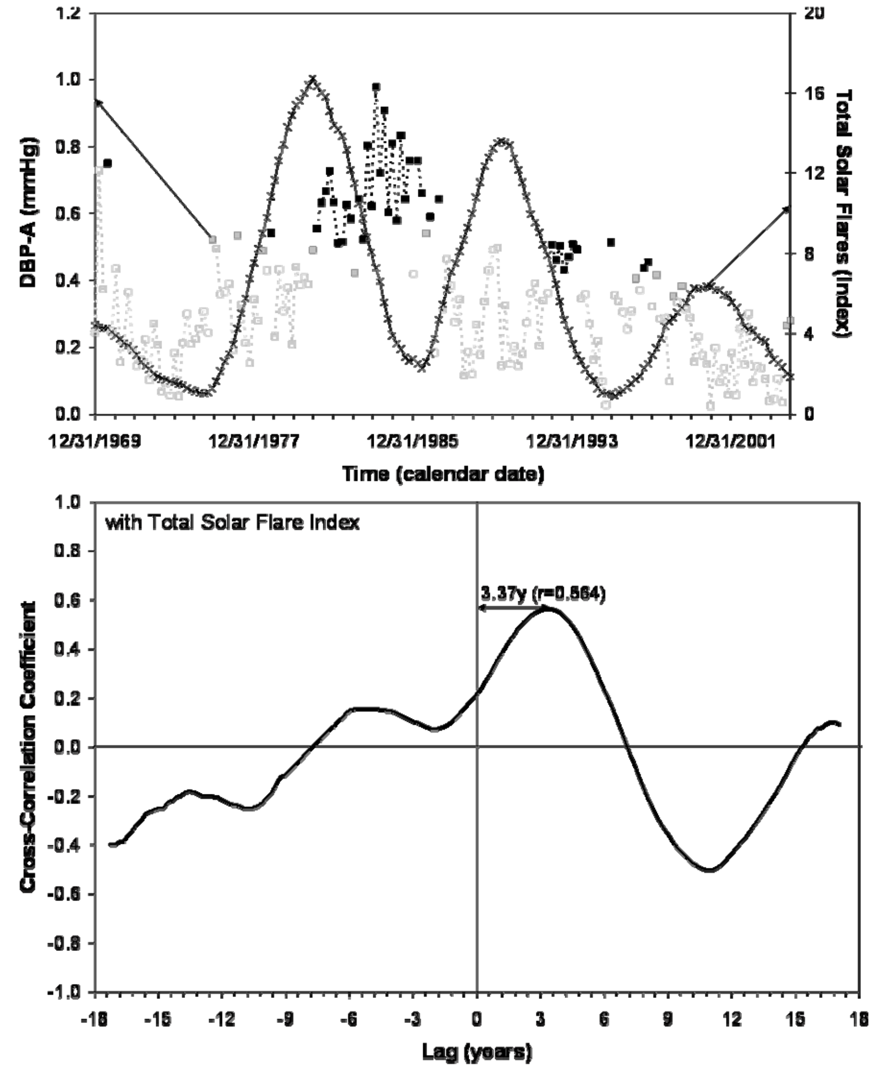


Figure 14. As also summarized in Figure 1, the cis-half-year amplitude of HR (bottom) shares an ~11-year cycle with Wolf numbers (top). © *Halberg*.

Human Diastolic Blood Pressure May Not Respond as Clearly as Heart Rate to the Schwabe Cycle

Cis-Half-Year (cHY) Amplitude (A) of Diastolic Blood Pressure (DBP) of Healthy Man (RBS)* Correlates Maximally with Solar Flares (SF) after about 3.2-Year Shift**



* Assessed in 4-year intervals moved by 0.2-year over 39 years (1968-2006).

** Top: Time course of RBS' DBP-A(cHY) (squares) and SF Index (crosses). Data are weekly averages analyzed in 209-week intervals moved by 11 weeks. DBP-A(cHY) estimated by 3-component model consisting of cosine curves with periods of 1.0, 0.5, and 0.41 year(s). P-values from zero-amplitude test <0.05, 0.05<P<0.10, or P>0.10 are shown as solidly-filled, lightly-filled, or open squares, respectively. SF are 209-week moving averages, computed every 11 weeks, to match HR-A(cHY). Bottom: Cross-correlation coefficients of DBP-A(cHY) versus SF show a maximum at 3.37 years.

RBS: Clinically healthy man who measured his HR about 5 times a day on most days since May 1967 when he was 20.5 years old.

Figure 15. Similarly to HR, the cis-half-year amplitudes of DBP are cross-correlated with solar flares, reaching a peak association of 0.564 at 3.37-year lag after the total solar flare index. © *Halberg*.

META-ANALYSIS OF HORREBOW'S AND SCHWABE'S SCHOLARSHIP WITH A VIEW OF SAMPLING REQUIREMENTS

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Jarmila Siegelova[2], Pavel Homolka[2], Jiri Dusek[2], Bohumil Fiser[2]

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Abstract

Christian Pedersen Horrebow (1718-1776), a Danish astronomer, son of Peder (Nielsen) Horrebow (1679-1764), whom he succeeded as head of the astronomical observatory associated with the University of Copenhagen, deserves credit for a thorough sunspot data collection between 1761 and the time of his death (16 years), continued by his successor only until 1777 (1). The rejection of the "no-cycle", i.e., "zero-amplitude" assumption, in sunspots with data covering, with gaps, not more than a single cycle is here documented by a chrono-meta-analysis as a statistically and, in retrospect, transdisciplinarily significant phenomenon. Samuel Heinrich Schwabe (1789-1876) started another series of sunspot numbers in 1826 and continued it for 17 years. He published data in 1838 without referring to a cycle (2). Meta-analyses demonstrate that his data over a single cycle suffice for establishing statistical significance. Schwabe would not have had to wait for 6 more years (3) before explicitly reporting a solar periodicity as he did in 1844. Both Horrebow's and Schwabe's meta-analyzed data are here discussed in the context of minimal sampling requirements on relatively long cycles that must be assessed in limited data covering but a single cycle or less, in the case of even shorter accumulating time series, if not in sunspots then in human heart rate (4).

Problem

In the early 1950s, it was relatively easy to gain the cooperation of members of a medical fraternity at the University of Minnesota to give blood at 90-minute intervals around the clock for one or two 24-hour spans and longer, in order to map their circadian rhythmic change in the count of certain blood cells. Even venipunctures every 90 minutes around the clock were tolerated without any blinking of eyes (5). We dealt with a large amplitude rhythm, not only in eosinophil cells but also in the cortical adrenal hormones that depressed them. Clinical laboratory practice ended up with a morning and/or evening cortisol, justified superficially by the 24-hour synchronization prevailing for the adrenal cortical cycle under ordinary conditions of life, albeit by reliance upon two spotchecks, one will lose invaluable diagnostic information not only in the case of cortisol but also in that of blood pressure.

The task of sampling about 10-year and about 35-year cycles (6, 7) is much harder when these are to be mapped on a given person. It then becomes necessary to consider what may be minimal sampling requirements to obtain a rough estimate of a given component's characteristics on the basis of limited data that may cover less than a full cycle. In particular, given components covering three decades or more, we aim at assessing them as soon as possible.

Background

Carl Friedrich Gauss (1777-1855), whose least-squares procedures we use herein for curve-fitting, was born the year after Christian Pedersen Horrebow died (in 1776). Joseph Fourier at that time was 8 years of age. Horrebow provided a first series of sunspot numbers, with gaps, at the time probably examined only by eyeballing, without Fourier's approach or Gauss' curve-fitting. Horrebow's counting of sunspots was continued for only a little while after his death, perhaps a year, since Clar. Baggio, Horrebow's immediate successor, had other interests, according to Thorwald Nicolai Thiele (1838-1910), then a student of astronomy (later an actuarial mathematician and statistician in addition to being an astronomer, and eventually Horrebow's successor as director of the astronomical observatory of the University of Copenhagen, from 1875 to 1907) (8). As Thiele wrote (1859): "Anno 1770 Horrebovius obiit *Clar*. *Baggio*, qui ei successit, aliis rebus intento, nullae vel paucae sequentibus annis macularum observations factae sunt."

Horrebow, cited by Thiele, had written that "... astronomers to date have taken too little care to make frequent observations of sunspots, undoubtedly because they think nothing can be accomplished thereby which would be of great importance to astronomy or physics. ... It is, however, to be hoped, by making diligent observations in this matter, that a definite cycle of heavenly bodies will be discovered; then at last it will be time to investigate as to how [heavenly] bodies, which are governed and illuminated by the sun, are brought into existence by the sun spots." (... astronomis adhuc parum curae fuit crebras macularum observationes facere, sine dubio quod nihil inde effici posse iis videbatur, quod astronomiae aut physicae magno opere interesset. Sperandum tamen est, diligenter observando etiam hac in re, ut in motibus ceterorum corporum coelestium periodum certam inventum iri; tum demum tempus erit inquirere, quonam modo corpora, quae a sole reguntur et illustrantur, maculis solis efficiantur." The follow-up visualized by Horrebow was realized by Samuel Heinrich Schwabe, who provided additional data that can be examined to focus on the length of sunspot series available in the 18th and 19th centuries that are required with modern computational tools to document a sunspot cycle in the circadecadal range of periodicities.

As a minimum, to detect a cyclic component of anticipated period (or a period near it), the zero-amplitude (no-rhythm) assumption needs to be rejected, usually at a probability level of 5% or less. Unknown components can be detected by spectral analysis or other similar procedure (9-11), in which case they need further validation, on the basis of complementary data, or if the time series is long enough, by the separate analysis of different sections. Several methods are available for rhythm detection and parameter estimation, as well as for model building when multi-frequency components characterize a given data series. The extended cosinor is used herein to examine several sets of related sunspot data published by Thiele (1), Schwabe (2, 3), and Hoyt and Schatten (12, 13), respectively. It seems interesting, in connection with Thiele's article first, that there is no bibliography and a reference to Schwabe is found only in the text, without a citation of prior publications.

Analysis of Horrebow's data

A time plot (chronogram) of the data tabulated by Thiele (Figure 1, top) shows about 1.5 sunspot (solar activity) cycles (with gaps), guesstimated from Horrebow's 204 monthly values between 1761 and 1776 and the addition of Baggio's data from 1777 (1). A least squares (14, cf. 9-11) spectrum (Figure 1, middle) reveals peaks corresponding to periods of about 9.5, 4.2 and 2.0 years.

Nonlinear analyses resolve the 9.4-year and the 2.1-year components but not the 4.2-year component. Periods and their 95% confidence intervals (CIs) are 9.554 [8.75, 10.36] and 1.971

[1.85, 2.09] years, with corresponding amplitudes of 4.47 [3.44, 5.50] and 1.26 [0.27, 2.25] (sunspots). The resulting two-component model is fitted to the data in Figure 1 (bottom).

All three components can be resolved nonlinearly after log-transformation ($y = \log_{10}(x+1)$), with periods and 95% CIs of 8.863 [7.80, 9.93], 5.037 [4.21, 5.87] and 2.153 [1.99, 2.31] years and corresponding amplitudes of 0.42 [0.32, 0.51], 0.17 [0.07, 0.27], and 0.09 [0.01, 0.17] (sunspots), when fitted concomitantly. Figure 2 illustrates the 3-component model fitted to the log-transformed data. Figure 3 shows the same model after back-transformation together with the original data.

Analyses of data from Hoyt and Schatten

Hoyt and Schatter (12, 13) provide three monthly data sets, the standard Wolf numbers (WN), the Group numbers (GN), and the Group Wolf numbers (GWN) from 1761 to 1777. The Group numbers coincide with the data published by Thiele (except for one small discrepancy of 0.2 for one of the monthly values). Because GN and GWN were both available on the same months but had missing values, one additional series was considered, consisting of the usual Wolf numbers (available for all months) omitting the monthly values when those were not available for the GN and GWB. A plot of the data as a function of time reveals a much sharper and higher maximum for the GWN than for the WN, Figure 4.

Least squares spectra (Figure 5) show peaks corresponding to an about 9.4-year component for WN and GWN, shifted to a slightly shorter period of about 8.9 years in decimated WN (to match the GWN data). About 4.1-year and about 2.1-year components characterize all three data sets, and an about 1.15-year or 1.16-year smaller peak is also detected for WN (not accounting for multiple testing), whether all data or the decimated data are analyzed, respectively, but not for GWN. An about 2.7-year peaklet is also found for WN. Nonlinear analyses validate the about 9.4- and 4.1-year components but not those with periods of about 2.7 and 1.15 years. The about 2.1-year component is resolved for GWN but not for WN, Table 1. The fact that this component is detected with borderline statistical significance for the decimated WN but not for the original WN suggests that it may be artifactual, related to the missing data.

Nonlinear analyses of the log-transformed data yield a 3-component model that differs between the WN (original or decimated) and the group WN. In the former case, the three components have periods of about 9.2, 4.5 and 3.1 years (the 3.1-year component being statistically significant when fitted singly, but reaching only borderline statistical significance when fitted concomitantly with the other two components), whereas in the latter case, the periods are about 9.2, 4.5 and 2.1 years. The same difference in model is found whether the components are fitted separately or concomitantly. Results from the concomitant fit of the three major components characterizing the log-transformed WN, decimated WN, and GWN are listed in Table 2. Figure 6 shows the 3-component models fitted to the original (top) and log-transformed (middle) data. Figure 6 (bottom) shows the original data and the model obtained for the log-transformed data after back-transformation. As can be seen from Figure 6, the model seems to provide a better fit for the original or decimated WN than for the GWN. It is possible that the three components selected for WN represent harmonics of the solar activity cycle and describe a non-sinusoidal waveform, even though they were fitted as independent components. This was not the case for GWN, and there appears to be an overfit during 1762-1764, when data were missing. This overfit is also observed for the Horrebow data in Thiele (1) (Figure 3), but to a much smaller extent.

Analyses of Schwabe's data

Two series (1826-1837 and 1838-1843) of yearly sunspot numbers were combined into one and analyzed by linear-nonlinear least squares rhythmometry (9-11). We wished to find the minimal number of yearly data on whose basis the solar activity cycle could have been documented by rejecting the no-cycle (zero-amplitude) assumption, had Schwabe used the method of least-squares that had been available since 1801 when Gauss had developed it to locate Ceres, the asteroid that was lost after Giuseppe Piazzi (1746-1826) initially observed it (14). A trial period of 11 years was used. The results in Figure 7 need to be qualified by the fact that using a trial period of 11 years assumes the existence of prior information, which was not the case at the time of the original documentation of a cycle in solar activity, unless Schwabe knew about Horrebow's data. Moreover, if he knew about Horrebow's observations, he could have used the equivalent of a cosinor spectrum and located a peak around 9.4 years. Against this background, several time series were prepared using all 18 data and progressively removing one value starting from the latest available (the early data were always kept). The shortest series contains the first 5 values. An 11-year cosine curve was fitted nonlineary to each time series, covering the entire 18-year span or only the first 17, 16, 15, … or 5 years, to obtain estimates of the period as well as of the MESOR, amplitude and acrophase. Results are shown in Figure 7 as a function of the decreasing observation span, for the MESOR (top), the estimated period length (middle), and the corresponding amplitude, each with a measure of its CI. An about 9-year cycle can be documented with as few as 9 values (9 years), Figure 7.

Thorvald Nicolai Thiele (1838-1910) -- of Thiele differential equation fame ("the fundament of modern life insurance mathematics"; 8) -- concluded: "Sed antequam postera aetas huic rei plus lucis attulerit, in periodo regulari decem fere annorum acquiescendum esse videtur" (But until a subsequent age adds more light to this matter, it seems necessary to be satisfied with a regular period of about ten years) (1). It seems pertinent to note that both Horrebow's and Schwabe's data allowed by 1838 the demonstration of a circadecadal cycle with a measure of its uncertainty on the basis of data covering only 9 years.

In Thiele's and Schwabe's time, the circadecadal cycle in sunspot numbers was shorter than its average length in all available data. The higher resolution of Figure 8 versus Figure 9 using a 12-year versus a 35-year interval suggests that in 1826, the solar activity cycle was actually the shortest between 1799 and 1947 (15).

In any event, we must not resign ourselves that data covering a full cycle is invariably required for the demonstration of cycles that characterize major features of solar variability. We certainly must not generalize to the detection of their reflection in the biosphere. With the linear-nonlinear extended cosinor, the zero-amplitude assumption could be rejected for a circatridecadal BEL cycle in the heart rate of an elderly man based on only 22 years of measurements (4), i.e., with only 73.3% of the cycle's total length covered by the data.

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Table 1:
Periods characterizing sunspots counted by Hoyt and Schatten
(components fitted separately)

Series	Period [95%CI] (years)	Amplitude [95%CI] (sunspots)
Trial Period: 9.4 years		
Wolf numbers (WN)	9.374 [8.90, 9.84]	42.65 [35.46, 49.84]
Decimated WN (matching GWN)	8.914 [8.40, 9.42]	46.63 [38.78, 54.48]
Group WN (GWN)	9.492 [8.71,10.28]	52.99 [41.18, 64.80]
Trial Period: 4.1 years		
WN	4.129 [3.64, 4.62]	13.30 [2.33, 24.27]
Decimated WN	4.201 [3.73, 4.68]	18.29 [5.11, 31.47]
GWN	4.152 [3.54, 4.77]	18.45 [1.39, 35.50]
Trial Period: 2.1 years		
WN	2.023 [1.87, 2.17]	9.88 [-1.40, 21.16] NS
Decimated WN	2.050 [1.88, 2.22]	13.07 [-0.04, 26.19] BS
GWN	2.068 [1.92, 2.22]	18.00 [1.10, 34.91]

Table 2:
Composite model characterizing sunspot numbers in the 18th century (Hoyt and Schatten)
Analysis of $\log_{10}$-transformed data

Series	Period [95%CI] (years)	Amplitude [95%CI] (sunspots)
Wolf numbers (WN)	9.356 [8.72, 9.99]	0.44 [0.35, 0.53]
	4.540 [4.21, 4.87]	0.20 [0.11, 0.29]
	3.122 [2.79, 3.46]	0.09 [-0.00, 0.18]
Decimated WN (matching GWN)	9.122 [7.79,10.45]	0.46 [0.33, 0.60]
	4.762 [3.77, 5.75]	0.19 [0.08, 0.30]
	3.105 [2.56, 3.65]	0.08 [-0.04, 0.20]
Group WN (GWN)	8.566 [7.45, 9.68]	0.63 [0.46, 0.80]
	5.155 [4.34, 5.97]	0.30 [0.12, 0.48]
	2.189 [2.04, 2.34]	0.15 [0.03, 0.27]

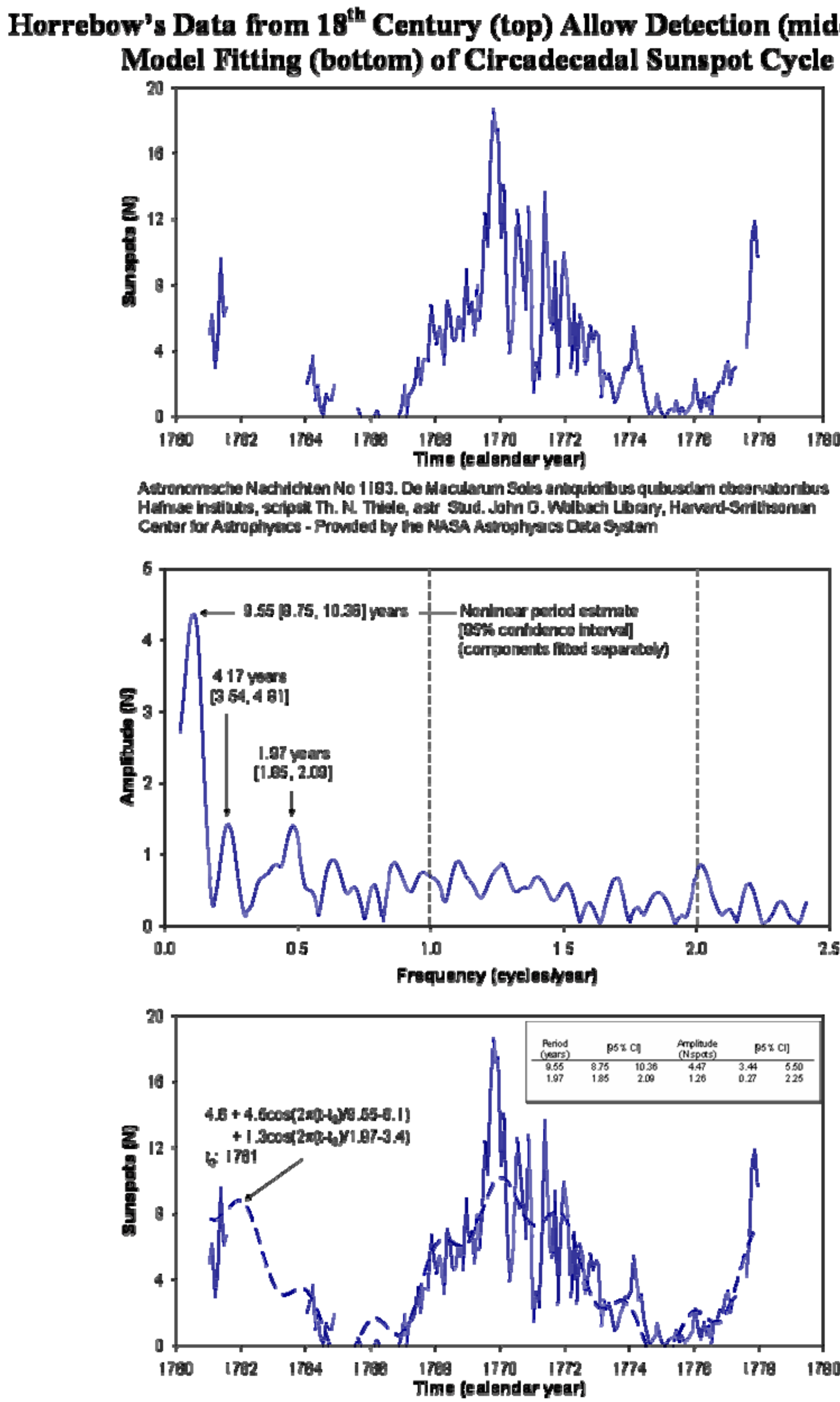
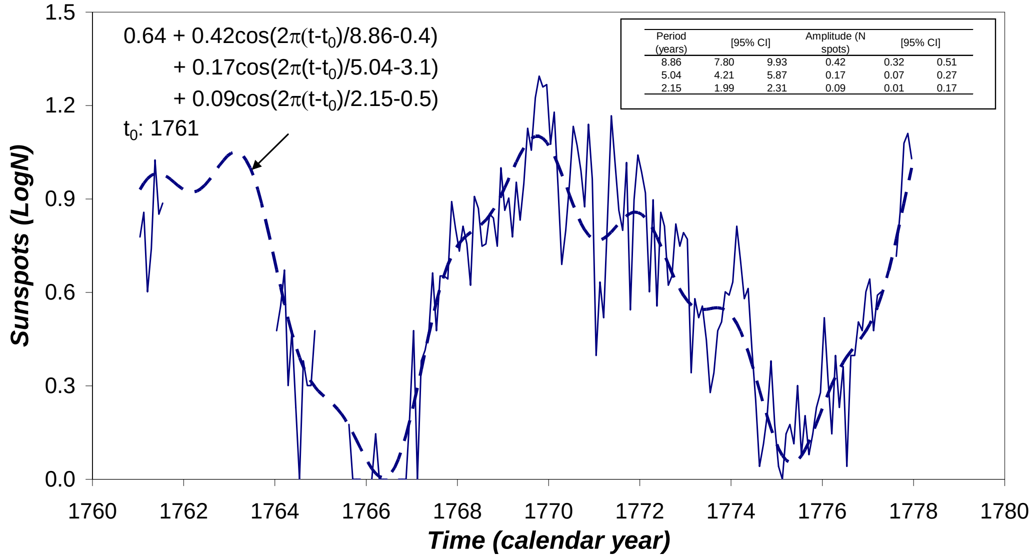


Figure 1. Yearly sunspot data (with interruptions) from Horrebow (published by Thiele) (top) are characterized by three spectral peaks corresponding to periods of about 9.55, 4.17, and 1.97 years validated nonlinearly when considered separately (middle). The composite 2-component model is fitted to the data (bottom). © *Halberg.*

Three-Component Model Fitted to Horrebow's Data on Sunspots (Published by Thiele) *



Astronomische Nachrichten No 1193. De Macularum Solis antiquioribus quibusdam observationibus Hafniae institutis, scripsit Th. N. Thiele, astr. Stud. John G. Wolbach Library, Harvard-Smithsonian Center for Astrophysics - Provided by the NASA Astrophysics Data System

* Data log10-transformed prior to analysis

Figure 2. After log-transformation, a 3-component model validated nonlinearly is fitted to the sunspot data from Horrebow. © *Halberg.*

Three-Component Model Fitted to Log-transformed Data Shown after Back-transformation with Original Horrebow's Data (Published by Thiele)

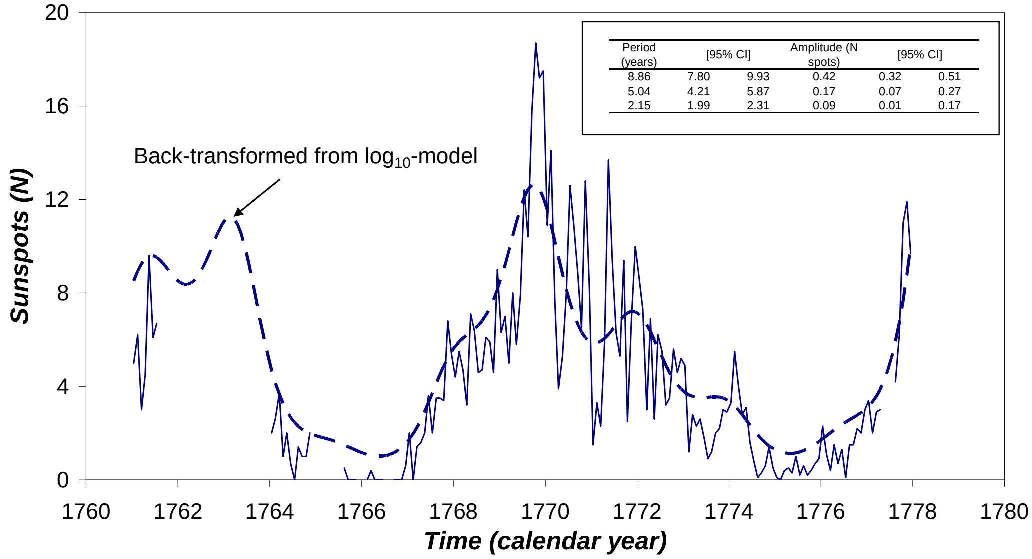


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Figure 3. The 3-component model fitted to the log-transformed sunspot data from Horrebow is back-transformed to be displayed with the original data. Note slight overfit at the beginning of the record when data are missing. © *Halberg.*

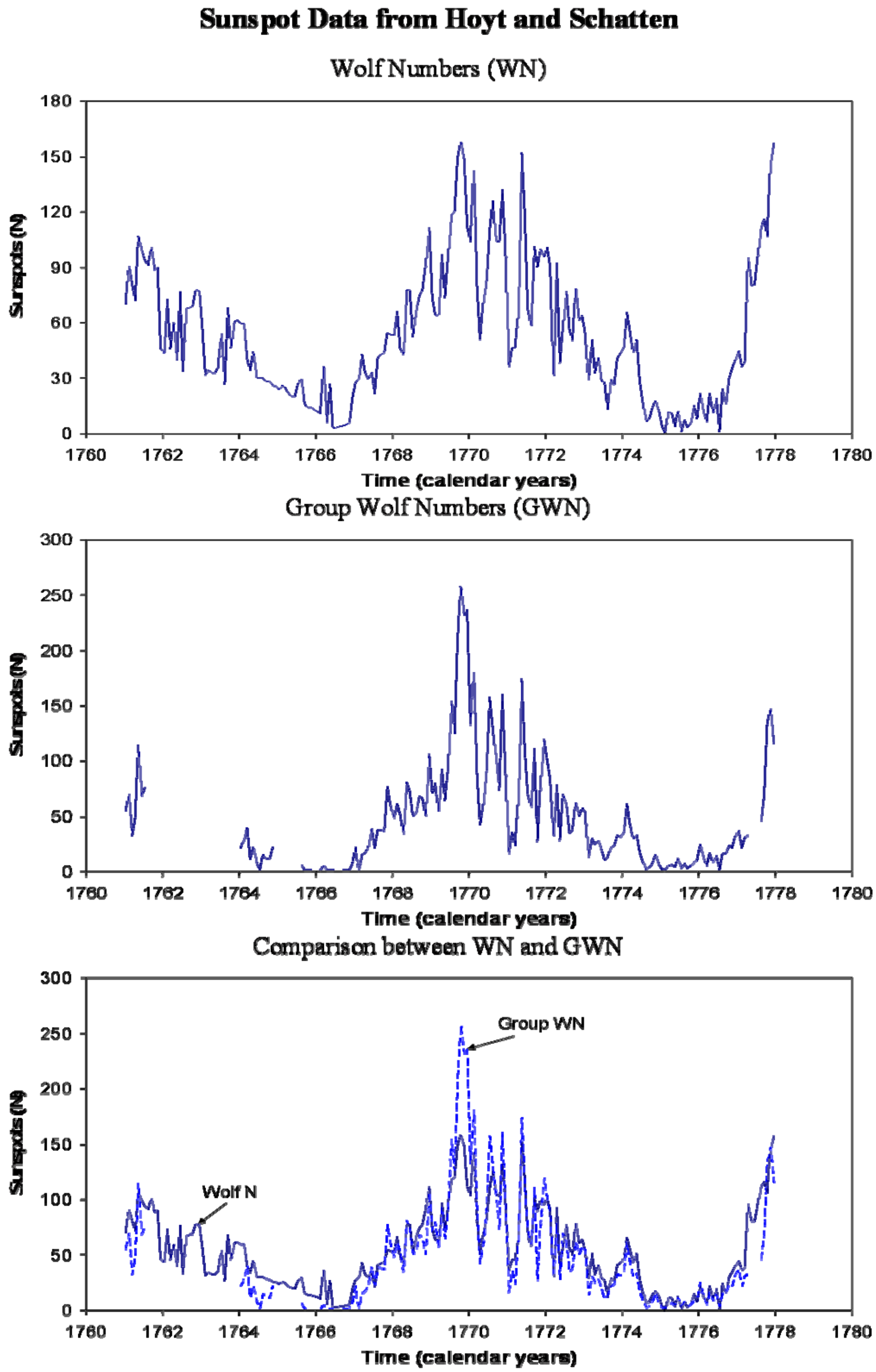


Figure 4. Yearly sunspot numbers (WN) and group sunspot numbers (GWN) reported by Hoyt and Schatten. As some yearly values are missing for GWN, the WN data have been decimated to match the GWN data in order to assess any influence of gaps on the assessment of the solar activity cycle. © *Halberg*

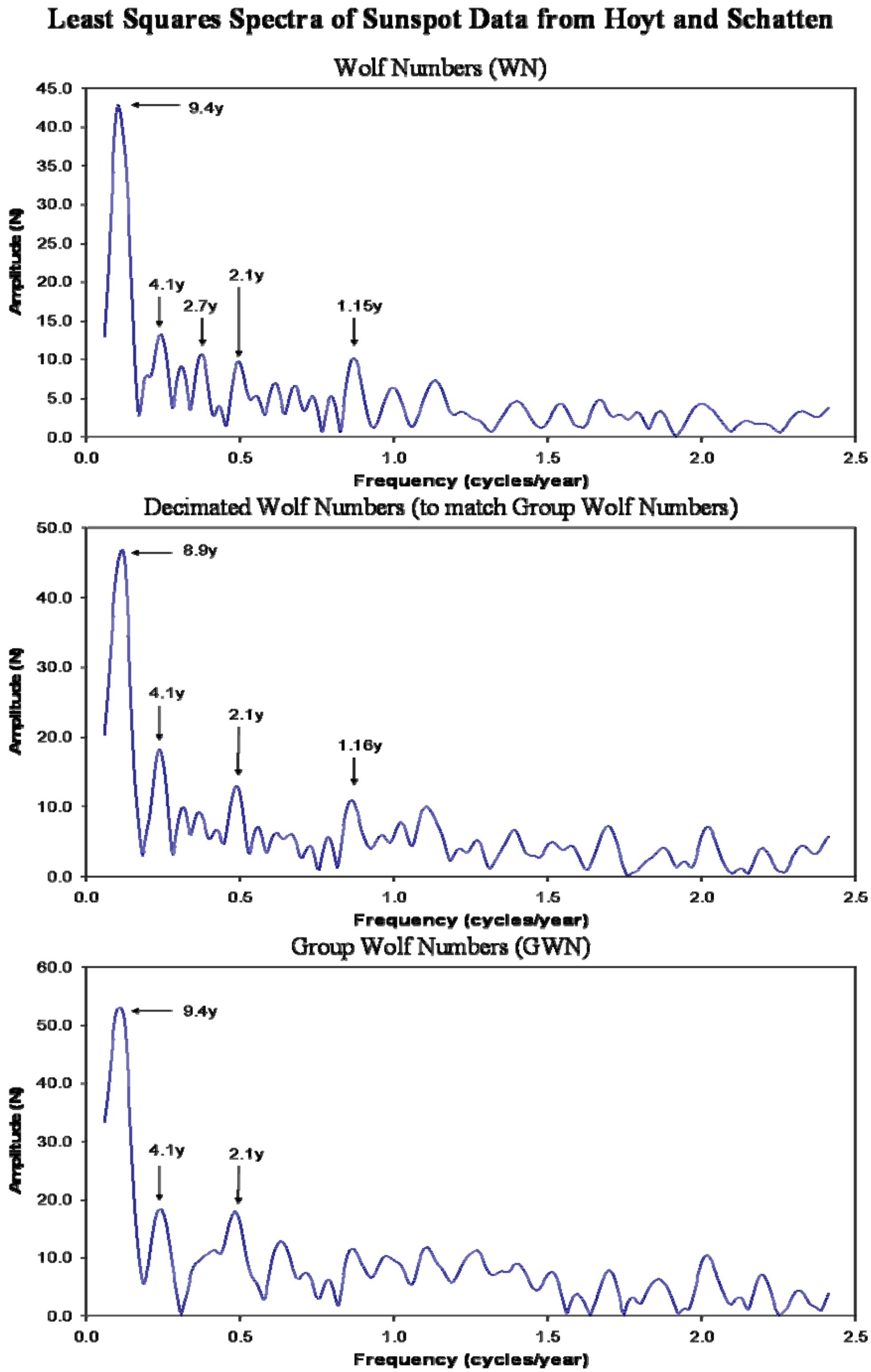


Figure 5. Least squares spectra of sunspot numbers (WN) and group sunspot numbers (GWN) reported by Hoyt and Schatten reveal the presence of similar cyclical components, as well as some differences. Small differences are also observed in relation to the missing values, suggested by a comparison of spectra of the original and decimated WN (to match GWN). © *Halberg.*

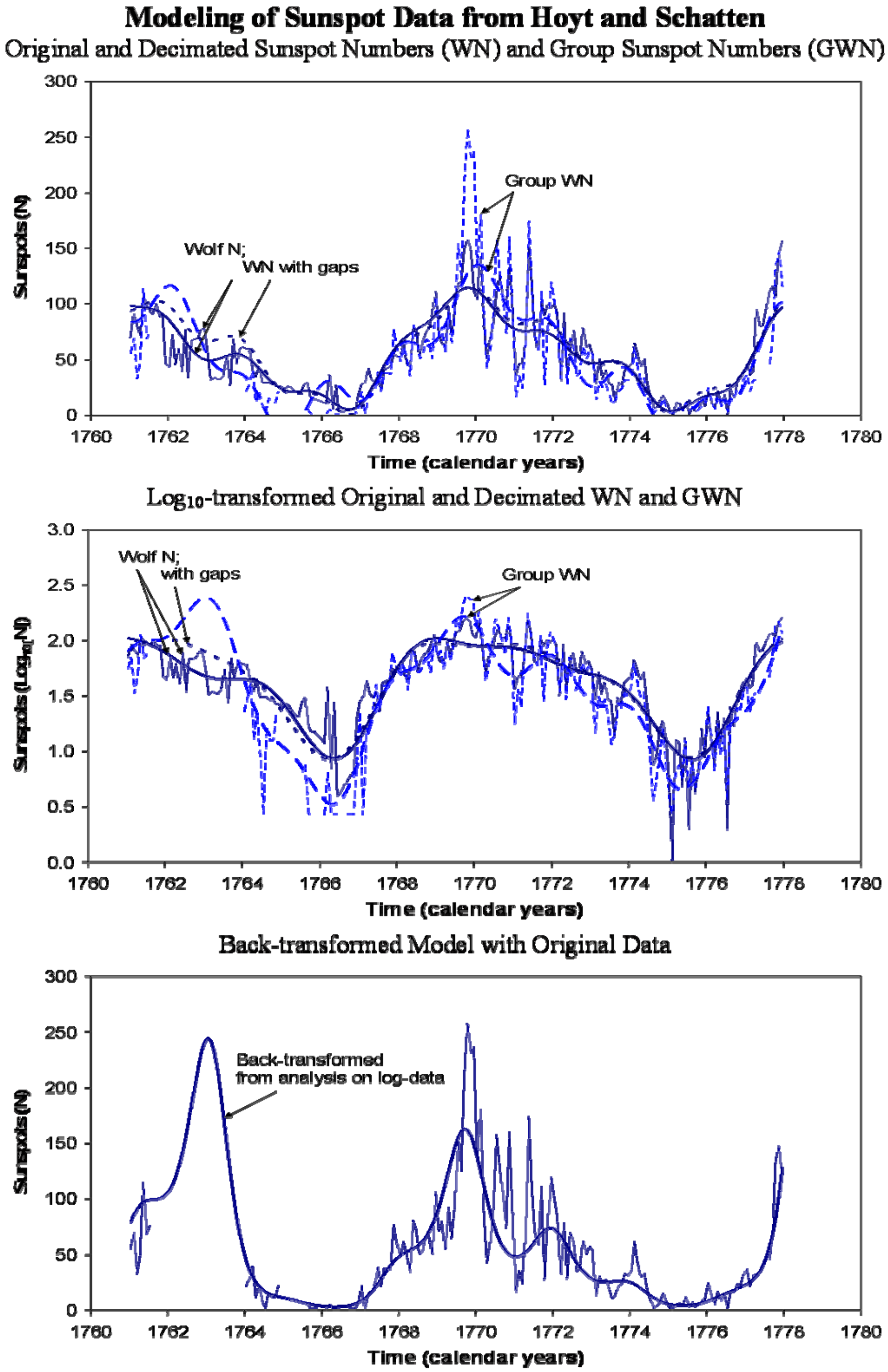
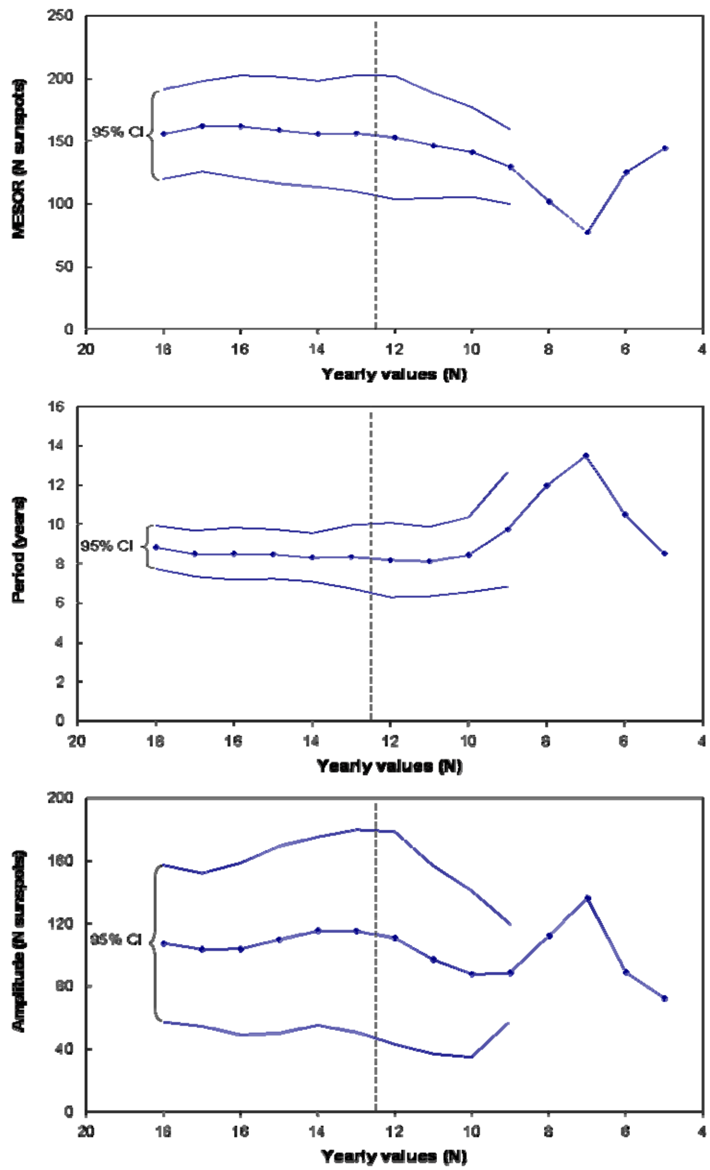


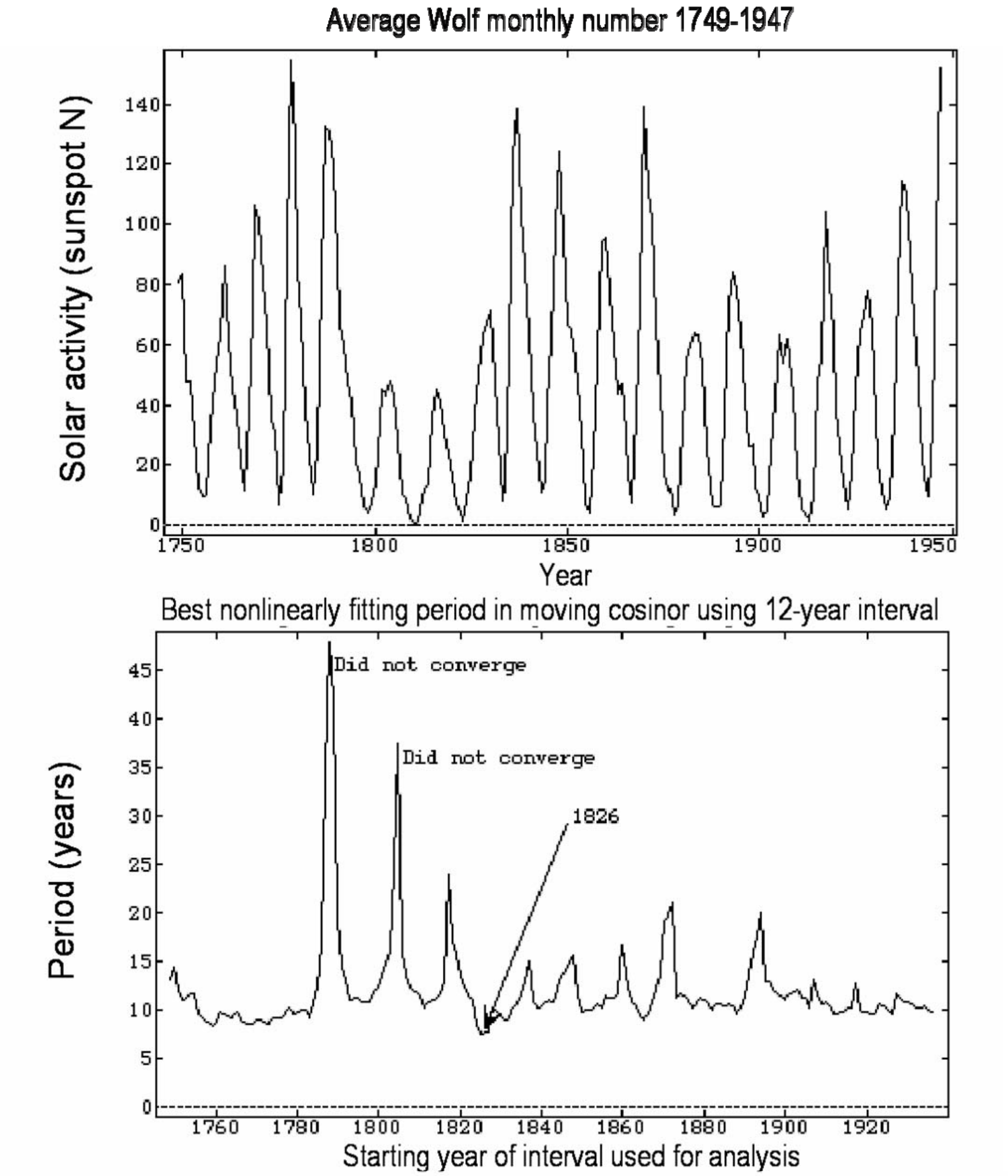
Figure 6. Three-component model fitted to the original (top) and log-transformed (middle) sunspot (WN) and group sunspot (GWN) data reported by Hoyt and Schatten. Model obtained on log-transformed data is back-transformed for display with original data (bottom). As for the data from Horrebow (Figure 3), there is even a more pronounced overfit at the beginning of the record, in association with the gap in the data series. © *Halberg.*

Using Gauss' Least Squares, Schwabe Could Have Validated a Periodicity in Sunspots with His First 9 Years of Data *



* Time series of yearly sunspot numbers (1826-1837 and 1838-1843) were combined for the nonlinear fit of a single cosine curve with a trial period of 11 years (that could not then but can now be anticipated) to all 18 values and after the progressive removal of the latest value. Nonlinear estimates of the MESOR (top), period (middle) and amplitude (bottom) with their respective 95% confidence intervals (95%CI) (when the zero-amplitude assumption could be rejected with $P<0.05$) shown as a function of the decreasing number of data indicate that relatively stable estimates are obtained with 9 or more years of data.

Figure 7. Results from nonlinear analyses of Schwabe's data, analyzed over the entire 18-year span and on progressively shorter series obtained by removing each time the last yearly value, in an attempt to determine what is the shortest series suitable for an assessment of the solar activity cycle at the time. Even with only the first 9 yearly data, it is possible to derive point and 95% confidence intervals for all parameters. Results shown for the MESOR (top), period length (middle), and amplitude (bottom). © *Halberg.*



Best period estimated by moving nonlinear least squares cosinor fits using 12 years of data. The starting values were the periods of best fit from linear least squares cosinor analyses at 50 equally spaced frequencies between 1/35 and 1/6 cycles per year (periods 6 to 35 years). The gaps at years 1788, 1789, and 1805 near the start of long cycles indicate the fit did not converge in 100 iterations.

Figure 8. Chronomic serial section estimating by nonlinear least squares the cycle length of Wolf numbers based on 12-year intervals. For measurements starting in 1826 when Schwabe made his observations, the solar activity cycle happened to be the shortest, in keeping with results in Figure 7. Had Schwabe examined 12 years of sunspots at other times, he may have had to wait longer to observe a full solar activity cycle or he may have been unlucky if the span coincided with one of the few instances when convergence could not be reached. © *Halberg.*

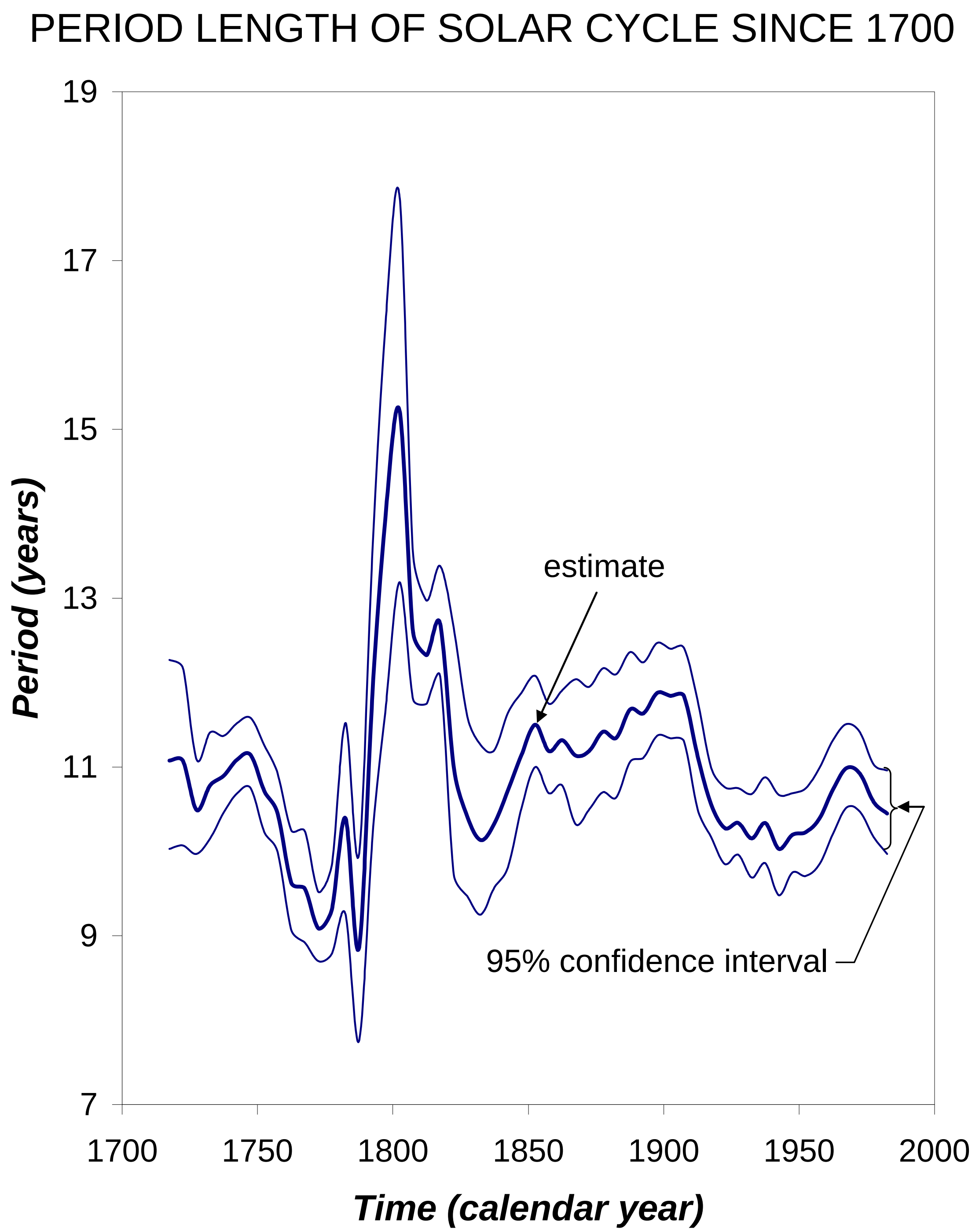


Figure 9. Nonlinear estimate of the solar activity cycle length, gauged by Wolf numbers analyzed in intervals of 35 years progressively displaced by 5 years throughout the time series. Results plotted at the midpoint of each interval. At the time of Schwabe's data, a shorter solar activity cycle is again found, but its length is somewhat longer as data over a longer interval of 35 years (rather than 12 years in Figure 8) was considered for analysis. With such a longer interval, convergence is invariably achieved. © *Halberg.*

TRANS-TRIDECADAL, DECADAL AND TIME-VARYING CIS-HALF-YEARLY, CIS-YEARLY AND TRANS-YEARLY COMPONENTS IN SOLAR FLARES WITH BIOSPHERIC SIGNATURES

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Aim. As a step toward aligning and examining mechanisms of possibly interacting environmental and biospheric periods, the latter involving sudden cardiac death (SCD) and cardiac arrhythmia, we analyze the longest series of the total solar flare index (SFI) available to us.

Background. Aeolian behavior has been described as time-varying in amplitude (A) by waxing and waning, in acrophase (ϕ) by jumping, if not drifting, and in period (τ) by drifting, bifurcation, rejoining, disappearance and reappearance. As noted in moving spectra by Mursula and Zieger (1), a given periodicity can change its period from 1.7 to 1.5 years, and in our analyses (2) even further to 1.3 years. To account for such drifts over a wide range of periods, far-transyears have been defined as components with periods such that 1.2 years ≤ [τ - CI {95% confidence interval}] < [τ + CI] < 1.9 years, whereas near-transyears are defined as 1.00 year < [τ - CI] < [τ + CI] < 1.20 years (2). By "τ - CI" or "τ + CI", we mean the lower or upper limit of the 95% confidence interval of the period, in keeping with the notation of a mean given ± 1SE or ± 1SD. The actual width of the error (uncertainty) is then 2SE or 2SD. As for large-sample normally-distributed data sets, 95% confidence limits can be approximated as the mean ± 2SE, the entire width of a 95% confidence interval is then 2CI. By analogy, the nonlinear period estimate is given as τ ± CI, and the entire width of the 95% confidence interval of τ is 2CI.

About 154-day periodicities also have biospheric counterparts (Table 1). These cis-half-years (from cis = on this side of the half-year) are found in some cases of cardiac arrhythmia (2-4) and SCD (ICD10, code I46.1) (2, 4-6). A range for the cis-half-year period has not been given yet because of the great variability of this component, which also prompted an attempt of studying its time-varying behavior in the solar flare index by a chronomic serial section. Such an examination is important since signatures of both far-trans-years and cis-half-years in cardiac arrhythmia recorded as such (Table 2) (2) or by implanted devices in which they trigger therapy (3; cf. 7) are found intermittently. It remains to be seen whether and, if so, how environmental change may be associated with biospheric consequences. Cis-half-years in the incidence pattern of arrhythmia triggering therapy from implanted devices are geographic site-dependent (3). In Minnesota, a site where the incidence patterns of both arrhythmia and SCD have been examined, a cis-half-year is found in both. Cis-half-year and trans-year components also characterize SCD in Tokyo (5), Hungary (2), Austria (6), and, transiently, in the Czech Republic (2). Furthermore, a cis-half-year was found in human heart rate studied around the clock for over 40 years and was modulated by a circadecadal Horrebow-Schwabe sunspot cycle, being statistically significant mostly with a lag of slightly over 3 years after the times of maximal solar activity (8).

Methods. Daily data on the total solar flare index, available from 1966 to 2007 were averaged over consecutive weekly intervals. The latter were analyzed by the extended cosinor (9-11). A least squares spectrum was obtained, using a fundamental period of 42 years. Periods of spectral peaks corresponding to anticipated components were used as initial values in the nonlinear program to obtain point and 95% confidence intervals for the periods. In order to examine how the characteristics of some of these components changed as a function of time, single- and multiple-component (chronomic) serial sections were carried out.

Results. The least squares spectrum of SFI is shown in Figure 1, suggesting the presence of a BEL cycle (12-16) with a period of about 35 years, only slightly shorter than the total length of the time series. A prominent spectral peak at a period of about 10.5 years corresponds to the Horrebow-Schwabe cycle. Other spectral peaks of less prominence include a trans-year of about 1.7 years, a cis-year of about 0.7 year, and multiple components in the cis-half-year spectral region, shown in greater detail in Figure 2. Each component considered separately was further assessed nonlinearly. Point and 95% confidence intervals of the periods are listed next to the spectral peaks in Figures 1 and 2. Chronomic serial sections served to study how the characteristics of the trans-year, cis-year, and the sole cis-half-year validated nonlinearly varied as a function of time. For this purpose, a relatively long interval of 7.2 years had to be chosen, which was displaced in 0.72-year increments,

Figure 3. The MESOR, displayed on top (left), is readily seen to vary according to the about 10.5-year solar activity cycle. The amplitudes (left) and acrophases (right) of each component of the cis-half-year (second row), cis-year (third row), and trans-year (bottom row) are shown with different symbols depending on whether the zero-amplitude test was rejected at the 0.05 probability level or not (Figure 3).

As seen in Figure 3 (row 2, left), the 0.42-year component has the largest amplitude for a while, around 1980, the time of Rieger et al.'s finding (17), predicted by Charles L. Wolff (18), Table 1. All three components can intermittently be detected with statistical significance (filled symbols), notably around 1982 when the cis-half-year is most prominent. The alternation between statistical significance and lack of statistical significance (empty symbols) does not seem to occur at random. The 0.42-year component tends to be detected with statistical significance at times of overall peak incidence in solar flares. Albeit not globally, the 0.42-year component assumes amplitudes (of up to 2.5 arbitrary units) larger than those of the cis-year and trans-year (reaching a maximum of only about 1.5 arbitrary units). At the beginning of the record, however, statistical significance is reached in only 5 intervals for the 0.42-year component, and in only 2 intervals for the 0.71-year cis-year, whereas it is more consistent, lasting until the mid-1980s for the 1.74-year trans-year. The Aeolian nature of all three components is best seen from the time course of the acrophases (Figure 3, right), showing mostly abrupt phase jumps for the cis-half-year, phase jumps and drifts for the trans-year, whereas the acrophase of the cis-year is more consistent, at least when this component is detected with statistical significance.

Discussion. BEL cycles in human health and other affairs, some congruent with those in solar flares, lend further weight to original data by Brückner (12). His original data are shown macroscopically in Figure 4 (top), as part of a set of transdisciplinary transtridecadal cycles assessed time-microscopically, with results from our spectral analyses also shown in Figure 4 (bottom). These include analyses of four decades of heliogeomagnetics (13), 2,556 years of international battles published by Wheeler (19), a 2,189-year record of tree rings (20), a 173-year record of military-political affairs compiled by Chizhevsky (21), a 460-year record of the South English Price Index gauging an aspect of economics (22, 23), as well as biospheric data, namely four decades of around-the-clock self-measurements of heart rate (14-16) and of a mental function (1-minute time estimation) (16, 24) by a clinically healthy man, and three decades of blood pressure and body weight of a clinically healthy man (25).

Space weather, mirrored in the circulation of human blood, can be tracked biologically as a dividend from self-assessed preventive health care, involving the manually (16) (or preferably automatically and ambulatorily) recorded heart rate and blood pressure for detecting and treating heretofore ignored vascular variability disorders (VVDs). In exchange for the data, the BIOCOS project (corne001@umn.edu) currently provides cost-free analyses for those motivated to survey themselves and can also serve any community with a computer-savvy member so as to start focus for the population on problems of societies' as well as individuals' health. Biospheric variability includes spectral components with a length of about three decades mapped in Figure 4 (16). Whereas they are signatures of our environment, these may also be partly built-in, as are circadian rhythms. In Brückner's data, the frequency of cold winters has a point estimate of its period outside the 30- to 40-year range, but its CI covers part of that range. By the same token, the point estimate of the aurora over nearly a millennium is slightly shorter than 30 years (not shown), but its CI extends beyond the length of 30 years (26) and in the analysis of a 500-year span, the point estimate of the period is transtridecadal (27).

Similar periods do not necessarily mean causal relations, and any parallelisms of their behavior are best studied over long time spans. The circumstance that the environmental spectral components are non-stationary to the point of intermittency allows the study of the biospheric consequences of their presence and absence. Environmental cycles also vary in terms of geography. The latter aspect is apparent for far-transyears that, in some locations, may coexist with a calendar-yearly component and in other sites may replace the calendar year, whereas in yet other geographic locations, or in other variables, the calendar year stands out most prominently or alone (16).

Table 1 lists only part of the very large literature revolving around the cis-half-year in physics, most of it without measures of the uncertainty of the periods on hand and without consideration of spectral components other than a cis-halfyear. Figure 5 compares acrophases of the cis-half-year, cis-year, and trans-year, each component fitted separately. The relatively narrow CIs in most cases are qualified by the fact that a single-component model is fitted, using different intervals for each component. Notably for the cis-half-year and the cis-year, the interval used for analysis in Figure 5 is shorter than the 7.2-year span considered in Figure 3, where all three components were fitted concomitantly. In view of the prominent about 10.5-year cycle characterizing solar flares reflecting changes in solar activity, it was of interest to compare the least squares spectra of solar flares (Figure 1) and of Wolf numbers recorded during the same 42-year span (Figure 6) to see whether both variables also shared similar BEL cycles. Whereas a BEL cycle is apparent in both variables, its amplitude is much larger in solar flares (more than 50% of the about 10.5-year amplitude) than in Wolf numbers (less than 20% of the about 10.5-year amplitude). Other differences between Figures 1 and 6 require further study for their biospheric associations, to be mapped further.

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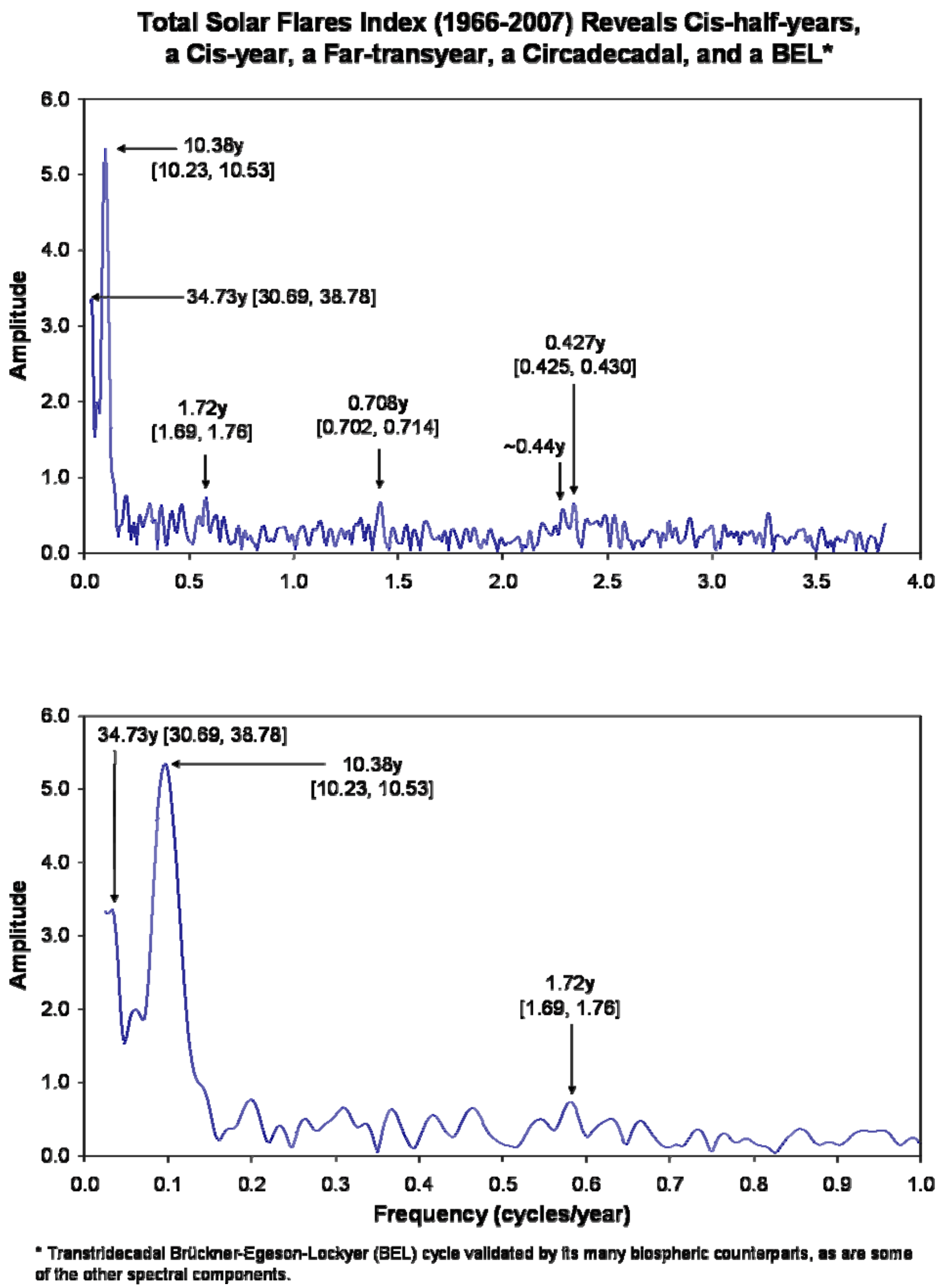


Figure 1. Least squares spectrum from extended linear-nonlinear cosinor of the total solar flare index. © *Halberg*

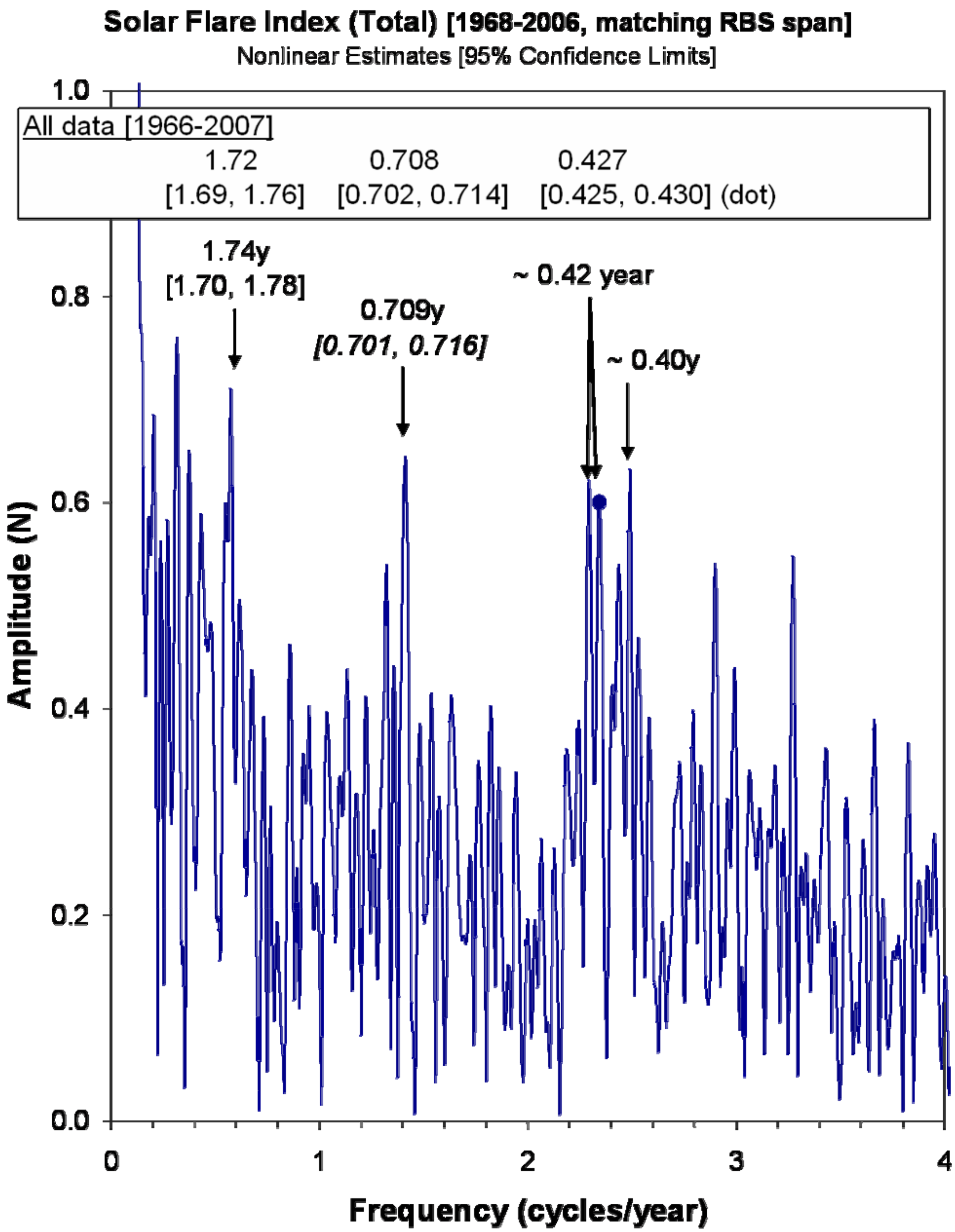


Figure 2. Focus upon the spectral region around 0.4 year reveals multiple peaklets, prompting the chronomic serial section in Figure 3. © *Halberg*

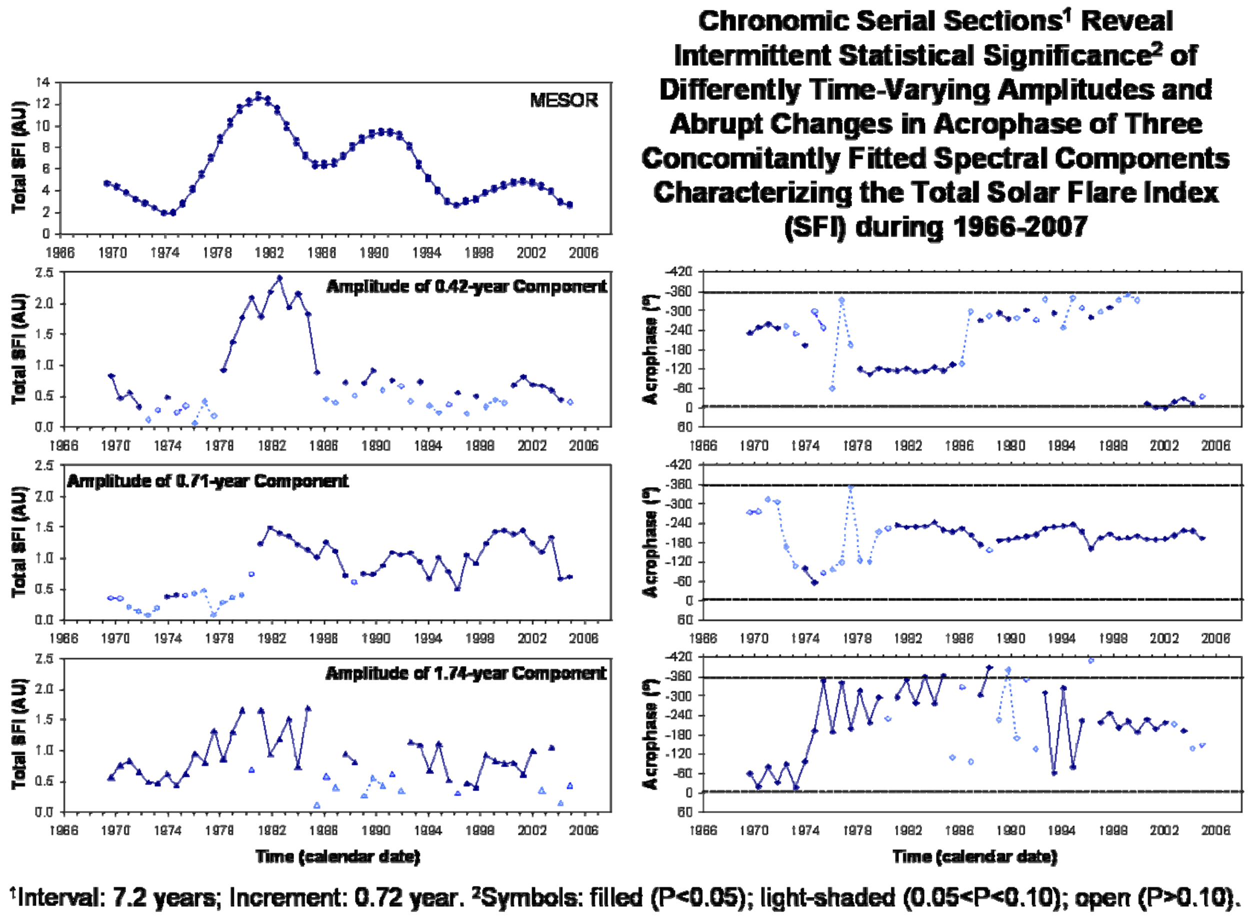


Figure 3. Intermittency of statistical significance of three spectral components fitted concomitantly. © *Halberg*

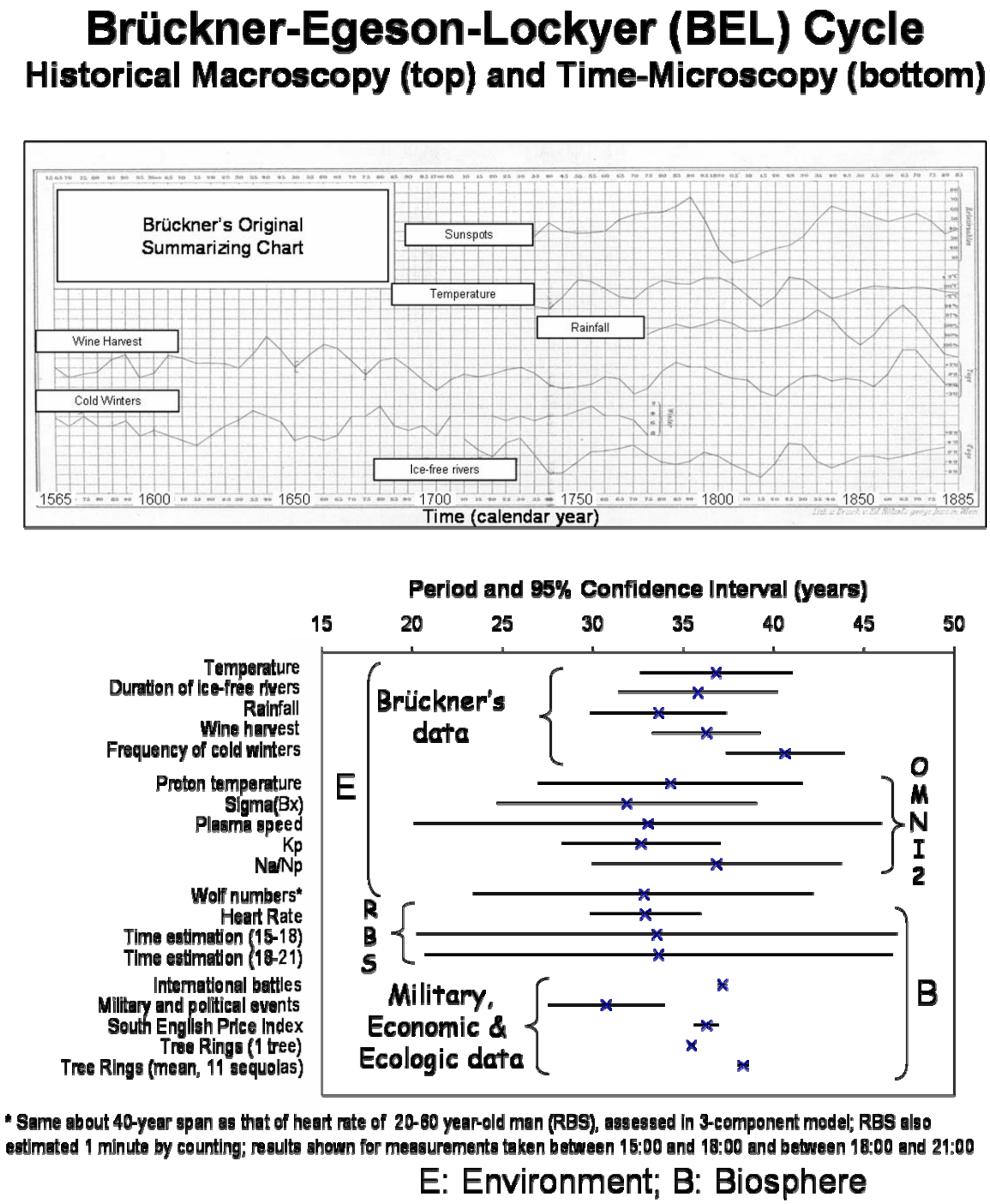


Figure 4. Degree of generality of the BEL transtridecadal cycle in Brückner's original data and beyond. © *Halberg*

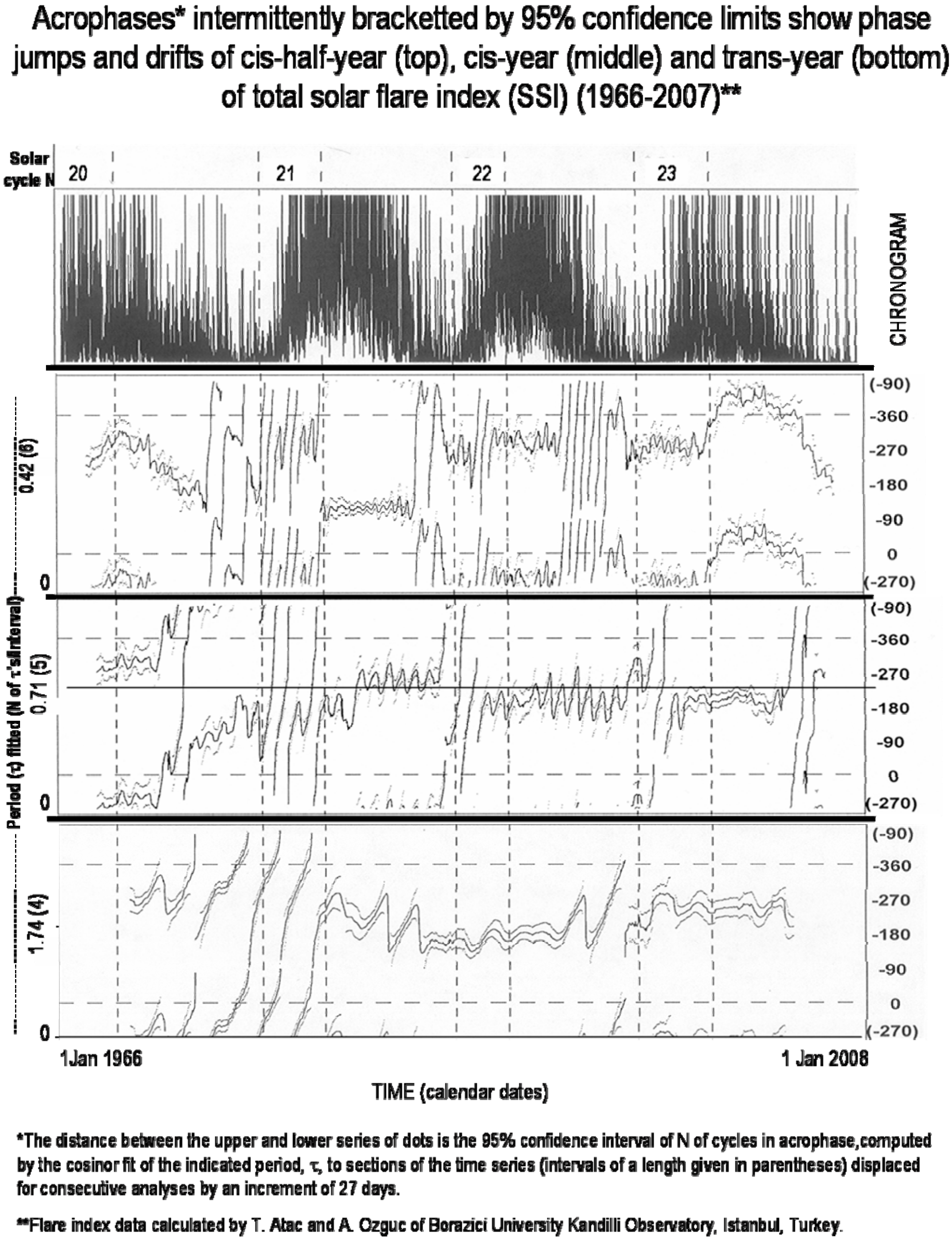
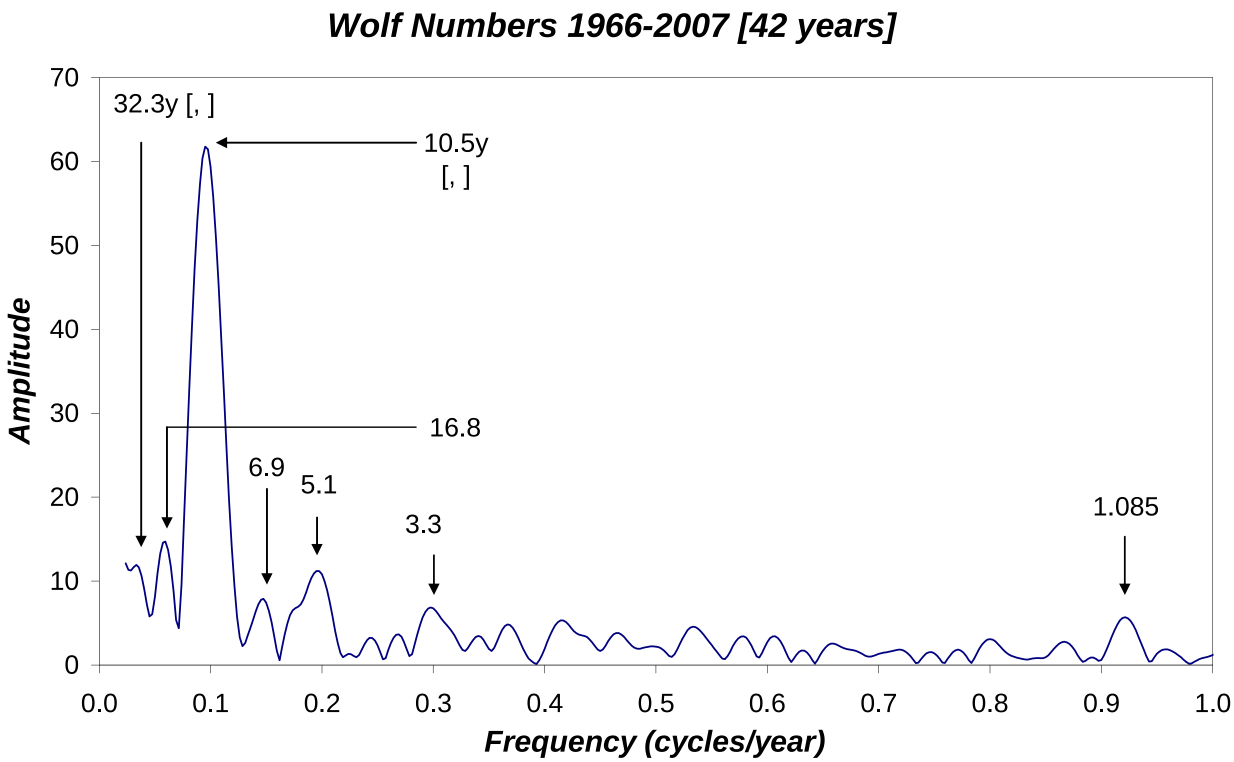


Figure 5. Time course of acrophases of three spectral components, each fitted separately. Acrophases are bracketed by their 95% confidence intervals. © *Halberg*



* Transtridecadal Brückner-Egeson-Lockyer (BEL) cycle validated by its many biospheric counterparts, as are some of the other spectral components.

Figure 6. Least squares spectrum of Wolf's relative sunspot numbers over 42-year span matching record of solar flare index (spectrum shown in Figure 1). © *Halberg*

Table 1: Point estimates of a cis-half-year (about 154-day) periodicity, sometimes given with estimates of uncertainty and hypothesis testing

Period (in days, except where noted)	Reference
154.3	Wolff CL. The rotational spectrum of g-modes in the sun. Astrophys J 1983; 264: 667-676.
154	Rieger A, Share GH, Forrest DJ, Kanbach G, Reppin C, Chupp EL. A 154-day periodicity in the occurrence of hard solar flares? Nature 1984; 312: 623-625.
158	Kiplinger AL, Dennis BR, Orwig LE. Detection of a 158-day periodicity in the solar hard X-ray flare rate. Bull Am Astronom Soc 1984; 16: 891.
152	Bogart RS, Bai T. Confirmation of a 152-day periodicity in the occurrence of solar flares inferred from microwave data. Astrophys J 1985; 299: L51-L55.
152-158	Dennis BR. Solar hard X-ray bursts. Solar Physics 1985; 100: 465-490.
152	Bai T, Sturrock PA. The 152-day periodicity of the solar flare occurrence rate. Nature 1987; 327: 601-604.
near 155	Lean JL, Brueckner GE. Intermediate-term solar periodicities -- 100-500 days. Astrophys J 1989; 337: 568-578.
152	Özgüç A, Ataç T. Periodic behavior of solar flare index in solar cycles 20 and 21. Solar Physics 1989; 123: 357-365.
154 (± 0.6)	Bai T, Cliver EW. A 154 day periodicity in the occurrence rate of proton flares. Astrophys J 1990; 363: 299-309.
near 155	Carbonell M, Ballester JL. A short-term periodicity near 155 day in sunspot areas. Astron Astrophys 1990; 238: 377-381.
153	Dröge W, Gibbs K, Grunsfeld JM, Meyer P, Newport BJ, Evenson P, Moses D. A 153 day periodicity in the occurrence of solar flares producing energetic interplanetary electrons. Astrophys J Suppl Ser 1990; 73: 279-283. Applying Rayleigh test for periodicity.
155	Silverman SM. The 155-day solar period in the sixteenth century and later. Nature 1990; 347: 365-367. "[A]lthough values between 150 and 160 days have been reported, I refer to it here as the 155-day period, for convenience"
154	Bai T, Sturrock PA. The 154-day and related periodicities of solar activity as subharmonics of a fundamental period. Nature 1991; 350: 141-143.

Period (in days, except where noted)	Reference
154	Kile JN, Cliver EW. A search for the 154 day periodicity in the occurrence rate of solar flares using Ottawa 2.8 GHz burst data, 1955-1990. Astrophys J 1991; 370: 442-448.
152-158	Verma VK, Joshi JC, Uddin W, Paliwal DC. Search for a 152-158 days periodicity in the occurrence rate of solar flares inferred from spectral data of radio bursts. Astron Astrophys Suppl Ser 1991; 90: 83-87.
near 155	Carbonell M, Ballester JL. The periodic behaviour of solar activity: the near 155-day periodicity in sunspot areas. Astron Astrophys 1992; 255: 350-362.
152	Verma VK, Joshi JC, Paliwal DC. Study of periodicities of solar nuclear gamma ray flares and sunspots. Solar Physics 1992; 138: 205-208.
154	Bai T, Sturrock PA. Evidence for a fundamental period of the sun and its relation to the 154 day complex of periodicities. Astrophys J 1993; 409: 476-486.
151-155	Lou YQ. Rossby-type wave-induced periodicities in flare activities and sunspot areas or groups during solar maxima. Astrophys J 2000; 540: 1102-1108.
153.9	Hady AA. Analytical studies of solar cycle 23 and its periodicities. Planetary and Space Science 2002; 50: 89-92.
near 160	Ballester JL, Oliver R, Carbonell M. The near 160 day periodicity in the photospheric magnetic flux. Astrophys J 2002; 566: 505-511.
near 5-month	Han Yanben, Han Yonggang. Time variation of the near 5-month period of sunspot numbers. Chinese Sci Bull 2002; 47 (23): 1967-1973. "Many scholars ... found similar periods of solar activity from other observations of the Sun. However, these periods are different, such as about 152-, 154-, 156-day, etc. Here we name it a near 5-month period (N5MP) since it is not definite."
153	Bai T. Periodicities in solar flare occurrence analysis of cycles 19-23. Astrophys J 2003; 591: 406-415.
near 160	Ballester JL, Oliver R, Carbonell M. Return of the near 160 day periodicity in the photospheric magnetic flux during solar cycle 23. Astrophys J 2004; 615: L173-L176.

This incomplete list (added contributions are cited in the references provided) suffices to indicate the variable nature of the period being discussed. Specifications of the solar (Schwabe) cycle in which they are found point indirectly to the intermittency of the components being discussed.

Table 4. **Do we need more than heating and air conditioning? Do we have to compensate for magnetics?**
Periodicities in human electrocardiograms show a circa-cis-semiannual (cis-halfyear) cycle matching the rhythm of hard solar flares, but no transyear, in one about10-year Schwabe cycle stage and vice versa in another stage: in most of various cardiac arrhythmias, a transyear (TY) is prominent during a span of maximal solar activity (1989–1990) and a cis-halfyear during the descending phase of solar cycle #22 (1983–1984)*

Arrhythmia	Period = 1 y			TY (trial period = 1.3 y)						Cis-halfyear (trial period = 0.42 y)					
	P	A	ϕ	Period (95% CI)			A (95% CI)			Period (95% CI)			A (95% CI)		
1983-1984															
S	0.034	0.058	-234	0.932	0.647	1.216	0.06	0.00	0.13	0.431	0.400	0.462	0.11	0.04	0.18
Ps	0.079	0.042	-228	0.974	0.605	1.343	0.04	-0.02	0.10	0.439	0.413	0.464	0.12	0.06	0.17
V1	0.002	0.087	-207	1.024	0.760	1.288	0.09	0.01	0.16	0.432	0.401	0.463	0.12	0.05	0.20
Vm	0.034	0.056	-214	1.000	0.647	1.353	0.06	-0.01	0.12	0.438	0.408	0.467	0.11	0.05	0.18
Pv	0.255	0.008	-70	1.000	0.484	1.516	0.00	0.00	0.02	–	–	–	–	–	–
Pp	0.151	0.009	-230	1.000	0.546	1.454	0.00	0.00	0.02	–	–	–	–	–	–
1989-1990															
S	0.386	0.024	-11	–	–	–	–	–	–	0.528	0.456	0.599	0.06	0.00	0.11
Ps	<0.001	0.069	-64	1.347	1.042	1.652	0.09	0.03	0.14	–	–	–	–	–	–
V1	0.001	0.103	-66	1.439	1.044	1.834	0.13	0.04	0.22	–	–	–	–	–	–
Vm	0.162	0.036	-67	1.690	0.979	2.400	0.10	0.04	0.15	–	–	---	–	–	–
Pv	0..826	0.003	-5	–	–	–	–	–	–	0.361	0.331	0.390	0.02	0.00	0.04
Pp	0.095	0.016	-4	1.289	0.879	1.700	0.02	0.00	0.05	–	–	–	–	–	–

*Data from Tbilisi (Georgia) from Dr Levan Tvildiani. P: P-value from zero-amplitude (no-rhythm) test; A: Amplitude (in number of cases per day); ϕ: Acrophase, in (negative) degrees, with 360° period length; 0°= 1 Jan 1983. S: supraventricular extrasystoles; Ps: supraventricular paroxysmal tachycardia; V1: ventricular single extrasystoles; Vm: ventricular multiple extrasystoles; Pv: paroxysmal ventricular tachycardia; Pp: paroxysm of atrial fibrillation. A cycle with a period shorter than a half-year, also found in Wolf's relative sunspot numbers (see Cornélissen et al. 2005I) spectra on page S7 and described for hard solar flares by Rieger A. et al. 1984. If we find out how precisely these cosmic, perhaps solar, signatures act, we may shield from, or rather compensate for their unseen and not obviously identified effects as need be.

CIRCADIAN AND CIRCASEPTAN STAGE DETERMINE MISDIAGNOSES (PSEUDO-HYPERTENSION, PSEUDO-WHITE-COAT HYPERTENSION AND PSEUDO-NORMOTENSION)

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A cardiologist (YW) was found to have MESOR-hypertension (MH) in the last 5 months of around-the-clock blood pressure (BP) and heart rate (HR) monitoring at half-hourly intervals with interruptions, continuing for 22 years (1). MH was present on workdays, absent on Sundays and during a vacation (i.e., it was a workday-MH) (1). This finding on a physician constitutes a true “white-coat” hypertension. It constitutes a hint that with continuous BP and HR monitoring, chronobiology may perhaps develop criteria to determine whether the response to a "stimulus" (such as the everyday tasks of a cardiologist) is desirable (benetensive) or undesirable (maletensive) (2). In any event, this observation by Professor Watanabe documents that the diagnosis of MH can depend on the day of the week. Continuous chronobiologically-interpreted BP and HR monitoring may reflect Sir William Osler's "wear and tear" (3) and may serve to measure Hans Selye's (4) brilliant, genial, but as yet anecdotal separation of stress (wear; by stressors, in Selye's terminology) and strain, which may be welcome, as eustress, or undesirable if not harmful, as distress (tear), and to which Paul Rosch has added his scholarship in bioelectromagnetism (5).

Disciplined systematic self-measurements of BP and HR were and are feasible with conventional manually handled sphygmomanometers and were highly recommended in the absence of automatic monitors (6, 7). Automatic self-surveillance is easier and cost-effectively affordable when monitors are acquired by a circle of family and friends with cost-free analyses. With this opportunity currently offered by a project on The BIOsphere and the COSmos, there is no justification for a spotcheck diagnosis, even when the spotcheck includes a 24-hour profile (8). From the viewpoint of circadian rhythms, a 24-hour BP profile covers only a single cycle and from the viewpoint of the many infradian cycles, it covers only a very small fraction of a cycle, as if one took the pulse for only one second or for a small fraction of a second, respectively! A tabula rasa eliminating single BP measurements and even a single 24-hour profile is essential to reduce the large number of misdiagnoses. Reliance on a minimum of 7-day/24-hour records must be insisted on to validate health, whereas added weeks of monitoring are essential to confirm a diagnosis in the presence of abnormalities, such as vascular variability disorders (VVDs), and certainly to monitor the response to treatment. VVDs include MH. The reliable estimation of a BP-MESOR (short for Midline-Estimating Statistic Of Rhythm) is desirable to eliminate the blunders resulting from differences found as a function of the time of day of BP measurement in current conventional care delivery. Failure to consider the usually prominent circadian rhythm in BP leads to the misdiagnoses of hypertension, white-coat hypertension, and masked hypertension, pseudo-diagnoses resting on the quagmire of a single 24-hour profile that disregards the often present large day-to-day variability in BP, and hence eliminates neither false-positive nor false-negative diagnoses.

Figure 1 (9) shows theoretically that given systolic/diastolic (S/D) BP MESORs of 130/80 mmHg, the circadian rhythm results in contradictory diagnoses in the morning's vs. the afternoon's office hours, as documented also by a clinical example, Figure 2 (10). When the “white-coat” happens to be dental surgery performed on diurnally-active, nocturnally-resting patients, systolic or mean arterial white-coat hypertension in the morning can be white-coat hypotension in the afternoon, Figure 3, the difference in BP response being statistically significant. Somewhat similar results are observed for DBP and HR, Figure 3. In each case, the response to periodontal surgery was assessed for the given patient, taking into consideration both that patient’s usual circadian variation in BP and HR on days and at times other than surgery, and the effect of posture, patients being mostly in a reclined position during periodontal surgery (11, 12).

The data underlying Figure 3 stem from a study completed for an advanced degree by Frank Raab, DDS (11, 12, cf. 13), which included 24 presumably normotensive patients. Each patient had 3 dental appointments, the last one consisting of periodontal surgery. Consecutive appointments were kept at the same clock hour for each patient but differed among patients, with 6 groups of originally 4 patients each seen at one of 6 different clock hours. (Only one did not complete the first stage of the study.) Clinic hours were slightly extended to accommodate the study. Each appointment was bracketed with ambulatory BP and HR monitoring at 15-minute intervals, first for 4 days, then for 2 days, and finally for 3 days. During each appointment, measurements were taken more often, and at the end of the last appointment, additional dense measurements were taken in the supine and sitting position in order to make adjustments for the effect of posture when analyzing the data.

The response in BP and HR was determined as follows: Data during appointments were removed from each record to assess the circadian variation and to estimate values the BP and HR would have assumed at appointment times, were they taken under similar ordinary conditions. Data during appointments, corrected for posture, were averaged for each patient at each appointment. The response in BP and HR was determined as the difference between the actual (corrected) values during the last appointment (periodontal surgery) and the estimated value these variables would have been under usual conditions, Figure 3.

Because patients were randomly assigned to 6 different appointment times and because a circadian stage-dependent response rhythm was anticipated, the change in BP and HR seen in each patient could be assigned to the treatment time. The time effect is statistically significant, whether responses from all 23 patients were analyzed by one-way analysis of variance (a procedure checking only for a time effect without assuming a model, i.e., a necessarily circadian variation) or by the cosinor fit of a 24-hour cosine curve (14-16, a method assuming that the response follows a circadian variation), Figure 3. Patients having surgery in the morning have an increase in their BP and HR during surgery ("White-Coat HYPERtension"), whereas patients having surgery in the afternoon have a decrease in their BP and HR during surgery ("White-Coat HYPOtension"). Whether the response of a variable is an increase or decrease depends on both the subject's genetics (17) and social schedule. When specifying a time of day, one must specify the routine of living with respect to the circadian system, such as diurnal activity and nocturnal rest, as was the case in this study. From the viewpoint of infradian rhythms, it is also important to note the calendar date, with particular reference to any magnetic storm or excessive magnetic quiet (18).

With respect to the circadian stage-dependent response of BP and HR to a "white coat" in preparation for periodontal surgery, there was an intervention of greater severity than the exposure to a care provider, and hence the response may be more than a mere "white-coat effect". The results, however, are similar to those seen for a white-coat effect uncomplicated by an anticipated intervention. This is demonstrated in Figure 4, based on single casual measurements taken in the care office in the physician's presence that are compared with measurements taken 30 minutes later in the physician's absence. In the morning, the white-coat effect was an average rise in BP of a magnitude of about 20 mmHg. By comparison, comparable patients seen in the afternoon around 16:00 had an average white-coat effect of only 6 mmHg magnitude. The difference in response is statistically significant (P=0.005). These results are averages, and some patients seen in the afternoon actually responded by a decrease in SBP in the physician's presence, just like the dental patients undergoing periodontal surgery. This is actually what happened for HR that increased by 3 beats/min for patients seeing the physician in the morning but decreased by 4 beats/min for patients seeing the same physician in the afternoon.

Great inter-individual differences (19, 20) also need to be considered. As an illustrative example, Figures 5 and 6 show that not all subjects respond to sodium loading with an increase in BP. Not only are there some subjects who have no statistically significant change in BP, but some subjects also respond with a decrease in BP. Moreover, the response to sodium intake is also circadian stage-dependent. In a study by Kawasaki et al. (21), the usual daily salt intake was redistributed to have either higher intake at lunch and lower intake at dinner or vice versa. BP was measured by ambulatory monitoring. As compared to the span when subjects had their usual salt intake, there was only a small numerical (not statistically significant) increase in both SBP and DBP when these subjects had the same total daily salt intake but with a higher amount at lunch and a smaller amount at dinner. By contrast, when sodium intake was reduced at lunch and increased at dinner, both the SBP and DBP of these subjects were statistically significantly decreased, Figure 7. This finding must eventually further consider the also statistically significant inter-individual differences which we found with Frederic C. Bartter on his metabolic ward at the NIH, Figures 5 and 6 (10).

Concern about variability has merit far beyond its role in clarifying reasons for opposite or differing diagnoses or differences in dietary responses. Assessing variability in BP and HR uncovers risks of vascular morbid events assessed from actual outcomes within 6 years of the monitoring session. In addition to MH, other VVDs that are not currently screened for can increase vascular disease risk from about 5% to about 100%. This fact in itself warrants the determination of minimal sampling requirements, starting with a 7-day record in health and deserving continuous monitoring when abnormality is detected, as apparent from a follow-up study of the dental patients, Figure 8 (13).

The need for the minimal sampling requirement of one week becomes further apparent from a 7-day BP record of measurements every half-hour by day and every hour by night. The data stem from a 70-year old Japanese woman obtained within the scope of the BIOCOS project. By comparison to reference standards from peers matched by gender and age, her circadian SBP characteristics were acceptable overall as well as during the first 3 days of monitoring, but were abnormal during the last 4 days when systolic CHAT (Circadian Hyper-Amplitude-Tension) was diagnosed each day, Figure 9. Whether the goal is to improve the reliability of a diagnosis of a

VVD, to guide treatment, or equally importantly to practice "stress relief", novel endpoints of response are needed, such as the parameters of the many rhythms characterizing physiologic variables. Their alterations can serve to indicate earliest harbingers of risk elevation. A conventional stress test cannot invariably be a valid substitute (22). By detecting VVDs, the foe in terms of misdiagnosis becomes the friend by warning of increased risks, which await further testing on an appropriate scale. But the evidence already available (23) suffices to suggest that we must not fly blind (24, 25). A true white-coat hypertension is now documented in a cardiologist on himself (1). As to pseudo-hypertension and pseudo-white-coat hypertension, they are interim misdiagnoses prompting us to note that the first motto of health care is "Do no harm". Harm can be done when patients who are mistreated (in that the treatment induces a VVD) are placed at a higher risk and when patients in need of treatment do not get it, even if, on the average, there is some benefit to be anticipated from a polypill given to everyone above a certain age without measuring BP (26-28). "Flying blind" is bound to hurt some patients!

Acknowledgement: The authors are indebted to Professor Paul Rosch for an essay that prompted the consideration of pseudo-white-coat hypertension and of the different, sometimes opposite effects of sodium intake.

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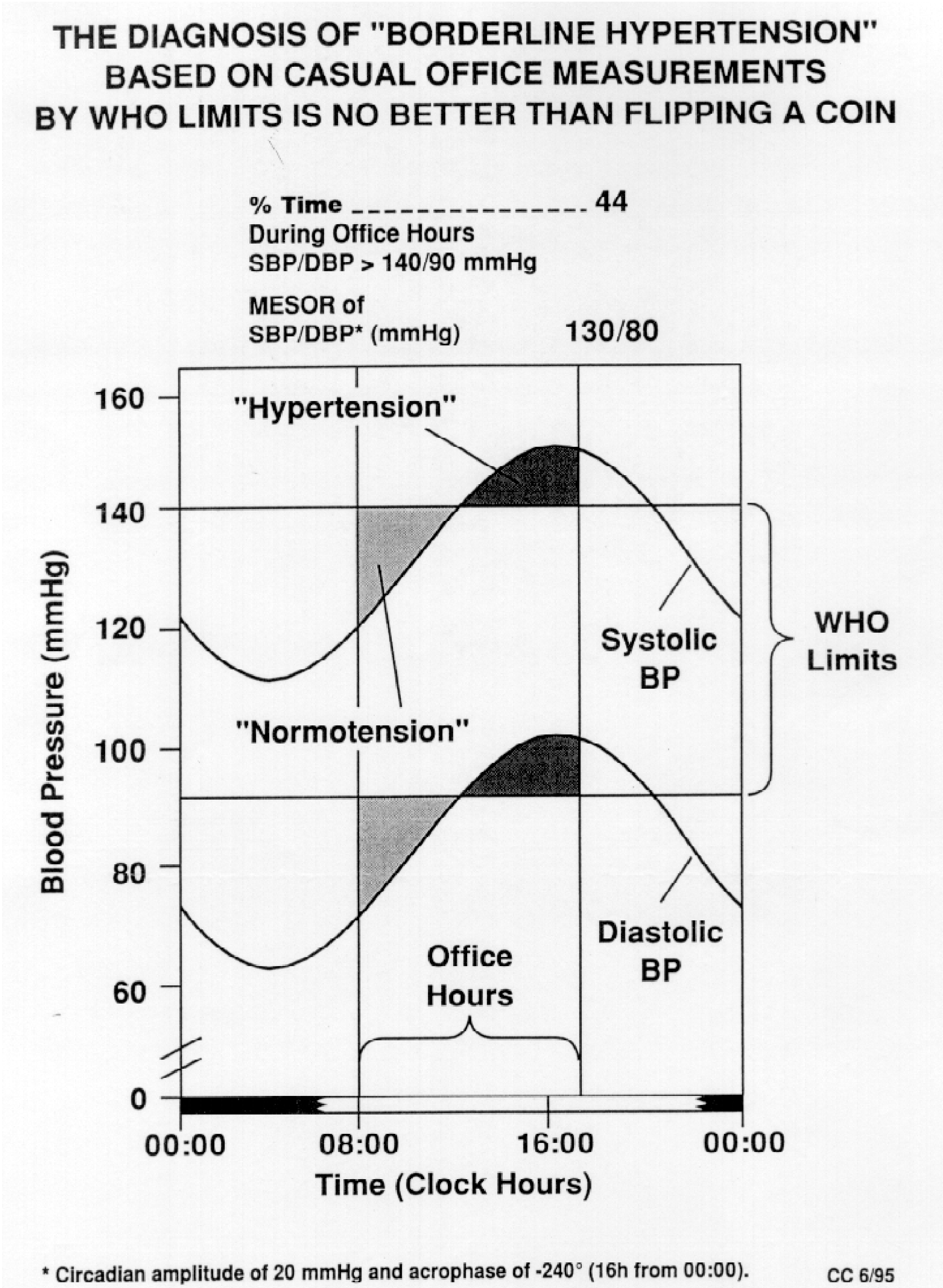

Figure 1. Abstract demonstration that for variables such as blood pressure that are usually characterized by a prominent circadian rhythm, the time of day can determine the diagnosis: normotension in the morning vs. hypertension in the afternoon when fixed limits are used to interpret single time-unspecified measurements. © *Halberg*.

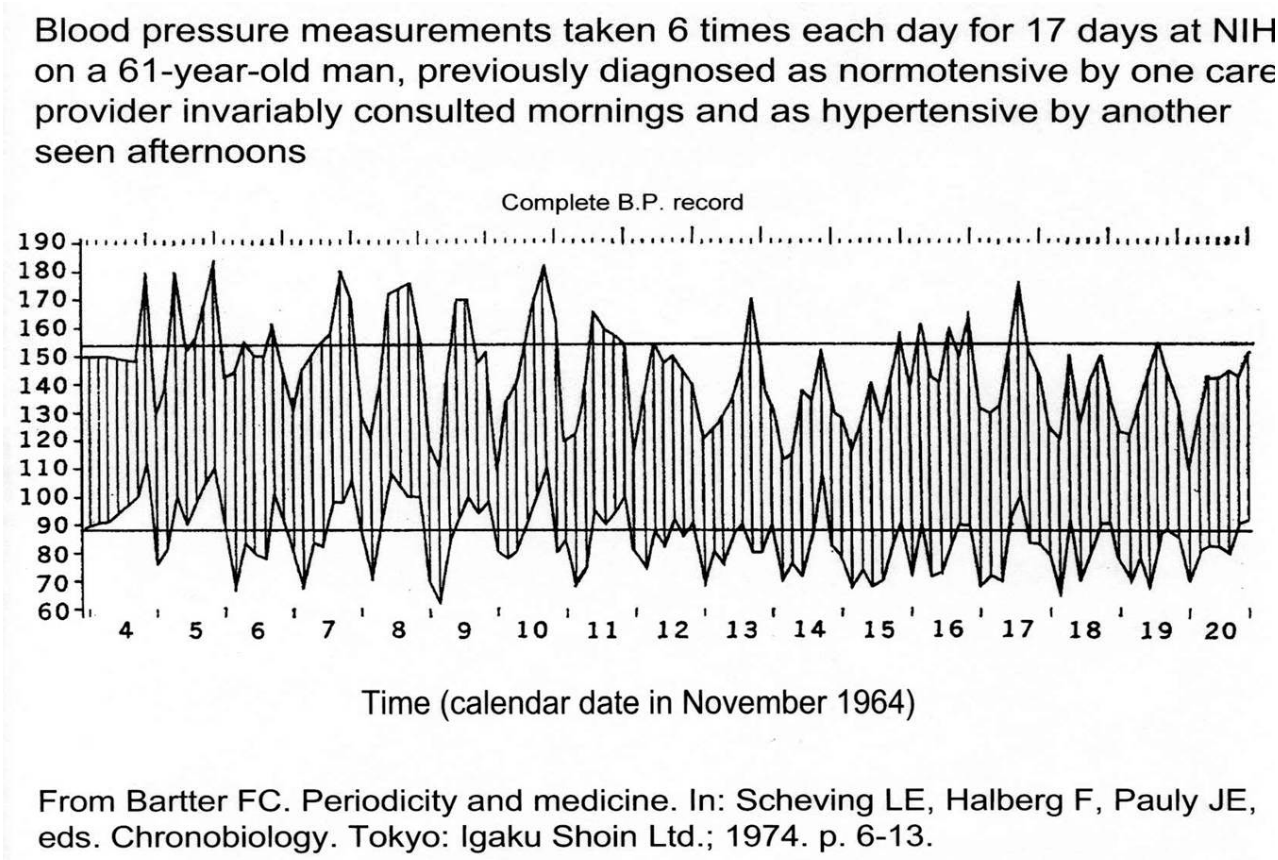

Figure 2. Clinical documentation that the diagnosis of normotension vs. hypertension can depend on the time of day of the blood pressure measurement(s), as illustrated in the abstract in Figure 1. © *Halberg*.

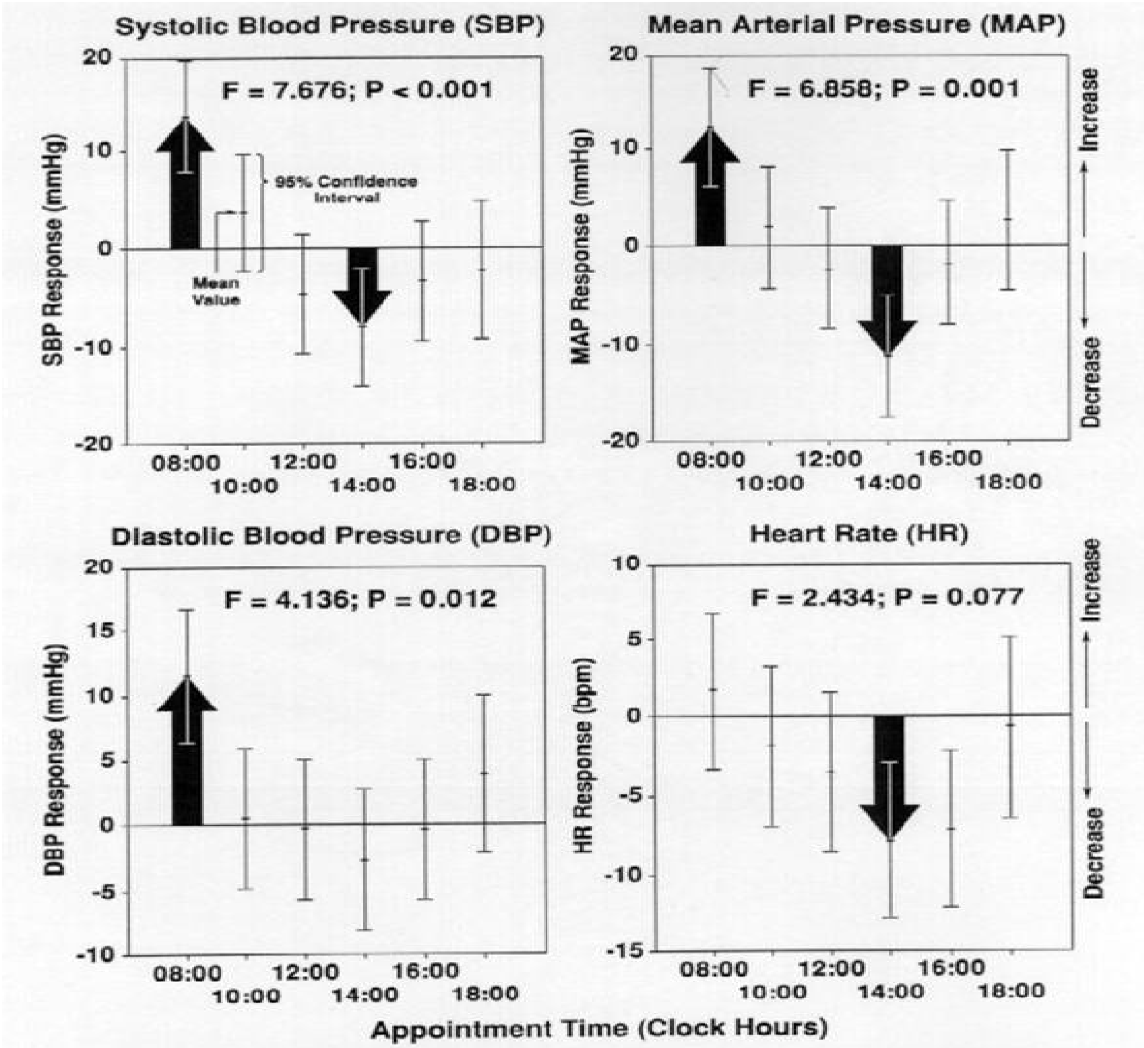

Figure 3. "White-coat hypertension" in the morning can be "White-coat hypotension" in the afternoon. In this study of dental patients, the "white-coat" effect is more than a response to the physician's presence, consisting of periodontal surgery. © *Halberg*.

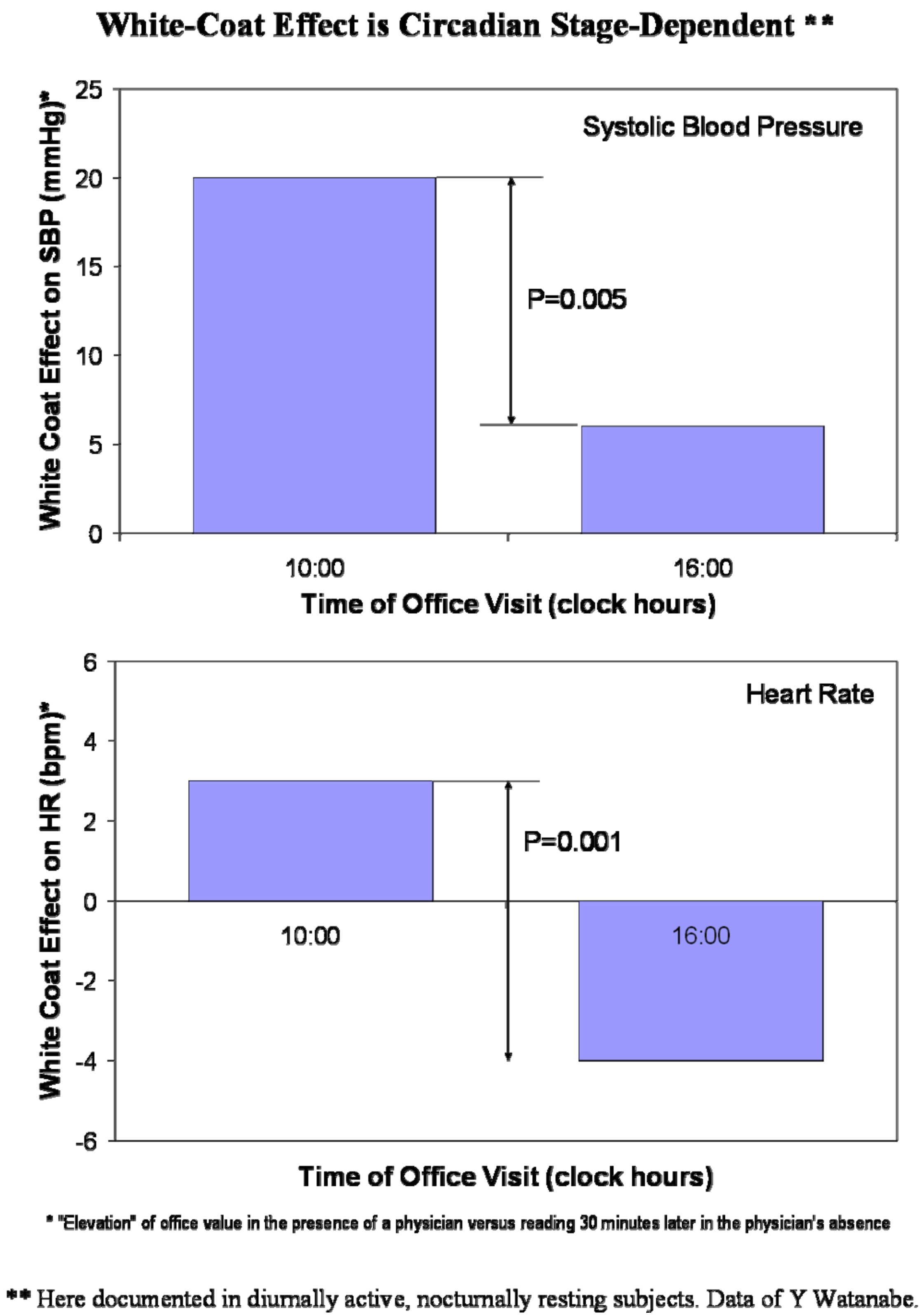

Figure 4. Regular uncomplicated "white-coat" effect. © *Halberg*.

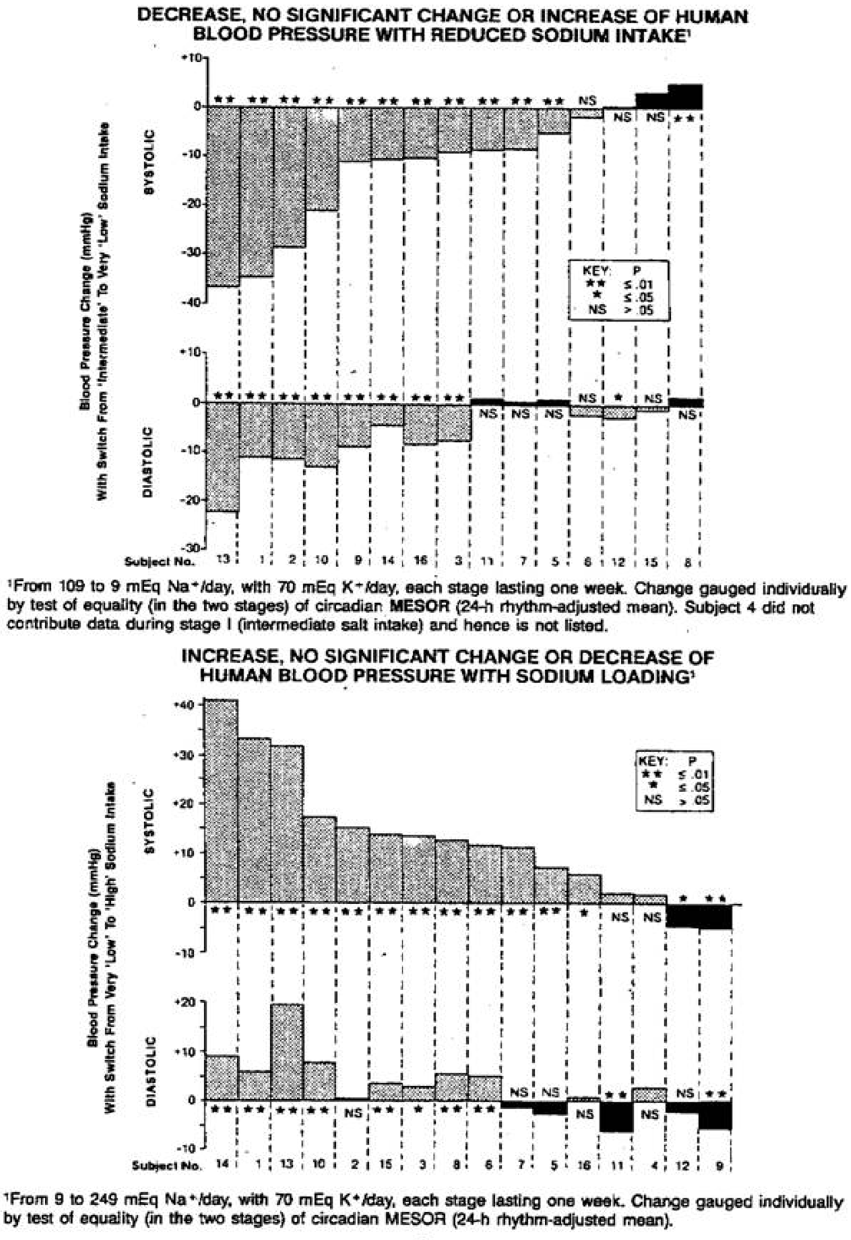

Figure 5. Inter-individual differences in response to sodium intake. © *Halberg*.

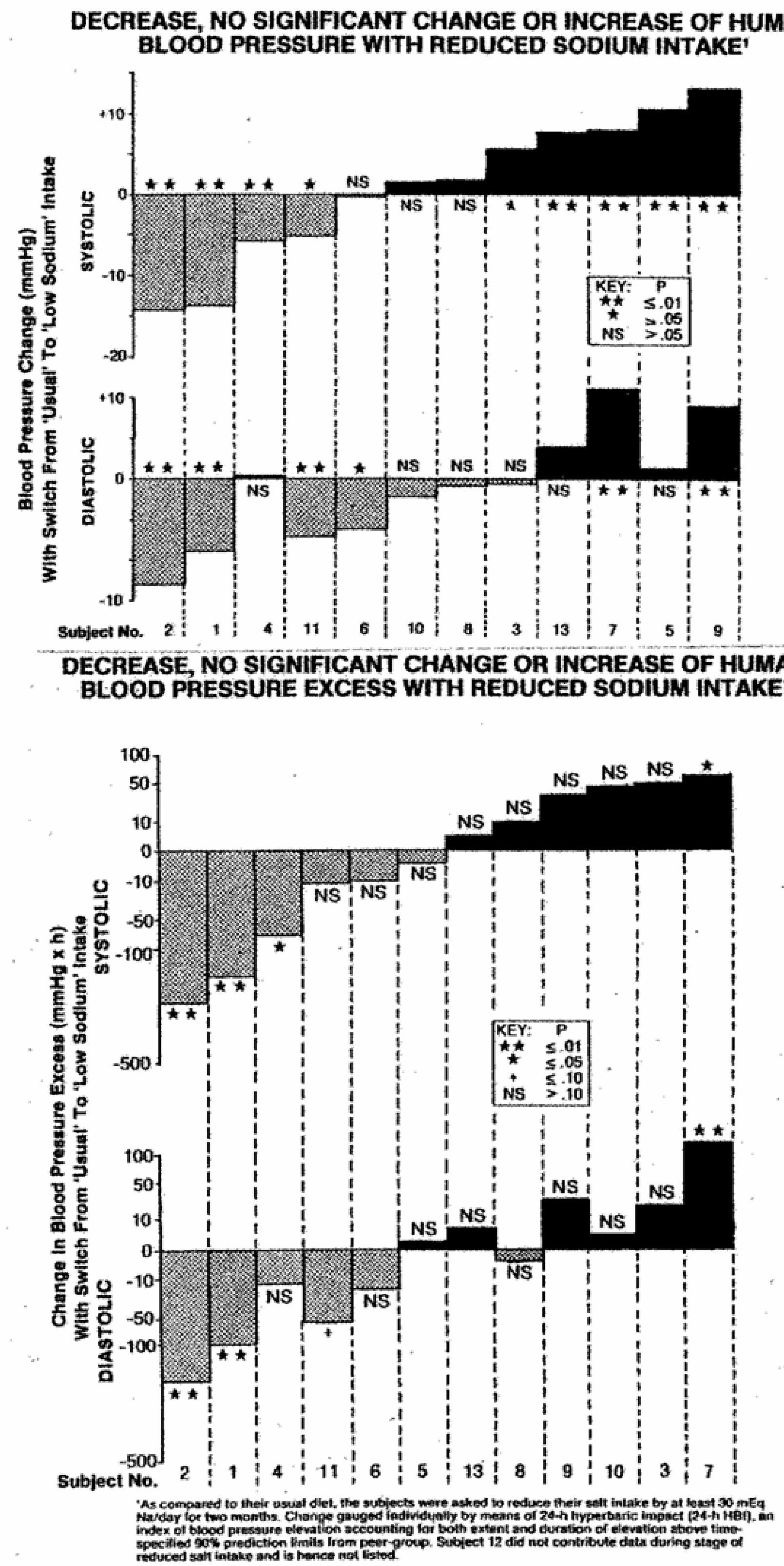

Figure 6. Inter-individual differences in response to sodium intake. © *Halberg*.

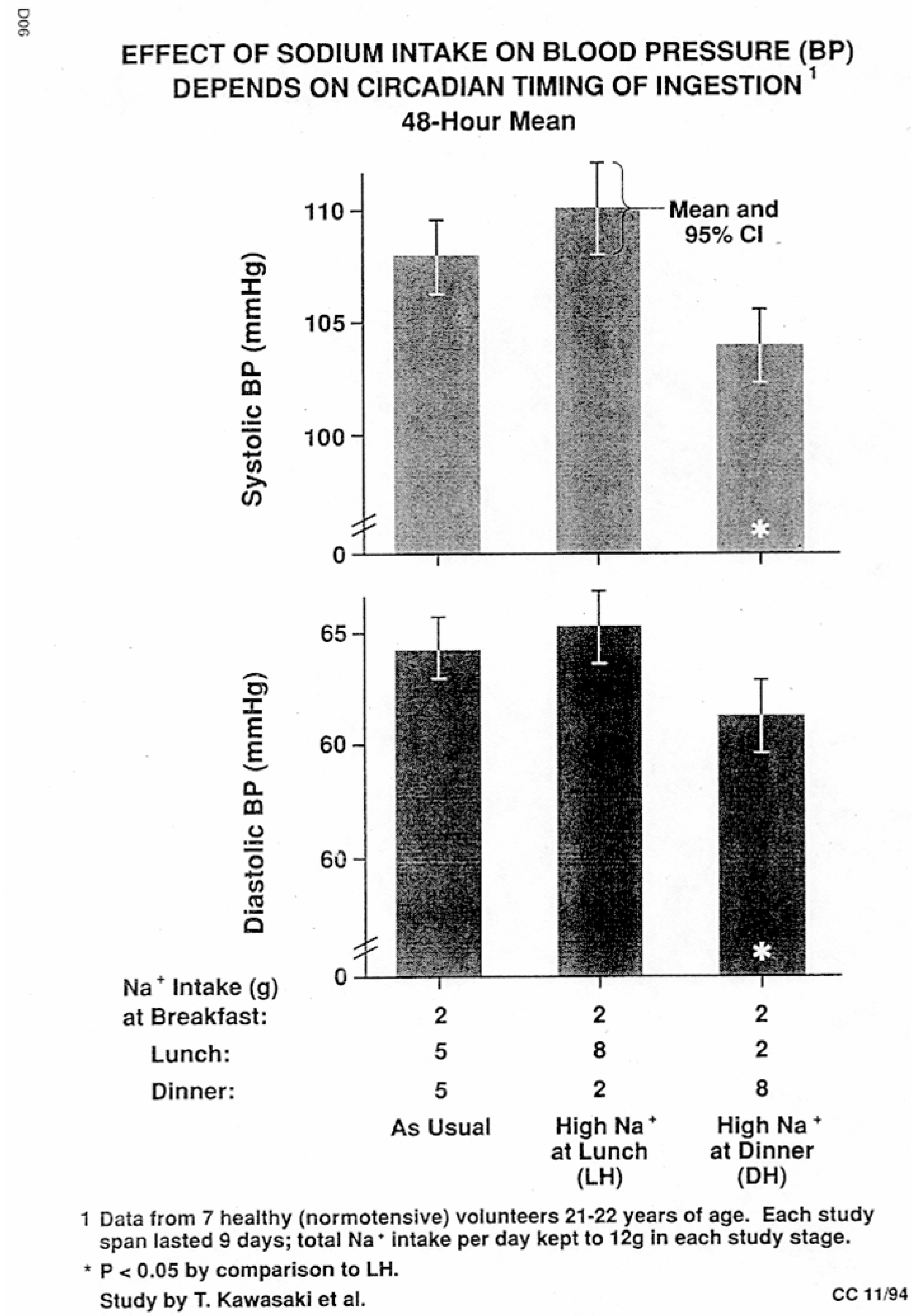

Figure 7. Circadian stage-dependent effect of sodium intake. © *Halberg*.

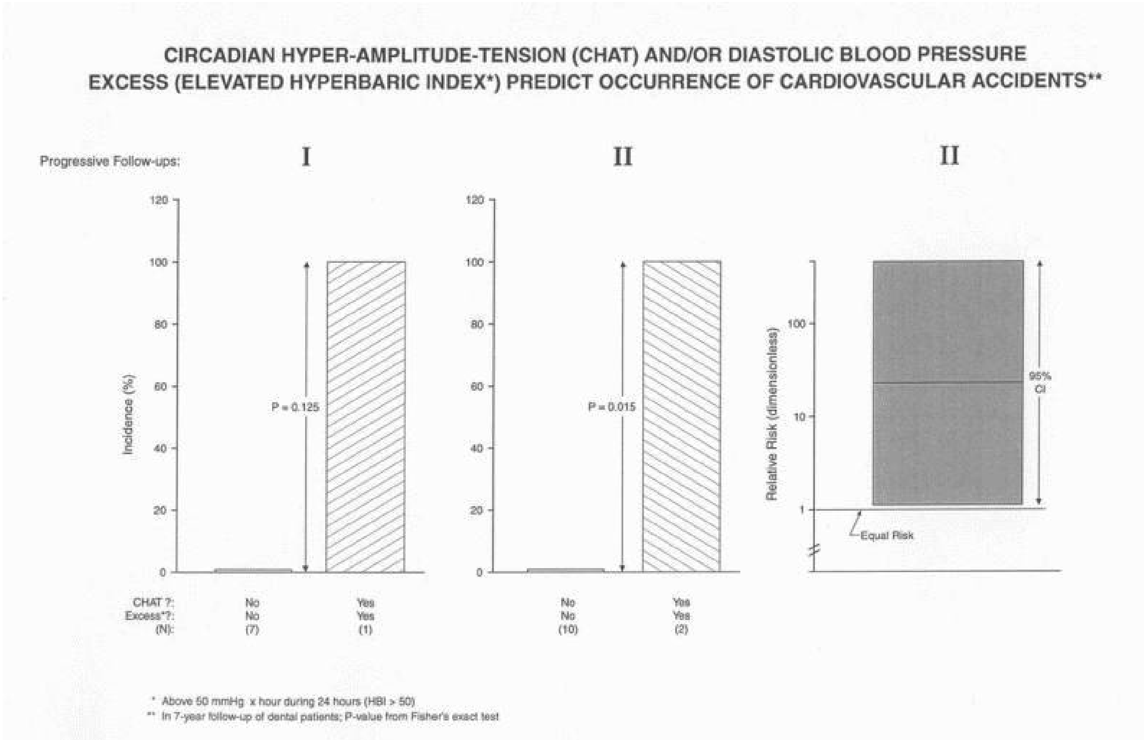

Figure 8. Follow-up study on dental patients, with focus on outcomes 7 years after monitoring assessed in two recalls (I and II, left and middle). No untoward event occurred among patients with blood pressure abnormality in two, one or none of the sessions, whereas both patients who experienced a vascular problem had been diagnosed with CHAT and/or other abnormalities in all three sessions (13). The prognostic value of a consistently (in three of three sessions) deviant chronobiological assessment is illustrated by the relative risk obtained as the ratio of incidences between the two groups being compared (right). P-values were derived using Fisher exact test. N: Number. CI: Confidence interval. © *Halberg*.

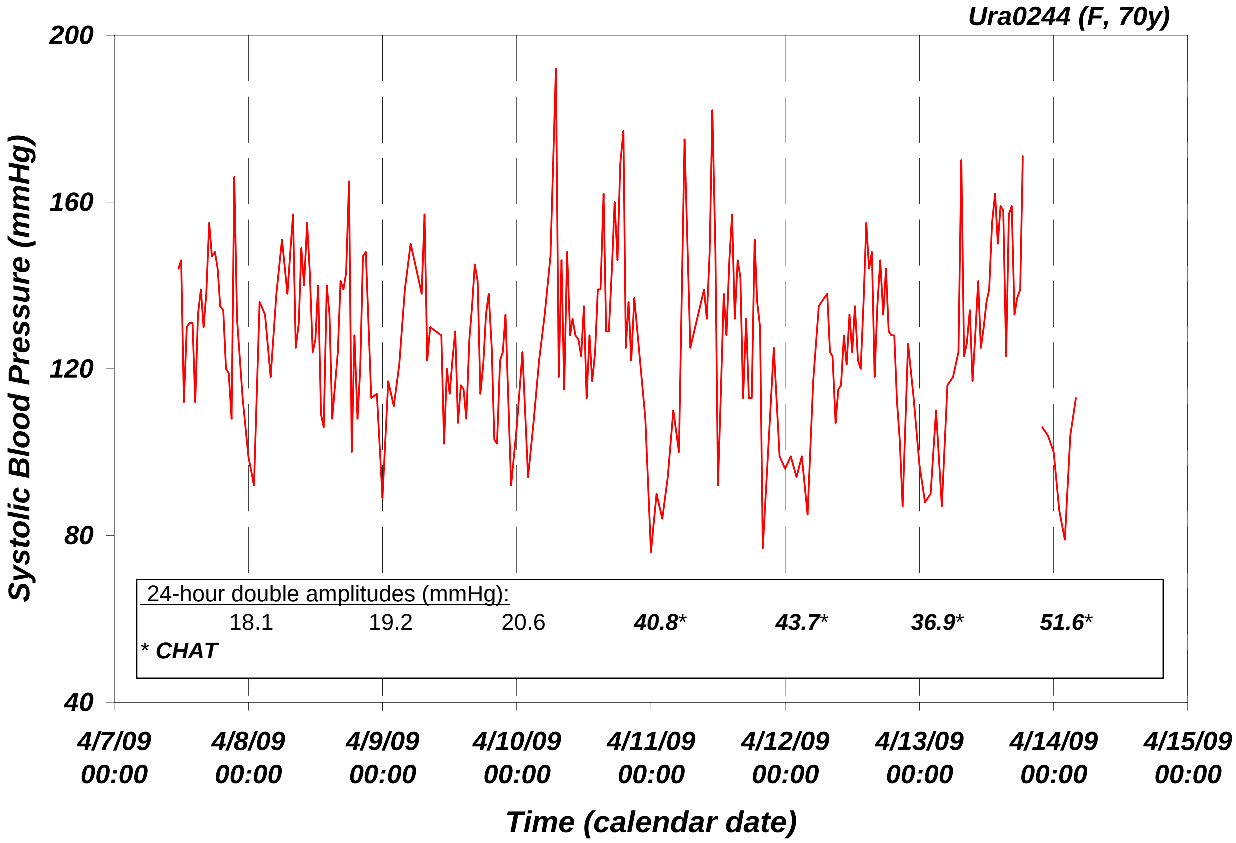

Figure 9. The need to determine minimal sampling requirements is illustrated by this case of a 70-year old Japanese woman who was monitored around-the-clock for 7 days. Overall, all parameters are within acceptable limits of clinically healthy peers matched by gender and age. Day-to-day analyses, however, indicate the presence of CHAT during each of the last 4 days but not during the first 3 days of monitoring. © *Halberg*.

E. CASE REPORTS

AMPLITUDE RATIOS OF HALF-WEEKLY VS. DAILY VARIABILITY IN DIASTOLIC BLOOD PRESSURE IN PUTATIVE MAGNETOLABILITY

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Aim. To find whether a set of self-measurements at about half-hourly intervals covering a week from a presumably magnetolabile 61-year-old woman (JF) has any spectral alteration of systolic (S) and diastolic (D) blood pressure (BP) and heart rate (HR) variabilities, reference ranges were computed, among others, for the ratios of the half-weekly vs. daily extent of change (double amplitude, 2A) approximated by the separate fits of 84-hour and 24-hour cosine curves. JF's DBP ratio was found to be outside the 95% prediction interval (PI) for 84-hour/24-hour A ratios of 178 week-long records from Brno, Czech Republic. It was also outside the PI computed on the basis of the 49 records from women in Brno. Results were replicated in a second weeklong record of measurements at 3-hour intervals. A histogram computed for the foregoing purpose may be of more general use as a reference standard and will have to be refined by age, ethnicity and geography.

Case Report. Figures 1A-1C are chronobiologic serial sections for SBP, DBP and HR. The original self-measurements are in the top row. Statistical significance from the zero-24-hour amplitude (no circadian rhythm) test is given in the penultimate row of P-values, with a dashed line indicating P=0.05. An interval of 24 hours was used for analyses, displaced by 3-hour increments, for the least-squares fit of a 24-hour cosine curve. A circadian rhythm is demonstrated most of the time (P<0.05) for HR (Figure 1C), also seen from the dots bracketing most of the 24-hour HR acrophases (third row of Figure 1C). As acrophases are circular variables, they are double plotted, their uncertainties overlapping 360˚. In Figures 1A-C, the MESOR (M; **m**idline-**e**stimating **s**tatistic **o**f **r**hythm) is displayed as the lower curve in the second row. The distance between the two curves represents the circadian amplitude. Dots below the lower curve and above the upper curve are the standard errors for M and A, respectively. In the case of SBP, statistical significance is reached only part of the time during the first few days (Figure 1A). A circadian rhythm in DBP is only detected with statistical significance in very few intervals (Figure 1B). The relatively dense self-measurements notwithstanding, there is a failure to demonstrate a circadian rhythm in BP most of the time. The acrophases drift but little, and only for BP when the circadian rhythm is statistically significant. Overall, a circadian rhythm is demonstrable nonlinearly by the extended cosinor for all three variables, Table 1.

When data are stacked over an idealized 24-hour span, they are within the limits of Caucasian peers matched by gender and age for SBP and DBP (Figures 2A and 2B), and are partly below the lower 5% prediction limit for HR (Figure 2C). Figure 3 allows a comparison of the three variables on consecutive days, while Figure 4 shows a spectral alteration found in JF, also found in a subsequent weeklong record of measurements at 3-hour intervals.

BIOCOS. In the course of a project on The BIOsphere and the COSmos (BIOCOS), automatic series of BP and HR were obtained at half-hourly intervals for 7 days, among others, on 178 patients in Brno. Whereas some were treated, most of them were clinically healthy and followed their usual routine of daily activity and nocturnal rest. A cosinor spectrum (1-4) was computed for each series linearly in frequency in the frequency range of 1 cycle in 7 days to 1 cycle in 4.8 hours. For the construction of a reference database, 178 weeklong records from Brno were used. The circadian (CD) and circasemiseptan (CSS) As of SBP and DBP were estimated and their ratios were computed as CSS-A/CD-A and $\log_{10}$-transformed to preserve symmetry. Histograms validate the approximate normality of the distribution of the log-transformed A ratios.

The CSS-A/CD-A of SBP, DBP and HR values from JF (9-15 June 2009) were similarly computed. For BP but not for HR, the CSS-A/CD-A is larger than unity, estimated as 1.065 (0.027) and 1.576 (0.198) for SBP and DBP, respectively ($\log_{10}$-transformed ratios given in parentheses).

In order to determine whether these ratios are larger than usually seen, PIs were determined from the Brno database. Using data from all 178 profiles, the average $\log_{10}$(CSS-A/CD-A) and PI are estimated as -0.552 [-1.220, 0.117] for SBP and -0.547 [-1.188, 0.093] for DBP. In view of known gender differences in average BP, PIs were also computed on the basis of data from women only, yielding estimates of $\log_{10}$(CSS-A/CD-A) and PI of -0.418 [-0.982, 0.146] and -0.551 [-1.110, 0.008] for SBP and DBP, respectively. Since some of the women in the database were on anti-hypertensive medication, limits were computed for untreated and treated women separately, yielding means and PIs of -0.486 [-1.043, 0.070] and -0.352 [-0.935, 0.230] for the SBP of untreated and treated women, respectively. For DBP, results were -0.569 [-1.072, -0.067] and -0.533 [-0.-1.171, 0.105], respectively, Figure 4. Whereas the $\log_{10}$(CSS-A/CD-A) of SBP of JF invariably resides within the PI of the reference database, that of DBP is always larger than the upper 95% prediction limit. The untreated women contributing data in the reference database were on the average 45.6 ± 12.1 (SD) years of age (range: 20-70 years). The treated women were on the average 54.2 ± 12.8 years of age (range: 20-77 years). JF is 61 years of age and takes 50 mg spironolactone, an antihypertensive medication, between 5am and 6am and again upon awakening, which recurred on a presumably free-running sleep-wake schedule progressively from 5pm to 9pm during the span of measurements. These results were replicated in a second weeklong record of measurements every 3 hours, with CSS-A/CD-A ratios of 1.383 (0.141) and 1.785 (0.252) for SBP and DBP, respectively.

Several factors may have contributed to the unusually larger circasemiseptan-than-circadian prominence in JF's BP, notably for DBP that exceeds the upper 95% prediction limit of peers. First, data were collected with a manual monitor that required waking up to take measurements during the rest span. Such a procedure is usually associated with higher BP readings, a fact contributing to a smaller circadian amplitude, since BP is usually lower during sleep. Moreover, in a comparison of self-measurements with automatic monitoring, there can be differences (5). Second, the rest-activity schedule of JF may also have been unusual, the rest span occurring at times differing from those of the reference population. It also may have differed from one day to another (although no deviation from 24 hours was found by nonlinear analyses of the data), another fact that can be expected to be accompanied by a smaller circadian amplitude. It is not likely that the actual number of measurements may have played a role: with 233 data collected during a week, this represents almost 70% of a full 7-day/24-hour record obtained automatically by ambulatory BP monitoring.

Circaseptan-to-circadian and circasemiseptan-to-circadian amplitude ratios are known to vary as a function of age, being larger early and late in life (6). At 61 years of age, JF is not expected to have a reversal of the circadian-to-infradian prominence yet. They are also known to differ between clinically healthy subjects and individuals with a depressed mood, the latter having a larger infradian prominence than the former (7). Whether the infradian prominence relates to magnetolability and/or to a state of not feeling well which has a tendency to recur in JF without any known underlying medical reason will require further monitoring, if not continued surveillance. Affordable automatic monitoring devices are urgently needed for this purpose so that the circadian variation can be assessed without the need to disturb the rest/activity cycle known to influence BP.

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Appendix: Self-description by JF, a putative magnetolabile woman

JF is a 61 year old Caucasian female who had a seemingly healthy childhood. She was reared in a stable home with two younger siblings, a stay-at-home mother, and a supporting blue-collar father. Social life was built around the church. Some maternal conflict based on personality differences occurred, but home life was mostly problem-free. School was a joy; grades were high.

JF married immediately following high school and continued her education by studying with her husband in his work on two graduate degrees. Early marriage was spent mothering two daughters and working in the churches where her husband served as pastor. Her healthiest time was during both pregnancies.

In the early 1980s JF and her husband founded an itinerant speaking and writing ministry that involved extensive national and international travel. JF found the ministry fulfilling and enjoyed the intensity of the travel. It was a mystery, however, why she could hike through busy airports one week without any problems, and in other weeks was hampered by leg and foot pain so intense that she could barely make it past two gates without stopping for a break. Observing the tides during an extended stay on the beach helped: she was able to hike miles along the sandy beach during the weeks midway between the new moon and the full moon, and between the full moon and the new moon; but near both the times of the full and new moon she was barely able to make it to the shore. Subsequently, this knowledge helped predict JF's ability to hike in airports.

Sometime in the late 1980s JF began to be unable to meet some of the travel demands. By 1990 her husband detected two specific time spans of her inabilities: Jan/Feb and Jun/Jul/Aug. Since the apparent semimonthly change seemed to have a geomagnetic connection, they first connected these spans with the solstices, but the timings seemed more consistent with the perigee and apogee of the earth's revolution around the sun. This knowledge was employed in scheduling engagements and also proved thoroughly faithful to predict JF's inability to participate if engagements were scheduled during the two seasonal spans.

By 2000 JF's very predictable semiannual physical symptoms that rendered her unable to function were dominating her life and the new inclusion of seizure-like events prompted serious evaluation. To provide better health insurance, JF's husband decided to take a hiatus from the traveling part of their ministry and secure part-time employment with a local firm that provides excellent medical coverage to part-time employees. While the medical help received during the following years provided relief from many symptoms, nobody was able to address the semiannual spans of abnormal sleep. JF decided to turn to science and to research as much as possible to find solutions.

On May 15, 2005, JF experienced many of the semiannual symptoms including muscle twitches, diagnosed as a myoclonus seizure. This was the first time JF experienced these symptoms outside of the Jan/Feb and Jun/Jul/Aug time periods. Later she observed a news article about an extreme solar storm that had occurred on that day. Once again a geomagnetic event appeared to trigger JF's symptoms and the planetary k-index became a dependable indicator for minor symptoms throughout the year and for intensified symptoms during the two semiannual time spans of illness.

By February 2009 JF and her family were beginning to sense that her older daughter (age 41) was experiencing some of the same semiannual changes that JF experienced at her age. These symptoms on a lesser level of intensity were also occurring in conjunction with an increase in the planetary k-index. Suspicion had also arisen that increases in the Kp were the cause of JF's granddaughter (age 2) awakening from her normal full night of sleep for no apparent reason desiring nothing more than to play.

Circasemiannual Cycle in JF's Health?

As JF has sought medical help for the myriad symptoms manifested during the semiannual time periods of Jan/Feb and Jun/Jul/Aug, it has become very clear that what ever is occurring during those time periods creates a break down in her immune system. Several documented events of poor health in JF's earlier years consistently fall into one of the two time periods:

Jun 1953	Mumps
Jan/Feb 1954	Hospitalization for kidney infection after 2 weeks of strep throat and sulfa drug treatment
Jun 1967	Kidney infection following birth of first child
Jun or Jul 1977-81	Repeated vaginal yeast infections
Jun 1985	Sought help from gynecologist for exhaustion and headaches
Jun 1986	Sought help from care giver for exhaustion and headaches

The multiple symptoms that occur and reoccur only during the semiannual cycles make it difficult to isolate the exact root cause of the problems. JF has been diagnosed and treated for carpal-tunnel syndrome, chronic fatigue syndrome, rheumatoid arthritis, kidney stones, myoclonus seizures, and meningitis induced by cytomegalovirus. She has been repeatedly placed on and taken off thyroid medication and has exhibited insulin resistance. Just recently she was tested for Vitamin D deficiency and found to be deficient. When each of these diagnoses was treated, there was improvement in the severity of her semiannual time spans of illness.

With these multiple symptoms treated, the following remains steadfast and untreated:

The onset of a semiannual "cycle" usually begins at a full moon or new moon with the following two weeks of complete exhaustion and sleeping day and night. Then a 7-9 hour sleep cycle is established and moves later each day, the later awakening with daily delay varying between 15 minutes and 1 hour. These sleeping hours are dictated by an excessive burst, presumably of stress hormones, that are described by JF as unbearable. In her own words: "When the time for sleep arrives I have a surge of what I assume is cortisol. [Her laboratory determinations of circulating cortisol for blood drawn during the then-usual sleep span are at the top, but within the normal range.] My body quivers both inside and out and it is as though I am driven to sleep in order to escape. (It is at these times that I have had myoclonus seizures in the past.) Sometimes the quivering is accompanied by heart palpitations. I have heart palpitations other times as well, but the quivering only occurs during the sleep time. I awaken several times throughout the sleeping hours with the same quivering and quickly go back to sleep to escape. Being awake when this is going on is unbearable. The myalgia is overwhelming and I often hyperventilate and cry. I do not have the capacity to communicate with my husband during this time. It reminds me of the physical stress that I saw in both of my daughters right after child delivery. It usually ends before my final awakening after 7-9 hrs of sleep." Eventually the time of these events leads to a 24 hour awake time. All of this cycle takes place in about a month. The monthly cycle is repeated twice in the winter and three times in the summer. There is not a gradual entrance nor exit with the semiannual spans of illness. They occur as though someone turned a switch off and then finally back on.

JF reports that during the awake hours of these time spans she experiences heart palpitations, myalgia, arthritis, brain fog, lethargy, nerve tingling, and neuropathy in varying degrees. Usually greater activity produces more intense symptoms. A rise in the planetary k-index will also increase the symptoms. There are usually 1-3 days of improved function in between the new moon and the full moon and the full moon and the new moon.

The semimonthly cycles experienced by JF seem to be dictated by the full moon and the new moon. These spans of 1-4 days involve much fluid retention accompanied by much pain throughout the body. They come to an abrupt end by excessive urination. Sometimes outside of the semiannual spans these semimonthly cycles are barely noticeable. Within the semiannual cycle periods they are quite intense.

JF is eager to find solutions to these problems and is committed to accomplish the task for herself and for science, and especially for her daughter and her granddaughter.

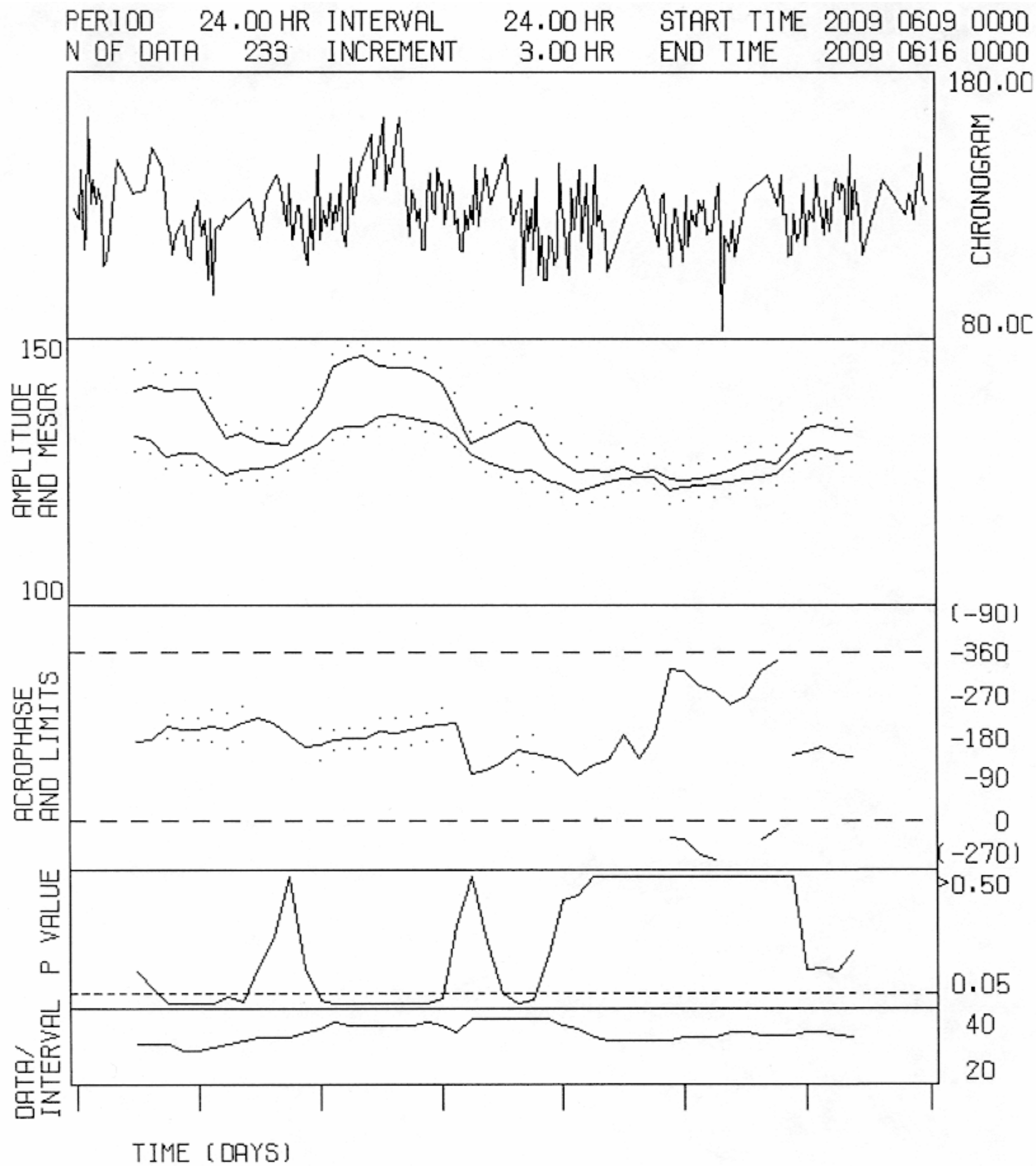

Figure 1A. Chronobiologic serial sections of JF's systolic blood pressure. © *Halberg*.

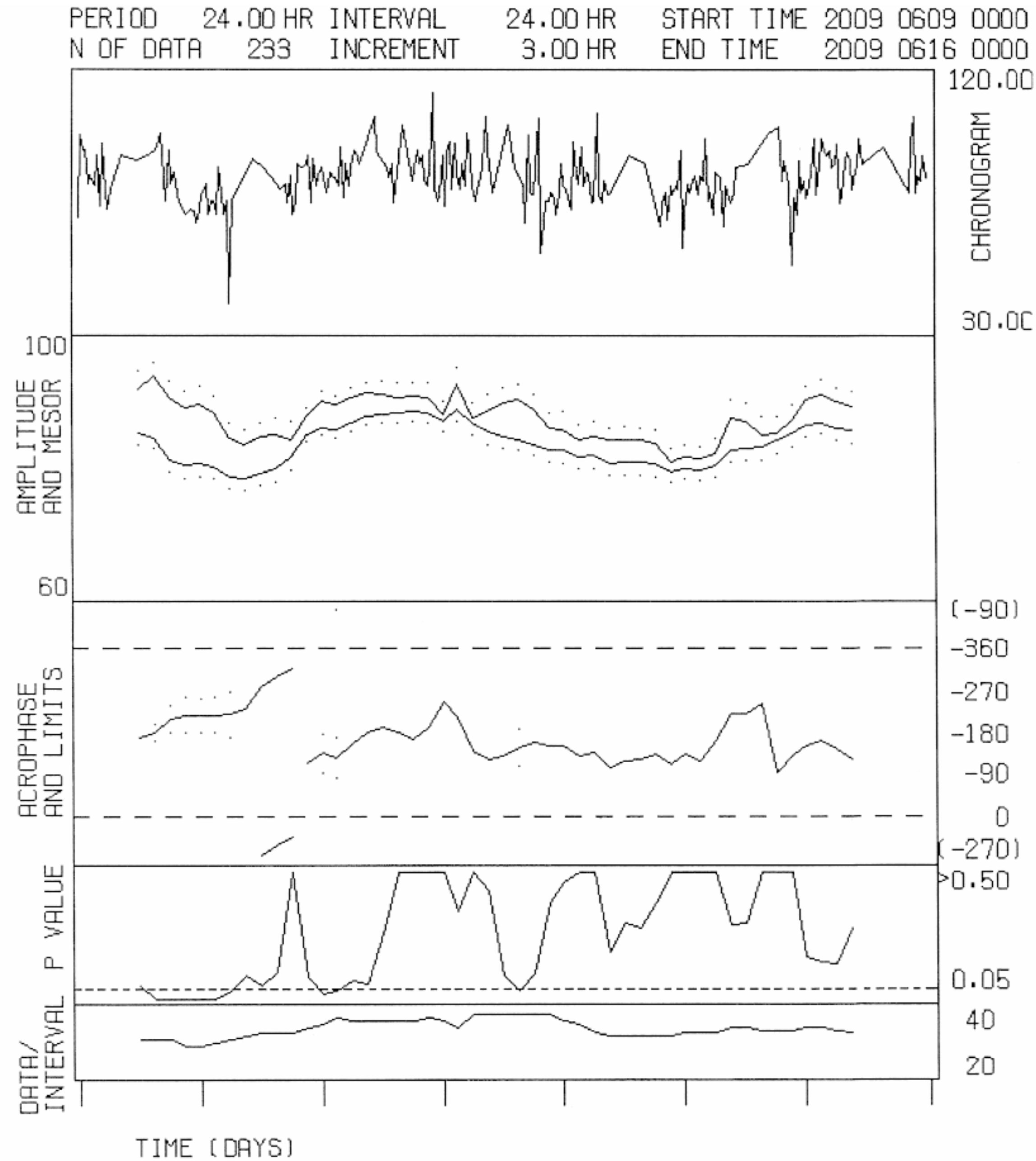

Figure 1B. Chronobiologic serial sections of JF's diastolic blood pressure. © *Halberg*.

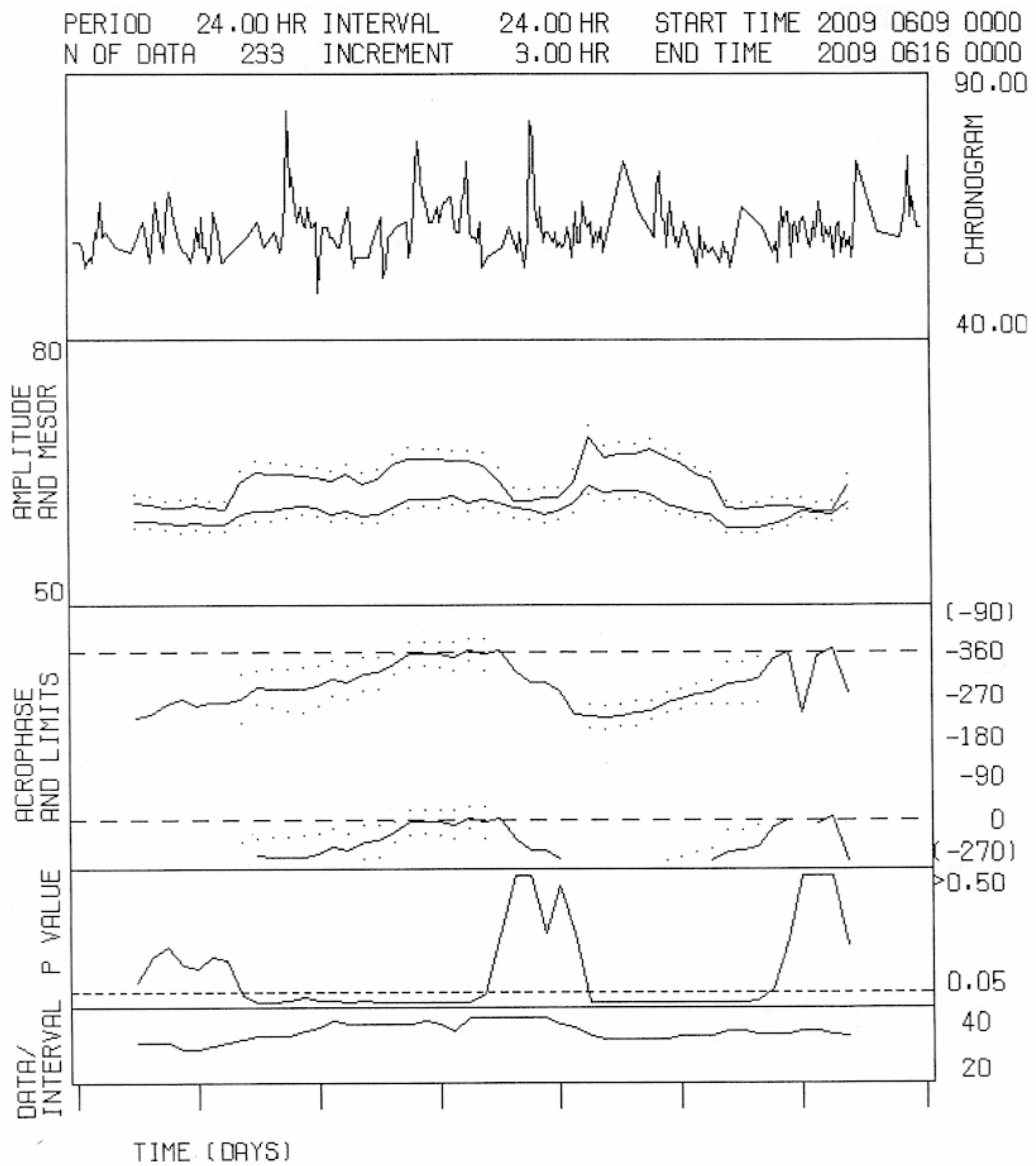

Figure 1C. Chronobiologic serial sections of JF's heart rate. © *Halberg*.

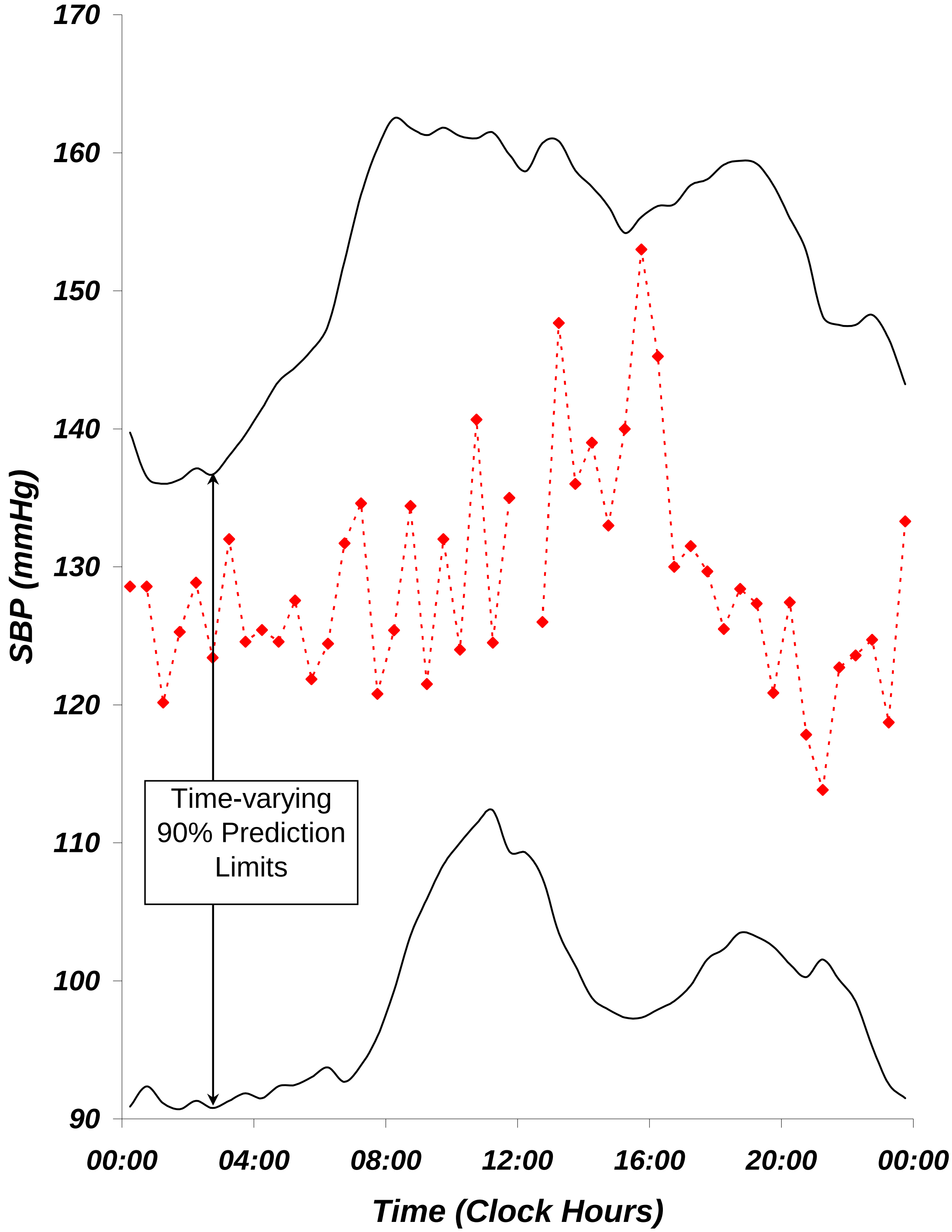

Figure 2A. Plexograms comparing JF's systolic blood pressure data (red) stacked over an idealized 24-hour day with reference values computed as time-specified 90% prediction limits derived on the basis of around-the-clock profiles from clinically healthy women of the same age group. © *Halberg*.

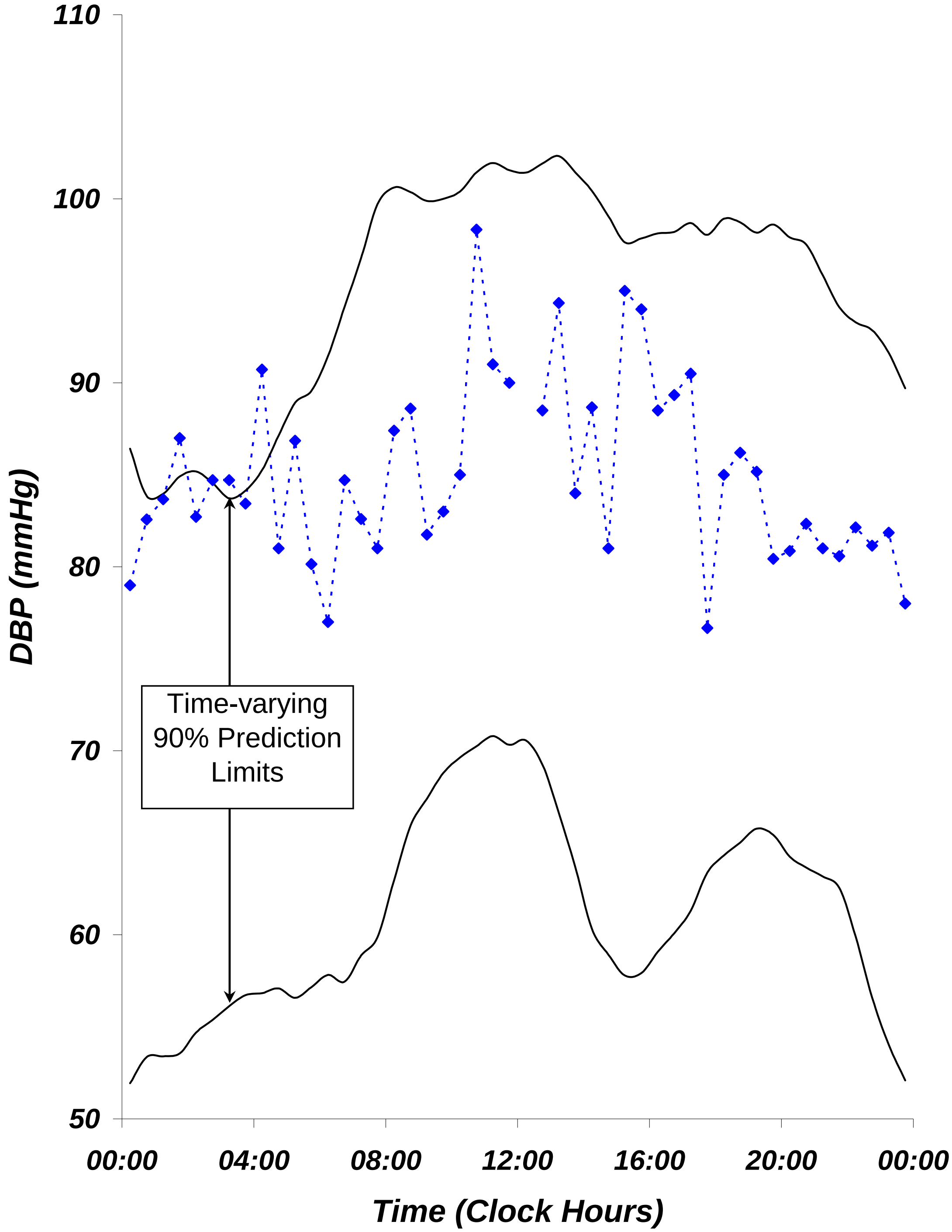

Figure 2B. Plexograms comparing JF's diastolic blood pressure data (blue) stacked over an idealized 24-hour day with reference values computed as time-specified 90% prediction limits derived on the basis of around-the-clock profiles from clinically healthy women of the same age group. © *Halberg*.

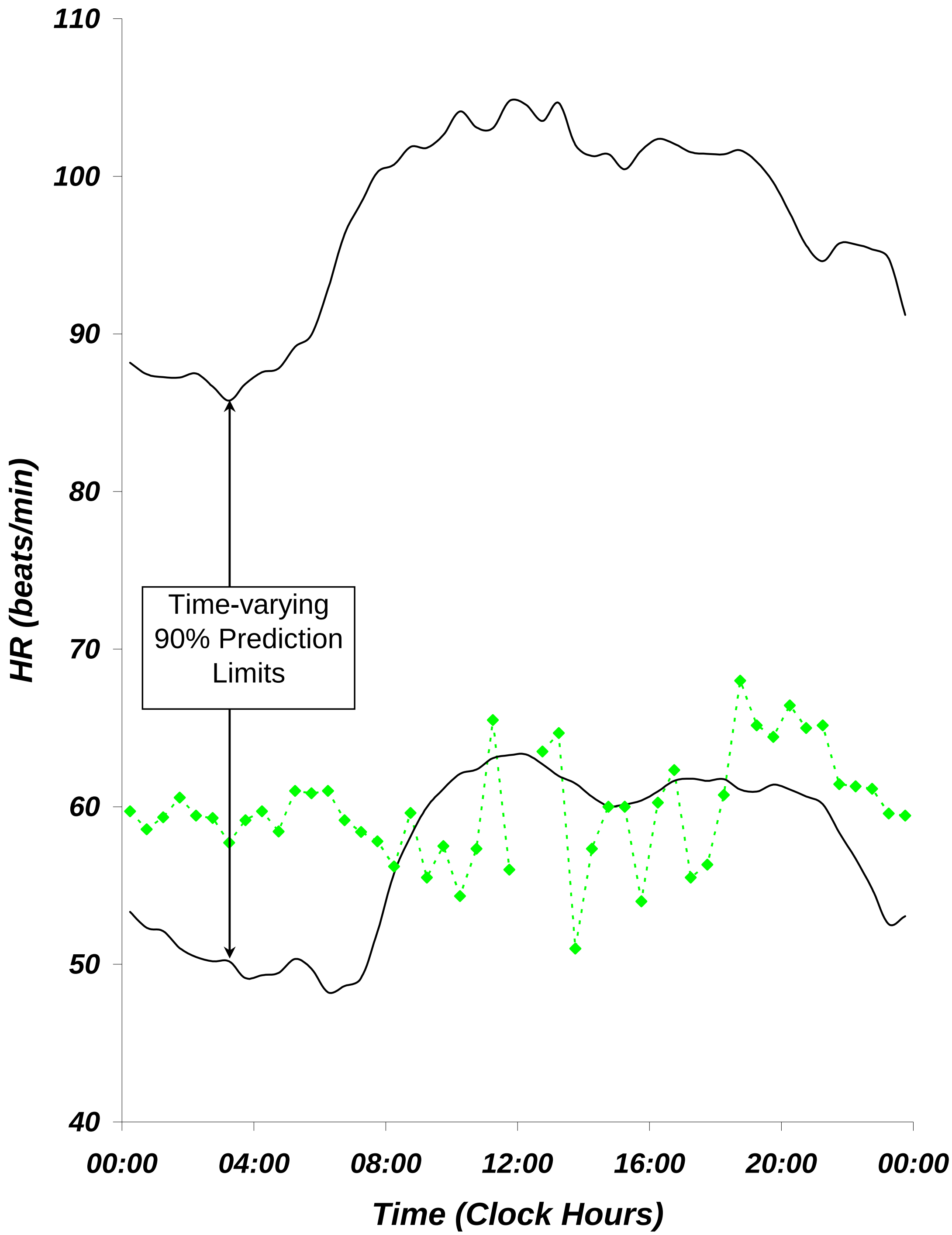

Figure 2C. Plexograms comparing JF's heart rate data (green) stacked over an idealized 24-hour day with reference values computed as time-specified 90% prediction limits derived on the basis of around-the-clock profiles from clinically healthy women of the same age group. © *Halberg*.

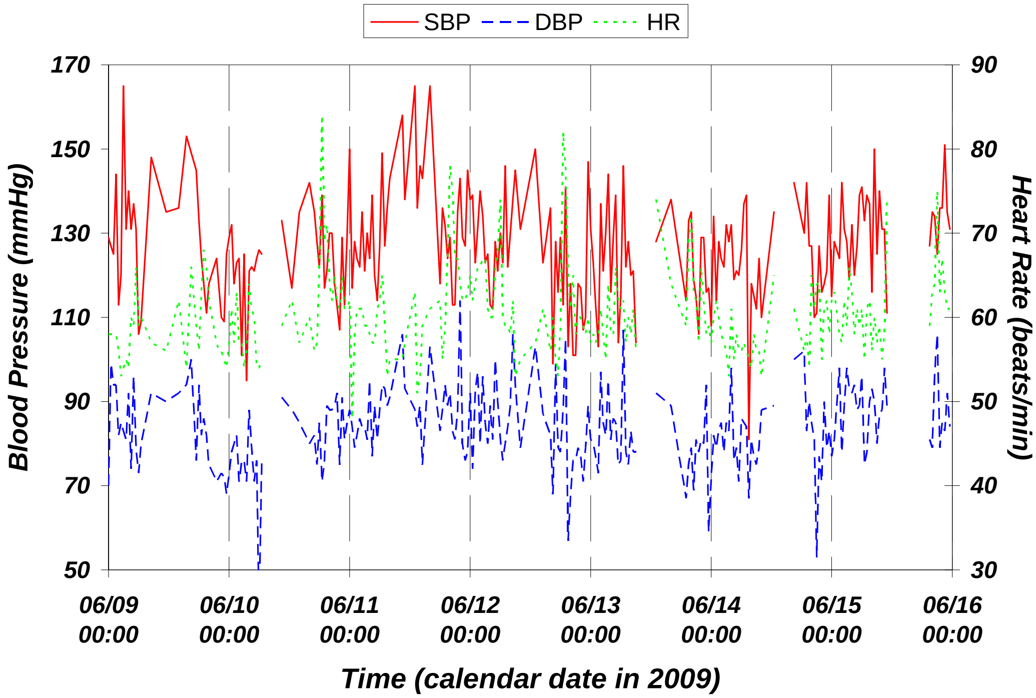

Figure 3. Time course of JF's systolic and diastolic blood pressure and heart rate. © *Halberg*.

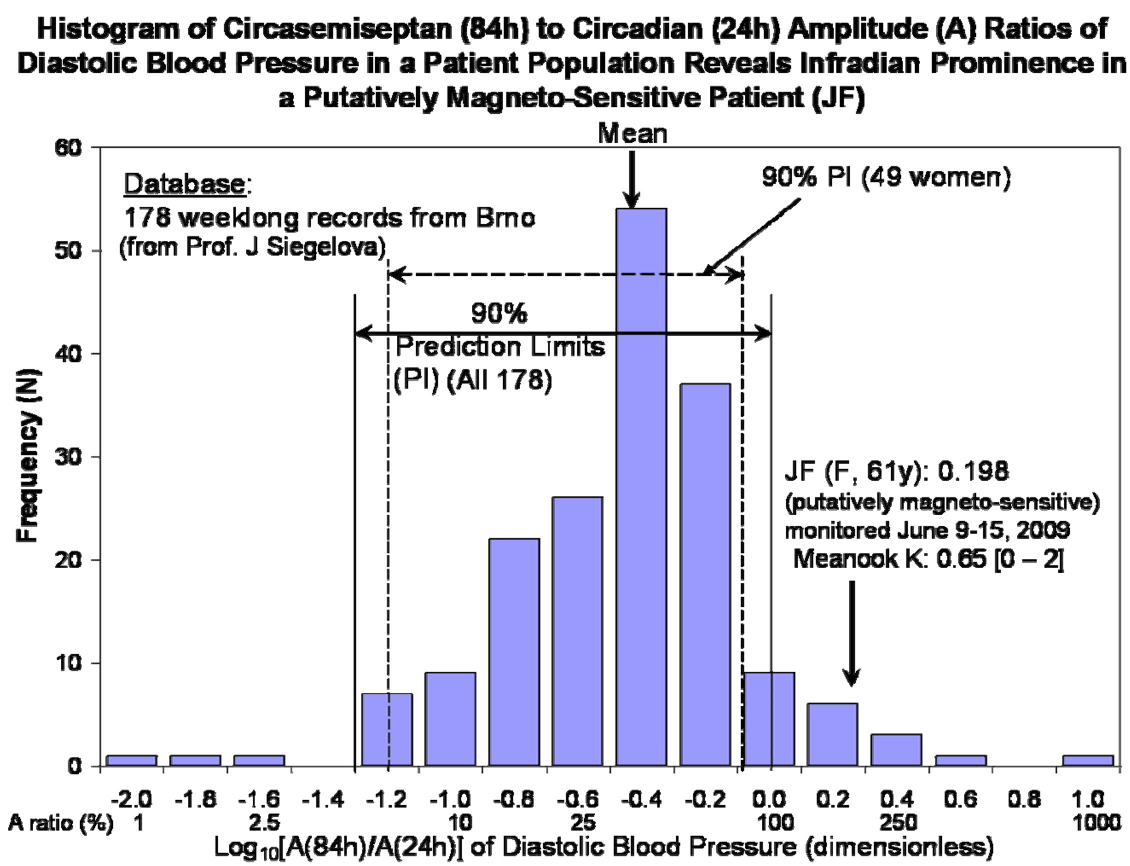

Figure 4. Histogram of circasemiseptan (84-hour) to circadian (24-hour) amplitude (A) ratios of diastolic blood pressure in a patient population reveals infradian prominence in a putatively magnetolabile patient (JF). © *Halberg*.

Table 1: Circadian characteristics with a measure of their 95% confidence intervals (CIs) of blood pressure (BP) and heart rate (HR) of a magnetolabile patient (JF, F, 61y)

Variable (units)	MESOR*	Period (hours) [CI]	Double Amplitude* [CI]
Systolic BP (mmHg)	128.5 [125.6, 131.3]	24.49 [23.22, 25.75]	10.6 [1.8, 19.3]
Diastolic BP (mmHg)	84.5 [82.3, 86.7]	23.38 [21.43, 25.32]	6.0 [0.1, 11.9]
HR (beats/min)	60.4 [59.2, 61.5]	24.40 [22.99, 25.81]	4.5 [1.8, 7.2]

*Decimals can be ignored.

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

CIS-HALF-YEAR IN THE SYSTOLIC BLOOD PRESSURE OF A YOUNG ADULT

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Around the clock monitoring of systolic (S) and diastolic (D) blood pressure (BP) and heart rate (HR) with the TM-2421 ambulatory monitor from A&D (Tokyo, Japan) served for mapping the circadian system of a few variables of the circulation of a young adult (DG). Data were collected around-the-clock, mostly at 30-minute intervals, with interruptions and averaged over consecutive 2-hour intervals for almost one year. The data were analyzed by the extended cosinor (1-3), with particular focus on the cis-half-year component with an anticipated period of about 0.42 year, previously reported for circulating melatonin (4) and the incidence of sudden cardiac death (5).

As a large-amplitude circadian component characterizes all three variables (Figure 1), initial values used in the nonlinear analysis included a fixed 24-hour component and a 0.42-year cis-half-year. Parameter estimates with their 95% confidence intervals (CIs) are summarized in Table 1.

Table 1
Nonlinear estimates of the cis-half-year assessed concomitantly with a fixed 24-hour component

Variable (units)	24h double amplitude [CI]	"Cis-half-year" period [CI] (years)	Cis-half-year double amplitude [CI]
SBP (mmHg)	21.60 [18.58, 24.62]	0.428 [0.376, 0.480]	6.68 [3.72, 9.64]
DBP (mmHg)	14.76 [12.78, 16.72]	0.619 [0.456, 0.782]	2.86 [0.84, 4.86]
HR (beats/min)	10.42 [8.44, 12.40]	0.490 [0.367, 0.613]	2.52 [0.66, 4.38]

A cis-half-year was detected in these data covering slightly less than one year only for SBP and not for DBP or HR. DBP had a trans-half-year, whereas HR had a half-year component. There appears to be a putative selective congruence in the para-semiannual range of the spectrum of a clinically healthy adult, as reported earlier for the circadecadal range for another clinically healthy adult (RBS) (6) and in the circaseptan range of an elderly man (GSK) (7). Different variables of the circulation of a given person can lock into synchrony with different environmental periodicities. In this case of DG, his HR locked into the geomagnetic half year, while his SBP showed a solar cis-half-year. The CI of the trans-half-year is also compatible with the presence of a signature of the solar 0.56-year predicted by Charles Wolff as a beat of solar rotation periods (8).

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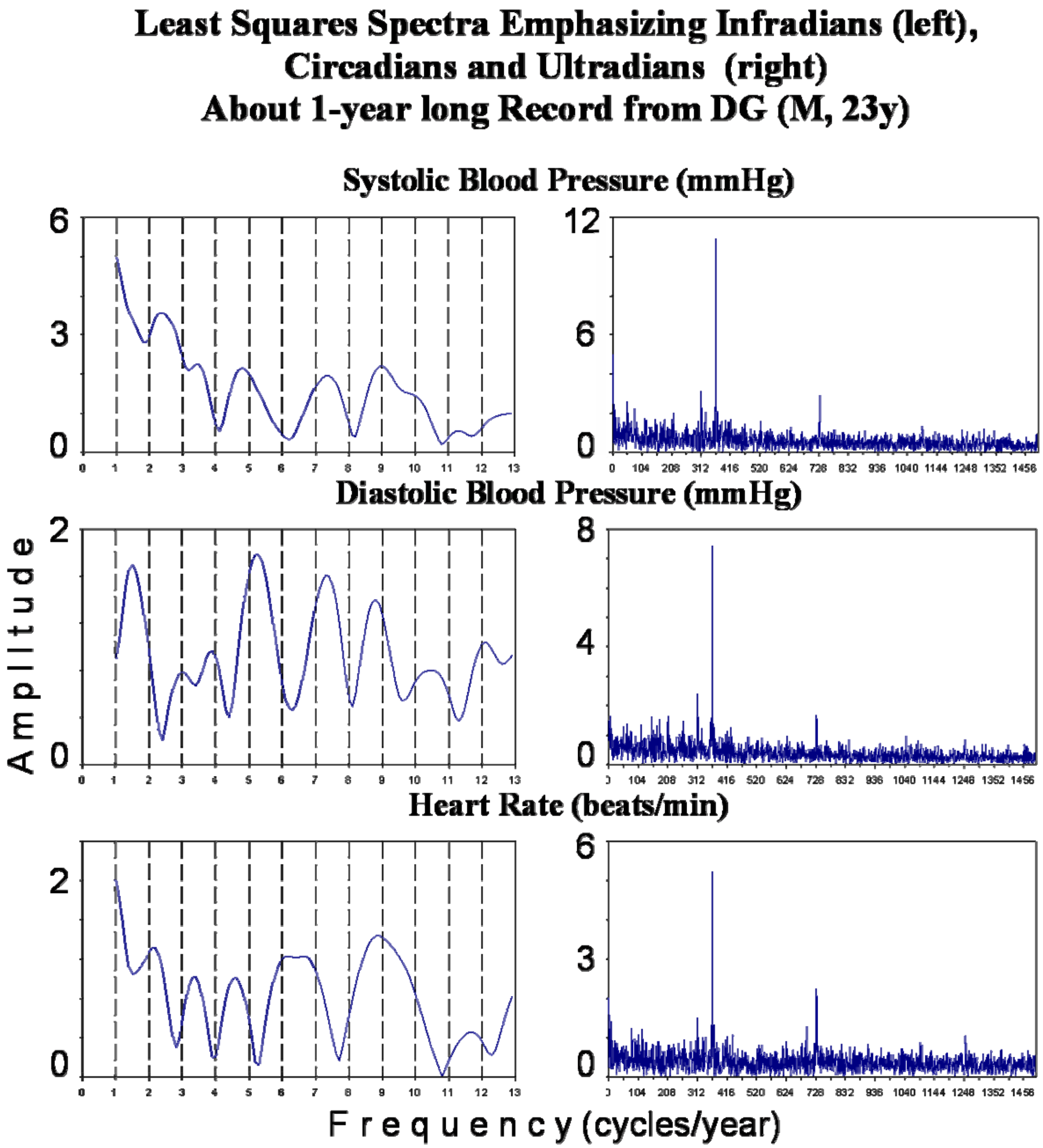

Figure 1. A prominent circadian rhythm is readily apparent (at a frequency of 365.25 cycles/year) (right) for all three variables. The second harmonics with a period of about 12 hours can also be seen. A cis-half-year is detected for systolic blood pressure (top left), corresponding to a peak at a frequency between 2 and 3 cycles/year. © *Halberg.*

SOLAR SIGNATURES IN A BOY'S BLOOD PRESSURE AND HEART RATE

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Running title: Solar signatures in circulation

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Abstract

Objective. To track, in a boy's circulation, components with a period, τ, of ~1.3 years, far-transyears, and ~5 months, cis-half-years, found in adults' sudden cardiac deaths and circulating melatonin as a putative signature of the solar wind's speed.

Design. The time course during childhood and adolescence of signatures of a 1-year cycle and of periodicities of about ~16 and ~5 months, the latter also reported for the incidence of solar flares, is here explored longitudinally in daily measurements during 8 years of the systolic (S) and diastolic (D) blood pressure (BP) and heart rate (HR) of a boy, FW.

Setting. On awakening at home.

Results. Original data show an increase in BP removed by the fit of a linear trend and a decrease in HR detrended by a second-order polynomial and further the anticipated components in the detrended data.

Main findings. When original or detrended data are analyzed by linear-nonlinear spectral cosinor analysis, a far-transyear, an about (~) 16-month cycle is most prominent in SBP and DBP and a calendar year is more prominent in HR, and a cis-half-year, i.e., an ~5-month cycle is third in prominence. When the cis-half-year is investigated by a chronobiologic serial section, consisting of the least-squares fit of a cosine function with a period determined nonlinearly, it is consistently statistically significant ($P<0.010$) mostly for SBP, less so, only intermittently for DBP, and is restricted to only a few of the intervals analyzed for HR.

Conclusion. Statistically significant transyears and cis-half-years coexist with a 1-year synchronized spectral component and in the case of BP, but not of HR, the transyear is most prominent.

How interpreted. Selective congruence with different environmental cycles characterizes the human circulation and differs among variables; non-photic transyear components can exceed in childhood and adolescence the prominence of the calendar year in a boy living in Tokyo. **304 words.**

Key words: solar activity, childhood, adolescence, blood pressure, heart rate, periodicity, chronomics

Background

In several geographic locations like Minnesota but not in others (Halberg et al. 2006), among others, components with a τ of ~1.3 and of ~0.42 year(s) characterize the incidence of human sudden cardiac death (SCD) after revision 10 of the International Classification of Diseases

(ICD10), code I46.1. The broadly defined far-transyear range (1.2 years ≤ [τ - CI {95% confidence interval}] < [τ + CI] < 1.9 years) has a component in Minnesota and Tokyo in the absence of a calendar-yearly component while in Arkansas and in the Czech Republic, the far-transyear coexists with a 1-year component, and in North Carolina, USA, only an ~1-year component is found during the spans examined, Figure 1 (Halberg et al. 2006). The cis (= on this side of)-half-year is found in Austria, Hungary, Minnesota (USA) and Tokyo (Japan) (Halberg et al. 2005, 2006; Cornélissen et al. 2007b; Hamamatsu et al. 2007) and during part of the span examined in the Czech Republic. Both nonphotic components are also found in cardiac arrhythmia again intermittently in the Republic of Georgia (Halberg et al. 2006). In Minnesota but not overall, arrhythmias triggering a therapeutic response from implanted pacemaker-cardioverter-defibrillators show a cis-half-year (Cornélissen et al. 2007a), as do arrhythmias in the Republic of Georgia (Halberg et al. 2006).

A cis-half-year is also found in the BP of two elderly men, FH (Halberg et al. 2006) and GK (Katinas et al. 2008), in the 17-ketosteroid excretion of an adult man over 15 years (Halberg et al. 2008; cf. Halberg et al. 1965), in the melatonin circulating in the blood of 172 patients, each studied for only a day at 4-hour intervals (Cornélissen et al. 2008) and in the HR of a man studied over 40 years (Sothern et al. 2008), in the latter only when the fit of the cis-half-year is carried out concomitantly with the fit of coexisting 1.0 and 0.5-year periods, with the latter converging to an 0.4 year (unpublished). We here explore the cis-half-year and the far-transyear (cf. Watanabe F. et al. 2008) during childhood and adolescence in a boy (FW) and demonstrate, during ages 8-15 years, a particularly prominent far-transyear in BP, Table 1, an anticipated signature of changing patterns in the solar wind's speed (Halberg et al. 2006) and a cis-half-year, notably in SBP, also a signature of solar flares (Rieger et al. 1984), as extensively confirmed (Kiplinger et al. 1984; Bogart and Bai 1985; Dennis 1985; Bai and Sturrock 1987) with slightly varying results due to nonstationarities and a modulation by the ~11-year Horrebow-Schwabe cycle in sunspot numbers (unpublished).

Case report

FW's paternal grandfather died at 47 years of age of renal failure with malignant hypertension associated with a pheochromocytoma. His maternal grandfather took medication for high BP; his maternal grandmother had breast, gastric and uterine cancer by the time of her death. His paternal grandmother underwent six surgeries for uterine cancer, colonic cancer and degeneration of the spine and of each knee joint. His mother had surgery for breast cancer in the summer of 2006. The boy's BP and HR were monitored around the clock, mostly at 30-minute intervals for 40 days (October 20-November 28, 1992) during the first 40 days of his life (Watanabe et al. 2003).

Method

Linear imputation spectra revealed an anticipated far-transyear of 1.35-year length in SBP and DBP in both original and detrended data and an ~0.39-year cis-halfyear that led to serial sections of each time series, with a 4-year interval displaced by 1-week increments throughout the time series. Below the original data shown in the top row, serial sections are shown in the second rows of Figures 1-3, prepared with the fit of a τ of 0.4 year found to be near the peak in a first imputational cosinor spectrum (Halberg et al. 1965).

Results

Table 1 presents a summary of analyses of all data showing the relatively small amplitude of the cis-halfyear in all variables as compared to the prominence of a putative signature of solar wind speed, a far-transyear of ~1.3-year length. For comparison, the characteristics of a coexisting component with a τ of precisely 1 year are also tabulated.

In SBP, the cis-half-year is statistically highly significant in nearly all intervals, each of about 4 years, displaced for consecutive analyses by increments of 1 week. The third to fifth rows of Figures 1-3 show results of detrended data (by the fit of a straight line for SBP and DBP and a second-order polynomial for HR). When fitted as such only, rather than with other components, the cis-half-year is prominent and statistically highly significant in SBP (Figure 1), as seen from the penultimate row of P-values in which a dashed horizontal line represents 5%; practically all values hug the 0.01 bottom line. Statistical significance is equally apparent from the fact that in the fourth row after detrending, the acrophase (double) plot shows three lines, the middle one for the acrophase as such, while the bracketing two lines document the 95% confidence limits of the SBP acrophase, with very few interruptions in spots where in the row of P-values below, there are peaklets or peaks that penetrate above the 5% level, the latter indicated by a dashed line. There is still a majority of bracketed acrophases in Figure 2 for DBP, but very few intervals have bracketed acrophases for HR in Figure 3.

Discussion

Many differences in the time structures or chronomes of BP versus HR were reviewed earlier elsewhere (Schwartzkopff et al. 1998). Figures 1-3 and Table 1 show new differences concerning the far-transyear and cis-halfyear in SBP and a lesser extent in DBP vs. a much less consistent component in HR, all here demonstrated during human childhood and adolescence.

In monitoring oneself, there is much to learn; some of it, in the case of YW, FW's cardiologist father has been communicated in 152 publications noted in order to stimulate the interest of others to follow in his steps for their own and others' health care (Watanabe et al. this issue). Monitoring the activity of the cosmos can be done with the very same data that are useful primarily to detect earliest alterations as **v**ascular **v**ariability **d**isorders, VVDs, prompting interventions by health care (Halberg et al. 2009). In FW, notably in his BP, cycles found as characteristics of solar wind speed and of solar flares as yet are only of basic interest, until reference values are obtained in clinical health from many other children and adolescents. The broad basic scope of far-transyears is apparent from the scholarship of Prof. Miroslav Mikulecky, who has extended their scope to natality in two geographic locations (Mikulecky and Florida 2005; Mikulecky 2006) and to epilepsy (Kovac and Mikulecky 2006) and stroke (Kovac and Mikulecky 2005) in Slovakia.

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Legends

Figure 1. Chronobiologic serial section of systolic blood pressure of a boy, FW, revealing a somewhat consistent cis-half-year by values in the row of P-values (second from bottom) mostly below the dashed 5% line and by a 95% confidence interval bracketing the acrophases shown in the 4^{th} row from the top. There is only a single interruption corresponding to a single P-value above the dashed line. © Halberg.

Figure 2. Chronobiologic serial section of diastolic blood pressure of a boy, FW, revealing an intermittent cis-half-year by the 4^{th} row of P-values when the curve remains only intermittently below the dashed line corresponding to 5%. © Halberg.

Figure 3. Chronobiologic serial section of heart rate of a boy, FW, with the demonstration of a cis-half-year limited to a very few intervals analyzed. © Halberg.

Table 1: Periods detected by extended cosinor in the circulation of FW*

Variable	Trial period (years)	Period [95% CI]	Double amplitude [95% CI]
SBP (orig)	0.400	0.384 [0.382, 0.386]	3.50 [1.38, 5.62]
DBP (orig)		0.389 [0.387, 0.390]	2.54 [1.10, 3.98]
HR (orig)		0.385 [0.382, 0.388]	1.34 [-0.12, 2.80]
SBPres	0.400	0.384 [0.382, 0.385]	3.74 [1.82, 5.66]
DBPres		0.389 [0.387, 0.390]	2.56 [1.26, 3.88]
HRres		0.385 [0.383, 0.388]	1.40 [0.14, 2.66]
SBPres	1.000	0.9998 [.9911, 1.0085]	4.04 [2.06, 6.00]
DBPres		0.9947 [.9865, 1.0030]	2.88 [1.52, 4.22]
HRres		0.9911 [.9845, 0.9977]	**3.40** [2.14, 4.66]
SBPres	1.300	**1.301** [1.292, 1.309]	**6.86** [4.90, 8.82]
DBPres		**1.340** [1.330, 1.351]	**3.92** [2.60, 5.26]
HRres		1.221 [1.208, 1.234]	2.50 [1.20, 3.80]

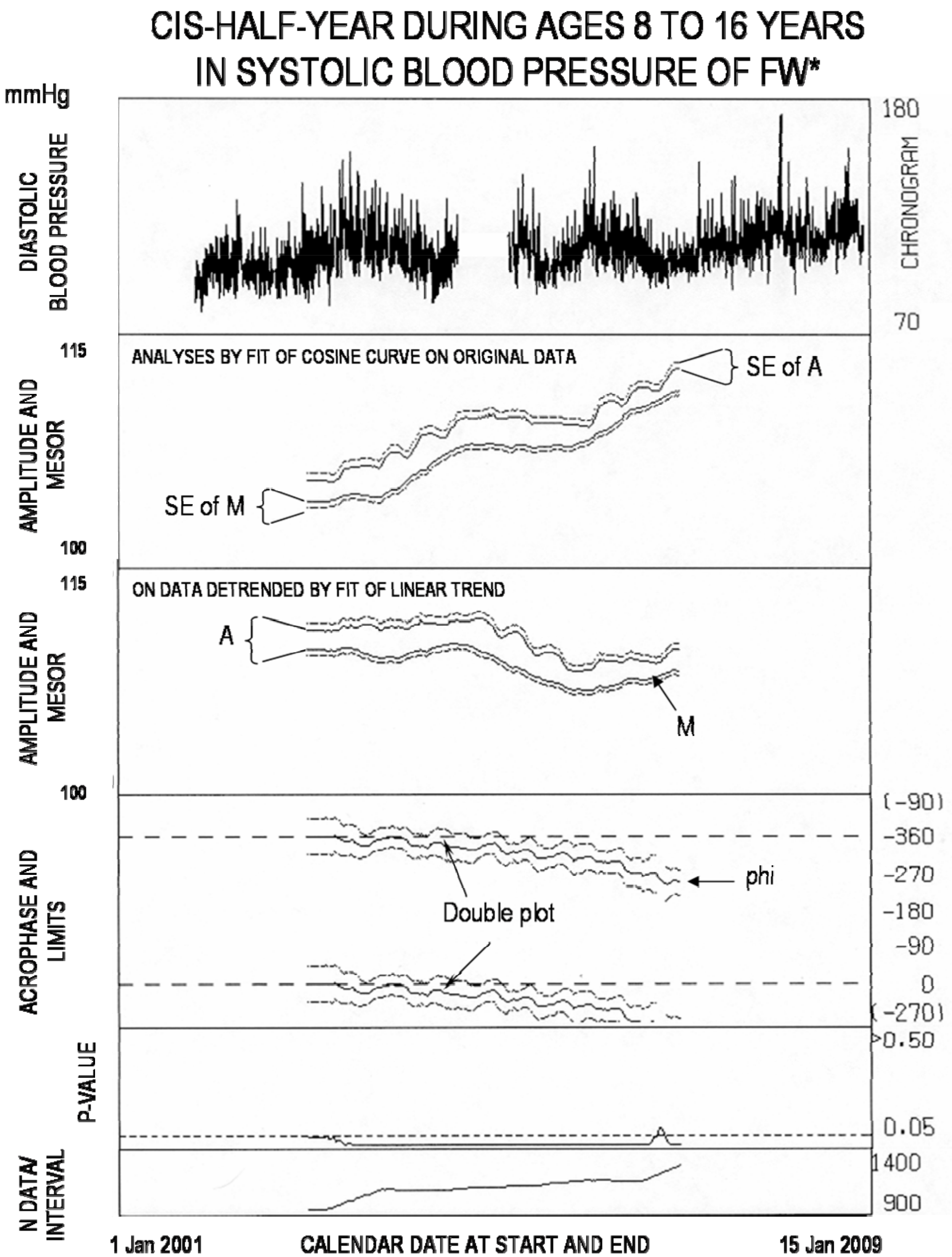
*CI: confidence interval; orig: original data; res: residual. There is a larger peak for HR at a period slightly shorter than the cis-half-year range. Para-annual components with amplitude larger than that of the coexisting annual component are shown in bold, as is the tallest component in HR.

Table 2: Point estimates of a cis-half-year (~154-day) periodicity, sometimes given with estimates of uncertainty and hypothesis testing

Period (in days except where noted)	Reference
154.3	Wolff CL. (1983). The rotational spectrum of g-modes in the sun. Astrophys J 1983; 264: 667-676.
154	Rieger A, Share GH, Forrest DJ, Kanbach G, Reppin C, Chupp EL. (1984). A 154-day periodicity in the occurrence of hard solar flares? Nature 312: 623-625.
158	Kiplinger AL, Dennis BR, Orwig LE. (1984). Detection of a 158-day periodicity in the solar hard X-ray flare rate. Bull Am Astronom Soc 16: 891.
152	Bogart RS, Bai T. (1985). Confirmation of a 152-day periodicity in the occurrence of solar flares inferred from microwave data. Astrophys J 299: L51-L55.
152-158	Dennis BR. (1985). Solar hard X-ray bursts. Solar Physics 100: 465-490.
152	Bai T, Sturrock PA. (1987). The 152-day periodicity of the solar flare occurrence rate. Nature 327: 601-604.
near 155	Lean JL, Brueckner GE. (1989). Intermediate-term solar periodicities -- 100-500 days. Astrophys J 337: 568-578.
152	Özgüç A, Ataç T. (1989). Periodic behavior of solar flare index in solar cycles 20 and 21. Solar Physics 123: 357-365.
154 (± 0.6)	Bai T, Cliver EW. (1990). A 154 day periodicity in the occurrence rate of proton flares. Astrophys J 363: 299-309.
near 155	Carbonell M, Ballester JL. (1990). A short-term periodicity near 155 day in sunspot areas. Astron Astrophys 238: 377-381.
153	Dröge W, Gibbs K, Grunsfeld JM, Meyer P, Newport BJ, Evenson P, Moses D. (1990). A 153 day periodicity in the occurrence of solar flares producing energetic interplanetary electrons. Astrophys J Suppl Ser 73: 279-283. Applying Rayleigh test for periodicity.
155	Silverman SM. (1990). The 155-day solar period in the sixteenth century and later. Nature 347: 365-367. "[A]lthough values between 150 and 160 days have been reported, I refer to it here as the 155-day period, for convenience"
154	Bai T, Sturrock PA. (1991). The 154-day and related periodicities of solar activity as subharmonics of a fundamental period. Nature 350: 141-143.

Period (in days except where noted)	Reference
154	Kile JN, Cliver EW. (1991). A search for the 154 day periodicity in the occurrence rate of solar flares using Ottawa 2.8 GHz burst data, 1955-1990. Astrophys J 370: 442-448.
152-158	Verma VK, Joshi JC, Uddin W, Paliwal DC. (1991). Search for a 152-158 days periodicity in the occurrence rate of solar flares inferred from spectral data of radio bursts. Astron Astrophys Suppl Ser 90: 83-87.
near 155	Carbonell M, Ballester JL. (1992). The periodic behaviour of solar activity: the near 155-day periodicity in sunspot areas. Astron Astrophys255: 350-362.
152	Verma VK, Joshi JC, Paliwal DC. (1992). Study of periodicities of solar nuclear gamma ray flares and sunspots. Solar Physics 138: 205-208.
154	Bai T, Sturrock PA. (1993). Evidence for a fundamental period of the sun and its relation to the 154 day complex of periodicities. Astrophys J 409: 476-486.
151-155	Lou YQ. (2000). Rossby-type wave-induced periodicities in flare activities and sunspot areas or groups during solar maxima. Astrophys J 540: 1102-1108.
153.9	Hady AA. (2002). Analytical studies of solar cycle 23 and its periodicities. Planetary and Space Science 50: 89-92.
near 160	Ballester JL, Oliver R, Carbonell M. (2002). The near 160 day periodicity in the photospheric magnetic flux. Astrophys J 566: 505-511.
near 5-month	Han Yanben, Han Yonggang. (2002). Time variation of the near 5-month period of sunspot numbers. Chinese Sci Bull 47 (23): 1967-1973. "Many scholars ... found similar periods of solar activity from other observations of the Sun. However, these periods are different, such as about 152-, 154-, 156-day, etc. Here we name it a near 5-month period (N5MP) since it is not definite."
153	Bai T. (2003). Periodicities in solar flare occurrence analysis of cycles 19-23. Astrophys J 591: 406-415.
near 160	Ballester JL, Oliver R, Carbonell M. (2004). Return of the near 160 day periodicity in the photospheric magnetic flux during solar cycle 23. Astrophys J 615: L173-L176.

This incomplete list (added contributions are cited in the references provided) suffices to indicate the variable nature of the period being discussed. Specifications of the solar (Schwabe) cycle in which they are found point indirectly to the intermittency of the components being discussed.



* 8-16 years of age; Period=146.6 days = 0.4 year; Interval = 209 weeks; Increment = 1 week.
MESOR: M; Amplitude: A; Acrophase: phi.

Figure 1

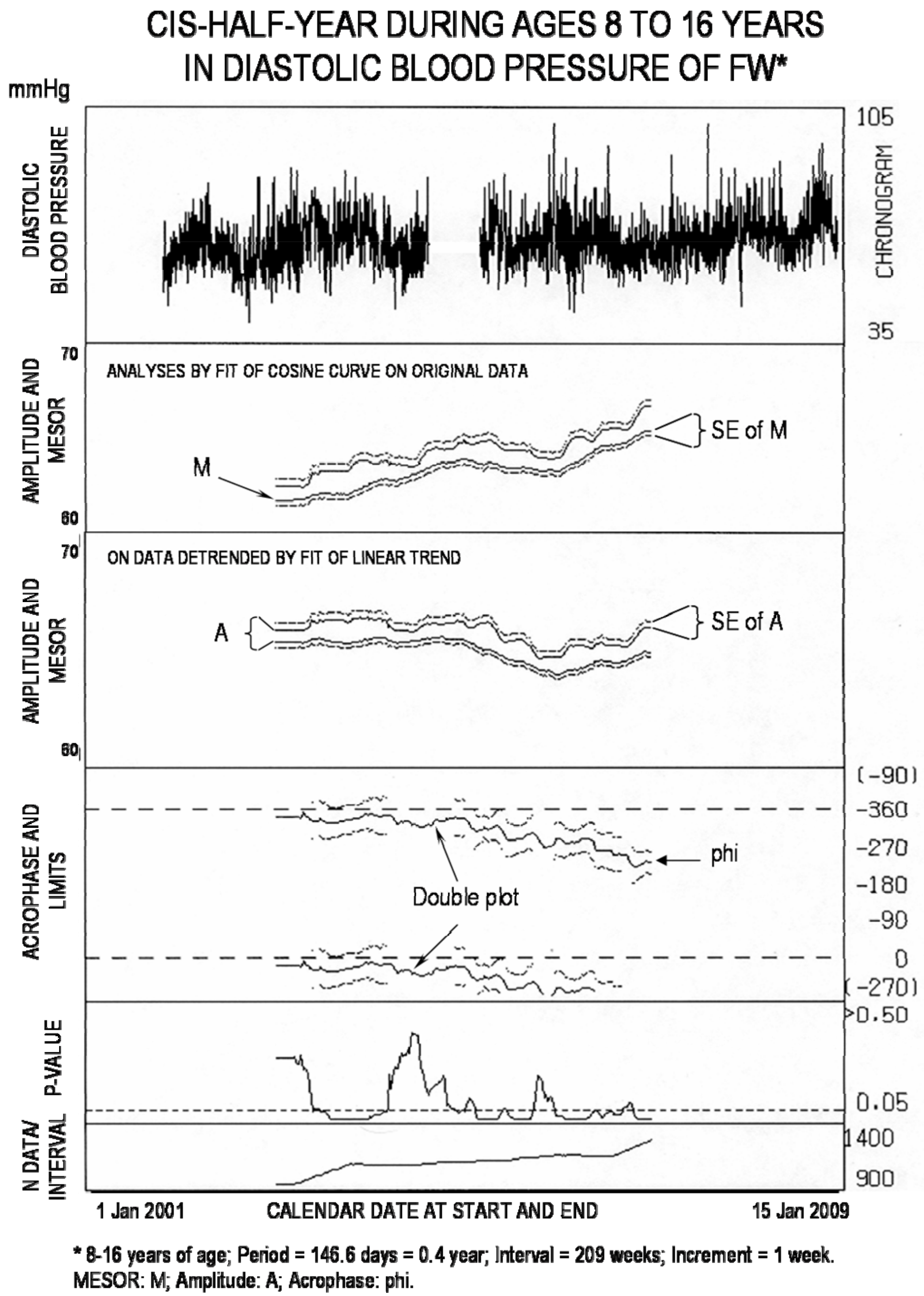
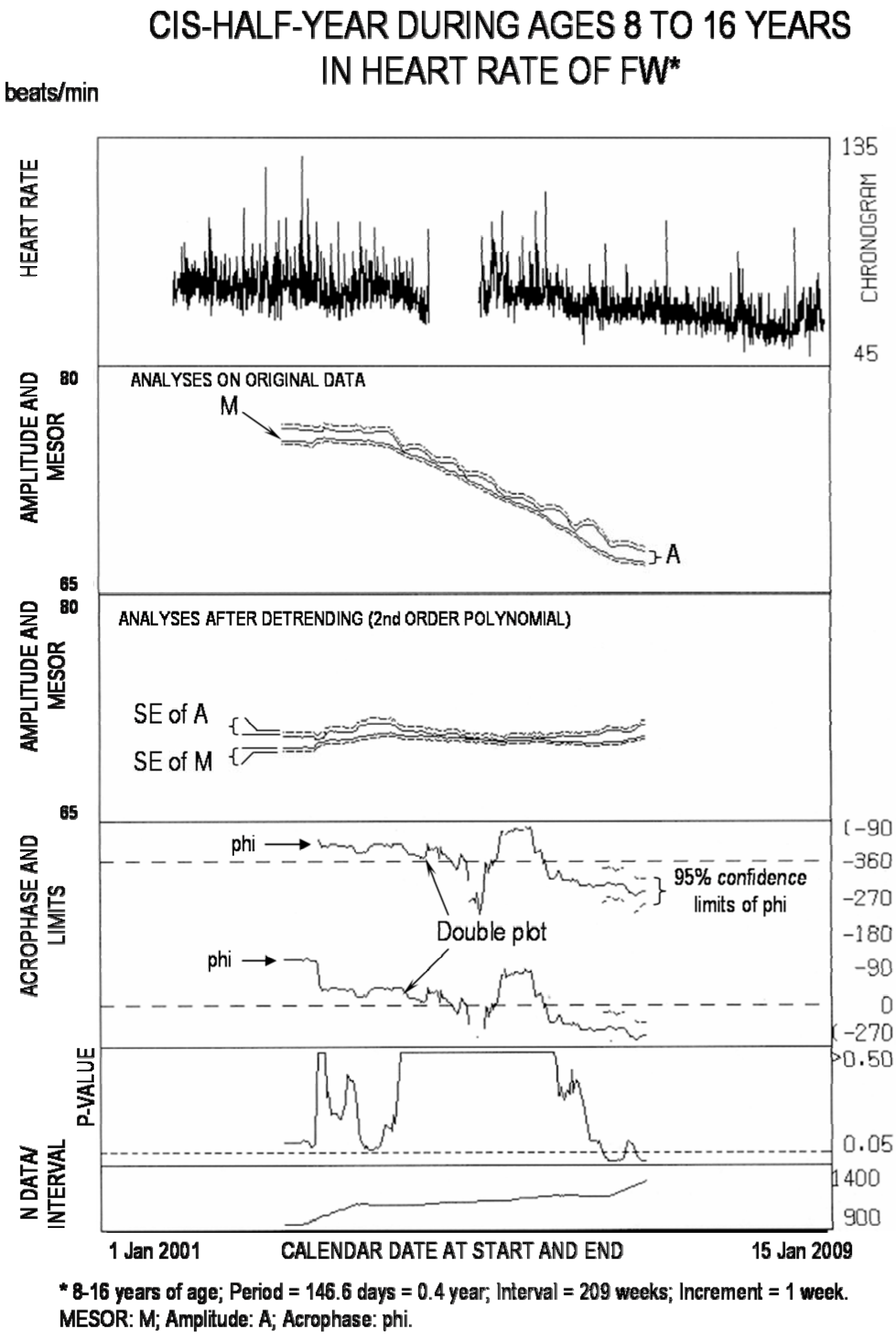

CIS-HALF-YEAR DURING AGES 8 TO 16 YEARS
IN DIASTOLIC BLOOD PRESSURE OF FW*
mmHg
DIASTOLIC BLOOD PRESSURE
105
35
CHRONOGRAM
AMPLITUDE AND MESOR
70
60
ANALYSES BY FIT OF COSINE CURVE ON ORIGINAL DATA
M
SE of M
ON DATA DETRENDED BY FIT OF LINEAR TREND
A
SE of A
ACROPHASE AND LIMITS
(-90)
-360
-270
-180
-90
0
(-270)
phi
Double plot
P-VALUE
>0.50
0.05
N DATA/ INTERVAL
1400
900
1 Jan 2001
CALENDAR DATE AT START AND END
15 Jan 2009
* 8-16 years of age; Period = 146.6 days = 0.4 year; Interval = 209 weeks; Increment = 1 week.
MESOR: M; Amplitude: A; Acrophase: phi.

Figure 2



CIS-HALF-YEAR DURING AGES 8 TO 16 YEARS
IN HEART RATE OF FW*
beats/min
HEART RATE
135
CHRONOGRAM
45
AMPLITUDE AND MESOR
80
ANALYSES ON ORIGINAL DATA
M
A
65
80
ANALYSES AFTER DETRENDING (2nd ORDER POLYNOMIAL)
SE of A
SE of M
65
ACROPHASE AND LIMITS
phi
(-90)
-360
95% confidence limits of phi
-270
Double plot
-180
-90
0
(-270)
P-VALUE
>0.50
0.05
N DATA/ INTERVAL
1400
900
1 Jan 2001
CALENDAR DATE AT START AND END
15 Jan 2009
* 8-16 years of age; Period = 146.6 days = 0.4 year; Interval = 209 weeks; Increment = 1 week.
MESOR: M; Amplitude: A; Acrophase: phi.

Figure 3

WHITE-COAT HYPERTENSION IN A CARDIOLOGIST: DECADES OF MONITORING LEAD TO TRANSIENT OCCUPATIONAL MESOR-HYPERTENSION ABSENT DURING VACATION: STRAIN TEST

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Running title: MESOR-hypertension: strain test

Support: GM-13981 (National Institutes of Health) (FH),

University of Minnesota Supercomputer Institute (GC, FH)

Abstract

Objective. To change the recording of blood pressure (BP) and heart rate (HR) from spotchecks to continuous electronically implemented cost-effective self-surveillance.

Design. Parametric and complementary non-parametric assessment of results from inferential statistical approaches by cosinor.

Setting. Everyday clinical practice by a cardiologist (YW).

Results. In a busy cardiologist's circulation, systolic (S) and diastolic (D) MESOR-hypertension, MH, can be transient, i.e., absent during vacation.

Main findings. The rare opportunity of following the development of transient MH, shows that it can differ in months-long records of the same individual. Hence, continued self-surveillance should become routine and should be implemented in the population as a whole.

Conclusion. A spotcheck evidence-based health care awaits replacement by one based on continued inferential statistical surveillance of the individual. The P-values and 95% confidence intervals that are currently indispensable in publications of research are applicable to the individual, in whose care, cost-effectively by self-surveillance, they are equally indispensable.

Introduction

Half-hourly around-the-clock BP and HR values, surveilled over 7 days or preferably over longer spans, are 24-hour synchronized in most time series. Hence, one can fit a 24-hour cosine curve to the data to obtain (parametrically) estimates of the **m**idline-**e**stimating **s**tatistic **o**f **r**hythm, i.e., the MESOR, M; the amplitude, A, and acrophase, ϕ, measures of the extent of rhythmic change and of its timing, respectively. The data can also be stacked along the 24-hour scale (non-parametrically) for comparison with time-specified reference values from clinically healthy peers matched by gender and age. Measures of the extent of abnormality, if any, are thus obtained by the hyperbaric (or hypobaric) indices, summarizing BP excess (or deficit). These indices consist of the integrated area between the time-varying prediction limits and any part of the BP curve where it lies outside the limit. Parametric endpoints are also compared with those of clinically healthy peers of the same gender and age group for the foregoing circadian (and any broader infradian as well as ultradian) chronobiologic assessment separately of systolic (S) and diastolic (D) BP and HR.

YW, a clinically healthy chrono-cardiologist/scientist, 56 years of age, is in the 21st year of **c**ontinued **c**hronobiologically-interpreted **a**utomatic half-hourly around-the-clock, ambulatory as well as resting **m**onitoring (with relatively few interruptions) of his **BP** and HR (C-ABPM). At the age of 55 years in an about (~) 7.5-month section of his record, he had by cosine fitting (of a 2-component model, consisting of cosine curves with periods of 24 and 12 hours) and by stacking, both compared with reference standards of clinically healthy peers matched by gender and age, a complete (parametric and non-parametric) SBP-**M**ESOR (M)-**h**ypertension (S-MH) and an incomplete (parametric, but not non-parametric) D-MH. In an immediately following ~5-month record at the age of 56 years, he has incomplete (only parametric) S-MH and DBP MESOR-normotension, MN (D-MN).

Months-long records in everyday life can differ as a function of professional and other loads. For YW, this assumption is in keeping with the finding that, during 4 days of vacation away from work at home, there is complete S-MN and D-MN, due to a statistically significant lowering of the BP-M and only a slight numeric increase in the hyperbaric index of DBP. Thus, the monitoring during as well as before and after a vacation constituted a professional strain test. His varying complete vs. incomplete (both parametric and nonparametric vs. only parametric) S-MH or his incomplete (only parametric) vs. absent D-MH can be interpreted as an occupational MESOR-hypertension. We are dealing with a reversible D-MH that can be readily "treated", i.e., that is eliminated by a change in routine.

Background

A 21-year record is available for YW, whose father died of renal failure with malignant hypertension associated with a pheochromocytoma at the age of 47 years. Apart from his other publications, including a book in Japanese about BP for the general reader, YW's cooperation with the Halberg Chronobiology Center at the University of Minnesota resulted in a steady list of 152 publications, many based on automatic BP and HR monitoring, some started on himself at age 35. YW's productivity, of interest in itself, should motivate others in a preventively useful and scientifically rewarding surveillance of oneself and of others. YW's data fully support the recommendation that a minimal 7-day record length for the initial monitoring of BP and HR should be only a transient substitute for continuous unobtrusive, affordable surveillance, C-ABPM, warranted at least by a positive family and/or personal history of cardiovascular disease and/or interest in research, or preferably both, as in the case of YW, as suggested by a long series of international consensus meetings (e.g., Halberg et al. 1995, 2004, 2009; Chibisov, 2005). Sooner rather than later, sufficient records will become available for the use of the same data for the biotic monitoring of the cosmos.

Method

YW wears an automatic monitor from A&D (Tokyo) around the clock with few interruptions. His most recent summary (Watanabe et al., 2008a) serves as a reference standard for the data accumulated in the interim of ~5 months, including 4 days of vacation from work at home. YW's chronobiologic summaries at ages 55 and 56 years include a sphygmochron carried out with both a parametric approach, from the fit of a two-component model (consisting of cosine curves with periods of 24 and 12 hours) and a nonparametric one by stacking, both interpreted by comparison with clinically healthy peers matched by gender and age, Figure 1, as done routinely in the project on The BIOsphere and the COSmos, BIOCOS (Halberg et al., 2000a).

Results

Figure 2 stacks the data along an idealized 24-hour scale from the 3 spans summarized by the bottom halves of the three sphygmochrons in Figure 1. Thus, the first of the 48 dots in the top row is the average of all values collected between 00:00-00:30 during 7.5 months; the next dot summarizes all data collected between 00:30-01:00, etc. The 7.5-month recordings caught a glimpse of an interesting time span when most SBP clock-time mean values are above the time-specified limit of peers matched by gender and age, while, with just 3 exceptions from 48 clock-time mean values, the DBPs are near but just below the upper 95% prediction limit.

The diagnosis made on August 8, 2008, at age 55 (top) differed, inferentially statistically but hardly clinically, from the one made on January 15, 2009, 5 months later. At age 55 years, it was a complete (parametric and non-parametric) S-MH and an incomplete (parametric but not nonparametric) D-MH seen in the top parts of sphygmochrons of Figures 1 and 2. These findings could not be confirmed parametrically for DBP in the added 5 months of data that became available in January 2009, nor did the nonparametric approach find any abnormality in SBP or DBP in the last ~5 months of data, Figures 1 and 2. The extent of nonparametric excess during 24 hours below 50 mm Hg x h is acceptable. Thus, the diagnosis of 2008 changed in early 2009 to an incomplete parametric but not non-parametric S-MH and (complete, both parametrically and nonparametrically) DBP MESOR-normotension.

All abnormality of BP or HR was absent during 4 recent vacation days, summarized in the bottom third of Figures 1 and 2. Table 1 compares the parameters of the three spans, revealing self-explanatory statistically significant differences among the 48 mean values from each span. Means rather than original values were compared to minimize artifactual differences due to relatively large numbers (what has been referred to as stochastic statistical significance). The desirability to assess and compare diagnoses with their uncertainties in inferential statistical terms cannot be overemphasized, yet a statistically significant difference in itself does not imply clinical or scientific signification (Halberg et al., 1991; Cornélissen et al., 1994), as in this case in January 2009.

Discussion

Whether back pain which was more prominent during the first ~7.5-month span summarized in August 2008 contributed to the high BP is in keeping with the detection of a threshold in another physician-scientist who suffered from back pain and whose BP-MESOR did not increase and HR-MESOR did not decrease until a certain measure of self-rated pain was reached (Katinas et al., 2008). The role of any of the many infradian spectral components, summarized in earlier publications, that may also have contributed to the differences between the top two versus the bottom sections of Figures 1 and 2 remains to be evaluated. A sharp rise of HR in the morning, when he often runs to catch the train on his way to work, seen in the last column of Figure 2 on top and in the middle, is not seen at the bottom when he stayed at home.

Further analyses warranted in YW's and others' time series, covering decades, may answer the question about the degree of generality with which a deviation (e.g., an elevation) in A alone or concomitantly with M (Cugini et al., 1998) leads to MH. Consecutive sphygmochrons to pursue the development of a VVD remain to be computed. In the laboratory, in the spontaneously-hypertensive stroke-prone rat (SHR-SP), an increase in A precedes the one in M (Halberg J et al., 1980). This sequence of A elevation preceding an elevation of M also occurs for BP and other telemetered variables, albeit with a lag of only a very few days, in the saline and desoxycorticosterone-induced hypertension of the rat (unpublished). Likewise, a higher BP-A is associated with intermediate values of the left ventricular mass index (LVMI), whereas a higher BP-M (above 140 mmHg) is seen only for larger LVMI values in humans (Kumagai et al., 1992). This association has now been qualified by the finding around a SBP-M of 120 mmHg of an increase in both A and M associated with minimal change retinopathy, discovered by Cugini and interpreted by him as constituting a pre-hypertension (Cugini et al., 1998). Similarly, pre-diabetes has been documented by focus upon the detection of circadian VVDs (Sanchez de la Peña et al., 2004; Gupta et al., 2008). More than single subjects will have to be longitudinally investigated by systematic monitoring as newborns (Halberg et al., 1990; Watanabe et al., 2003) and at school age (Halberg et al., 1973, 2000b) to explore any sequences in the development of incomplete to complete S-MH and D-MH, started in adulthood, now in the perspective of decades in YW.

The effect of loads like pain and/or a busy professional schedule must be quantified (Halberg et al., 2003; Maschke et al., 2003; Katinas et al., 2008). Any load consisting of dietary ingredients, notably the effect of sodium intake (Cornélissen et al., 1993) that is circadian stage-dependent (Itoh et al., 1996), remains to be further tested. The removal of the load of professional activity can normalize BP in certain individuals: this should be explored further with replications in YW's vacations and in other individuals.

Much investigation remains to be done when we focus upon the earliest infradian as well as circadian alteration of BP and HR characteristics. There is already evidence that an ~35-year Brückner-Egeson-Lockyer cycle and a ~21-year Hale cycle in the bipolarity of sunspots are mirrored in the human circulation (Halberg et al., 2006). There is also evidence in YW's son FW of an ~5-month cycle in his SBP, putatively related to solar flares, as he aged from 8 to 15 years (Watanabe et al., this issue).

The effect of loads upon human BP has been described as bene- or maletensive (Halberg et al., 2003), and for YW, the 4 days away from his professional work appear to have been benetensive, i.e., normalizing. It remains to be investigated in the light of outcomes whether the transitions from S-MN and D-MN to an incomplete or complete S-MH or D-MH, under the load of professional activity may indicate if not quantify certain limits around which benetensive stimuli become maletensive. Alternatively, pertinent limits for a change in intervention by non-drug or drug treatment may be resolved only when days of vacation are no longer associated with a return of MN.

An answer to these questions may place Hans Selye's (1974) distinction of "stress" vs. "distress" on a quantifiable basis. To be sure, monitoring for a longer span away from challenging conditions must be examined for any effect. Moreover, different individuals may react differently to the same stimulus that is also likely to be circadian stage-dependent (Lee JY et al., 1982; Lee MS et al., 2003). An indirect strain test, C-ABPM, comparing endpoints on vacation days with those on weekdays at occupational activities, which is documented for YW, must be further investigated on YW and/or others and is not generalized. A span longer than 4 days seems desirable, preferably with alternations between at least a week without a load to be tested, bracketed by at least week-long spans of monitoring during "everyday life" with the load. In routine clinical practice, the length of the test span, away from the stimulus constituting a load, may need to be individualized by sequential procedures. A CUSUM (Cornélissen et al., 1997) may eventually find when, e.g., BP reaches the limit of a decision interval for its MESOR, circadian or other amplitude. Sequential tests applicable to other characteristics of dynamics such as phase or period remain to be developed.

The frequency and sequence of superficially spontaneous alternations between incomplete or complete S-MH vs. D-MH, that probably depend on factors like grief or conflict during the daily routine, constitute still other problems to be explored in decades-long time series like that of YW. It will be interesting to find out from earlier long sections of the 21-year record whether loads are associated with differences in the infradian M and/or A or ϕ as well (e.g., by comparing infradian characteristics such as those of an ~5-month cis-half-year from data collected only during weekdays vs. weekends and holidays). Also to be further explored is the question of the sequence, if any, in which SBP vs. DBP, their A, ϕ and M and their non-parametric endpoints, such as the hyperbaric index (HBI), change, if they do not alter concomitantly. The exploration of sequences in which the foregoing changes occur in any longitudinal records of others collected systematically with diaries depends on the development of affordable, unobtrusive instrumentation for continuous automatic BP and HR monitoring.

Follow-up longitudinal studies with outcomes will be critical to assess the relative importance of SBP vs. DBP alteration. Whether or not, as suggested from thorough albeit non-chronobiologic epidemiologic studies, SBP shows a more important influence than does DBP (Kannel, 2007) must be examined longitudinally with continued around-the-clock sampling. A transverse chronobiologic study of actual hard outcomes showed the numerically greater risk of a circadian DBP overswing (DBP-CHAT) as compared with SBP-CHAT or a conventionally diagnosed "hypertension" (Otsuka et al., 1996). "Hypertension" was associated with a fourfold increase in risk of ischemic stroke, whereas that risk increased six- or eight-fold with SBP-CHAT and DBP-CHAT, respectively (Halberg et al., 1995).

Questions may also be raised whether waiting for both the occurrence of a double (parametric and nonparametric) failure of SBP and/or DBP to return to normal after load removal, may be warranted before instituting treatment. The institution of drug treatment may be warranted by an abnormality not reversed by load removal restricted to one approach such as parametric MH, in SBP or DBP alone. A work-dependent alteration detected by both approaches in either SBP or DBP would seem to warrant treatment once it persists for spans of time yet to be determined.

In viewing the half-hourly averages for SBP on top of Figure 2, a literal (time-varying) "borderline" BP elevation may give this term new, perhaps more solid meaning, although it may seem arbitrary to assign a certain percentage of the 48 means as the upper acceptable limit prompting intervention. Before setting up complicated outcome studies prompting the initiation of treatment with both a parametric and a nonparametric limit with institution prompted by any one of them separately, it seems reasonable to explore what happens in cases like that of YW longitudinally. The merits of a chronobiologic surveillance are illustrated in Table 1, wherein the absence of professional work during a vacation is the treatment.

For drug treatment, Figure 3 (Watanabe et al., 2008b) reminds us that first we must do no harm and that this commandment requires self-surveillance leading not only to avoiding harm by timing but also to deriving benefit thereby. Much systematic detailed work on a true personalized chronotherapy of vascular variability disorders, VVDs, guided by marker rhythms in BP for picking and validating the kind, dose and timing and the response to treatment remains to be done.

As for comparisons of groups, inferential statistics applied to the individual, can also mislead. Half-hourly around-the-clock measurements during two consecutive spans of several months, one of ~7.5, the other of ~5 months, respectively, reveal statistically significantly differing diagnoses. The scientific and clinical signification of these differences may be questioned, since they may be expected to occur naturally when analyses of longitudinal records as a whole revealed the presence of several infra-annual components described elsewhere (Watanabe et al., 2008c).

Nonetheless, analytical statistical testing of any differences in diagnoses should become indispensable in clinical practice, as it is already in research, and as it was recommended specifically by Bartter (1974) for the case of BP. Ruling out chance as much as possible in everyday care may be at least equally important, as it is in research aimed at the same care and the same testing is now rendered possible for the case of the individual by accumulating time series from at least 7-day and preferably longer-term monitoring. Of course, statistical significance, albeit a sine qua non, does not imply clinical significance or scientific signification (Halberg et al., 1973, 1991; Lee JY et al., 1982; Cornélissen et al., 1994). From those viewpoints and from that of stress versus distress (Selye 1974), the findings in YW remain to be further evaluated in the light of continued surveillance. The question whether occupational hypertension requires treatment remains to be further assessed. Whether a relaxation test consisting of 10 consecutive measurements within 10 minutes on a fully relaxed person (Scherf et al., 2006) can do the same as ABPM did in this study should also be checked. The effect of vacations, notably when these are associated with celebrations, such as New Year's Eve, has been associated with hypertension (Hecht et al., 2007) with a higher cardiac mortality (Phillips et al., 2004).

Conclusion

Under the assumption of homeostasis rather than rhythms, it may be anticipated that diagnoses based on monitoring spans of 5 or more months will be consistent. Chronobiologically, they can be expected to be possibly statistically significantly different in the light of a broad spectrum of infradian rhythms that has as yet been incompletely mapped in relatively few subjects. Rhythms with infradian as well as circadian frequencies can blur the effect of loads that may be tested quantitatively in some subjects like YW by a comparison of vacations from work with weekdays. The normalization of the BP during 4 days of vacation from work at home in YW is just one case showing the desirability of continuous monitoring so that any changes requiring intervention are acted upon, notably when, contrary to what happened in YW during the time span here reported, the normalization on Sundays and during a vacation fails to occur. We must not fly blind (Fossel, 1998) when "seeing" may enter the state of the art in terms of both affordable, unobtrusive hardware and software on a website for automatic analysis (Halberg et al., 2009), both planned by the Phoenix Study Group, composed of volunteering members of the Twin Cities chapter of the Institute of Electrical and Electronics Engineers (http://www.phoenix.tc-ieee.org), to whom this paper is dedicated.

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Legends

Figure 1. Sphygmochrons of a man in everyday professional life as a cardiologist at ages 55 and 56 years, summarizing first 7.5 (top) and 5 months (middle), respectively, of mostly half-hourly around-the-clock data, stacked and averaged for 48 consecutive (half-hourly) bins of an idealized 24-hour day. Data during 4 days at home away from everyday activity extracted from the second record were used to derive sphygmochron shown at the bottom. The abnormal MESOR in bold on top and in the middle is no longer seen in the sphygmochron at the bottom. The unintentional "treatment" by a vacation at home eliminated all systolic, diastolic, parametric and non-parametric MESOR-hypertensions. © Halberg.

Figure 2. Nonparametric summary by stacking of half-hourly around-the-clock means along an idealized 24-hour day at ages 55 and 56 years for blood pressure (BP) and heart rate (HR) during regular professional life (top and middle) and during a vacation of 4 days at home (bottom). Data during all 4 days of vacation are included in the 5-month record (middle). © Halberg.

Figure 3. Harm or benefit in the same patient from the same doses of the same antihypertensive drug combination (Hyzaar) as a function of timing its administration, with about 1 month on each of 5 administration times and half-hourly chronobiologically interpreted ABPM during the last week of each drug timing tested (Watanabe et al., 2008b; http://web.fnusa.cz/files/kfdr2008/sbornik_2008.pdf; p. 149-167). If such chronotherapeutic surveillance is ignored, "first do no harm" is violated. © Halberg.

SPHYGMOCHRON-TM Monitoring Profile over Time; Computer Comparison with Peer Group Limits

Blood Pressure (BP) and Related Cardiovascular Summary.

Name:---------------------- Patient #: YW
Age: 55 Sex: M
Monitoring From: 1/4/2008 9:30 To: 8/18/2008 2:30
Comments:

Everyday life, ~7.5 months

CHRONOBIOLOGIC CHARACTERISTICS

	SYSTOLIC BP (mmHg) Patient Value	Peer Group Reference Limits	DIASTOLIC BP (mmHg) Patient Value	Peer Group Reference Limits	HEART RATE (bpm) Patient Value	Peer Group Reference Limits
ADJUSTED 24-h MEAN (MESOR)	142.5	98.4-135.1 (Range)	87.3	60.3-87.2 (Range)	74.6	56.4-91.2 (Range)
PREDICTABLE CHANGE (DOUBLE AMPLITUDE)	23.61	6.4-39.40 (Range)	11.83	4.84-29.80 (Range)	10.43	5.26-36.20 (Range)
TIMING OF OVERALL HIGH VALUES (ACROPHASE) (hr:min)	16:05	11:48-17:40 (Range)	15:22	11:08-16:48 (Range)	16:14	11:44-17:20 (Range)

	STD (MIN; MAX)*	STD (MIN; MAX)*	STD (MIN; MAX)*
PERCENT TIME OF ELEVATION	78.3%	3.1%	0.0%
TIMING OF EXCESS	22:46 (hr:min)	23:30 (hr:min)	0:00 (hr:min)
EXTENT OF EXCESS DURING 24 HOURS HBI*	65 (mmHg x hour)	1 (mmHg x hour)	0 (mmHg x hour)
10-YEAR CUMULATIVE EXCESS	236 (mmHg x hour)(in 1,000's units)	4 (mmHg x hour)(in 1,000's units)	0 (mmHg x hour)(in 1,000's units)

Individualized bounded indices: (STD = Standard)(Min = Minimum)(Max = Maximum)(HBI = Hyperbanic Index)

Name:---------------------- Patient #: YW
Age: 56 Sex: M

Everyday life, including vacation, ~5 months

Monitoring From: 8/18/2008 5:30 To: 1/11/2009 4:00
Comments:

CHRONOBIOLOGIC CHARACTERISTICS

	SYSTOLIC BP (mmHg) Patient Value	Peer Group Reference Limits	DIASTOLIC BP (mmHg) Patient Value	Peer Group Reference Limits	HEART RATE (bpm) Patient Value	Peer Group Reference Limits
ADJUSTED 24-h MEAN (MESOR)	139.7	98.4-135.1 (Range)	86.8	60.3-87.2 (Range)	75.5	56.4-91.2 (Range)
PREDICTABLE CHANGE (DOUBLE AMPLITUDE)	26.84	6.4-39.40 (Range)	16.02	4.84-29.80 (Range)	11.02	5.26-36.20 (Range)
TIMING OF OVERALL HIGH VALUES (ACROPHASE) (hr:min)	16:22	11:48-17:40 (Range)	15:47	11:08-16:48 (Range)	16:46	11:44-17:20 (Range)

	STD (MIN; MAX)*	STD (MIN; MAX)*	STD (MIN; MAX)*
PERCENT TIME OF ELEVATION	44.5%	0.8%	0.0%
TIMING OF EXCESS	21:13 (hr:min)	19:17 (hr:min)	0:00 (hr:min)
EXTENT OF EXCESS DURING 24 HOURS HBI*	33 (mmHg x hour)	0 (mmHg x hour)	0 (mmHg x hour)
10-YEAR CUMULATIVE EXCESS	121 (mmHg x hour)(in 1,000's units)	0 (mmHg x hour)(in 1,000's units)	0 (mmHg x hour)(in 1,000's units)

Individualized bounded indices: (STD = Standard)(Min = Minimum)(Max = Maximum)(HBI = Hyperbanic Index)

4 vacation days

Monitoring From: 12/31/2008 8:22 To: 1/3/2009 23:30
Comments:

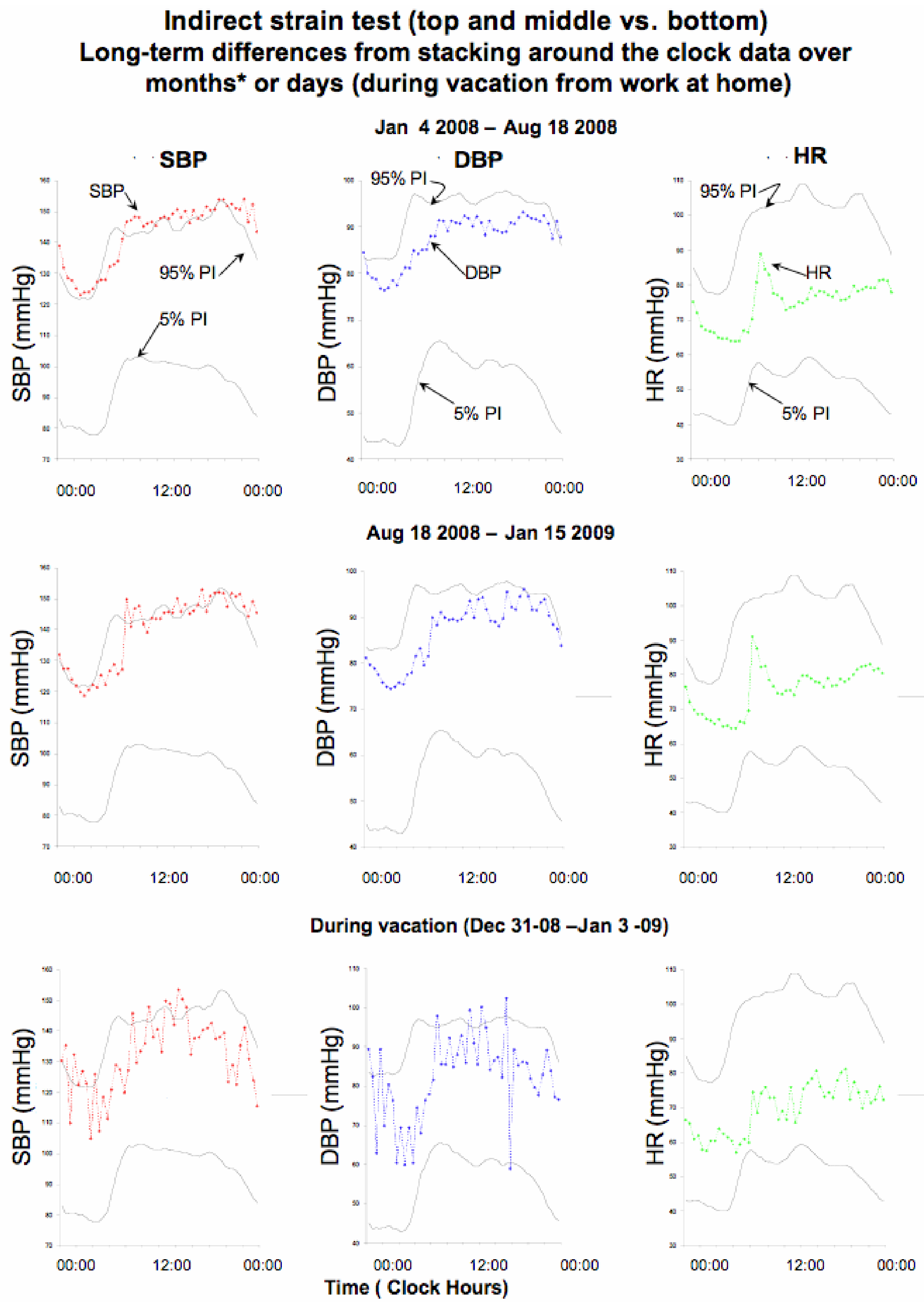
CHRONOBIOLOGIC CHARACTERISTICS

	SYSTOLIC BP (mmHg) Patient Value	Peer Group Reference Limits	DIASTOLIC BP (mmHg) Patient Value	Peer Group Reference Limits	HEART RATE (bpm) Patient Value	Peer Group Reference Limits
ADJUSTED 24-h MEAN (MESOR)	132.0	98.4-135.1 (Range)	82.0	60.3-87.2 (Range)	69.8	56.4-91.2 (Range)
PREDICTABLE CHANGE (DOUBLE AMPLITUDE)	25.10	6.4-39.40 (Range)	19.00	4.84-29.80 (Range)	15.66	5.26-36.20 (Range)
TIMING OF OVERALL HIGH VALUES (ACROPHASE) (hr:min)	14:43	11:48-17:40 (Range)	14:52	11:08-16:48 (Range)	16:35	11:44-17:20 (Range)

	STD (MIN; MAX)*	STD (MIN; MAX)*	STD (MIN; MAX)*
PERCENT TIME OF ELEVATION	22.6%	8.6%	0.0%
TIMING OF EXCESS	13:51 (hr:min)	18:50 (hr:min)	0:00 (hr:min)
EXTENT OF EXCESS DURING 24 HOURS HBI*	20 (mmHg x hour)	5 (mmHg x hour)	0 (mmHg x hour)
10-YEAR CUMULATIVE EXCESS	73 (mmHg x hour)(in 1,000's units)	18 (mmHg x hour)(in 1,000's units)	0 (mmHg x hour)(in 1,000's units)

Individualized bounded indices: (STD = Standard)(Min = Minimum)(Max = Maximum)(HBI = Hyperbanic Index)

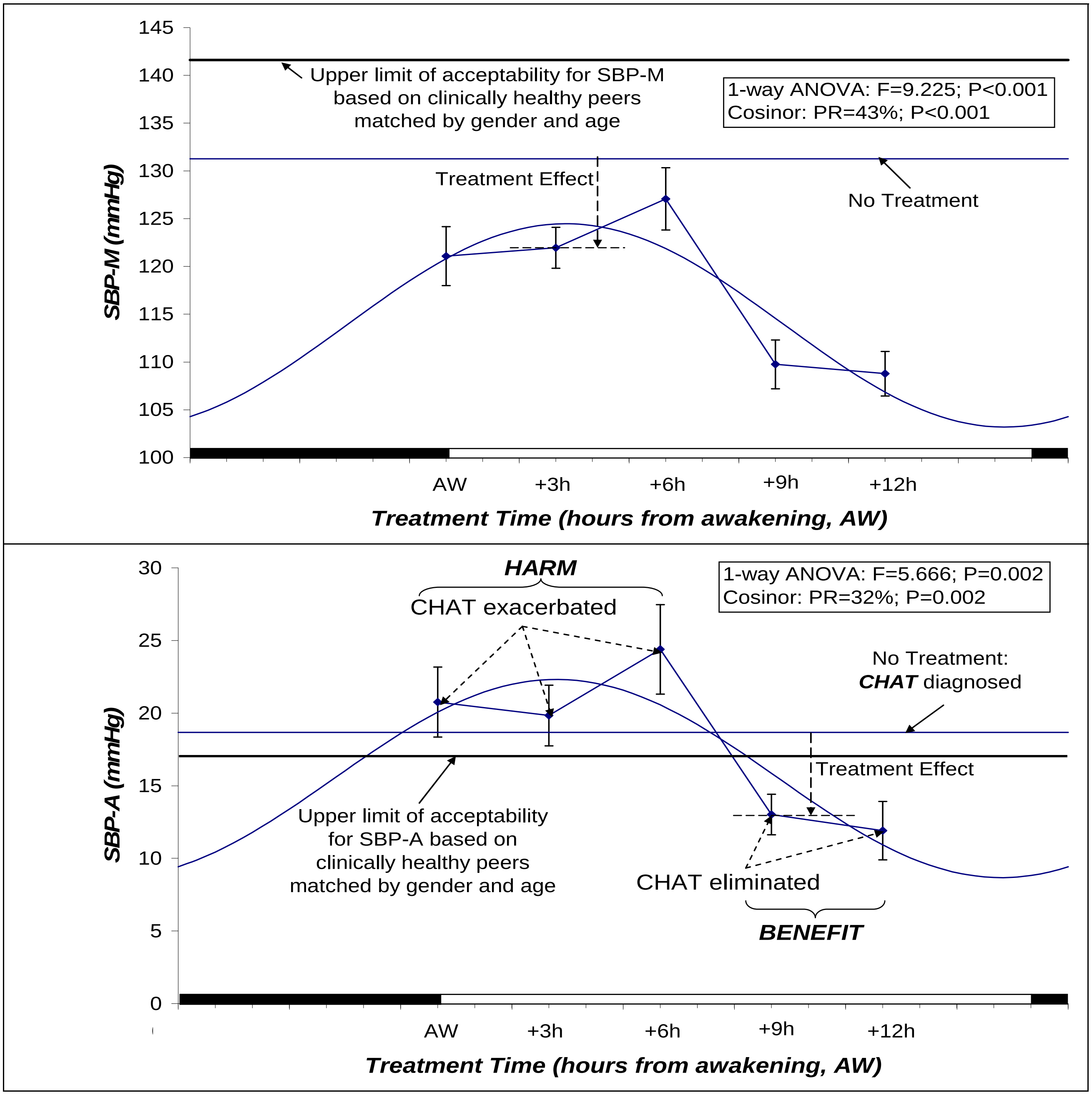
Figure 1



*revealed better by spygmochrons than by eyeballing in circadian profiles of systolic (S) and diastolic (D) blood pressure (BP) and heart rate (HR) of physician-scientist, YW, 55 years of age in January 2008, during ~7.5 months (top), ~5 months (middle) and 4 days (bottom) of around-the-clock half-hourly monitoring. Dots: original values; PIs: prediction limits according to Nelson W, Cornélissen G, Hinkley D, Bingham C, Halberg F. Construction of rhythm-specified reference intervals and regions, with emphasis on "hybrid" data, illustrated for plasma cortisol. Chronobiologia 1983; 10: 179-193.

Figure 2

Chronotherapy Individualized by Monitoring of a Patient (Su, M, 66y) with Circadian Overswing (CHAT*) Finds Best Treatment Times for Lowering both MESOR (top) and an Excessive Circadian Amplitude (bottom)



* CHAT: Circadian Hyper-Amplitude-Tension, a vascular variability disorder. Bottom: Note that a treatment can be useful when given in the evening, but is actually harmful when taken on awakening and later in the morning, when it exacerbates CHAT, a condition that carries a risk of morbid events greater than an elevated mean value of blood pressure.

Figure 3

Table 1: Comparison of rhythm parameters among 3 spans in Figures 1 and 2*

		Systolic Blood Pressure (mmHg)			
Span		MESOR	24h-A	24h-ϕ	(A,ϕ)
1. Jan-Aug 2008		142.6	11.76	-246	
2. Aug 08-Jan 09		140.1	13.56	-251	
3. Holiday (2008-09)		132.1	12.54	-226	
1 vs. 2 vs. 3					
	F	32.174	0.440	4.598	2.501
	P	<0.001	0.645	0.012	0.045
1 vs. 2					
	F	4.247	1.029	0.392	0.708
	P	0.042	0.313	0.533	0.495
2 vs. 3					
	F	29.504	0.246	7.073	3.886
	P	<0.001	0.621	0.009	0.024
		Diastolic Blood Pressure (mmHg)			
Span		MESOR	24h-A	24h-ϕ	(A,ϕ)
1. Jan-Aug 2008		87.3	5.94	-236	
2. Aug 08-Jan 09		86.9	8.11	-242	
3. Holiday (2008-09)		81.9	9.08	-226	
1 vs. 2 vs. 3					
	F	13.248	1.896	1.129	1.457
	P	<0.001	0.154	0.327	0.219
1 vs. 2					
	F	0.324	5.029	0.618	2.827
	P	0.571	0.027	0.434	0.065
2 vs. 3					
	F	13.581	0.254	1.740	0.949
	P	0.001	0.616	0.192	0.391
		Heart Rate (beats/min)			
Span		MESOR	24h-A	24h-ϕ	(A,ϕ)
1. Jan-Aug 2008		74.9	4.92	-246	
2. Aug 08-Jan 09		75.8	5.28	-253	
3. Holiday (2008-09)		69.6	7.95	-253	
1 vs. 2 vs. 3					
	F	21.029	2.543	0.146	1.355
	P	<0.001	0.082	0.865	0.253
1 vs. 2					
	F	0.785	0.053	0.187	0.120
	P	0.378	0.819	0.667	0.887
2 vs. 3					
	F	37.279	3.392	0.001	1.697
	P	<0.001	0.069	0.975	0.189

/...

A: Amplitude; ϕ: Acrophase, expressed in (negative) degrees, with 360˚ ≡ 24 hours, 0˚ = 00:00. Results from parameter tests (Bingham C, Arbogast B, Cornélissen Guillaume G, Lee JK, Halberg F. Inferential statistical methods for estimating and comparing cosinor parameters. Chronobiologia 1982; 9: 397-439). For this time-microscopic assessment, the data during the 4 days of vacation in span 3 were removed from span 2 prior to analysis. Any discrepancy between estimates of M, A and ϕ in this table versus in Figure 1 may stem from the fact that original data are analyzed by means of a 2-component model in Figure 1, whereas for this analysis a single 24-hour cosine curve was fitted to the 48 half-hourly mean values obtained by stacking in each span separately.

Table 2: Comparison of vascular endpoints on Sundays with weekdays reveals acceptability of blood pressure (BP) on Sundays by contrast to weekdays in YW, a physician-scientist

Sphygmos	SBP-M	DBP-M	HR-M	SBP-2A	DBP-2A	HR-2A	S-HBI	D-HBI	TCI
1. Sun	132.9	83.0	72.2	20.03	9.10	10.30	5	1	0
2. Mon	138.8	86.9	74.2	28.15	19.86	11.25	53	11	0
3. Tue	140.9	88.2	76.2	29.58	18.05	14.23	70	12	0
4. Wed	138.6	86.2	75.0	28.33	18.33	10.46	51	9	0
5. Thu	141.4	88.3	75.2	22.85	10.78	8.07	80	6	0
6. Fri	143.0	88.4	77.0	27.52	17.70	8.84	80	5	0
7. Sat	141.0	85.6	78.5	30.86	19.30	16.17	57	5	0

*S: systolic; D: diastolic; BP: blood pressure; M: MESOR, a midline-estimating statistic of rhythm; 2A: double circadian amplitude, HR: heart rate; HBI: hyperbaric index; TCI: tachycardic index. A lower value on Sundays for BP was also found for 30 series from 25 individuals, when the data of each subject were expressed as a percentage of their mean values, examined as a group by a one-way analysis of variance: the lower MESOR was statistically significant for DBP below the 5% and for SBP below the 10% level. In the same 30 series, the 2A of HR was higher on Sundays and Saturdays than on other days of the week ($P<0.05$).

ACCEPTABLE CONVENTIONAL STRESS TEST OUTCOME MAY NOT DISPEL INDICATIONS OF A SPHYGMOCHRON

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Abstract. A high risk of a myocardial infarction was detected by a chronobiologically-interpreted around-the-clock cost-free blood pressure (BP) profile, a sphygmochron, but not by a conventional "stress test" that requires special equipment and provider's time (and perhaps a co-payment). Currently a sphygmochron can be carried out cost-free via a project on the BIOsphere and the COSmos (BIOCOS; corne001@umn.edu), in exchange for the data, and, better yet, eventually automatically via a website (http://www.sphygmochron.org/) being built by the Phoenix Study Group, composed of volunteering members of the Twin Cities chapter of the Institute of Electrical and Electronics Engineers (http://www.phoenix.tc-ieee.org). With proper education of all concerned via the same website, any computer-savvy person could serve any circle of family and friends for cost-free surveillance, until an abnormality is found and could thus prompt action by the also-copied care provider with added monitoring, whenever chronobiologic abnormality occurs, irrespective of the outcome of a conventional stress test. Inaction in the case here reported was associated with a hard event. This case report should stimulate interest in chronobiology by the public, the care provider, the health care industry and the government. The informed care recipient should convince the other three entities that cases such as the one here reported, now almost certainly the rule, may become the exception, both in terms of the brevity of the record and the neglect of its warning message, neglected based on the acceptable outcome of a conventional stress test. We propose that continuous vascular BP and heart rate (HR) monitoring, if chronobiologically interpreted, may constitute a stress test in its own right.

Introduction and Background. A comparison of the relative diagnostic and prognostic value of a cardiovascular stress test administered by a care provider with that of a sphygmochron, a chronobiologic summary as a function of time of BP and HR, should have been the topic of clinical trials on an appropriate scale long ago. More so, since there are retrospectively analyzed trials originally carried out for other purposes with outcomes or proxy outcomes showing the merit of chronobiologic diagnostics and prognostics in Table 1 on 2,354 patients, in sets of 297, 2,039 and 18 (1), 50 (2) and 12 (3) individuals. The opportunity of a prompt outcome in a special case to assess the merits of a conventional vs. a chronobiologic approach in Table 2 (2) is hence likely both representative and illustrative, and deserves comment further in the light of differences in BP vs. HR and further between workdays and holidays, a comparison of the latter days during at least several months or preferably years or rather decades constituting a stress test in its own right in some persons (4, 5).

Case report. BR, a computer scientist who came to our center could not be persuaded to monitor for more than one or two days. In a first short profile over a weekend, he had a circadian overswing near 40 mmHg, which for his gender and age is too high and is hence shown in bold type in Table 2. He was strongly advised to monitor again and did so, albeit again for a relatively short span on barely two workdays (rather than for an entire week, as we wished, i.a., to detect transient abnormality and to implement another workday vs. holiday comparison). The overswing that in the first profile was limited to systolic (S) BP now involved diastolic (D) BP as well. Furthermore, the MESOR (a rhythm-adjusted mean) of his SBP was now also deviant (elevated). The difference between the two profiles is visualized for his SBP only in Figure 1, which presents the abnormal values in black.

The Sunday vs. weekday difference in the MESOR and circadian double amplitude of BP (BP-M and BP-2A) likely contributes to what otherwise appears as a rapid progression of disease. Statistically significant Sunday or holiday vs. workday differences were found in around-the-clock surveillance for the last 5 months of a 22-year-long half-hourly record of a self-monitoring cardiologist (YW) (5) as a presumably first case of true professional white-coat MESOR-hypertension. This finding prompted the analyses of a set of 30 automatically monitored around-the-clock series each covering about 30 days that showed great inter-individual differences. While on Sundays the BP-M is on the average lower than during weekdays, one cannot generalize, as the weekend vs. weekday difference was neither consistently statistically significant nor always in the same direction; at least numerically, Sunday's average BP was not invariably lower than the average BP during weekdays (in preparation). With the qualification that in BR, both profiles were too short, in retrospect, from the follow-up history, the diagnosis could be made of a fulminating circadian BP overswing together with workday MESOR-hypertension, a co-occurrence of two Vascular Variability Disorders (VVDs) that made his condition a Vascular Variability Syndrome (VVS).

Note in Figure 1 (top) the increase (arrow) in the BP-M and in the circadian BP-2A (a measure of predictable extent of within-day change) from profile 1 to profile 2 ($P<0.001$). The increase also occurs for both SBP and DBP in the nonparametric hyperbaric index (HBI), based on stacking data along the 24-hour scale, Table 2, as also seen for SBP in Figure 1 (bottom).

BR was again strongly advised, first and foremost, to continue monitoring and, if the VVS persisted, to be treated, until the VVS was eliminated. Instead of further monitoring, he went to a care provider who gave him a stress test which proved negative. He was advised that there was no reason for concern, in keeping with the lack of action of the profession for which a chronobiologic diagnosis is not in the guidelines and hence can be ignored. (This status quo has been compared with the neglect of Ignaz Semmelweis' insistence on antisepsis.) A few months later, BR called and asked to be monitored for a week. We inquired why he changed his mind when he was previously reluctant to monitor for more than a couple of days. He told us that in the interim he had had a myocardial infarction.

Discussion. In the course of NIH-sponsored research, we also diagnosed a circadian BP overswing in several pregnant women, and could usually avoid or minimize problems by bedrest, continued monitoring and treatment. In one case, however, with a (relatively low) 48-hour SBP-M of 115 mmHg, the obstetrician did not put the mother to bed and did not continue monitoring as in other cases. She developed pre-eclampsia, gave birth in the 27th week of pregnancy, and her baby boy was hospitalized off and on for several years, with his care costing about U.S. $1 million, more than half cost-accounted, Figure 2 (6). Other evidence is summarized in Table 1, upon which the evidence to be used in the clinic rests. More of the same approach in specially designed clinical trials is needed. The brevity of the records in Table 2 and the figures is illustrative of the status quo, unacceptable for drawing inferences concerning individuals (7, 8). Conventional practice is reflected in the discussion of several recent articles (9-13), all revolving around the fiction of "**the true"** BP and ignoring VVDs, including MESOR-hypertension, the topics of last year's consensus at this conference (14).

Certainly doing something about "hypertension" is much better than doing nothing and has saved many lives (15). This merit does not detract from the fact that very many millions of the same "hypertensives", among others, remain untreated because VVDs are unknown and false positive and false negative diagnoses based on the spotcheck of a single 24-hour profile are excused as white-coat or masked hypertension, respectively. But the latter diagnoses can also be false since there is day-to-day variability in BP. *Quo usque tandem?*

Marcus Tullius Cicero, whose oration we just cited, took an aggressive stand and, like Semmelweis, died under unclement circumstances. Instead, as did Oliver Wendell Holmes in his fight for antisepsis, and we in our endeavor toward chronobiologic self-help in health care, simply note that "medical logic ... does not seem to have been either taught or practiced in our schools" (16; cf. 17).

Elsewhere, Larry A. Beaty makes the point that the home use of a device in a significantly different way from that in which it is used by care providers (the vast majority of whom measure the fiction of "a true" static BP) constitutes a hurdle to overcome in the case of home chronobiologic ABPM 7/24. Another hurdle is "Give blood pressure drugs to all (and do not measure at all)" (18). Hurdle, yes, but if the public is reached and awakened to the opportunity of cyber-aided cost-free self-help before a myocardial infarction rather than thereafter, the care receiver remembering VVDs may be the vehicle to convince the provider of the merits of not flying blind (7).

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Legends

Figure 1. Weekday (left) vs. workday (right) around-the-clock profiles provide a warning of a high risk of a hard vascular event, which in this case was not accompanied by an abnormal result of a conventional cardiologist's stress test. © Halberg.

Figure 2. Diagnosis of CHAT (short for Circadian Hyper-Amplitude-Tension) in the profile of the mother of the partly cost-accounted "million-dollar baby" (6); even when it is associated with an acceptable BP MESOR, CHAT can be a useful warning in pregnant women and in very many others of both genders. © Halberg.

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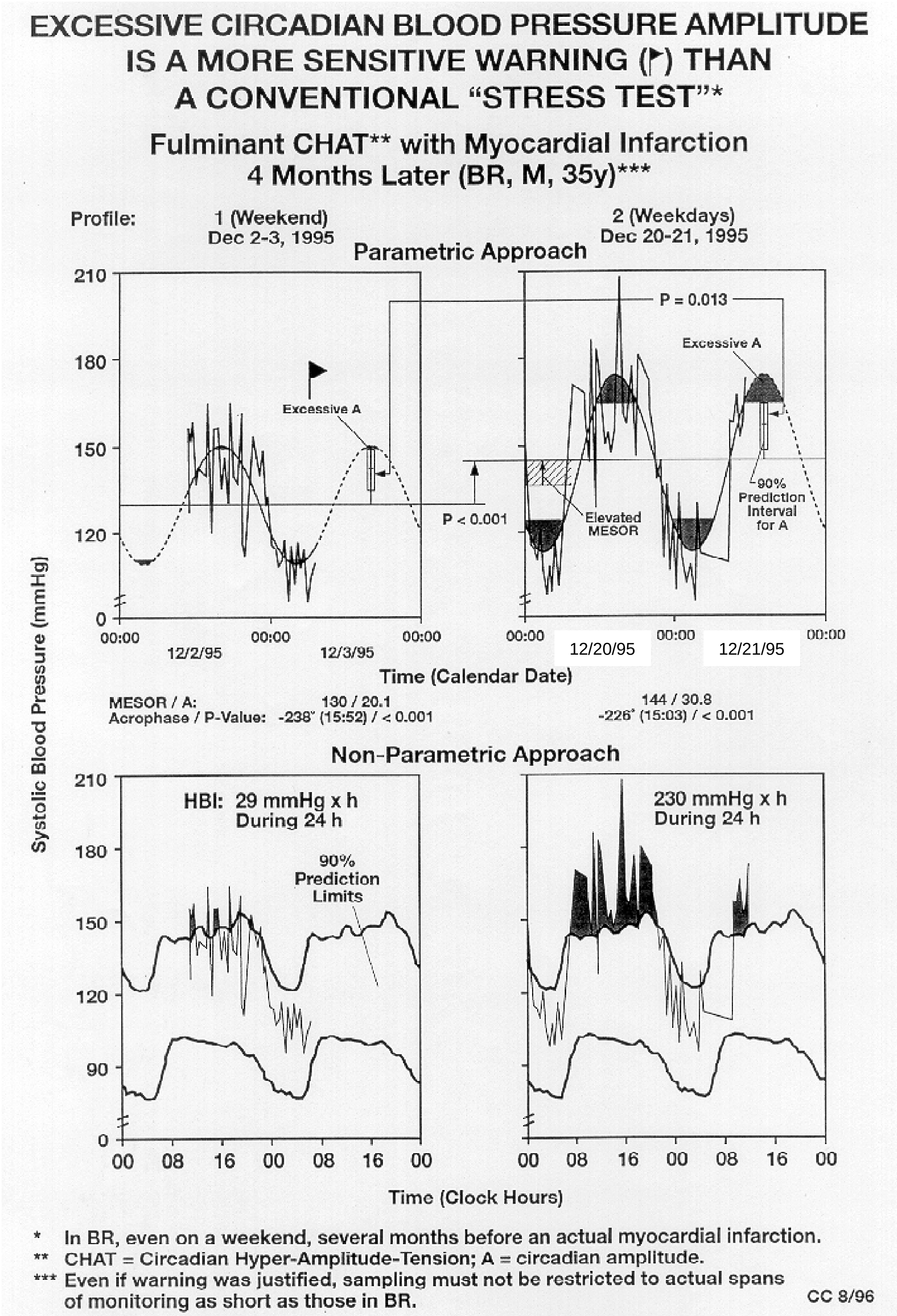
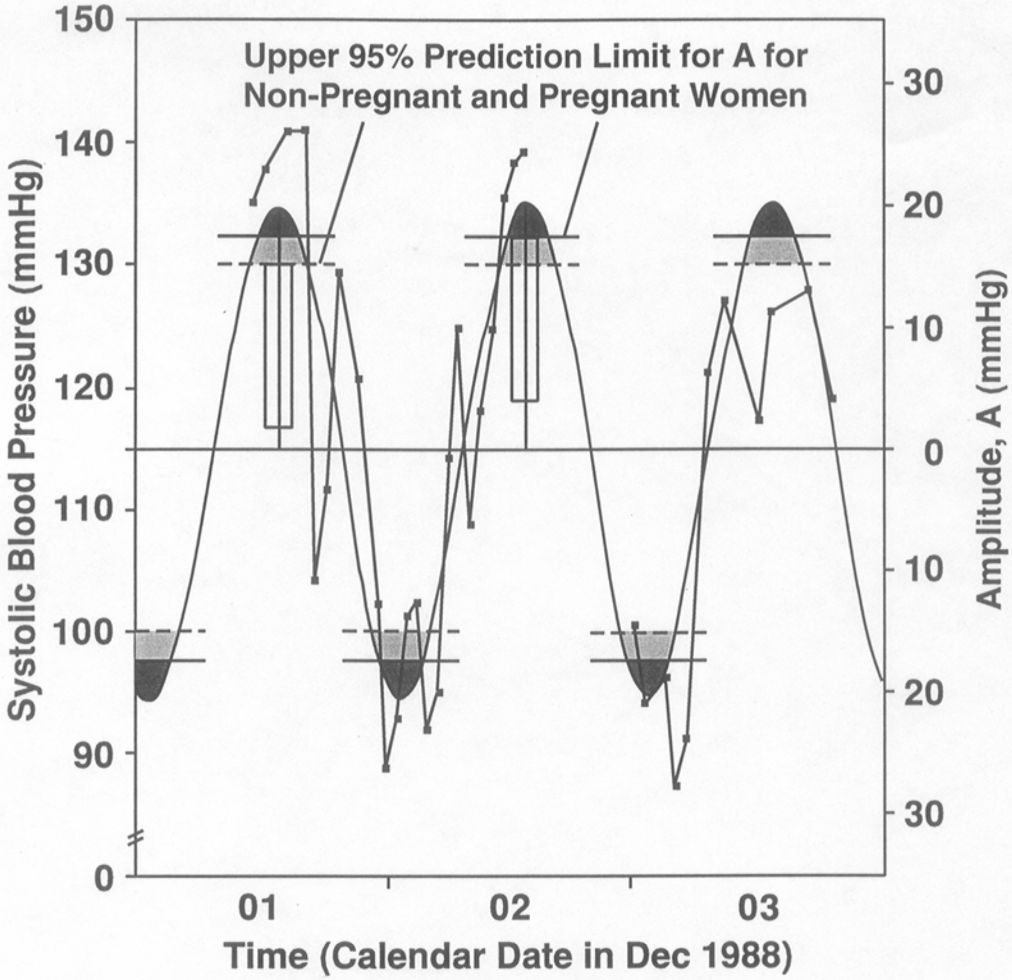

EXCESSIVE CIRCADIAN BLOOD PRESSURE AMPLITUDE IS A MORE SENSITIVE WARNING THAN A CONVENTIONAL "STRESS TEST"*
Fulminant CHAT** with Myocardial Infarction 4 Months Later (BR, M, 35y)***
Profile:
1 (Weekend) Dec 2-3, 1995
2 (Weekdays) Dec 20-21, 1995
Parametric Approach
P = 0.013
Excessive A
Excessive A
P < 0.001
Elevated MESOR
90% Prediction Interval for A
Systolic Blood Pressure (mmHg)
12/2/95
12/3/95
12/20/95
12/21/95
Time (Calendar Date)
MESOR / A: 130 / 20.1
Acrophase / P-Value: -238° (15:52) / < 0.001
144 / 30.8
-226° (15:03) / < 0.001
Non-Parametric Approach
HBI: 29 mmHg x h During 24 h
230 mmHg x h During 24 h
90% Prediction Limits
Time (Clock Hours)
* In BR, even on a weekend, several months before an actual myocardial infarction.
** CHAT = Circadian Hyper-Amplitude-Tension; A = circadian amplitude.
*** Even if warning was justified, sampling must not be restricted to actual spans of monitoring as short as those in BR.
CC 8/96

Figure 1

AN UNHEEDED CHRONOBIOLOGIC WARNING: ECLAMPSIA FOLLOWED OVERSWINGING OR CHAT (BRIEF FOR *C*IRCADIAN *H*YPER-*A*MPLITUDE-*T*ENSION)*



MESOR:	115 mmHg
Double Amplitude:	41 mmHg
Acrophase:	-202° (13:29)
P-Value:	< 0.001

* 8 weeks later, appearance of convulsions, delivery of boy in 27th gestational week, whose cost-accounted care during first 13 months totals U.S. $615,000; 26-month hospitalization may have raised cost to about U.S. $1 million.

Figure 2

Table 1. Outcomes of Chronobiological Screens of Blood Pressure and Heart Rate*

N of patients	N at follow-up	Sampling	N measurements: Total (outcomes)	Finding
10	10 (up to 5 years)	5/day daily	Up to 9,125 (only partially analyzed)	Among P. Scarpelli's patients, the 4 who died with malignant hypertension had a larger circadian BP amplitude than the 6 who were still alive (SBP: t=1.84; P=0.103; DBP: t=2.99; P=0.017)
63	21 after 28 years	~q4h for 2 days	756 (252)	9 of 10 subjects without CHAT are alive while 7 of 11 subjects with CHAT are dead 28 years later (chi-square=6.390; P<0.01)
56	56: Concomitant LVMI	q15 min for 24 h	5,376 (5,376)	Classification by Y. Kumagai of patients by LVMI (<100; 100-130; >130 g/m^2) reveals elevation of circadian amplitude at LVMI in 100-130 range whereas MESOR elevation occurs only at LVMI >130.
221	221 (time of delivery)	q1 h/48 h in each trimester of pregnancy (336 profiles)	16,128 (16,128)	In addition to an 8 mm Hg difference in mean value between women who will or will not develop complications (gestational hypertension, preeclampsia) already observed during the first trimester of pregnancy, the occurrence of complications is also associated with BP profiles characterized by an elevated circadian BP amplitude. In particular, one case (JK) of CHAT where warning was not heeded, was followed 8 weeks later by severe pre-eclampsia, premature delivery and 26 months of hospitalization of offspring at a cost of about $1 million
297	297 after 6 years	q15 min for 48 h	57,024 (57,024)	CHAT or a reduced circadian standard deviation of heart rate, or an excessive pulse pressure (>60 mm Hg) are large risk factors (larger than hypertension) for cerebral ischemic events, nephropathy and coronary artery disease, even when the blood pressure is within acceptable limits.
2039	2039 Concomitant LVMI	Hourly averages for 24 h	48,936 (48,936)	LVMI is increased in patients with CHAT, a reduced circadian standard deviation of heart rate, or an elevated pulse pressure. The relation between LVMI and the circadian endpoints is nonlinear.
23	12 after 7 years	q15 min for 9 days	19,872 (10,368)	10 of 20 patients with no consistent BP abnormality are alive and well; 2 of 3 patients with consistent BP abnormality reported an adverse vascular event (P=0.015 by Fisher's Exact Test).
80	80 Response to treatment administered 2 h before daily BP peak vs. control group treated 3 times a day	q4 h for 24 h before and on treatment	960 (960)	With smaller doses of medications, BP was lowered by R. Zaslavskaya to a larger extent and treatment was accompanied by fewer complications. Treatment: propranolol, clonidine, or alpha-methyldopa (P<0.05 for each effect)
18	18 (12 weeks)	q30 min (≥24h) on 3 regimens	≥2592 (≥2592)	Treating CHAT may prevent adverse vascular events: As compared to placebo, nifedipine (1 mg b.i.d. at 08 & 20) increases and benidipine (4 mg/day at 08) decreases the circadian amplitude of blood pressure. The resulting increase vs. decrease in the incidence of CHAT on nifedipine vs. benidipine may account for the corresponding difference between the number of stroke events of 7.6 vs. 3.5 and the total number of cardiovascular events of 20.4 vs. 8.8 per 1,000 person-years.
Totals:				
2,807	2,754		160,769 (>141,636)	

*SBP and DBP: Systolic and Diastolic Blood Pressure; HR: Heart Rate; CHAT: Circadian Hyper-Amplitude-Tension, a condition defined by a circadian amplitude exceeding the upper 95% prediction limit of acceptability (in healthy peers matched by gender and age); LVMI: Left Ventricular Mass Index. By comparison with several classical studies, the number of measurements in chronobiological work completed thus far is likely to be larger, and confounding by inter-subject variability smaller.

Table 2: Case report: A 35-year-old man (BR) was monitored for 1 day (of a weekend; Profile 1: 12/2/1995) and (18 days later) for 2 added days (midweek; Profile 2: 12/20/1995), 4 months before a myocardial infarction in April 1996

Endpoint (units)	SBP (mmHg)		DBP (mmHg)		HR (beats/min)	
Profile	1	2	1	2	1	2
MESOR	130.3	144.0**	81.0	86.5*	70.5	82.4***
2A (amplitude)	40.5	57.5*	20.0	45.8***	27.1	29.2
ϕ (hr:min)	15:39	15:06	16:34	14:52	15:25	15:33
PTE (%)	17	54.8	8.5	35.8	0	9.2
tEx (hr:min)	14:49	14:59	22:56	16:23	-	15:57
Index (HBI or TCI)	29	230	7	92	0	15

*PTE: percent time elevation (of blood pressure or heart rate above time-specified reference limit computed as upper 95% prediction limit); tEx: timing of excess; index: extent of excess measured as area under the curve delineated by time-specified upper reference limit (chronodesm) and profile whenever it exceeds the limit; for SBP and DBP, HBI = hyperbaric index in mmHg x hour during 24 hours; for heart rate TCI = tachycardic index, in beats/min x hour during 24 hours.
Values in **bold** are outside chronodesmic (time-varying and time-specified) reference limits.
P: *<0.05, **<0.01. In BR's first profile, only the SBP-2A was deviant; 18 days later, the SBP-MESOR and both the SBP-2A and DBP-2A and HBIs were deviant. From (2).

A TRANSTRIDECADAL BEL CYCLE IN HUMAN BLOOD PRESSURE AND BODY WEIGHT

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Aim. To explore the presence of non-photic cycles and in particular of a BEL cycle of a length between 30 and 40 years in the body weight and blood pressure of a MESOR-hypertensive man using hypotensive medication, 52 years of age at start of mostly daily measurements for the ensuing decades.

Background. Chronomics, a cartography of chronomes (time structures, consisting of rhythms, trends and chaos), has yielded a fledgling atlas of transdisciplinary rhythms that cover a wide range of frequencies: some are photic in origin, such as circadians and circannuals, now broadly recognized as entities in their own right; others are non-photic components of particle radiation from the sun and the galaxy, broadly of helio-geomagnetics, gravitation, UV flux, and/or of any other unseen yet measurable weather in extraterrestrial space. Pairs or multiple congruent periods, in two or more time series, defined as having overlying or at least partly overlapping CIs (95% confidence intervals) of their periods are seen when these series are analyzed with the extended linear-nonlinear cosinor. They are found, i.a., among helio-geomagnetic activity indices themselves and among these and vascular spectral components, notably in blood pressure and heart rate (studied over decades) in the spectral regions of 1 cycle in I. about 7 days, the circaseptans; II. about 5 months, the cis-half-years; III. more than one year but less than two years, the transyears (longer than [beyond = trans] a calendar year); and IV. decades, with the transtridecadal BEL of about 30-40 years currently extensively documented (1-9).

Earlier (10-13), we had focused upon transyears -- periods longer than a year but shorter than 1.9 years. These can be far-transyears (1.2 years $\leq [\tau$ {period} $- CI] < [\tau + CI] < 1.9$ years) with the CI of τ within these limits or near-transyears (1.00 year $< [\tau - CI] < [\tau + CI] < 1.20$ years) with the CI of τ not overlapping these limits. We had also focused on cis-half-years, slightly shorter than a half-year (12; cf. 14, 15). Far-transyears predicted by Wolff (14) and found by other physicists in solar flares (15, 16) and in the solar wind (17, 18) have congruent periods detected in physiology (11-13, 19, 20). They were discovered in sudden cardiac death in some locations and in cardiac arrhythmia during some time spans during some solar cycle stages (12, 13). Near-transyears found in biology, prompted their discovery in the solar wind, solar magnetism and geomagnetics (12, 21).

Subject and method. A physician (WRB) began self-monitoring body weight (BW) and systolic (S) and diastolic (D) blood pressure (BP) when he was a few months short of 52 years of age and continued for over 30 years. During the most recent 12 years, he also recorded his heart rate (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 cosinor analyses was presented earlier (10). Here, we focus on the broader spectrum, including the transtridecadal BEL (1-9).

Results. Figure 1 displays the original data covering 3 decades for SBP, DBP and BW. Eyeballing sees changes that differ in BW from those in BP, but objective analyses are needed. 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, but the most prominent component in DBP has a period of about 16.7 years, the possible signature of a global Makarov and Sivaraman (22) cycle. A cis-half-yearly component is further seen in SBP (Figure 2, top) with a period of about 0.37 year as well as in DBP along with a second cis-half-year 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 cis-half-year at a period of 0.45 year. 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 cis-half-year, and no calendar-yearly component. Other anticipated non-photic components seen in Figures 1 and 2 suffice to suggest that non-photic effects were prominent in several variables in the subject investigated, awaiting nonlinear analysis. 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 (23-25), using 35 years as trial period, yielded a transtridecadal spectral component only for SBP, the period [CI] being estimated as 30.56 [29.24, 31.87] years and the amplitude (A) as 9.03 [8.46, 9.60] mmHg. For BW, the period was 28.14 [26.66, 29.63] years and the amplitude was 1.79 [1.67, 1.92] lb. Analyses failed 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 period of 32.17 years, results were compatible with the presence of a BEL cycle, as shown in Table 1.

Table 1. Transtridecadal periods with the concomitatnt fit of a linear trend *

Variable (units)	Period (years) [CI]	A (units) [CI]
Diastolic blood pressure (mmHg)	31.68 [23.94, 39.42]	4.62 [2.63, 6.61]
Body weight (lb)	41.23 [31.25, 51.20]	3.31 [1.80, 4.81]

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

The about 30-year component in SBP and DBP and a component also qualifying as a transtridecadal by a CI of the period covering part of the 30-40 year range constitute an exciting new finding on a revisited forgotten yet vindicated BEL periodicity (26; cf. 1-9).

Discussion. The yearly progression of seasons in a mid-continental climate is anticipated to have a profound effect on our lives, and most certainly would find expression in some measures of body function. 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 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. 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 (7; cf. 5, 6, 8, 9). In FH (12), another elderly man, a circannual component was absent in SBP, characterized only by transyears, which are prominent in WRB's HR as well.

In WRB's series, the BEL cycle is demonstrated for SBP and DBP and for BW, the demonstration for the latter two variables hinging on accounting for an also-present trend. 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 (27, 28). It persists in an analysis of temperature data measured since Brückner's time to that of this writing (9), and is thus pertinent as a background to discussions of climate change. It relates to economics (30) and to military-political affairs (31) as well as to international battles (32) and thus to diseases of society, as our meta-analyses (9) of invaluable data compiled by the scholarship of Alexander Leonidovich Chizhevsky and Raymond Holder Wheeler reveal.

Before generalizing from two elderly cases, WRB and also FH (12), and a younger adult (RBS), and considering age rather than high BP as accounting for the spectral difference between WRB and FH on the one hand, without dominating transyears in BP versus and RBS with a prominent circannual component on the other hand, many more time series will have to be collected, in the footsteps of Santorio (33), 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, and whose data, including those on his changes of weight that led to the discovery of insensible perspiration, could not be retrieved. RBS's, FH’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 (12). A major question revolves around selective congruence. Do different physiologic variables in RBS, WRB and FH show congruence with environmental cycles of differing lengths during the same multidecadal spans, and what may putative underlying mechanisms be?

Acknowledgement and comment

This is a rare acknowledgement wherein the two senior authors thank Dr. William R. Best (WRB), a co-author, not only because the data presented are those of the co-author, WRB. It is a pleasant task to clarify at the outset that WRB's motivation, which has now continued for over three 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 "pressure" for "glucose". The time of strict control of vascular variability disorders is also likely to come.

The senior author is further indebted to WRB for his publication of his studies on the response to epinephrine in 1950 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 gonadectomized mice of both sexes, where, in addition to a bilateral adrenalectomy, ectopic tissue next to the vertebral column and in the large ligaments or in the scrotal fat had also been removed.

When the failure to confirm the epinephrine test was reported by the senior author to his then department head, the late George W. Thorn, Hersey Professor of Medicine at Harvard, Thorn said that he admired the senior author's (FH) sticking to his guns, but all the others could not be wrong. In the case of the epinephrine test, the then majority was wrong. 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. Nontheless, 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 transtridecadal cycles and perhaps some new information thereby concerning the health of individuals and societies.

Support: GM-13981 (FH), University of Minnesota Supercomputing Institute (GC, FH), MSM0021622402

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Legends to Figures

Figure 1. Time plots of original data of WRB can be interpreted only subjectively. © *Halberg*

Figure 2. Linear least squares spectra of blood pressure of WRB. © *Halberg*

Figure 3. Linear least squares spectra of heart rate and body weight of WRB. © *Halberg*

Figure 4. Modeling of blood pressure and body weight of WRB reveal the presence of a BEL cycle. © *Halberg*

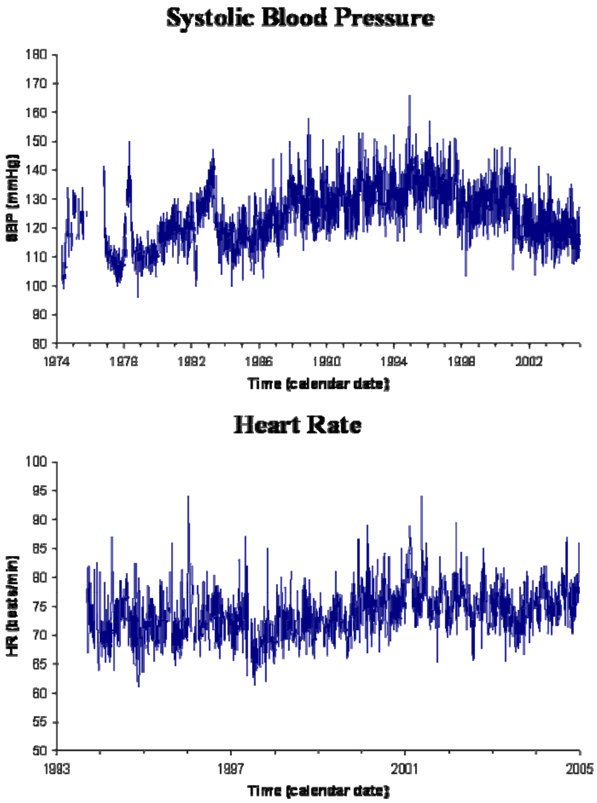

Systolic Blood Pressure
SBP (mmHg)
Time (calendar date)
Diastolic Blood Pressure
DBP (mmHg)
Time (calendar date)
Heart Rate
HR (beats/min)
Time (calendar date)
Body Weight
BW (lbs)
Time (calendar date)

Figure 1

Non-Photic Components in the Circulation of a MESOR-Hypertensive Man (WRB) Awaiting Further Analyses

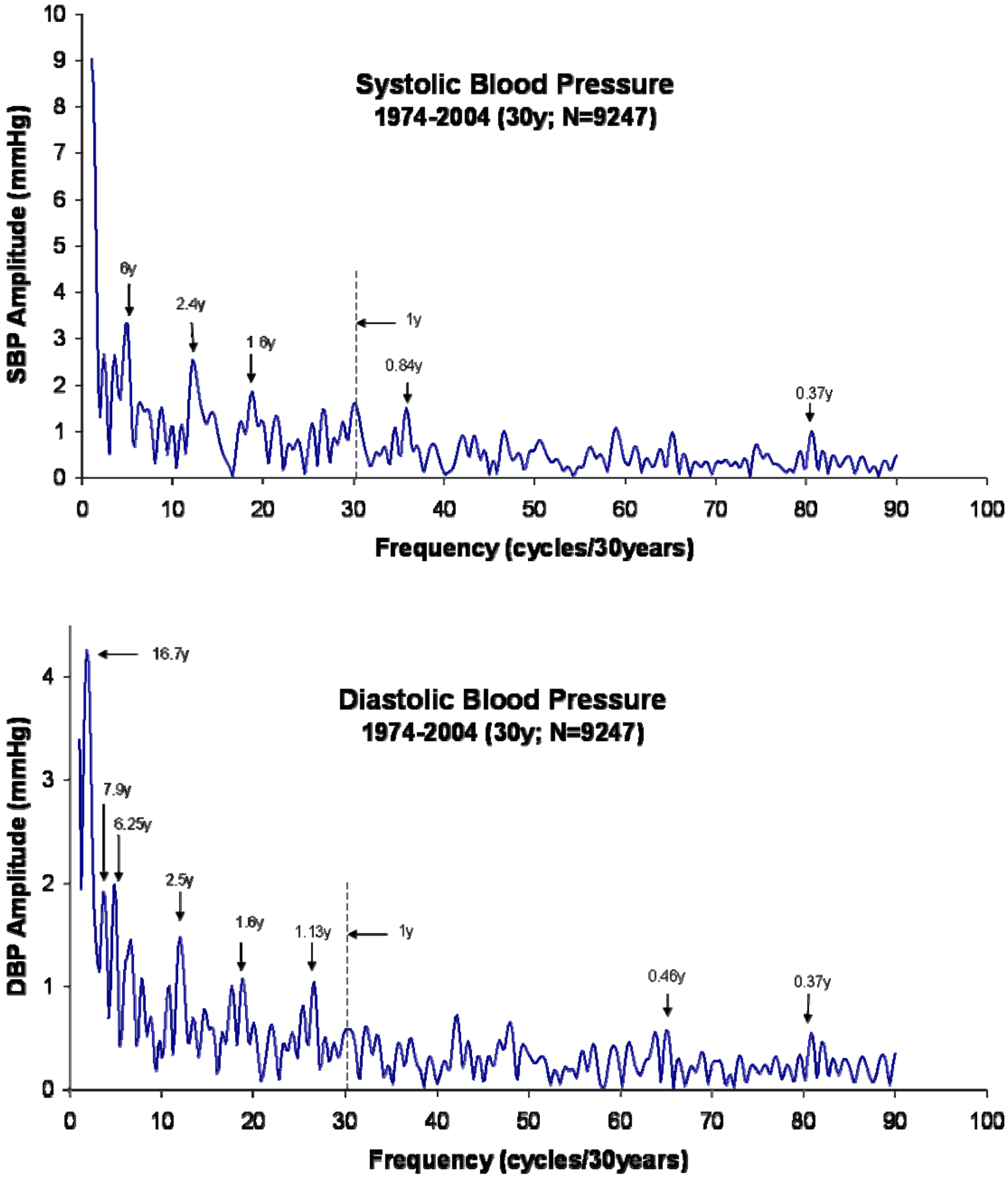


Figure 2

Non-Photic Components in the Physiology of a MESOR-Hypertensive Man (WRB) Awaiting Further Analyses

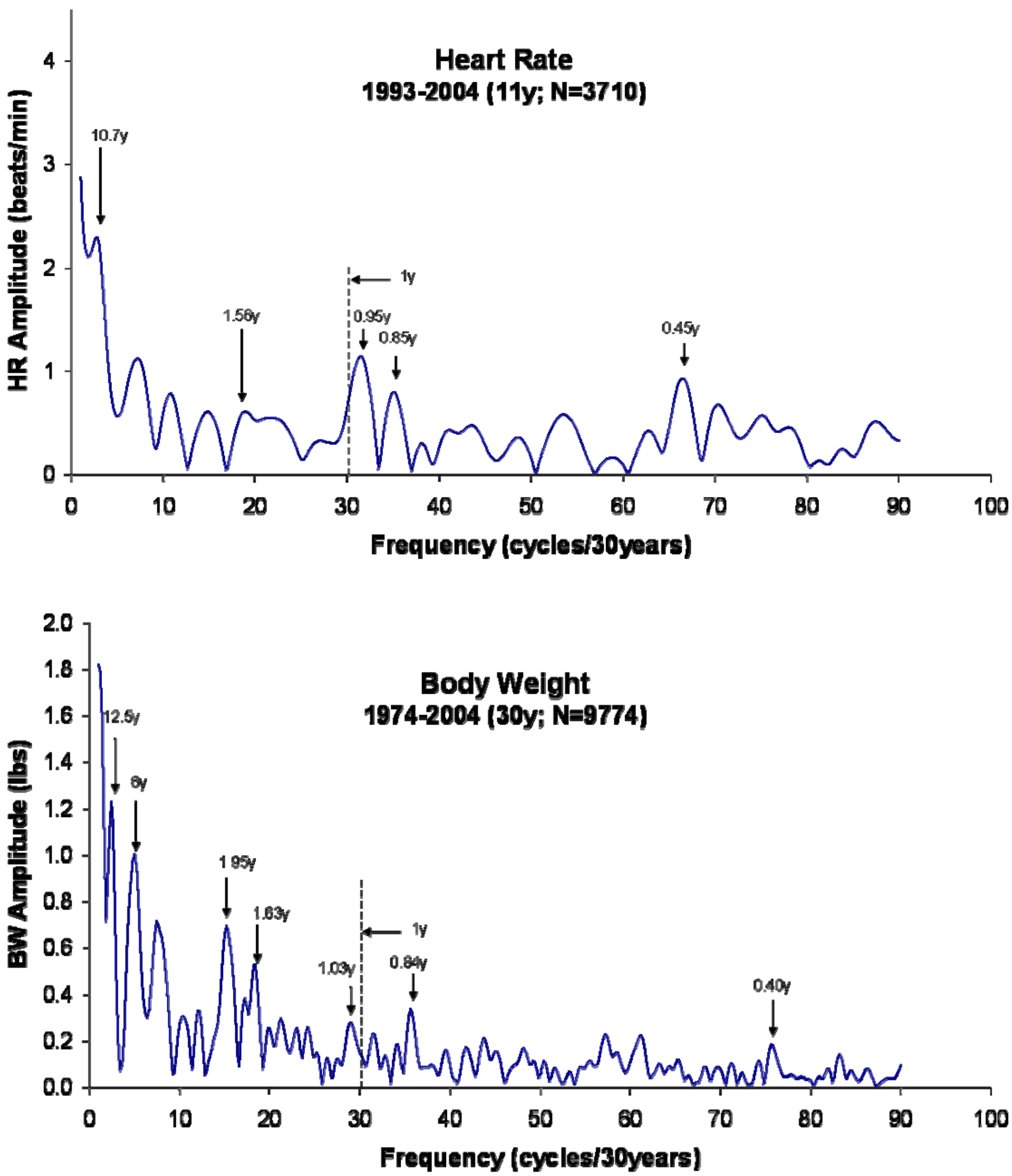
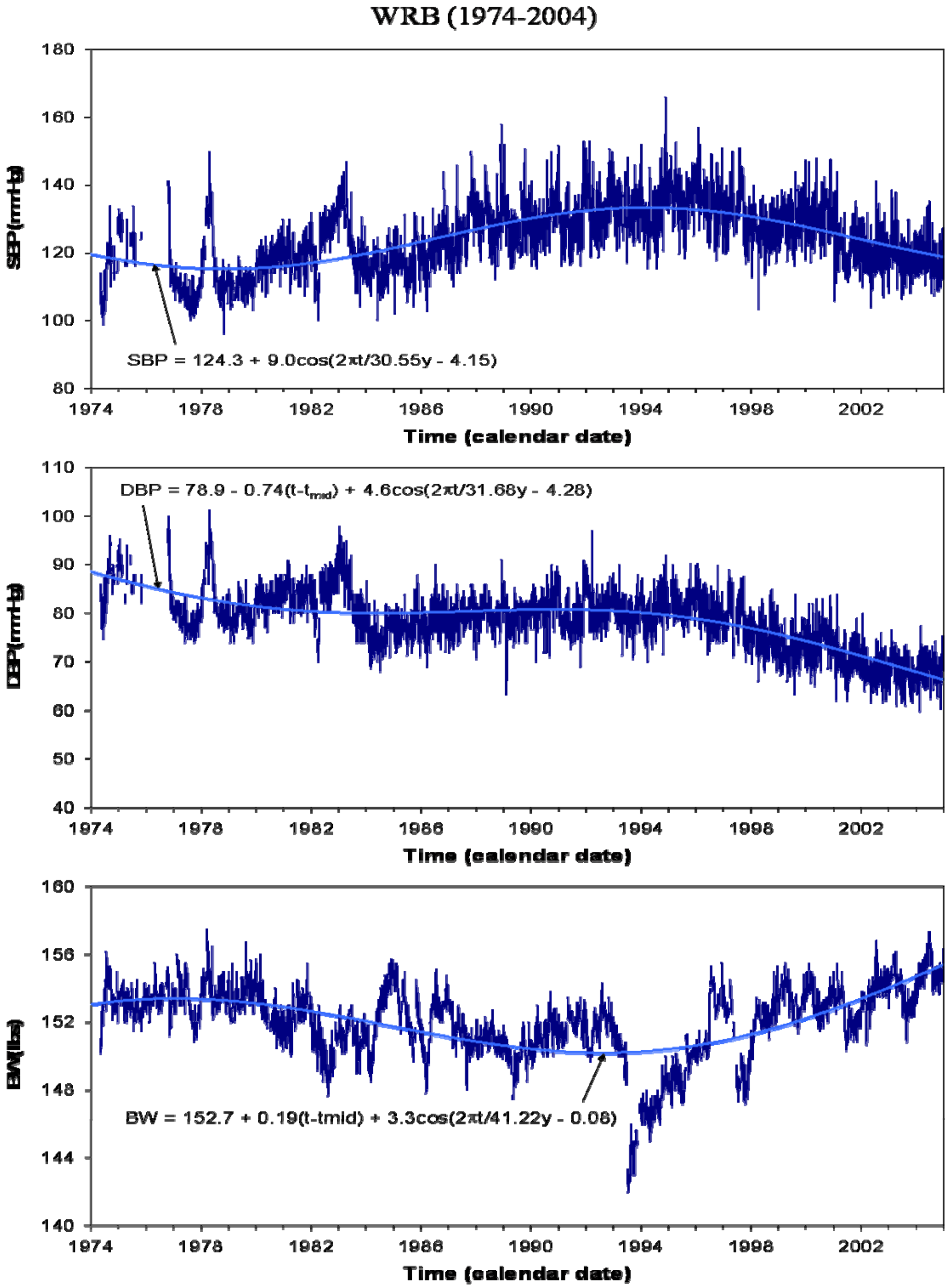


Figure 3



WRB (1974-2004)
SBP(mmHg)
SBP = 124.3 + 9.0cos(2πt/30.55y - 4.15)
Time (calendar date)
DBP(mmHg)
DBP = 78.9 - 0.74(t-t_mid) + 4.6cos(2πt/31.68y - 4.28)
Time (calendar date)
BW(lbs)
BW = 152.7 + 0.19(t-tmid) + 3.3cos(2πt/41.22y - 0.08)
Time (calendar date)

Figure 4

DIFFERENCES IN TIME STRUCTURAL ENVIRONMENTAL CONGRUENCE OF VASCULAR VARIABLES IN AN ELDERLY MAN

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Abstract. A wobbly about 30-year cycle in the heart rate (HR) of an elderly man (FH) measured around the clock with interruptions during 22 years is detected and validated, along with a 15-year (global?) cycle and a circadecadal (Horrebow-Schwabe) component characterizing the systolic (S) and diastolic (D) blood pressure (BP) of FH.

The extended linear-nonlinear cosinor (1-3) has been used to detect cycles and to provide point and confidence intervals for their parameters, namely their period (□) amplitude (A) and acrophase (□). The periods found in a first linear step (in a linear cosinor spectrum) were the input used as initial values into a nonlinear model that may then provide parameter estimates that can markedly differ from the original guesstimates. With the construction of artificial time series consisting of periodic components with known periods, amplitudes, and acrophases, one can check the output of the program (4). Thus, we analyzed by a linear cosinor spectrum a simulated series containing two components with close periods of 24.0 and 24.8 hours and with widely differing amplitudes over a span much shorter than the beat period. With additions of more and more noise, the linear spectrum finds three peaks, two of which are spurious. But when all three periods are used as input in the nonlinear program, the procedure converges to the correct model, one of the two spurious peaks showing as not significant and the other converging toward the correct frequency (4). The problem is the more interesting since our approach fared well in comparisons with other methods, as shown elsewhere (Table 1 in 3). The extended linear-nonlinear cosinor has been applied to infradian cycles with periods longer than 30 years, which were detected and validated by the rejection of the zero-amplitude assumption (5, 6). The minimal amount of data in terms of the number of cycles covered by a time series has been considered for the assessment of circadian rhythms as requiring a number of longitudinal replications, in order to reliably estimate the characteristics of the dynamics (7). In the case of tridecadal cycles, a longitudinal approach is often not possible and transverse analyses had to be used, replications being implemented across different similar individuals under similar conditions, rather than on the same individual. As a few test pilots practice continued surveillance of BP and HR, long enough time series have become available for the tentative scrutiny of the tridecadal cycle in these variables on an individualized basis, relying on results from other test pilots as prior information for the analysis on hand. Drawing a parallel with the study of circadians indicating that a reasonable assessment of parameters could be obtained from data covering no more than about 2/3 to 3/4 of a cycle (albeit with wide confidence limits), we here attempt to assess a tridecadal cycle in time series of BP and HR shorter than a full cycle.

Specifically, we analyzed SBP, DBP and HR data of an elderly man (FH), 70 years of age at the start of half-hourly around-the-clock measurements with interruptions (1987-2009, 22 years). For all three variables, the spectra show a circadecadal cycle, Figure 1. Linearly, spectral peaks are found at periods of about 11, 13, and 10 years for SBP, DBP, and HR, respectively. Using a trial period of 10 years in the nonlinear analysis, periods and their 95% confidence intervals [CIs] converge to 11.00 [10.32, 11.69], 15.31 [14.10, 16.52], and 10.14 [9.90, 10.39] years for SBP, DBP, and HR, respectively (Figure 2). Analyses with a trial period between 30 and 35 years invariably fail for SBP. In the case of DBP, even a trial period of 35 years converges to the 15.31-year component of Figure 2. In the case of HR, a different component is found with a period and CI of 25.40 [24.45, 26.36] years, Figure 3 (middle). When it is fitted together with the about 10-year cycle, both components are detected with statistical significance, but their periods are markedly changed to 30.01 and 7.3 years, Figure 3 (bottom). Thus, another BEL cycle is very tentatively suggested for HR from data covering only 22 years in FH. This elderly man's SBP follows a Horrebow-Schwabe cycle, his DBP a global Makarov and Sivaraman cycle (8) and his HR synchronizes with both a BEL and the third harmonic of the Hale cycle (9) as can be seen also by the unaided eye in Figure 3 (bottom).

The major question revolves around selective congruence. Different physiologic variables in a clinically healthy adult who at 20.5 years of age started self-measurements around the clock for 40 years (RBS) (5), a physician starting self-measurements mornings around 52 years of age for 3 decades (WRB) (6), and another yet older man (FH) show concurrently congruence of their SBP, DBP and HR with environmental cycles of differing lengths during the same multidecadal spans. Are these endocrine, neural or, as seems possible, neuroendocrine phenomena, involving i.a., the differential pineal and hypothalamic responses that can be detected during a magnetic storm, Figure 4 (10)?

The transtridecadal periods here described in the circulation of three men were documented thoroughly in climate by Brückner (11), reported a few months earlier by Egeson (12), and associated with changes in the length of the about decadal cycle in relative sunspot numbers by William and Norman Lockyer (13, 14), son and father, the latter the discoverer of helium and founder of the journal Nature. Hence, this cycle of about 30 years has been named the BEL cycle to honor its discoverers, remembered only by notable exceptions (15).

BEL cycles are found in records of environmental temperature up to today (16-18) and in our meta-analyses of time series bearing on economics (19) and military political affairs, including international battles (20, cf. 17).

Support: GM-13981 (FH), University of Minnesota Supercomputing Institute (GC, FH), MSM0021622402

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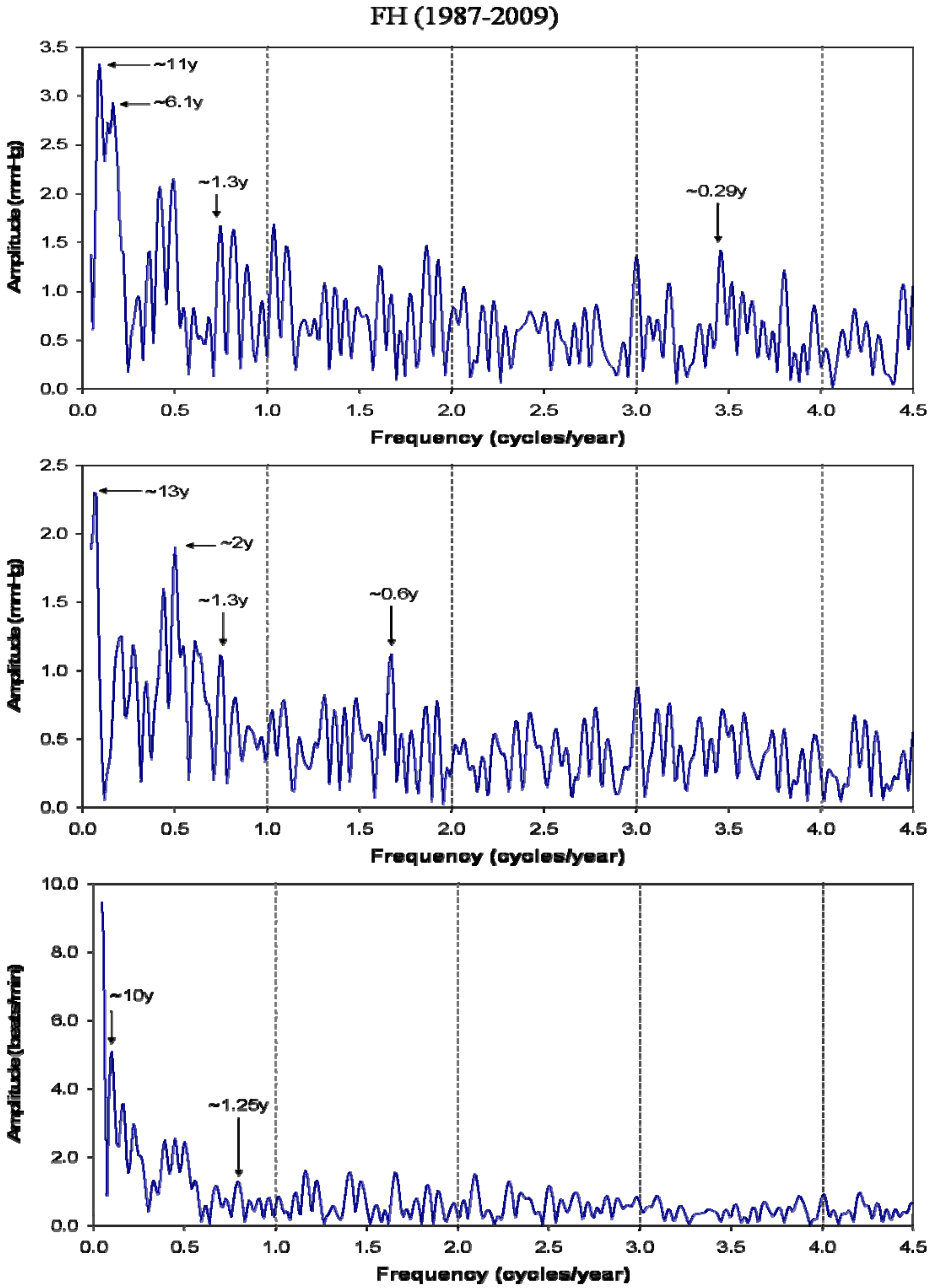


Figure 1. Least squares spectra of systolic blood pressure (top), diastolic blood pressure (middle) and heart rate (HR) of FH (M, 68 years of age at start of monitoring during 22 years, with interruptions) reveal the presence of a prominent about 11-year cycle, among other components. © Halberg.

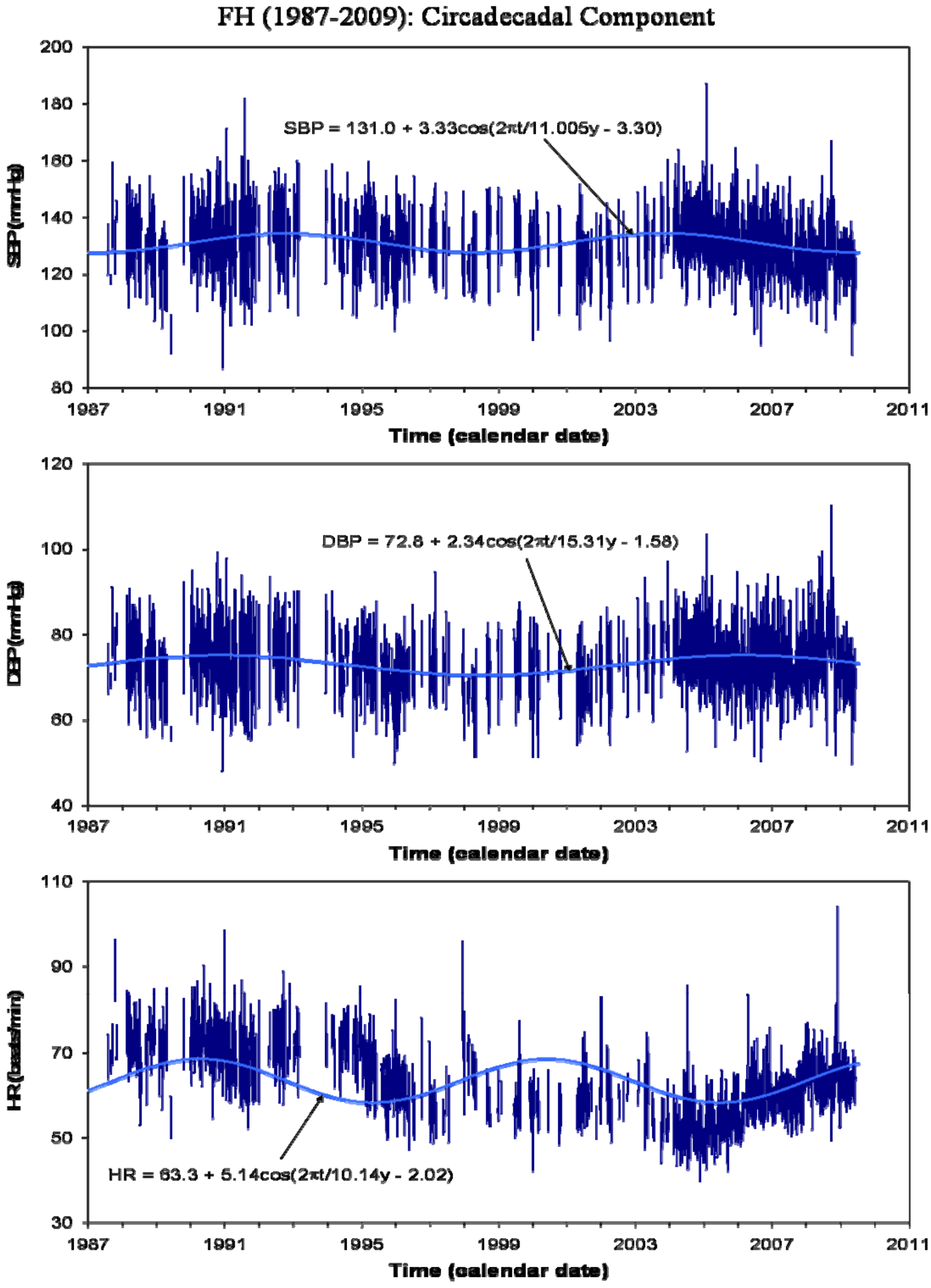


Figure 2. Nonlinear analyses confirm the presence of a Schwabe cycle for systolic blood pressure in the 22-year series of FH (M, 68 years of age at start of monitoring) (top). In the case of diastolic blood pressure, the model converges toward a global cycle with a period of about 15 years (middle). The fit of a Schwabe cycle to the heart rate data shows considerable lack of fit, suggesting the need to modify the model in this case (bottom). © Halberg.

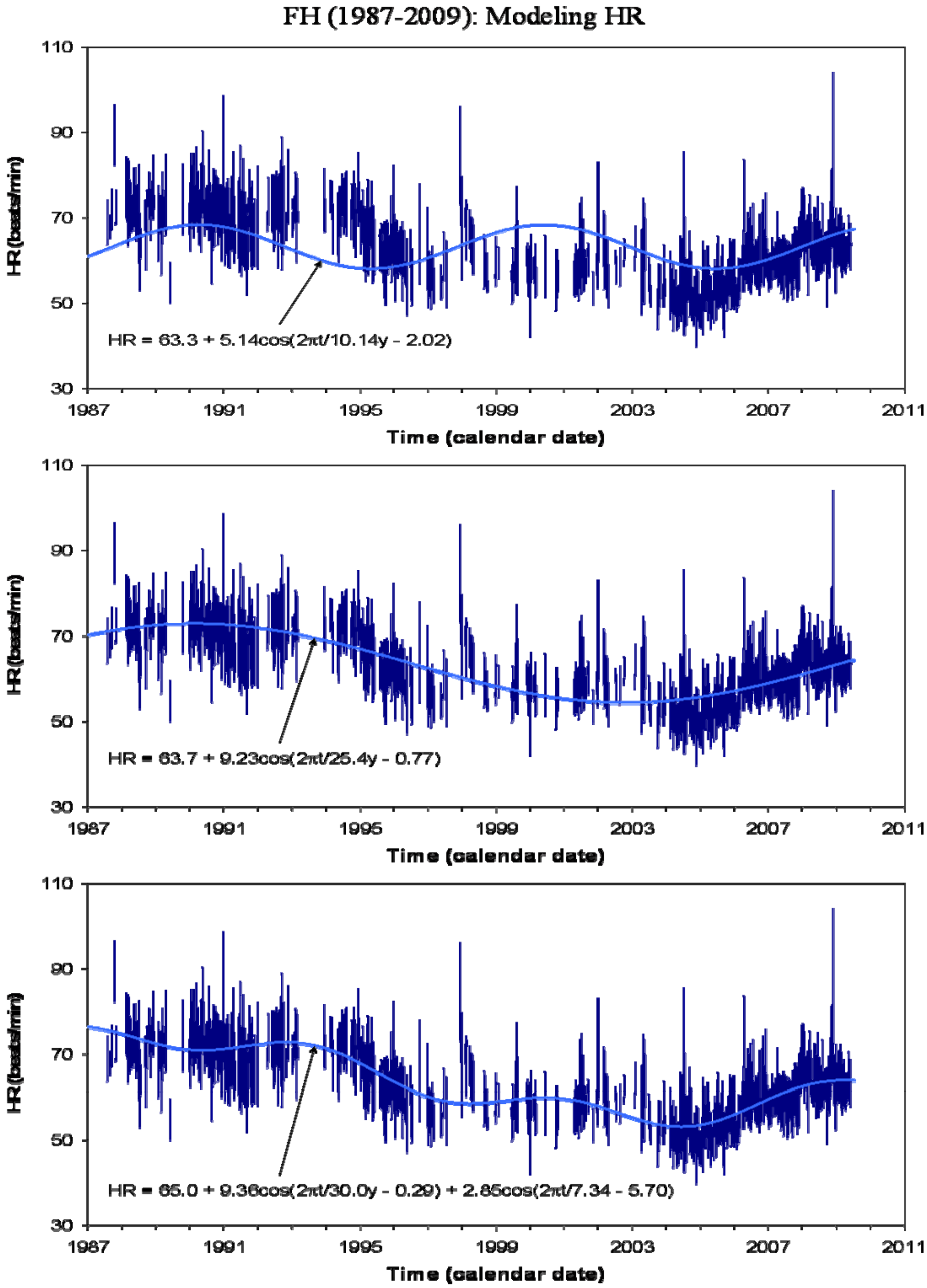
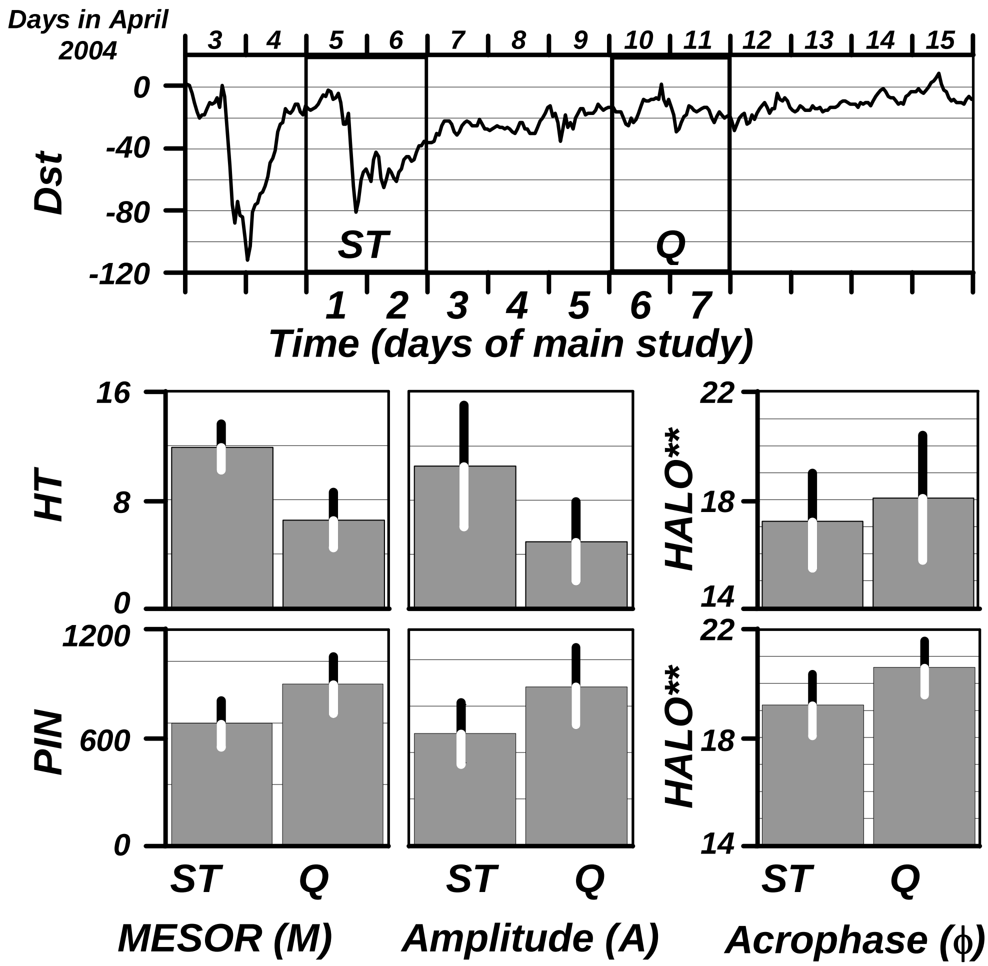


Figure 3. Modeling heart rate data collected during 22 years (with interruptions) by FH (M, 68 years of age at start of monitoring): anticipated components with periods of about 11 and 35 years are fitted separately (top and middle, respectively) and concomitantly (bottom). The composite model provides a better fit, converging towards periods that differ markedly from their estimates in the separate single-component models, including the anticipated BEL cycle of about 30 years. © Halberg.

MELATONIN DYNAMICS IN RATS' HYPOTHALAMUS (HT, middle) AND PINEAL (PIN, below) DURING MAGNETIC STORM (ST) AND QUIET (Q)



ST = 2 days of the second part of a moderate double magnetic storm, Q = 2 days of magnetic quiet, gauged by the geomagnetic equatorial disturbance index Dst in nT (plotted, top) of -115 and -80 and Kp (a planetary magnetic disturbance index of slightly above 6 in arbitrary units in each storm (Kp not shown).
*** HALO = hours after light on. Vertical lines straddling bars are 95% confidence intervals. P < 0.05 in each comparison, except for ϕ in hypothalamus.**

Figure 4. Using the equatorial geomagnetic disturbance index Dst as a gauge of magnetic storms (top), two subspans of 2 days each at the beginning and end of a 7-day study are selected to compare stormy (ST) and quiet (Q) conditions as they may influence hypothalamic (HT) and pineal (PIN) melatonin of rats kept in 12 hours of light alternating with 12 hours of darkness. Whereas geomagnetic disturbances are associated with lower melatonin concentrations and a dampened circadian variation in pineal melatonin as expected from other studies, melatonin concentrations are higher and the circadian rhythm is amplified in the case of hypothalamic melatonin. Data of R Jozsa. © Halberg.

DEATH FROM WOLFF-PARKINSON-WHITE SYNDROME DURING MODERATE MAGNETIC STORM: CASE REPORT WITH LITERATURE REVIEW

Germaine Cornélissen and Franz Halberg

Halberg Chronobiology Center, University of Minnesota, Minneapolis, MN, USA

A physician who died at 38 years of in Albuquerque, New Mexico, during a solar maximum, had a congenital conductive heart disorder, Wolff-Parkinson-White syndrome (WPW), with which he was diagnosed at 14 years of age. Putatively pertinent magnetic storm data framing the date of his death are here noted to stimulate others to investigate whether individuals with conductive heart disorders might be particularly and differentially susceptible to magnetic storms.

Background

Pioneering studies by Eliyahu Stoupel report on a relation of cardiac arrhythmia and geomagnetic activity (1) and on sudden cardiac death (SCD) and daily and monthly helio- and geomagnetic as well as cosmic ray activity (2). The detection of arrhythmias by implanted devices served this author's team to relate arrhythmia to cosmophysical findings (3). Pearson correlation coefficients constitute a major approach by Stoupel (4), usually without consideration of rhythms, a circumstance that limits inferences, Figure 1. With focus upon cycles and superposed epochs, arrhythmias triggered by implanted devices had been investigated earlier by others (5). Koukkari and Sothern (6) deserve credit for considering non-photic environmental (as well as societal) circaseptans (Saturday peak) with circadian and circannual rhythms in a review of cardiovascular disease broadly, Table 1. Photic about-daily and about-yearly patterns were documented earlier (7, 8), as were circasemiseptans by 1982-1983, Figure 2 (9; cf. 10).

The multi-frequency rhythmic element in the time structure (chronome) of the incidence of SCD (based on the code of the tenth revision of the International Classification of Diseases, ICD-10, code 146.1) reveals, in addition to an anticipated (photic) circadian rhythm (morning peak) and a circannual variation (winter peak) reviewed earlier (Table 1), also non-photic signatures (11-15), including transyears with periods longer than a calendar year (by a few weeks or by several months) and an about 0.42-year cis-half-year, detected in some but not all geographic locations examined thus far (13). ICD-10 rightly separates electrical accidents of the heart from a cardiac arrest associated with a myocardial infarction.

Before ICD-10, analyses by superposed epoch of 70,531 SCDs in Moscow, Russia, during 1979-1981 found an about 5.4% decreased incidence (P=0.012) two days after a southward turn of the North-South component (Bz) of the interplanetary magnetic field (16). This record was also characterized by an about 15.21-day variation validated by nonlinear least squares (95% CI: 15.14 - 15.28 days), apparently resonating with occasional frequency trapping with the about 14-day component in the local geomagnetic disturbance index K recorded concomitantly (17, 18), Figure 3.

Chronomic analyses of a pool of 5,503 cases of SCD (ICD-10 146.1 code) from 9 geographic locations between 1998 and 2003 corroborate a decreased incidence of SCD on days of high geomagnetic activity (Kp>5) (p<0.05 from the fit of a parabola to the relative SCD incidence on days -3 to +3 bracketing days when Kp>5 = day 0), Figure 4 (14, 15). This result is in keeping with a decreasing second-order polynomial trend in the relative incidence of SCDs as a function of Kp (R^2=0.604; P=0.040), Figure 5 (14, 15).

A smoothed (over 5 spectral lines) population-mean cosinor spectrum (across all 9 locations) in the frequency range of one cycle in 5 years to one cycle in 3.3 days identifies peaks at trial periods of about 1.25 years, 14.6 and 3.5 days. Prior to smoothing, the circannual (P=0.063), cis-half-year (P=0.054), and about 14.4-day (P=0.075) components are detected with borderline statistical significance, whereas other components related to the solar rotation, with periods of about 9, 7, 5 and 3.5 days are detected with statistical or borderline statistical significance (P<0.06) (14, 15).

Circadian, circaseptan, and circannual patterns have also been documented to characterize different kinds of cardiac arrhythmia (19, 20). Arrhythmias that may underlie SCD have been shown to follow patterns similar to those characterizing SCD (13-15). Paroxysmal supraventricular tachycardia is found to peak in the evening, later than the rather broadly classified ventricular arrhythmia but earlier than atrial fibrillation (19). Analyses of 811 cases of atrial fibrillation recorded between 1980 and 1989 (10 years) indicate a clear circannual component peaking in November (P=0.003). In addition, these data are also characterized by an about 1.35-year transyear

(P=0.050) and an about 7-year (P<0.001) component, Figure 6. During the same 10-year span, no circannual (P>0.50) but only about 2-year (P=0.021) and 0.45-year (P=0.009) components are found to characterize 353 cases of paroxysmal supraventricular tachycardia (P-values not corrected for multiple testing), Figure 7 (14, 15, 21). Transyears have also been found in all longitudinal blood pressure and heart rate series analyzed thus far (over 46), most covering 10 years or much longer (up to 40 years), Figure 8 (15). Analyses of long-term ECG and pacemaker-cardioverter-defibrillator records can also help assess the relative merits of different treatment modalities (5), notably once outcome measures also become available.

There is a precedent for such outcome studies in the case of ambulatory blood pressure monitoring. These studies have identified abnormalities in blood pressure and heart rate variability that can be treated, such as an excessive circadian amplitude of blood pressure (CHAT), an excessive pulse pressure, and a deficient heart rate variability, and also an odd timing of the circadian blood pressure rhythm, but not of that in heart rate. These conditions are associated with increased cardiovascular disease risk, even among MESOR-normotensive subjects (22-27). There is also a precedent for a decrease in heart rate variability associated with magnetic storms, as a factor putatively underlying myocardial infarctions (28-30). The patterns of arrhythmia are amenable to longitudinal study by chronomics, a microscopy in time that maps endpoints of timing in data from around as well as in us. With considerations of safeguarding privacy by using appropriate coding rather than personal identification, open access to archival and device data may serve not only for prediction of SCD, but also for the study of underlying mechanisms and thus for rational prevention. Against this background (14, 15), we present the following case report.

Case report. On the morning of 31 Jan 1978, the 38-year-old patient, diagnosed 24 years earlier with WPW, started to get out of bed and then collapsed. He was taken to the hospital by an ambulance and pronounced dead on arrival. Time of death was estimated to be around 07:30-08:30. The patient had been on quinidine and/or propranolol since age 14, and had a history of being able to convert back to a normal sinus rhythm by Valsalva or eyeball pressure. His WPW was complicated in that during his medical residency in Madison about six years earlier, he had broken his back in a freak bicycle accident. At the time of his accident, he was 6'4". Six years later, he had suffered such severe spinal compression that he was only 6' tall. As a result, he had been in considerable physical pain just prior to his death, and his wife attributed the lateness of his getting up to the back pain. At age 15, his granddaughter underwent cardiac catheterization for a conductive disorder.

As seen is Figure 8 (top 2 rows), on the day of death (marked by a black dot), Bz, the north-south vector of the interplanetary magnetic field, turns from positive to negative, a feature associated with a magnetic storm. A peak was also found in the planetary index of geomagnetic disturbance Kp, and a moderate trough in the equatorial index of geomagnetic disturbance Dst, both features in keeping with a magnetic storm. Wolf's relative sunspot numbers had sharply risen and there was a peaklet in the electric field. Solar wind speed peaked one day earlier while proton temperature, proton density and flow pressure were not remarkable. This set of conditions prevailing at the time of death of this patient with WPW syndrome is reported to stimulate the search for common denominators in the death of other patients with WPW. This pathological condition is characterized by abnormal pathways between the upper and lower chambers of the heart (the bundle of Kent, an accessory pathway), leading to abnormal communication between the atria and ventricles. To our knowledge, there are no previous investigations of magnetosensitivity (or sensitivity to other aspects of space weather) of WPW patients. Eliyahu Stoupel had previously investigated cardiac arrhythmia in relation to many helio-geomagnetic and other non-photic factors (1-3), whereas we have focused upon the periodicities in the incidence patterns of both cardiac arrhythmia and SCD. Both approaches are in agreement, documenting that overall in superposed epochs, magnetic storms may protect the patients with arrhythmia, Figure 3. But according to Figure 8, the death of at least one patient with WPW, or this syndrome itself, may be an exception. Only follow-up studies examining the heliogeomagnetic and other non-photic environmental constellation at the time of death of other cases of WPW syndrome can decide this question.

Acknowledgement Dr. David Sonntag, from the Asian Office of Aerospace R&D, Tokyo, provided the data here analyzed and a continuing stimulus to delve further into aligning frequency-windows related and stochastic resonances with non-photic as well as photic environmental factors.
Support: GM-13981 (FH) and University of Minnesota Supercomputing Institute (GC, FH), MSM0021622402

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Legends

Figure 1. The ever-present risk of different correlations on cyclic variables dependent upon the particular time span investigated is illustrated by correlations of the urinary excretion of 17-ketosteroids with solar activity that can display a high statistical significance (as in the second section of the display on the left) or no significant association (as in the rest of the display on the left), notwithstanding a cross-spectral coherence and the proper time relations with a maximum 17-ketosteroid following that in solar activity, both in keeping with a possible association. © Halberg.

Figure 2. About 3.5-day (circasemiseptan) rhythmic feature of sudden human death. Original data by Rabkin et al. (10), who examined records of 3,983 men for sudden cardiac deaths (SCD). 63 deaths occurred in the absence of information on previous ischemic heart disease (IHD) and 89 in the presence of IHD. For the 63 deaths without IHD and for the total of SCD, the original authors established differences by χ^2 test ($P<0.01$). They comment on the excess of SCD on Mondays. Meyers and Dewar (31) comment in turn on the role of a large consumption of alcohol on Saturdays. In Rabkin et al.'s data (10), a second peak on Thursdays is apparent to the naked eye. The frequency multiplication (doubling) of an internal circaseptan rhythm, which is merely synchronized by the burden of returning to work on Mondays and influenced by other factors is a working hypothesis. Note that the best-fitting period is 84 hours (1/2 week) rather than 168 hours (1 week). We are dealing with a frequency-doubled (circasemiseptan) change. This rhythm is apparent from the fact that the 95% confidence ellipse from the fitting of an 84-hour cosine curve does not cover the center (pole) of the cosinor plot. This result is in keeping with much evidence on the ubiquity of circaseptan and circasemiseptan rhythms, their free-running in human beings, their relative temperature compensation in the springtail and their frequency multiplication, e.g., in a fatal case of cardiac arrhythmia, studied after a triple coronary bypass operation. 7-day synchronized circaseptan-rhythmic mortality has also been documented by autocorrelations for homicides, motor- and non-motor-vehicle accidents and suicides. © Halberg.

P: probability of null hypothesis: amplitude = 0;

no obs: number of observations;

percent rhythm: percentage of variability accounted for by cosine curve;

95% CL = 95% confidence limits derived from cosinor ellipse.

†: MESOR ≡ 100%;

††: from midnight Sunday to Monday (≡0˚).

Figure 3. Circadiseptan pattern of sudden cardiac death: social (the bimonthly payday), environmental (the first harmonic of the solar relation rate at its equator) or both may contribute to the pattern (18). © Halberg.

Figure 4. Chronomic analyses of a pool of 5,503 cases of SCD (International Classification of Diseases, 10^{th} revision, code I46.1) from 9 geographic locations between 1998 and 2003 corroborate a decreased incidence of SCD on days of high geomagnetic activity (Kp>5) (P<0.05 from the fit of a parabola to the relative SCD incidence on days -3 to +3 bracketting days when Kp>5 = day 0) (14, 15). © Halberg.

Figure 5. A decreasing second-order polynomial trend characterizes the relative incidence of SCDs as a function of Kp (R^2=0.604; P=0.040) (14, 15). © Halberg.

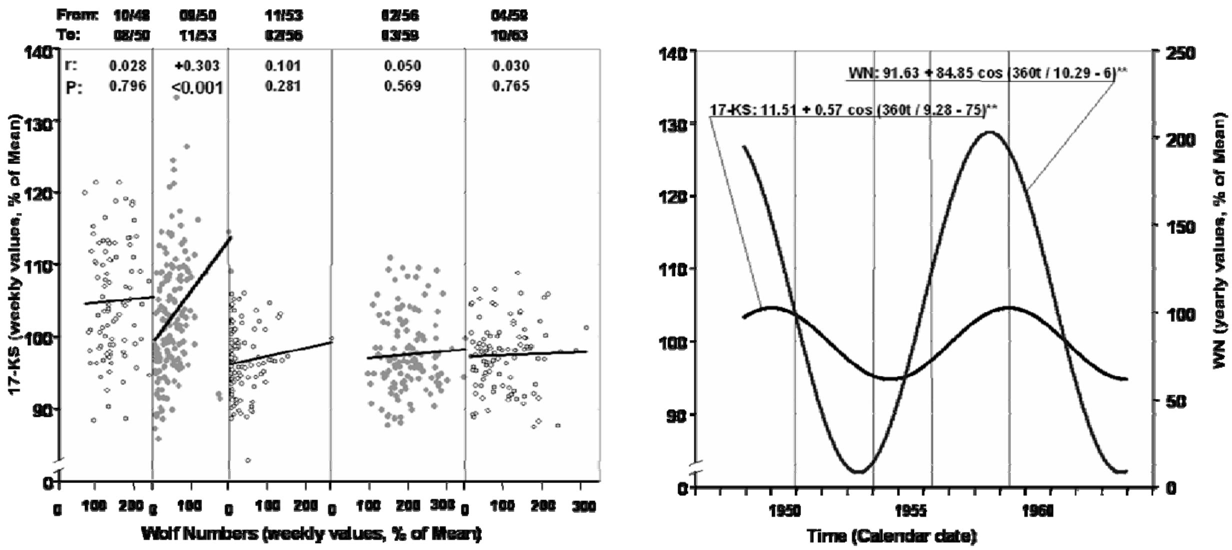
Figure 6. Least-squares spectra of atrial fibrillation (21). © Halberg.

Figure 7. Least-squares spectra of paroxysmal supraventricular tachycardia (21). © Halberg.

Figure 8. Mostly far-transyears (1.2 years ≤ [τ {period} - CI {95% confidence interval}] < [τ + CI] < 1.9 years) in 10 physical and environmental variables and in human physiology (14). © Halberg.

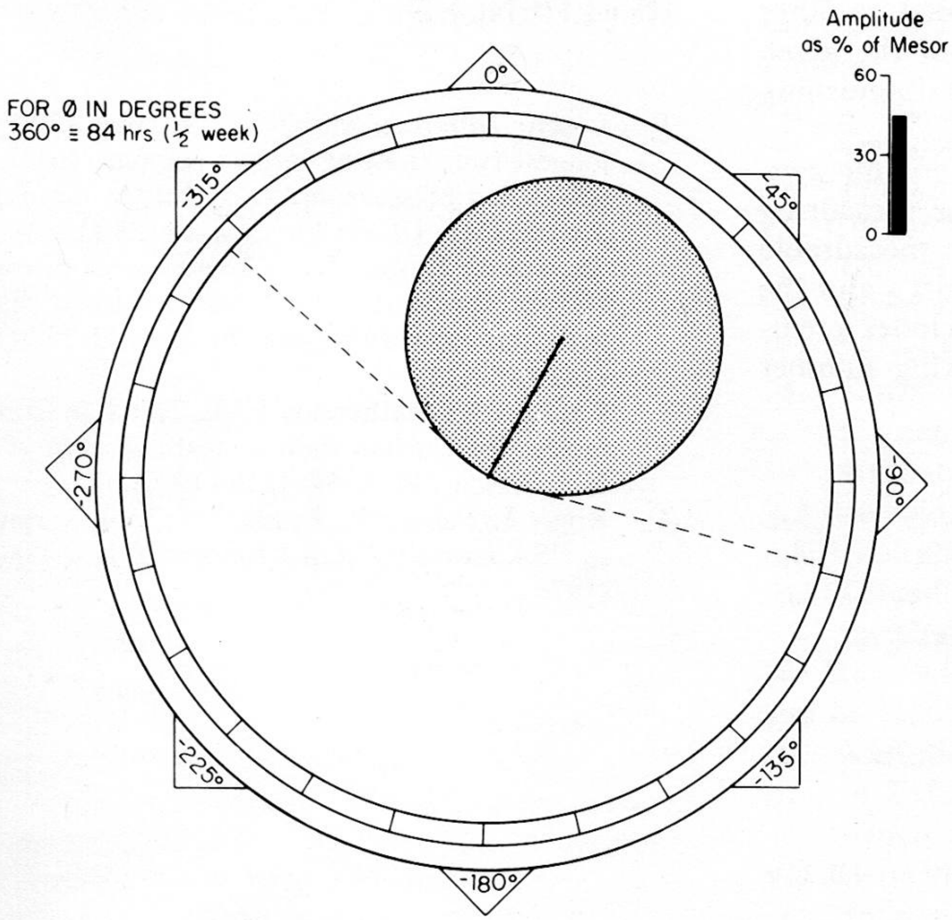
Figure 9. A case of Wolff-Parkinson-White syndrome or the syndrome itself may be an exception to the protective effect of magnetic storms in cardiac arrhythmia (Figure 3). © Halberg.

PRESENCE OF CYCLES IN BIOLOGICAL (e.g. 17-KS)
and/or ENVIRONMENTAL (e.g. WN) VARIABLES
UNDERLIES CHRONOME-UNQUALIFIED NONSENSE CORRELATIONS*



WN = Wolf numbers, gauging solar activity; 17-KS = urinary excretion of steroidal hormonal metabolites (17-ketosteroids); an association and mediation by geomagnetic activity (Kp) is supported by a cross-spectral coherence of 0.588 between
17-KS and Kp at 1 cycle in 4.3 weeks (away from spectral peaks).
* Both as a function of time (age; not shown) and between the two variables (r: correlation coefficient;
P: P-value from test of H_0: r = 0)
** Model validated nonlinearly, reference 21 Dec 1947.

Figure 1



SINGLE COSINOR

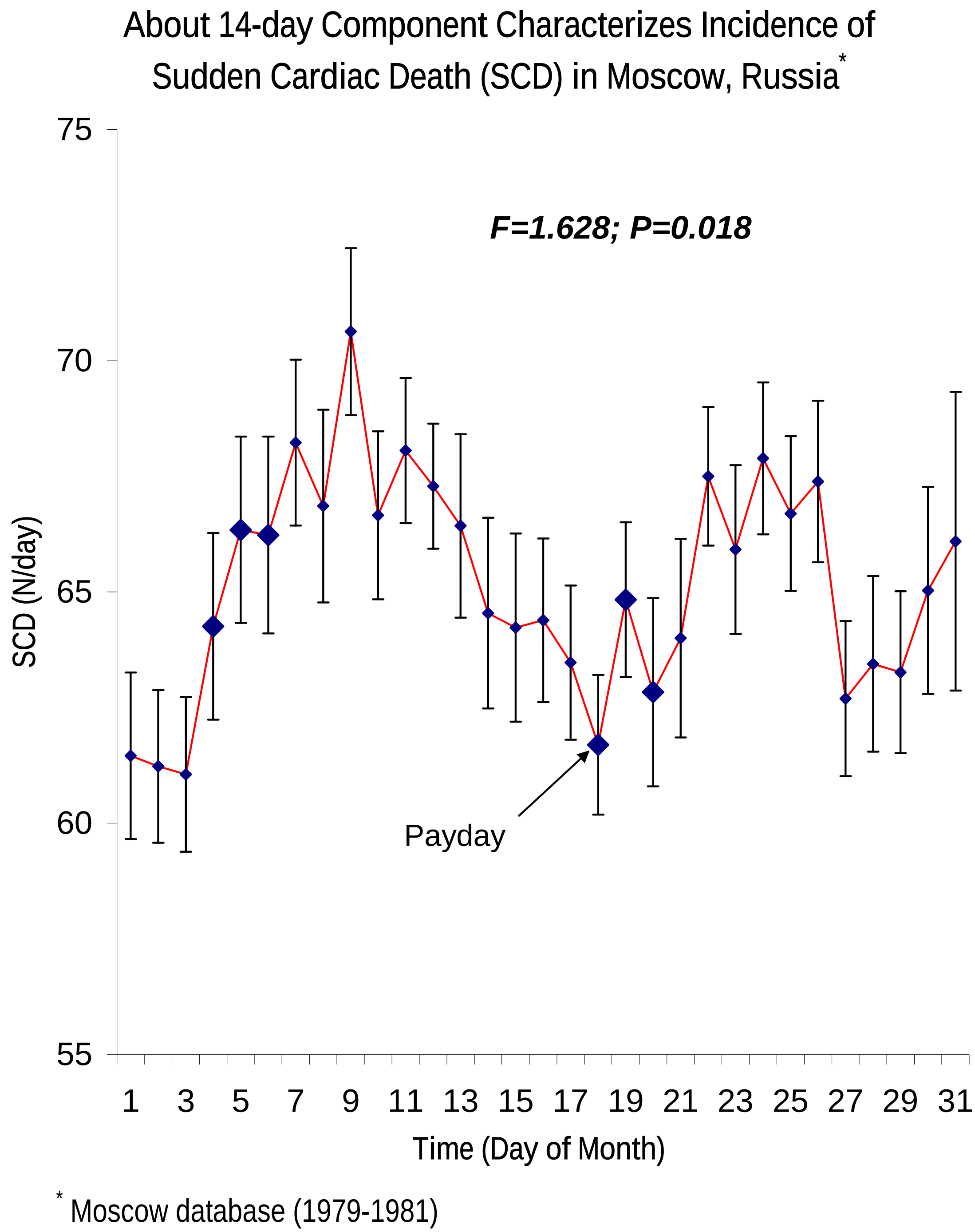
P	No. Obs.	Percent Rhythm	Amplitude, % of mesor† (94 % CL)	Acrophase, degrees††
0.05	14	41	44 (1.18, 87)	-28 (-311, -105)

P = probability of hypothesis: amplitude = 0 ; No. Obs = number of observations; Percent Rhythm = percentage of variability accounted for by cosine curve; 94 % CL = 94 % confidence limits derived from cosinor ellipse.

† *mesor ≡ 100 %.*

†† *from midnight Sunday to Monday (≡ 0°)*

Figure 2



About 14-day Component Characterizes Incidence of
Sudden Cardiac Death (SCD) in Moscow, Russia*
F=1.628; P=0.018
SCD (N/day)
75
70
65
60
55
Payday
1
3
5
7
9
11
13
15
17
19
21
23
25
27
29
31
Time (Day of Month)
* Moscow database (1979-1981)

Figure 3

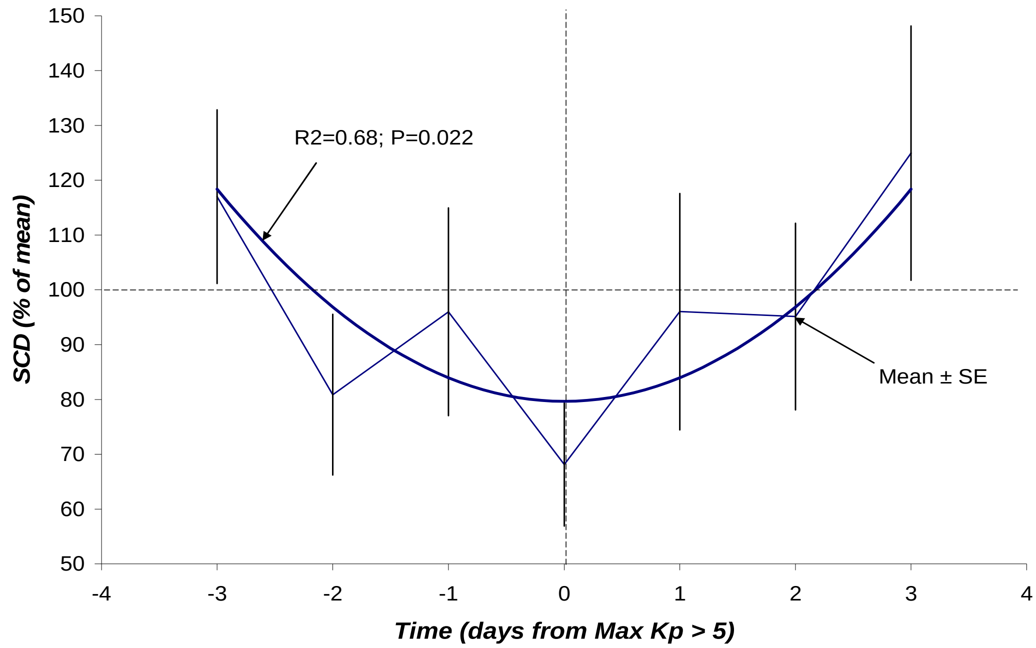


Figure 4

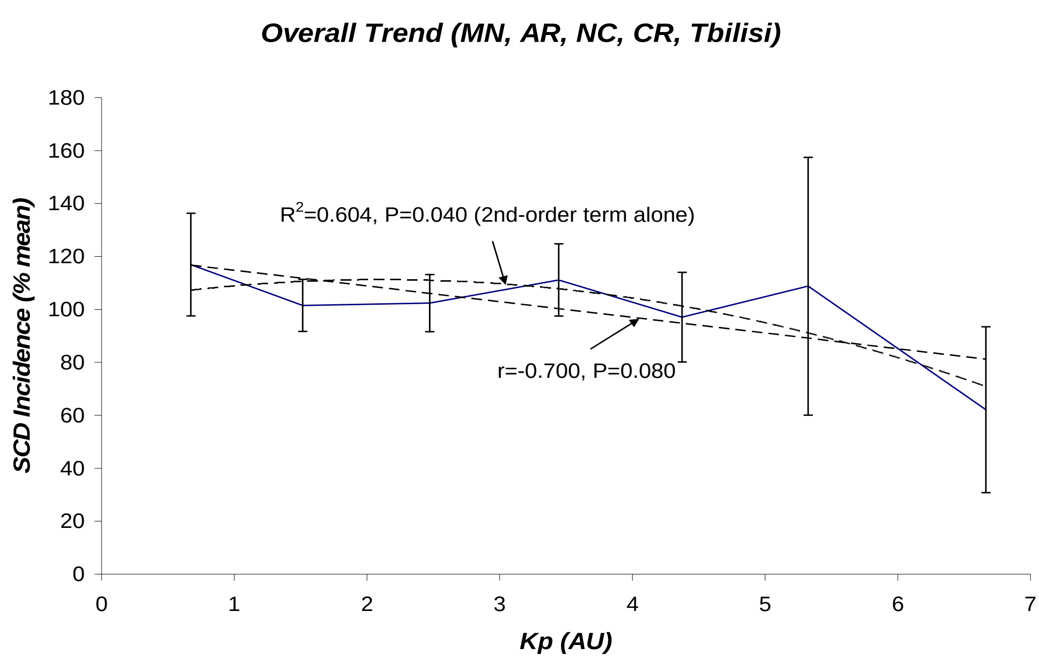


Figure 5

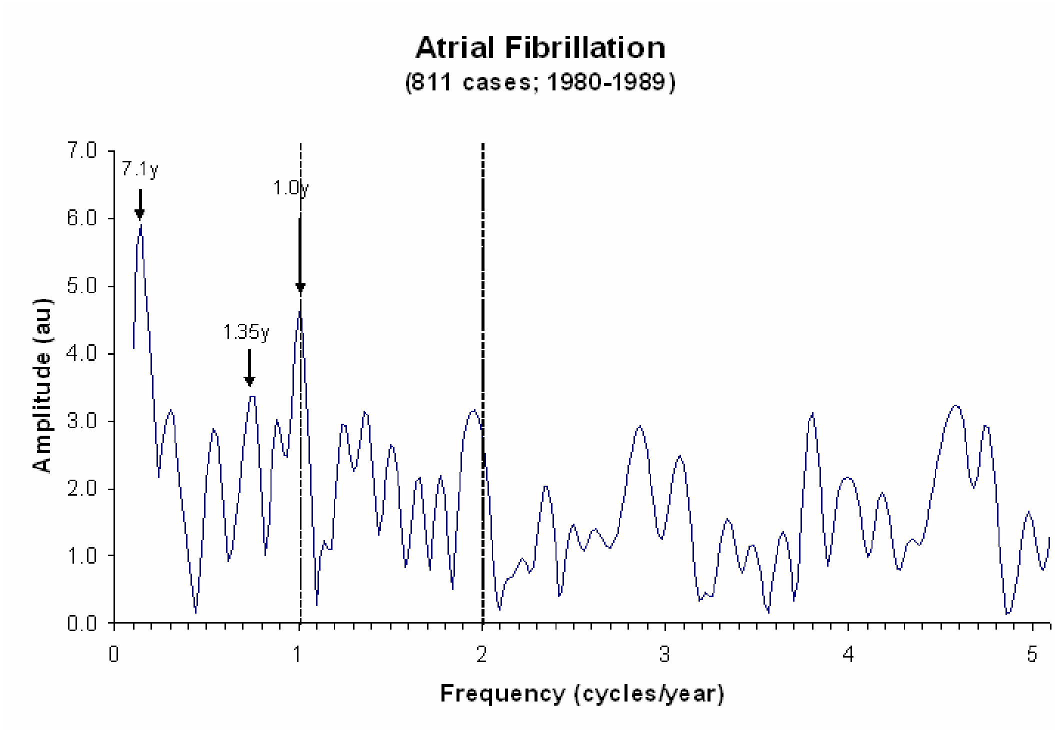


Figure 6

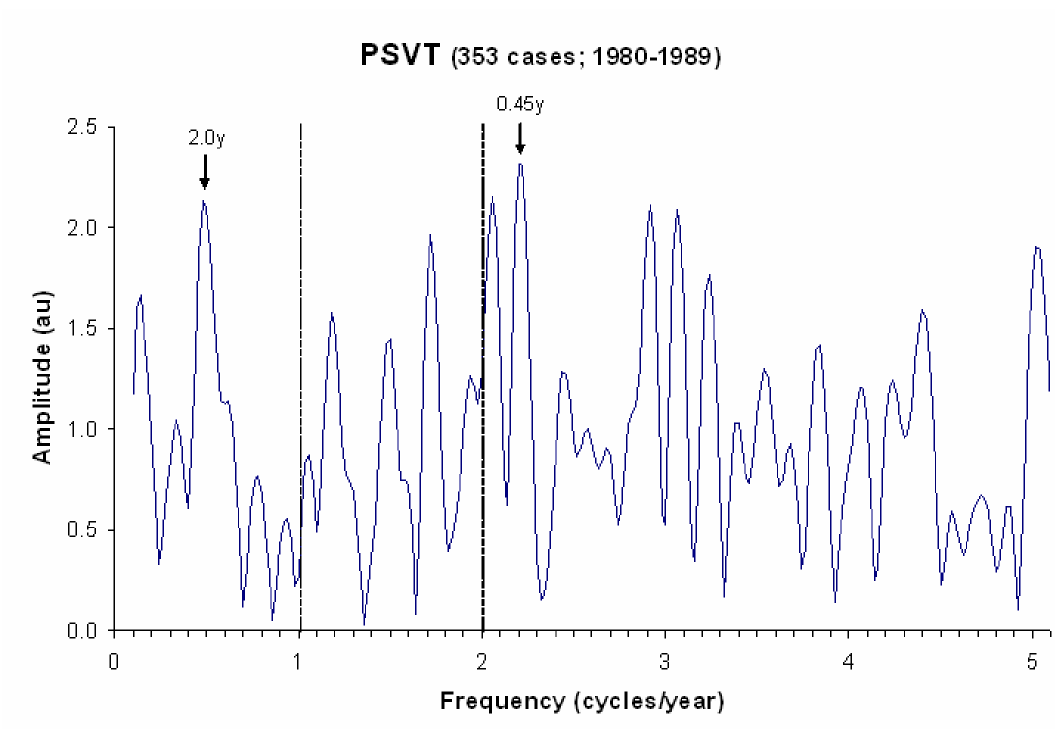
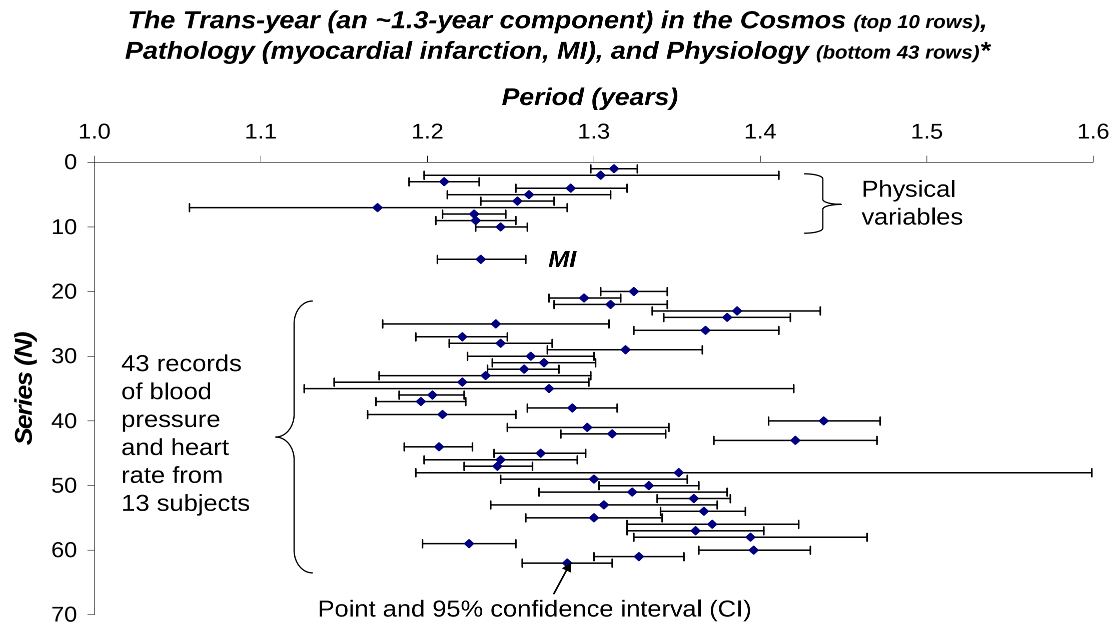


Figure 7



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

Figure 8

Death (dot) of a 38-year old case of Wolff-Parkinson-White Syndrome occurred at an extremum of the equatorial magnetic disturbance index Dst that is negatively related to magnetic storms, shortly after a peak in the planetary geomagnetic disturbance index Kp, and shortly before a peak in Wolf relative sunspot numbers; there were other extreme values of greater magnitude during 1978.

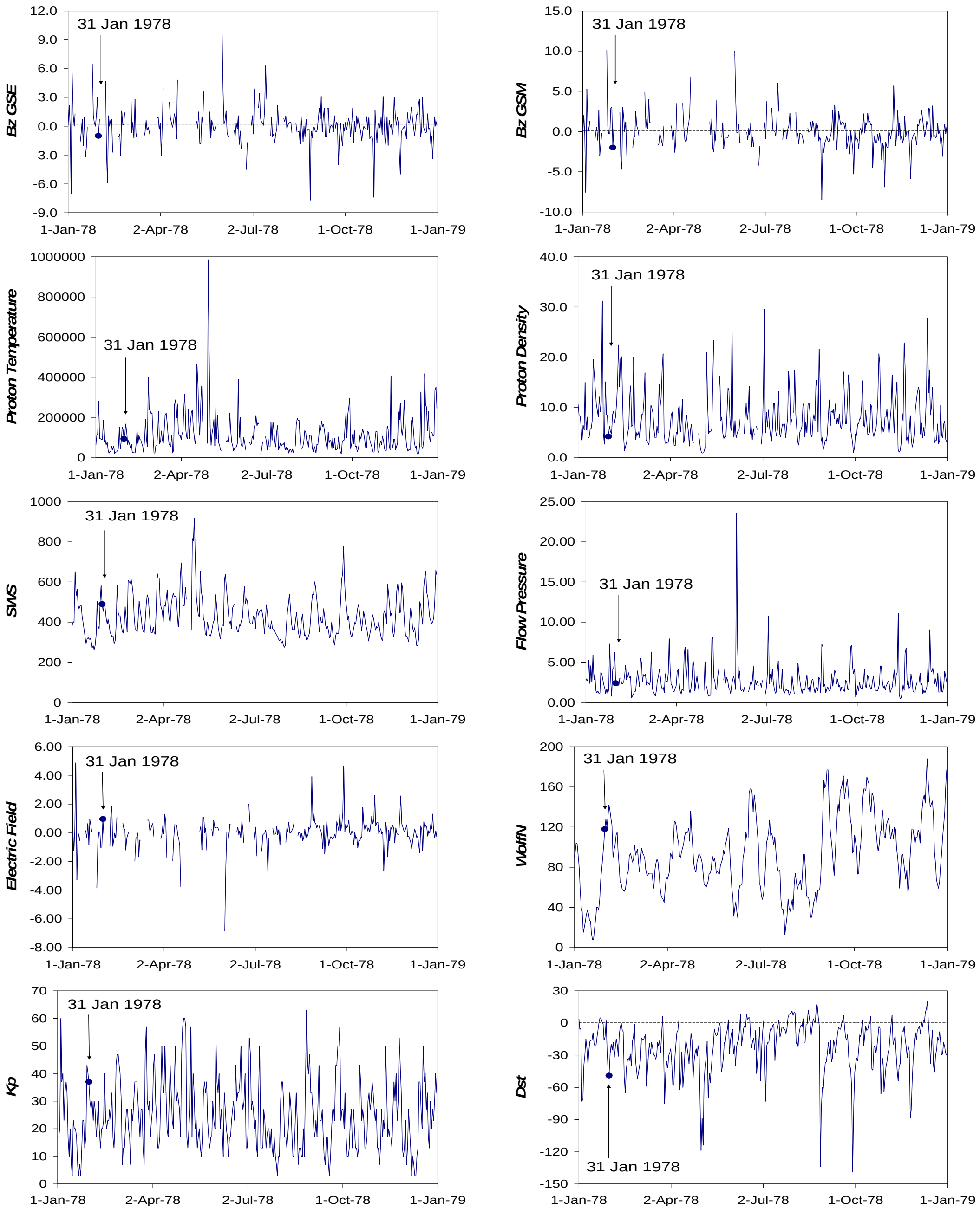


Figure 9

F. CHRONOBIOETHICS

CHRONOMICS OF CHURCH MEMBERSHIPS

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A rational scientific optimization may serve in ethics to the extent to which any mechanisms of reproducible since cyclic features of spirituality and of criminality as well as of other illnesses become measurable and eventually understood (1-5). Should either or both the 'good' or the 'bad' be found to be at least passively influenced by cyclic physical environmental factors, as is putatively the case (1, 2), these aspects of behavior may eventually become actively manipulable, perhaps utilizable for human survival. Toward this goal, chronomics, the study of aligned environmental and biological time series, has already mapped time structures in religious behavior, like proselytism (2). Such maps may lead to underlying geographic/geomagnetic latitude-associated mechanisms (2). The relative brevity of the available time series for earlier maps is a hurdle, and here, with further clearly insufficient data, we continue a plea for much longer and denser worldwide time series.

In the growth rate of membership in the Church of Jesus Christ of Latter-Day Saints (LDS), the linear-nonlinear cosinor (6-9) finds a spectral peak at a period of about 32.2 years, with a CI (95% confidence interval) extending from 26.8 to 37.5 years, Figure 1. The period estimate and most of its CI lie in the 30-40 year range. This finding qualifies it as a transtridecadal peak, or BEL. This peak is so named after Eduard Brückner, who published his extensive groundbreaking findings of an about 33-year cycle in 1890 (10); Charles Egeson (11), who described the cycle a few months earlier in 1889; and William J.S. Lockyer and Sir Norman Lockyer (12, 13), son and father, who described and reviewed, respectively, the history of an about 35-year cyclic variation in the length of the Horrebow-Schwabe cycle (14-16). Figures 2A-C show prior findings on cosmic signatures in church membership and Figures 3A-B summarize an about-didecadal component in religious proselytism (2). The data underlying Figures 2A-C are too short to assess any transtridecadals, but with this qualification, they yield signatures of sunspot cycles, albeit differing for different church memberships. Figure 2A hints at a circadecadal Horrebow-Schwabe cycle, whereas Figures 2B and

2C show about 19.0-year or 19.3-year cycles, respectively, with CIs overlapping both the global Makarov-Sivaraman (17) and the Hale bipolarity cycles.

In turning to Figures 3A-B, the zero-21.0-year-amplitude assumption is rejected (P<0.05) in 86 of 104 data series, the distribution of acrophases spanning less than 180° (half a cycle), a statistically significant finding in its own right. By population-mean cosinor, 35% of the total variability is accounted for by the about 21.0-year Hale cycle (P<0.001). Nonlinearly, the period is estimated at 20.39 years, its CI extending from 18.60 to 22.25 years (2). It is in keeping with a Hale cycle, as results in Figures 2B-C, prompting the consideration that the sunspot bipolarity cycle is mirrored in church memberships, the CI of periods overlapping 20-24 years for data analyzed in Figures 1, 2B-C and 3A-B.

Whether the LDS membership has both a Hale and a BEL signature will have to be scrutinized further, but the findings are compatible with at least the possibility that these periods alternate. A chronobiologic serial section carried out at a trial period of 32.2 years validates this period only for the last few (overlapping) 64-year intervals, Figure 4. The time course of MESORs (lower curve in row 2 of Figure 4) reveals a single cycle of about 100 years, in keeping with the spectral peak in Figure 1 (bottom). To the naked eye, the transtridecadal amplitude (distance between the two curves in row 2 of Figure 4) undergoes changes recurring also every about 32.2 years (CI: 29.6 – 34.8 years, with the qualification that amplitude estimates from the serial section were not independent).

Until geographic regions are separately documented for other church memberships, any latitude-dependence of parameters can be examined only for the proselytism data, Figure 5 (2). Several characteristics of the about 21.0-year Hale cycle are statistically significant related to geomagnetic latitude. It seems pertinent that when the adjusted growth rate of the LDS church is examined during the span from 1950 to 2008, 27.9-year and 17.0-year components (17) dominate (Figure 6), with the CI of the former period overlapping the 30-40 year range of the transtridecadal BEL cycle (18-21). The BEL has been validated in Brückner's original data (18, 21) and has been shown to characterize heliogeophysics (19), notably solar flares, also solar wind speed (19) and further psychophysiology (20-22), military politics and economics (23). It is extended by Figures 1, 4 and 6, to church membership dynamics, at least one aspect of religiosity.

Albert Einstein, among many others, explicitly regarded religion as a topic inappropriate for science, if not inapproachable or unassailable (24). Other physicists and academic engineers have addressed spirituality as intentionality (25; cf. 26). It is the more noteworthy that, in addressing scientists in 1983 (27), Pope John Paul II "spoke therapeutically toward the historical rift between the (Catholic) Church and science", providing more than an "apology to the memory of Galileo". Albert Di Canzio interprets this address as a bright ray of hope (which could become) a hint of “better things to come". First, the bright ray: "Let us think of how the results of scientific research help us to know the universe better, to understand better the mystery of man; think of the advantages which the new means of communications and contact among people offer to society and to the church; let us think of the ability to produce incalculable economic and cultural wealth, and especially to promote the education of the masses, and to cure diseases previously thought incurable. What admirable achievements. And the hint: yes, the church appeals to your capacities for research in order that no limit may be placed upon our common quest for knowledge" (27). Many pertinent data could be studied in this context, starting in earliest church records providing time series, which are still accumulating today and should become amenable to analysis.

Acknowledgement

Dr. David Sonntag, from the Asian Office of Aerospace R&D, Tokyo, provided the data here analyzed and a continuing stimulus to delve further into aligning frequency-windows related and stochastic resonances with nonphotic as well as photic environmental factors.

Support: GM-13981 (FH) and University of Minnesota Supercomputing Institute (GC, FH).
Supported by MSM0021622402

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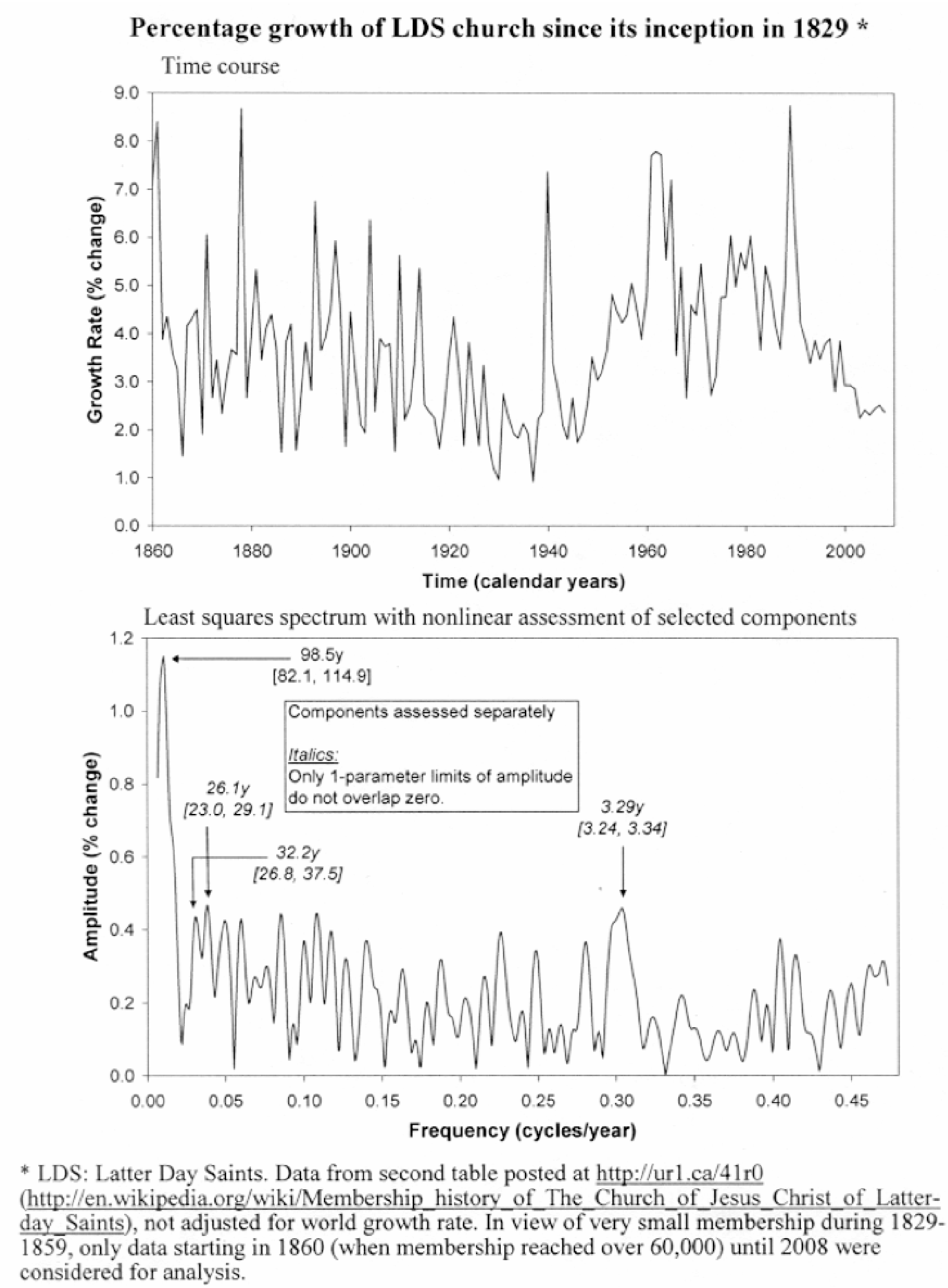


Figure 1. The growth rate of the Church of Jesus Christ of Latter-day Saints (LDS), shown on top, is resolved by linear-nonlinear cosinors into 3 spectral peaks, each putatively approximating a known solar cycle. The CI (95% confidence interval) of the first peak between 80 and 115 years could correspond to a Gleissberg cycle followed by a transtridecadal 32.2-year BEL (Brückner-Egeson-Lockyer) cycle. The peak with a 95% confidence interval reaching 23 years could correspond to a Hale cycle. © *Halberg*.

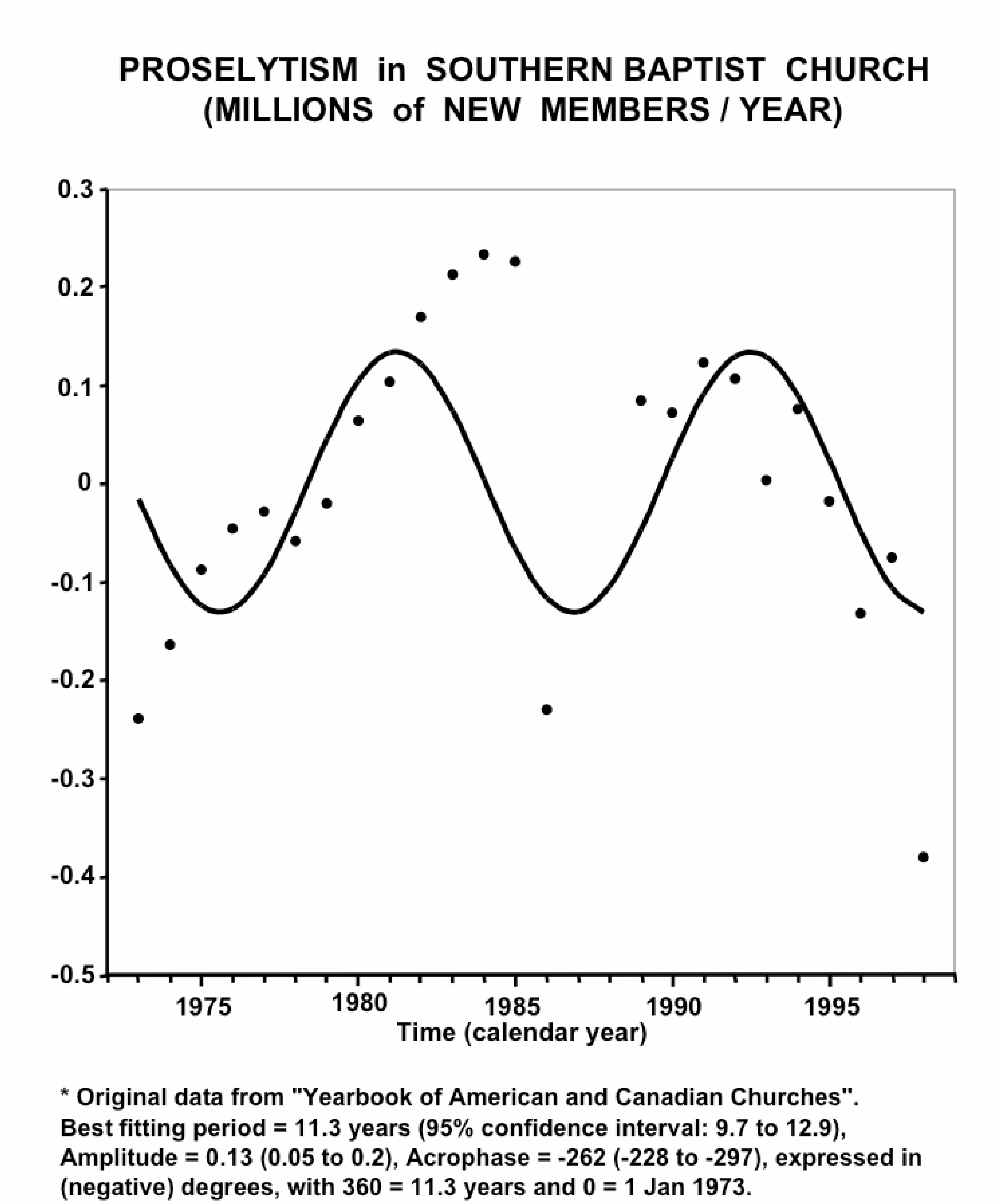


Figure 2A. Southern Baptist church membership hints at a circadecadal (circadecennian) cycle of about 11 years, based on limited data. The 95% confidence interval extends from 9.7 to 12.9 years. © *Halberg*.

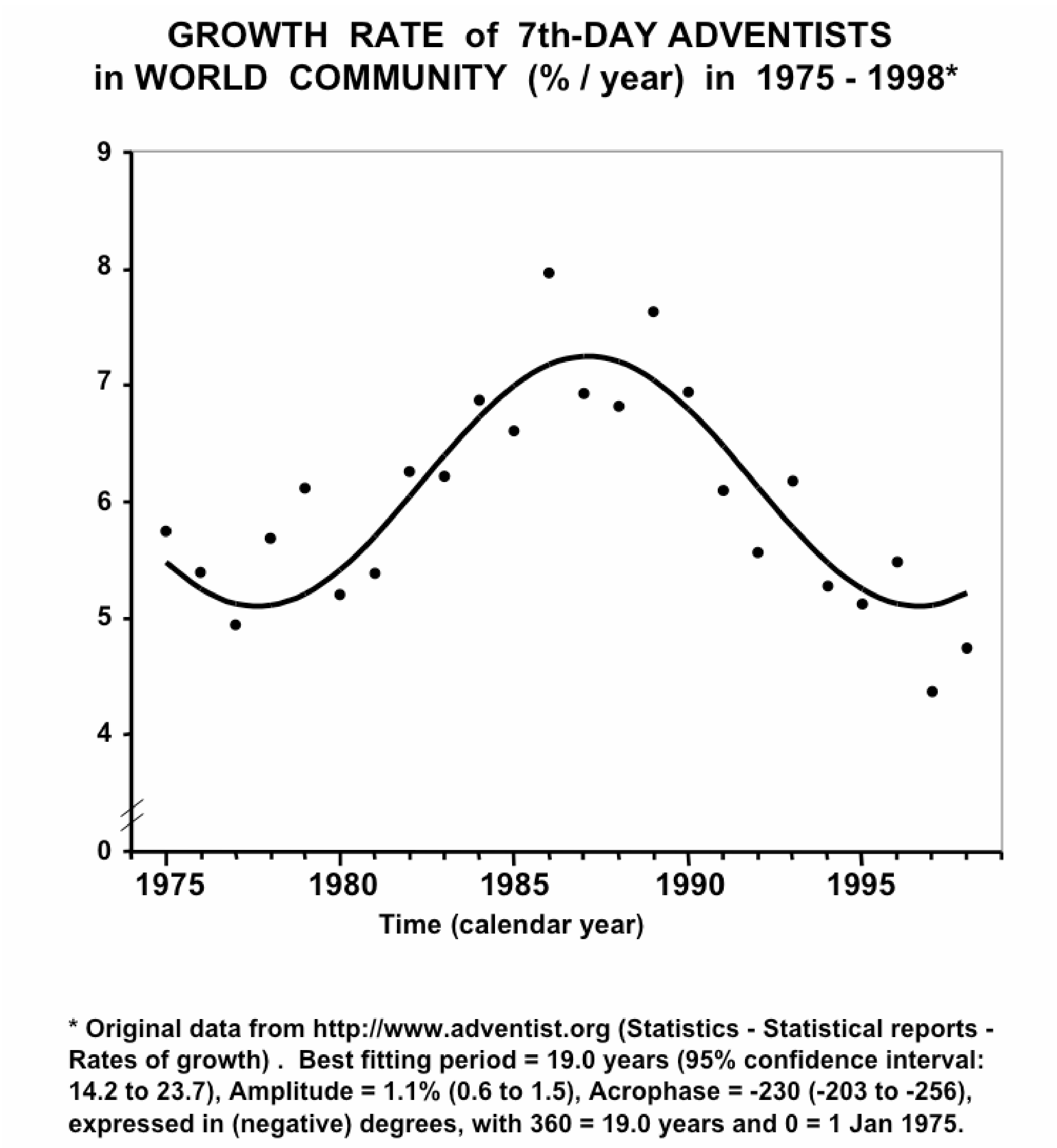


Figure 2B. Seventh-day Adventist church membership record hints at a much longer circadidecadal cycle of about 19 years. The 95% confidence interval of the period from 14.2 to 23.7 years does not overlap the corresponding estimate in Figure 2-A. © *Halberg*.

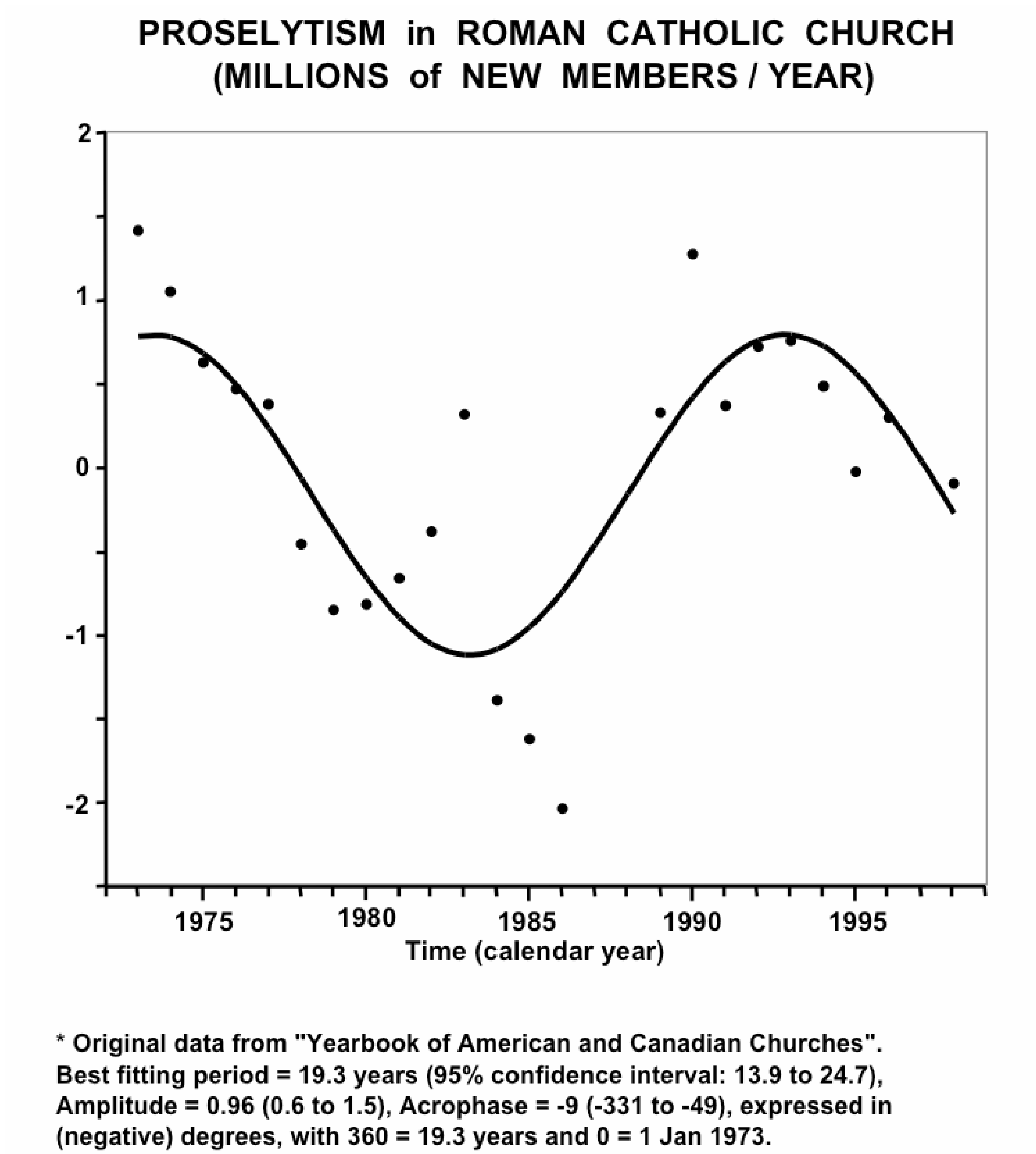


Figure 2C. Roman Catholic church membership shows a cyclic pattern of about 19 years, in keeping with the uncertainty of the circadidecadal peak in Figure 2-B. © *Halberg*.

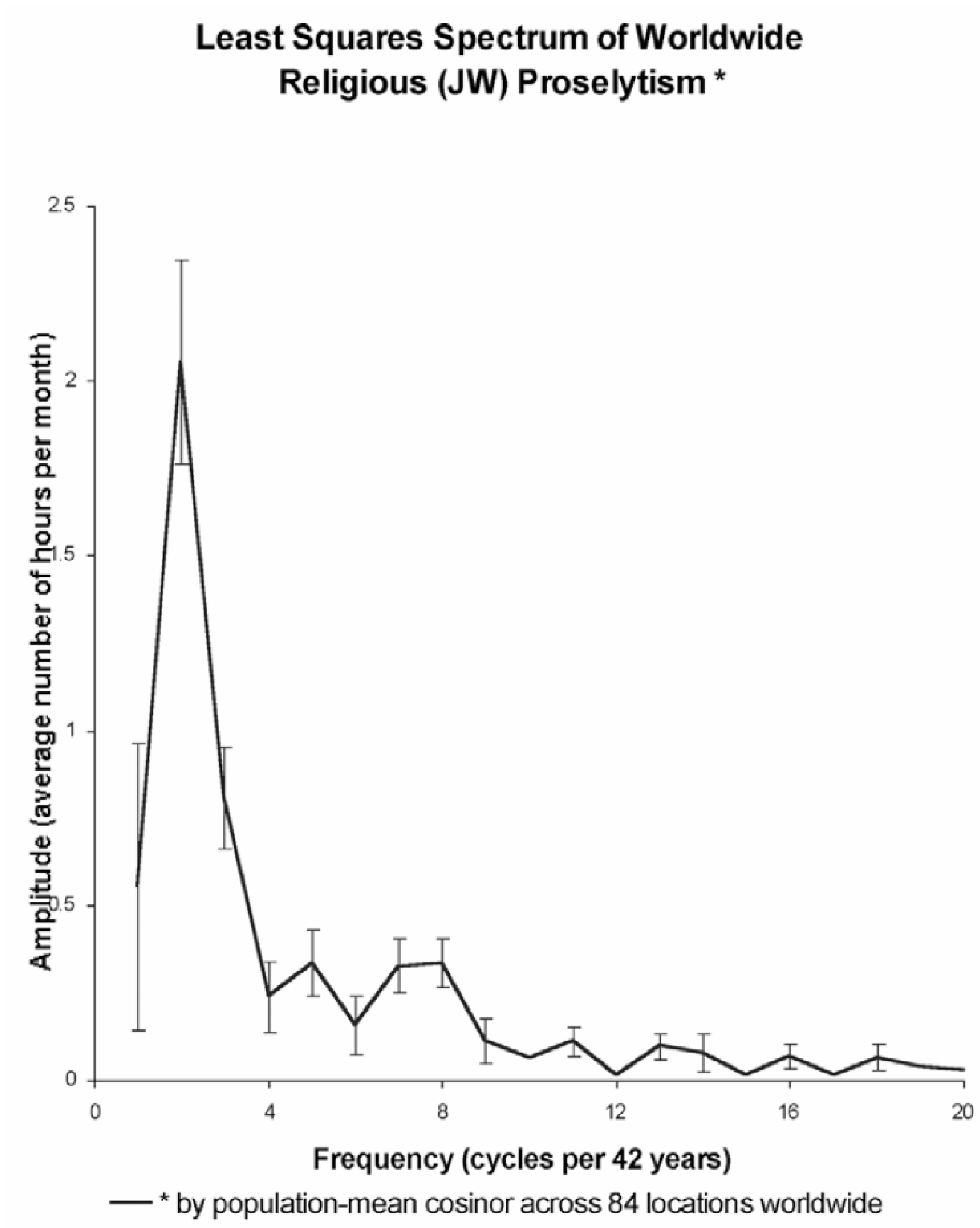


Figure 3A. Least squares spectrum by population-mean cosinor of the average number of hours per month spent working for their church by Jehovah's Witnesses (JW). Results stem from 84 of 103 available sites, including all time series spanning at least 35 years, i.e. over 85% of the fundamental period of 42 years, allowing rejection of the zero 21-year amplitude assumption. Amplitudes are phase-weighted, determined as the vectorial average of the (amplitude, acrophase) pairs across all 84 locations at each trial period. For ordering purposes only, without correction for multiple testing, components found to be statistically significant by the rejection of the zero-amplitude assumption are shown with their respective 95% confidence interval. © *Halberg*.

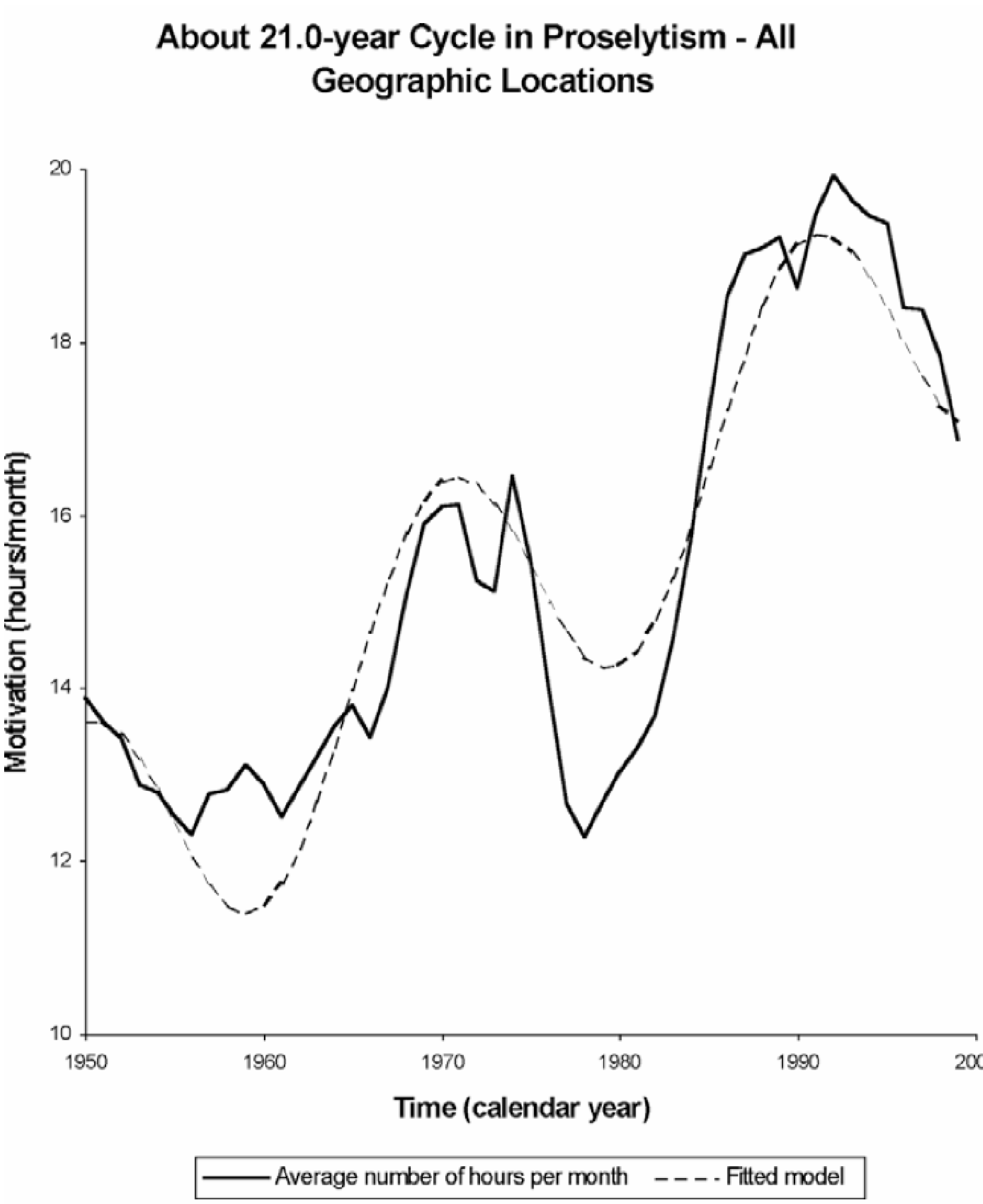
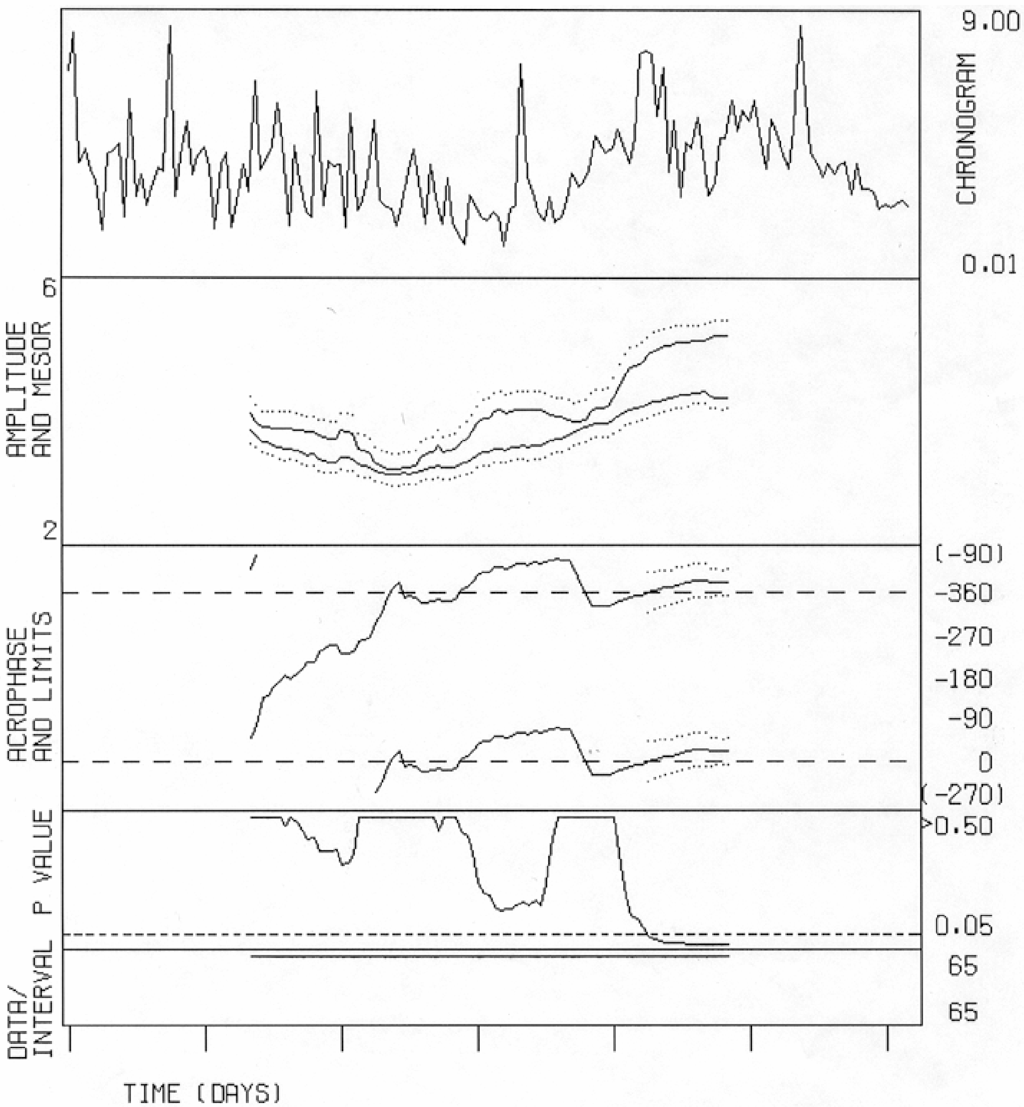


Figure 3B. Illustration of the about 20.39-year (95% confidence interval: 18.60-22.25) component in the average number of hours spent working for their church per month by Jehovah's Witnesses (JW) for the grand total, including other locations in addition to the 103 sites analyzed separately. Model fitted by non-linear least squares consists of linear trend and cosine curve with trial period of 21.0 years. Whereas a linear trend applies to the grand total, such a trend is statistically significant in only about 50% of the individual data series, and can be negative as well as positive. © *Halberg.*

PERCENTAGE GROWTH OF LDS CHURCH DURING 149 YEARS (1860-2008)*



*Chronobiologic serial section with fit of a 32.2-year period to intervals of 64.4 years displaced in increments of 1 year.

Figure 4. Original data (top) are fitted with a 32.2-year cosine curve in a 64.4-year interval (2 cycles) displaced in 1-year increments. The lower curve in the second row represents the MESOR (M, Midline-Estimating Statistic Of Rhythm). Changes in MESOR as a function of time hint at the presence of an about 100-year Gleissberg cycle (in keeping with the spectral peak at 98.5 years in Figure 1). The distance between the two curves represents the circatridecadal amplitude (A), which suggests the occurrence of about 3 cycles. Dots below the lower curve and above the upper curve represent the standard errors of M and A, respectively. Dots bracketting acrophases in the last 15 intervals (third row) are CIs indicating the statistical significance of the 32.2-year component during that time span, also shown by P-values (fourth row). © *Halberg*.

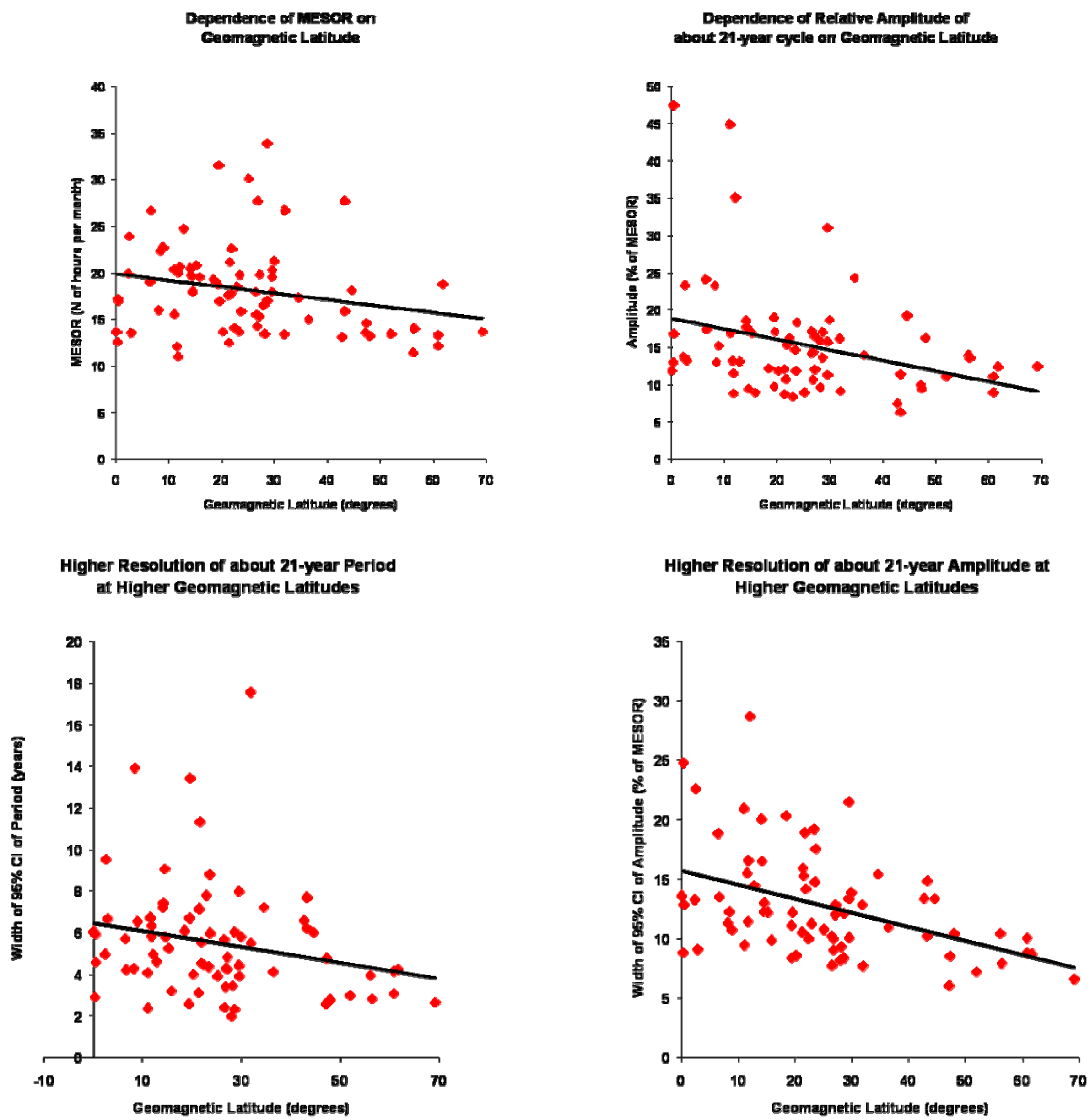
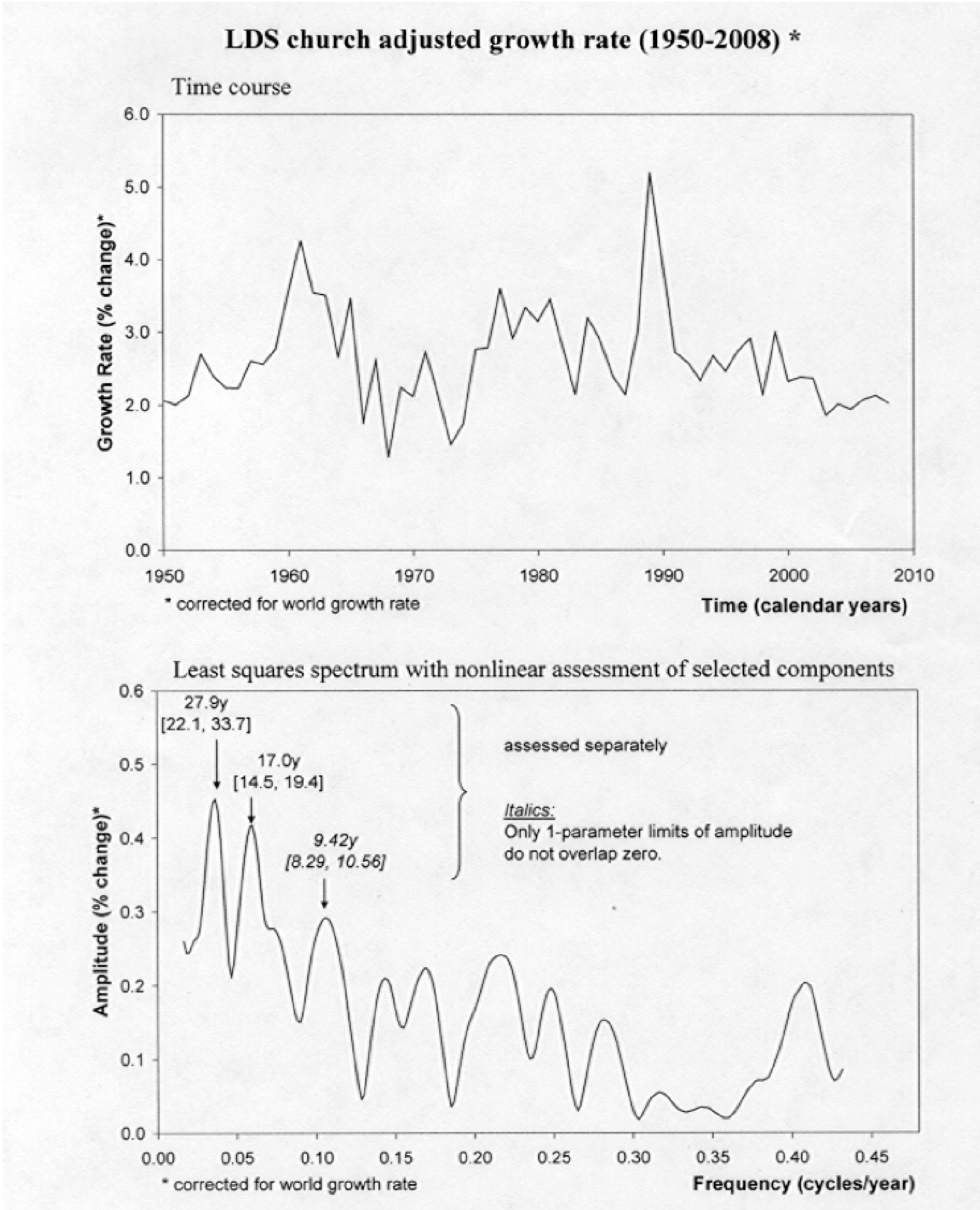


Figure 5. Dependence on the geomagnetic latitude of the MESOR (top left) (r = -0.236; P = 0.044) and relative amplitude (r = -0.318; P = 0.006) of the about 21.0-year component (top right) of the average number of hours spent working for their church per month by Jehovah's Witnesses, resolved by nonlinear least squares for each site separately. More time is spent at lower than at higher latitudes (top left). The about 21.0-year cycle is also more prominent at lower than at higher latitudes (top right). The dependence on the geomagnetic latitude of the width of the CIs of the period (r = -0.028; P = 0.052) (bottom left) is aligned with that of the relative amplitude of the about 21.0-year component (bottom right) (r = -0.436; P < 0.001). The CI's width tends to be smaller at higher than at lower latitudes, suggesting a higher resolution of this component at higher latitudes. © *Halberg.*



* LDS: Latter Day Saints. Data from first table posted at http://ur1.ca/41r0 (http://en.wikipedia.org/wiki/Membership_history_of_The_Church_of_Jesus_Christ_of_Latter-day_Saints) obtained by dividing the LDS growth rate by the world growth rate.

Figure 6. By contrast to Figure 1, which shows the growth rate of the Church of Jesus Christ of Latter-day Saints (LDS) starting 121 years earlier and not corrected for world growth rate, the data analyzed herein during the span from 1950 to 2008 are corrected for world growth rate (top). Their least squares spectrum (bottom) validates a BEL insofar as the CI of the 27.9-year period estimate overlaps the range of 30-40 years, including an about 33-year period estimate. © *Halberg*.

G. ADDENDUM

CIRCADIAN AMPLITUDE OF HUMAN HEART RATE ALONG A GERIATRIC DEPRESSION SCALE

G. Cornélissen[1], K. Otsuka[2], F. Halberg[1], G. Yamanaka[2], N. Hotta[2], S. Murakami[3], Y. Kubo[2], O. Matsuoka[2], E. Takasugi[2], T. Yamanaka[2], M. Shinagawa[2], S. Nunoda[2], Y. Nishimura[2], K. Shibata[2], H. Saitoh[2], M. Nishinaga[4], M. Ishine[5], T. Wada[5], K. Okumiya[6], K. Matsubayashi[7], S. Yano[8], S. Ishizuka[9], K. Ichihara[10], J. Siegelova[11]

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Abstract

For reducing the likelihood (if not for avoiding as far as possible) of nonsense correlations between variables undergoing deterministic variations such as a circadian and/or other cycle(s), associations are best based on rhythm characteristics (such as the MESOR or circadian amplitude) rather than on actual measurements. This approach is followed herein to explore any relationship between blood pressure (BP) and heart rate (HR) on the one hand and emotional depression on the other hand. A weak negative correlation is thereby found between the circadian amplitude of HR and a geriatric depression score.

Background

A depressive mood was found to be independently related to stroke and cardiovascular events in a chronoecological health watch started in April 2001 in the town of Urausu, Hokkaido, Japan (latitude: 43.45° N, longitude: 141.85° E) (1), involving 224 subjects (88 men and 136 women; mean age: 56.8 ± 11.2 years). Each participant underwent a 7-day/24-hour BP and HR monitoring session, starting on a Thursday. Readings were taken at 30-minute intervals between 07:00 and 22:00 and at 60-minute intervals between 22:00 and 07:00. Data stored in the memory of the monitor (TM-2430 from A&D, Tokyo, Japan) were retrieved and analyzed by sphygmochron (2). Subjects were asked to answer a self-administered questionnaire inquiring about 15 items of a geriatric depression scale (GDS) (3), at the start of study and again after 1-2 years. Subjects with an initial depression score of 5 or more and with a score higher by at least two points at the second versus first screening were classified as having an enhanced depressive mood. The other subjects served as the control group.

The mean follow-up time was 1,064 days at the November 30, 2004 follow-up. During this time, four subjects suffered an adverse vascular outcome (myocardial infarction: 1 man and 1 woman; stroke: 2 men). Among the variables used in the Cox proportional hazard models, a depressive mood, assessed by the GDS, as well as the MESOR of diastolic (D) BP and the circadian amplitude of systolic (S) BP showed a statistically significant association with the occurrence of adverse vascular outcomes (1). In univariate analyses, the relative risk (RR) of developing outcomes was predicted by a 3-point increase in the GDS scale (RR = 3.088, 95% CI: 1.375-6.935, P = 0.006). Increases of 5 mmHg in DBP-MESOR and of 3 mmHg in SBP-Amplitude were associated with RRs of 2.143 (95% CI: 1.232- 3.727, P= 0.007) and 0.700 (95% CI: 0.495-0.989, P = 0.043), respectively (1). In multivariate analyses, when both the second GDS score and the DBP-MESOR were used as continuous variables in the same model, GDS remained statistically significantly associated with the occurrence of cardiovascular death (1). After adjustment for DBP-MESOR, a 3-point increase in GDS score was associated with a RR of 2.172 (95% CI: 1.123-4.200). Monday endpoints of the 7-day profile showed a statistically significant association with adverse vascular outcomes: a 5 mmHg increase in DBP on Monday was associated with a RR of 1.576 (95% CI: 1.011-2.457, P = 0.045) (1).

Methods

Each 7-day/24-hour profile of BP and HR was analyzed by the extended cosinor method (4-6). The circadian rhythm characteristics were assessed by means of the least squares fit of a 24-hour cosine curve to the data. The MESORs and 24-hour amplitudes of SBP, DBP and HR were correlated with the initial GDS score (GDS1).

Results

Depression scores were available from 182 subjects. The 24-hour amplitude of HR was found to be negatively correlated with GDS1 (r = -0.215, P = 0.005), Figure 1. The correlation, although statistically significant, is rather weak. It is submitted for the record and for eventual further study elsewhere.

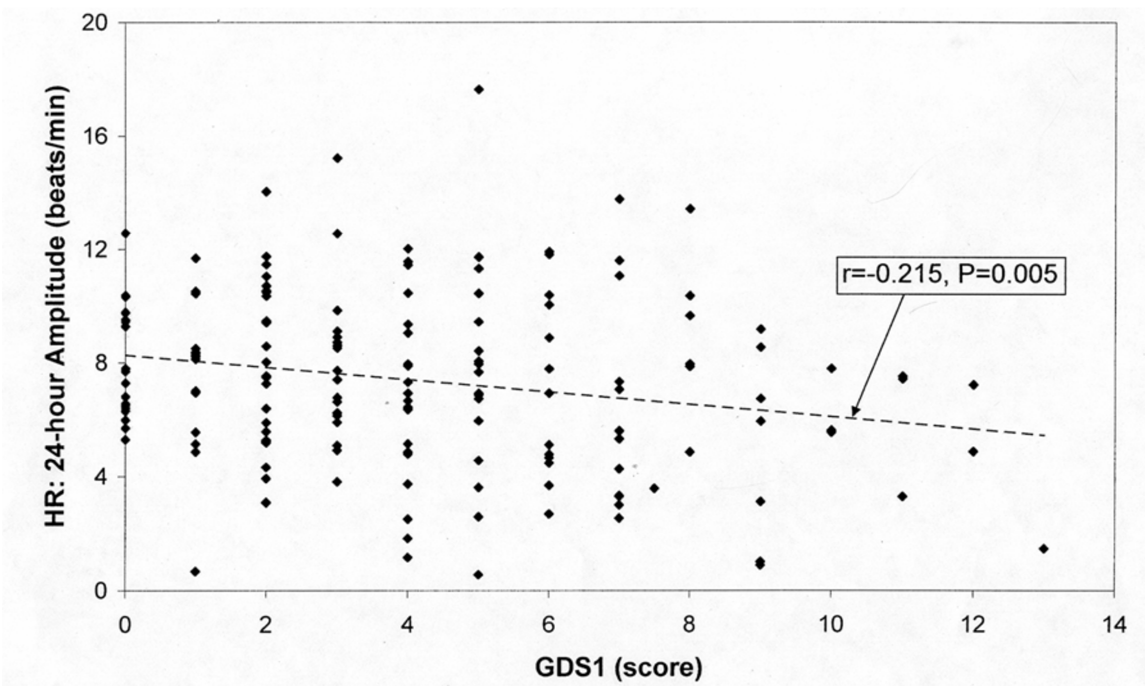

Figure 1

Discussion and Conclusion

Vascular monitoring for stroke prevention in a community allows the search for any associations with increased disease risk. An association of hypotension with positive and negative affect and depressive symptoms reported in the elderly by Jorm (7) could not be found in this population. Instead, we found a relation between the extent of daily variation in HR and a geriatric depression score in a community of mostly healthy residents. It is emphasized that the participants surveyed herein had no known clinical problems. Depressive subjects in this population were also reported to show a more prominent circaseptan variation in SBP and DBP as compared to the controls (8). Affordable unobtrusive ambulatory monitors for continued surveillance by everybody is needed to investigate such problems on a much larger scale.

Support: GM-13981 (FH), University of Minnesota Supercomputing Institute (GC, FH), MSM0021622402

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AN ESSAY ON SOME ASPECTS OF CHRONOBIOLOGY

presented by an every-day-physiologist in honour of Franz Halberg

Thomas Kenner (Graz, Austria)

Abstract

This essay is an attempt to summarize some thoughts in a short overview about the meaning of time and of system-time and to point out certain time dependent functions and additional conditions, all of which belong to chronobiology and thus, play an important role in physiology or pathology.

The headlines of the following text correspond to the key-words:

Time and System Time
Cycles, Aging, Oscillations and Variability
Variability Diseases
Synchronization
Evolution
Optimization
Similarity and Scaling
Symmetry and Asymmetry
Chronification and Chaos
Sudden and Unexpected Phenomena

Time and system-time

Life and time are essentially interdependent and can only been seen as an interacting complex. The recent consensus paper which was initiated by Franz Halberg (1), signed in Brno and published in Moscow is one signal of how important chronobiology is today within the whole context of health and disease. It should be recognized, that even the latin word for time – *tempus* – can be attributed to ancient medical practice as will be described in the following.

In an article with the title “Rhythmen und Resonanzen” in a book on Viktor von Weizsäcker , Friedrich Cramer (2) writes the following summary on the meaning of time, starting with the interpretation of Newtonian understanding of time.

“The absolute true mathematical time flows smoothly as such and according to its nature, without any relation to external entities. This understanding of time of Newtonian physics is ab-solute, that means it is detached from external objects. This understanding was not given before. The latin word *tempus* is derived from the temple region of the head – with the same latin name - temporal region. In the hippokratic medicine the arterial pulse was palpated on the temporal artery. Time as *tempus* originally was our system time (“Eigenzeit”), the rhythm of our heart beat, not detached from our personality. The new absolute meaning of time permitted to establish mathematical rules to describe movements and the paths of satellites. The Newtonian discoveries have enabled the technical epoch – even in medicine. However, this new point of view produced the effect, that everything living was excluded from scientific research. Apparently, this is what Viktor von Weizsäcker meant when he wrote: *Until now, a moment in a biological process cannot be localized in the objective time, in the sense that a biological period cannot be measured by an objective clock……This means that biological events and rhythms have to serve as a gauge for biological periods, whereas in physics time itself is the gauge for movement, velocity and accelerations*.”

The distinction between physical and biological time, which appears as the essential statement in this text by Friedrich Cramer, can further be underlined by the following three observations:

At least in the time of Renaissance, musical notation was used to describe the “medical quality” of arterial pulses. Examples can be found in a respective book on music and medicine (3). In the time of Renaissance there existed no metronomes. Therefore, the musician or the conductor of an ensemble had to use the time sequence of his own pulse to achieve an indicator of proper speed for a music performance.

Recently several articles on medical aspects related to chronobiology have been published, the title of whom refer to music. A book by Friedrich Cramer has the title “Symphonie des Lebendigen” (4). The list of similar titles also includes one article, recently published by Moser, Fruhwirth, Kenner with the title “symphony of life” (5).

The term “system-time”, which I used in the above translation of the German word “Eigenzeit” is more and more used. In 2002 a report on a Symposium with the title “Selbstorganisierte Systemzeiten” (self organized system times) was published (6).

Cycles, Aging, Oscillations and Variability

Periodic or random oscillations and variability are characteristic features of most if not all biologic variables.

On the one hand time dependent variations of biological variables may be generated or controlled by certain centers, like the autonomous circadian rhythm or the periodic heart beat. On the other hand, there may exist periodic or non-periodic external influences acting on our body. In all these phenomena synchronization of several oscillations may appear.

There is a list of characteristic time dependent functions of life with respect to chronobiology. Most prominent are cycles and aging and, more general, oscillations and variability. The description of the cyclic property of life and time can only be mentioned in some examples. The important role of cycles may be particularly found in ancient Egypt and also in Christian religion. The process of birth, growing and aging can be found in circular pictures in churches, which describe life from birth to death and can be described as life-time clocks. One such picture from the 16th century can be found in the orthodox church in Arbanassi (Bulgaria).

Recognizing the approaching end of his life, the Austrian Habsburg Emperor Karl 5th (1500 – 1558) had retired to the monastery San Yuste in Spain. He is reported to have tried to synchronize the many clocks, which apparently existed in different locations in this building. Apparently this procedure did not succeed, a fact, which he commented with the words: “clocks are as unreliable as humans”. About hundred years later Christian Huyghens (1629 – 1695) discovered the phenomenon of synchronisation when he observed in two pendulum clocks, which were hanging on one stick of wood.

Variability Diseases

It must be distinguished between controlled oscillations and oscillations which are due to some kind of instability. It can be assumed that any biological variable may, under certain conditions achieve instability. Prominent examples are the loss of the control of the equilibrium of the body, and excessive “spontaneous” variations of blood pressure or blood glucose. As discussed in the consensus paper (1), variability of biological oscillations may be disturbed by abnormal amplitudes, or by shift of phases, or by irregularities, which generate unexpected outbreaks.

Synchronization

It can be stated that more or less all oscillations have the trend to synchronize with each other (7). The best known example is the synchronization of heart beat and respiration (8). In this example the periods can lock in relations like e.g. 4:1, 5:1, however also 5:2. In order to explain in detail, 4:1 means that in each respiratory cycle, there are exactly 4 heart beats. A synchronization 5:2 means that two respiratory cycles are identically repeated: the first of the two respiratory cycles contains two and ½ cardiac cycle. The second respiration starts with the second ½ cardiac cycle and continues with further two cycles. During synchronization this configuration repeats. The appearance of these synchronization phenomena has the most close similarity to certain music rhythms. Namely the state of synchronization is characterized by the repeat of the same pattern in the period of one breath (when 4:1) or in the period of two breaths (when 5:2). Of course, further rhythms with longer repeats are also possible.

The consequence of an improved regularity during synchronization appears to be advantage in energy or information transfer.

Evolution

In this year 2009 we remember the 250th anniversary of the publication of Darwin's famous book "On the Origin of Species". His idea was, that evolution is possible by variation and consecutive selection. As one example we can observe, that the development of the cardiovascular system from a symmetric construction (fish) towards an asymmetric heart and an asymmetric aortic arch (mammals) apparently improves the efficiency of the system and the ability to adjust the function to changing load.

It can be seen that the following three further key words have to be involved in the considerations about evolution.

Optimization

Optimization of function or of the use of mass or energy in a biologic organism is as well a precondition as a consequence of the principle of evolution. The following example is chosen because of our special interest in the control of the cardiovascular system. In terms of the ventricular ejection one can show, that the time course of ejection under assumption of a certain given stroke volume and heart rate follows a path, which minimizes the energy expenditure (9). There is a more or less long list of examples, which permit to demonstrate the natural search for optimization of efficiency. Including the ability of adjustment to load, E.

Weibel (10) has coined the name “Symmorphosis”. This word expresses the importance of interaction between structure and function.

Similarity and Scaling

There exist between animal of different size so called allometric laws which describe the relation between body mass, energy consumption and other variables (11). It is quite interesting and important, that these laws also include what can be called individual system-time, and thus, permit to illustrate what the term system-time means. The larger an animal the slower is system time passing. The allometric laws support the idea, that structure and function of animals are optimally adjusted.

Symmetry and Asymmetry

As well in physiology as in pathology and other fields, the observation of the role of symmetry or asymmetry is of enormous interest. It was already mentioned above that, in the course of evolution, the asymmetric anatomy of the heart and the aorta served as a marked advantage for the adjustment of the cardiovascular system to variable load. There are, besides heart and aorta, several organs, which in mammals are markedly asymmetric. We have studied the effect of the asymmetry of the aortic impedance, which most probably is involved in the improvement of arterial blood transport (12).

Chronification and Chaos

There exists an interesting rather simple equation, the so called logistic equation, which is based on a feedback model where automatically the output of a calculation is fed back as the next input (13). The logistic equation describes a kind of circular process. The result of such a calculation depends on one parameter. Depending on the value of this parameter three characteristic types of result can be generated: A. increase from zero to a limit level, B. periodic oscillations or C. chaotic oscillations. Although this model is extremely simple, the processes of variability disorder (B) or chronification or chaos (C) can be explained.

Sudden and Unexpected Phenomena

Many diseases or pathologic events happen completely unexpected. The explanation or discussion of such phenomena is the most difficult task. Many pathologic events in medicine start unexpected, without warning. Examples are stroke, or heart attack. The so called sudden and unexpected death of babies is another example of such an event. In the Austrian province of Styria we have developed a project for the prevention of the sudden infant death (14). The attempt to initiate such a project includes the search for possible risk factors and the education of parents. It can be shown that there exist internal risk factors – there is a higher incidence around 3 month of age – and external risk factors, like prone position or smoking of parents.

SUMMARY

As initially stated, the attempt is made in this short essay, to list and shortly explain a – most probably incomplete – set of time dependent biologic (physiological or pathological) functions. All of these functions have to be considered as one unit. It can easily be seen that these functions or conditions interact. In any case most or all of them have to be taken into account if a special event should be evaluated.

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CHRONOBIOLOGY AND BAROREFLEX SENSITIVITY

Dedicated to Prof. Franz Halberg, Dr. M.D., Dr. h.c. multi

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Introduction

During the second half of the twenties century an opinion prevailed in the scientific community that role of baroreflex in hypertension is negligible despite the fact that baroreflex is the most important regulatory mechanism of blood pressure. This opinion was supported by the observation of baroreflex resetting. The resetting is in other words the shift of the curve of the relationship between carotid sinus pressure and systemic arterial pressure to the higher values of systemic arterial pressure. This opinion was not shared by all scientists; most prominent opponent professor Slight claimed that it is clear that all forms of hypertension – whether primary of essential or secondary to renal, hormonal, or environmental influences – have a neurogenic component. More recent evidence suggests that neural mechanisms, particularly impairment of arterial baroreflexes, play an important part.

In the recent years the long-term control of blood pressure was re-evaluated. The recent opinion is based on chronic electrical stimulation of carotid baroreceptor afferent fibers, on re-evaluation of time of chronic resetting lasting several days according the more recent experiments. Furthermore decreased baroreflex gain appears to precede hypertension.

Years ago baroreflex sensitivity was regarded to correspond to the capability of the parasympathetic nervous system to react to a gross stimulus and thus concerns primarily vagal reflexes. The measurement of baroreflex heart rate sensitivity in ms/mmHg was the adequate method. To study the blood pressure control function of baroreflex the determination of baroreflex gain is necessary.

The founder of modern chronobiology professor Franz Halberg demonstrated many years ago that the reliable diagnosis of blood pressure disorders can be performed on the basis of 24 hours blood pressure monitoring at least. (The recent Prof. Halberg studies suggest seven days monitoring to obtain a reliable estimates.)

The aim of a present paper was to determine the baroreflex open-loop gain during 24 hours in hypertensive patients and normotensive controls.

Methods

The blood pressure and heart rate were recorded in thirteen healthy subjects (N), mean aged 33±12.3 years, all men, body height 178±8 cm, body weight 81±6kg and 14 patients with essential hypertension (EH), all men, mean age 40±6 years, body height 181±8 cm, body weight 83±8kg in the supine position by means of Peňaz´s noninvasive blood pressure measurement. In EH medical tests and examinations excluded any other diseases and diagnosis of essential hypertension was made according to WHO criteria to rule out any form of secondary hypertension. All patients had been followed up at least 3 years prior to the study in clinic. All subjects gave their informed consent and the study was approved by the institutional ethical committee. Two inflatable cuffs were placed on both thighs. The cuff pressure was increased abruptly 180 mmHg for 5 min. the occlusion elicited the vasodilatation of vessels in the legs. Following the abrupt change in pressure in the occluding cuffs from 180 to 60 mmHg caused a decrease in blood pressure followed by an increase of heart rate. The changes in the blood pressure and heart rate were used for calculation of the BRS. (The pressure of 60 mmHg in the occluding cuffs prevented the stimulation of the low pressure receptors by the increased venous return.) The mean systolic pressure and mean cardiac interval were from 5 beats preceding the abrupt decrease in the cuff pressure. The difference between the mean systolic pressure before and the minimum systolic pressure after the change in the cuff pressure was calculated. The difference between the mean cardiac interval before and the shortest interval after the change in the cuff pressure was also computed. The BRS corresponded to the ration of these two differences and was expressed in ms/mmHg. The method is described elsewhere.

The BRS determination was repeated at 4-hour intervals during a 24-hour period. We started at 8 a. m. and finished at 8 a. m. the next day. The daily activities of the subjects between the measurements were unchanged. The subjects were sleeping during the night but wee awake during the measurements. The first measurement at 8 a. m. was not taken into account. Six measurements in each subject were used for further analysis.

The calculation of open-loop gain is based on following equation. Baroreflex gain (G) corresponds to the decrease of blood pressure elicited by 1 mmHg increase of pressure in carotid sinus:

$G = MBP\ (before) – MBP(after) = HR*SV*TPR – (HR-BRS_{hr})*(SV-BRS_{sv})*(TPR-BRS_{tpr})$,

MBP – mean blood pressure, HR – heart rate, SV – stroke volume, TPR - total peripheral resistance, BRS_{hr} – heart rate baroreflex sensitivity [Hz/mmHg], BRS_{sv} – stroke volume baroreflex sensitivity[ml/mmHg], BRS_{tpr} – total peripheral resistance baroreflex sensitivity[(mmHg*s/ml)/mmHg = s/ml].

By dropping the second orders terms the equation can be simplified:

$G = G_{hr} + G_{sv} + G_{tpr} = MBP*(BRS_{hr}/HR + BRS_{sv}/SV + BRS/TPR)$,

G_{hr} – gain of heart loop, G_{sv} – gain of stroke volume loop, G_{tpr} – gain of total peripheral resistance loop.

Our method enables the calculation of BRS_{hr} and G_{hr} only. $G_{hr} = MBP*(BRS_{hr}/HR)$.

The results are seen in Table I.

Baroreflex measured as BRS (ms/mmHg) increases during the night as well as duration of cardiac interval in normal controls, SBP and DBP decrease in both groups. The changes of baroreflex heart gain were not observed.

Discussion

Our method made not possible the calculation of the gain of TPR and SV because SV and TPR were not measured in our experiments but we suppose that the changes of all gains were similar. Nowadays we have possibility to use a device Task Force Monitor for measurements in our laboratory. Estimation of baroreflex set-point of MBF, which probably correspond to DBP night value, enables the calculation of the theoretical value of MBP without baroreflex and thus estimates the quantitative contribution of the baroreflex to the MBP value of an hypertensive subject.

Lower BRS in hypertension was observed by Gribbin et al. many years ago by means of phenylephrine. This finding was several times confirmed by noninvasive spectral method in our laboratory. This was in the past explained by the hypertension elicited remodeling of carotid arterial wall. The remodeling is firmly established fact as the negative correlation between intima-media thickness and BRS indicates. On the other hand our calculation indicates that lower baroreflex gain in the range of normal range of baroreflex in healthy people can make an important contribution to the blood pressure increase.

Second conclusion from our study indicates the necessity to re-evaluate the role of the blood pressure decrease during the night. Because process of resetting last of about 48 hours the night decrease of blood pressure influence the baroreflex resetting. The set point is surely lower than the night value and in subjects with normal blood pressure values during the night the shift of the carotid pressure-systemic pressure curve to higher values of pressure cannot occur. The normal chronobiology of blood pressure is so a factor protecting against hypertension.

This is an additional argument supporting the view that the diagnosis and treatment of hypertension ignoring chronobiology is bad for a patient.

Table 1 Day and night differences in cardiovascular parameters in normotensives (N) and hypertensives (EH)

	N n = 10		EH n = 14	
	day	night	day	night
I (ms)	921±181	1008±188	758±108	793±97
SBP (mmHg)	111±12	98±10	126±12	120±20
DBP (mmHg)	68±7	59±7	79±8	76±11
BRS (ms/mmHg)	11.64±4.95	20.90±21.80	8.42±6.52	8.35±5.34
G_{hr}	1.02±0.43	1.47±1.47	1.04±0.79	0.94±0.59

Healthy subjects (N), Patients with Essential Hypertension (EH), Cardiac Interval (I), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Baroreflex Heart Rate Sensitivity (BRS), Baroreflex Heart Rate Gain (G_{hr}).

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RELATIONSHIP BETWEEN CIRCADIAN BLOOD PRESSURE VARIATION AND AGE ANALYZED FROM 7-DAY MONITORING IN HEALTHY SUBJECTS AND PATIENTS WITH ISCHEMIC HEART DISEASE

Dedicated to Prof. Franz Halberg, Dr. M.D., Dr. h.c. multi

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INTRODUCTION

Franz Halberg, Germaine Cornélissen and BIOCOS scientific group provided strong evidence for the need to account for day-to-day changes in blood pressure and heart rate variables in the similar way as a circadian assessment considers the hour-to-hour variability [1-5]. The evidence led to the recommendation of around-the-clock monitoring for 7 days at the outset [6,7], to be continued whenever needed, until monitoring for a lifetime becomes more readily feasible.

By 1988, major findings had been summarized in a volume of annotated illustrations [8]. Methodology had developed concomitantly under Halberg chronobiology center leadership in Minnesota University. In particular, the "sphygmochron" [9] was introduced.

The sphygmochron is a computer summary of results from chronobiological analyses performed on BP and HR data collected around the clock by ambulatory monitoring. Two approaches are possible, one parametric (model-dependent), the other non-parametric (model-independent). The parametric approach entails the least-squares fit of a two-component model consisting of cosine curves with periods of 24 and 12 hours. Estimates are obtained for the MESOR (**m**idline-**e**stimating **s**tatistic **o**f **r**hythm), a rhythm-adjusted mean, and for the amplitude and (acro)phase of each component, measures of (half) the extent of predictable change within a cycle, and of the timing of overall high values recurring in each cycle, respectively.

The relationship between age and circadian blood pressure (BP) variation was described by us in 2004. One hundred eight seven subjects (130 males, 57 females), 20-77 years old, were recruited for seven-day BP monitoring. Colin medical instruments (Komaki, Japan) were used for ambulatory BP monitoring (oscillation method, 30-minute interval between measurements). Sinusoidal curve was fitted (least square method) and mean value and amplitude of the curve (the value of double amplitude shows approximately the day and night difference) were evaluated every day of monitoring. Average 7-day values of the mean (MESOR) and of double amplitude (2A) for systolic BP (SBP), diastolic BP (DBP) and heart rate (HR) were determined for each subject. Mean values of M (±SD) for the whole group were: SBP- 127±8, DBP – 79±6 mmHg, HR – 70±6 bpm; of 2A: SBP – 21±7, DBP – 15±5 mmHg, HR – 15±6 bpm. 2A of SBP and DBP was increasing with age up to 35 years, then the curve remained relatively flat up to 55 years (maximum at 45 years) and then decreased again (the difference between 45 and 77 years: SBP- 13mmHg, DBP-12 mmHg). Heart rate M and 2A were age-independent.
The aim of the present study is the evaluation of blood pressure variability by 7-day ambulatory blood pressure (BP) monitoring in healthy subjects and in patients with ischemic heart disease.

METHODS

The set being monitored consisted of 40 patients with ischemic heart disease (IM) of the age 63 ± 6,3 years (age between 41 and 77 years) and ejection fraction (43 ± 12,3) %.
The patients were subjected to phase II of cardiovascular rehabilitation (controlled ambulatory rehabilitation program) lasting two to three months with the frequency of three times a week at the Department of Functional Diagnostics and Rehabilitation of St. Anna Teaching Hospital. The duration of the training unit was 60 min and it consisted of warm-up phase (10 min), aerobic phase (25 min), toning phase (15 min) and relaxation phase (10 min).
In the course of rehabilitation the patients underwent 7-day ambulatory monitoring of blood pressure. During blood pressure recording they did not interrupt pharmacotherapy (ACE inhibitors, statins, betablockers, Ca antagonists).
The set of healthy subjects was composed of 44 healthy subjects (C, age between 40 and 77 years, mean age 54 years).
7-day monitoring of blood pressure was made by means of the instrument TM – 2421 of Japanese firm A&D operating on the principle of oscillometric analysis. The instrument

measured blood pressure for 7 days repeatedly every 30 min from 5 to 22 o'clock and once an hour from 22 to 5 o'clock. If a value not much probable from the point of view of the instrument setting was recorded, another check measurement was made (Siegelová et al. 2004).

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

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

RESULTS

A significant increase of systolic BP (SBP) MESOR with age was found in C ($r=0.39$, $p<0.01$), but not in IM ($r=0.23$) Fig.1. Diastolic BP (DBP) MESOR was not related to age in C ($r=014$) but a decrease of DBP with age in IM was observed ($r=0.362$, $p<0.05$) - Fig.2. Mean value of SBP MESOR was higher in C than in IM (128±9 vs. 121±8 mmHg, $p<0.01$), as well as DBP MESOR (81±7 vs. 74±7 mmHg, $p<0.01$). DA SBP decreased with age in C ($r=0.30$, $p<0.05$) but not in IM ($r=0.03$) - Fig.4. Similarly DA DBP decreased with age in C ($r=0.41$, $p<0.01$) and not in IM ($r=0.08$) - Fig.5. Mean values of DA were lower in IM (DA SBP: 21±10 vs. 16±8 mmHg, $p<0.01$; DA DBP: 16±8 vs. 12±5 mmHg, $p<0.01$). Heart rate (HR) was not age-related in both groups, difference in mean values of HR was not observed (C: 71±10, IM: 65±8 bpm) - Fig.3. DA HR was lower in IM (15±8 vs. 9±5 b.p.m) - Fig.6.

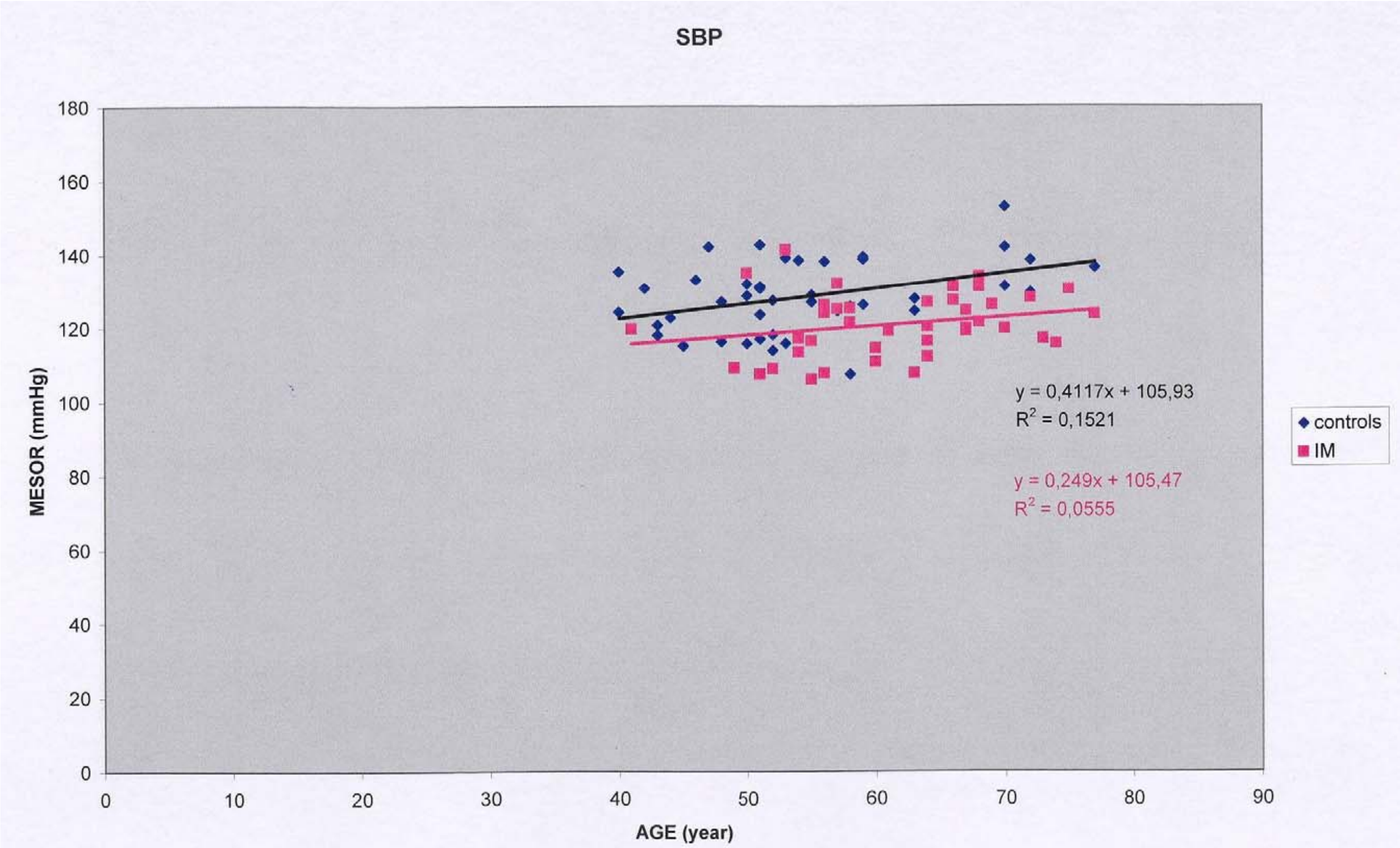

Fig. 1 Relationship between MESOR of systolic blood pressure(SBP, mmHg), measured by 7 day ambulantory blood pressure monitoring, and age (years) of patients with MI the subjects C.

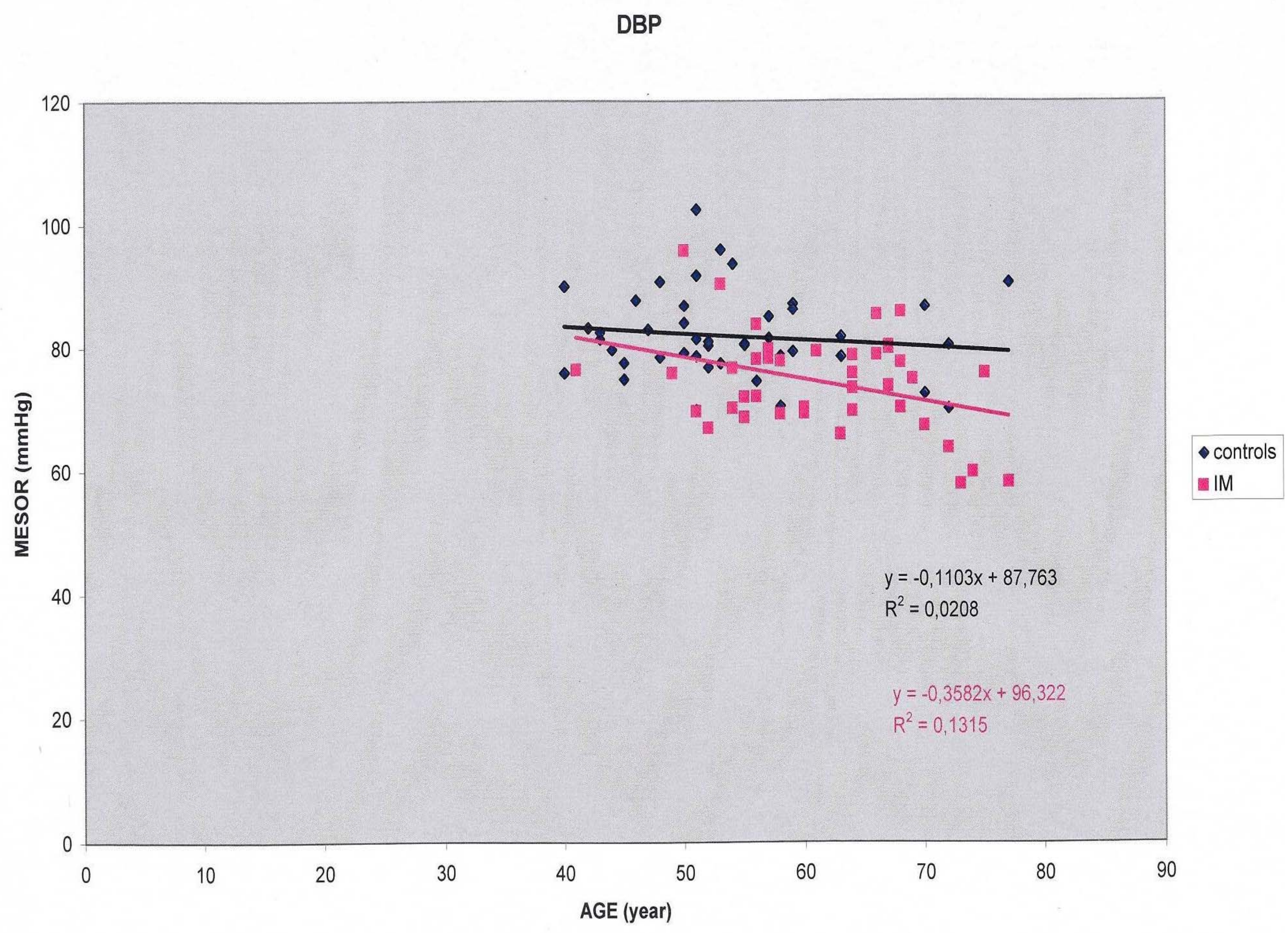

Fig. 2 Relationship between MESOR of diastolic blood pressure (DBP, mmHg), measured by 7 day ambulantory blood pressure monitoring, and age (years) of the MI and C subjects.

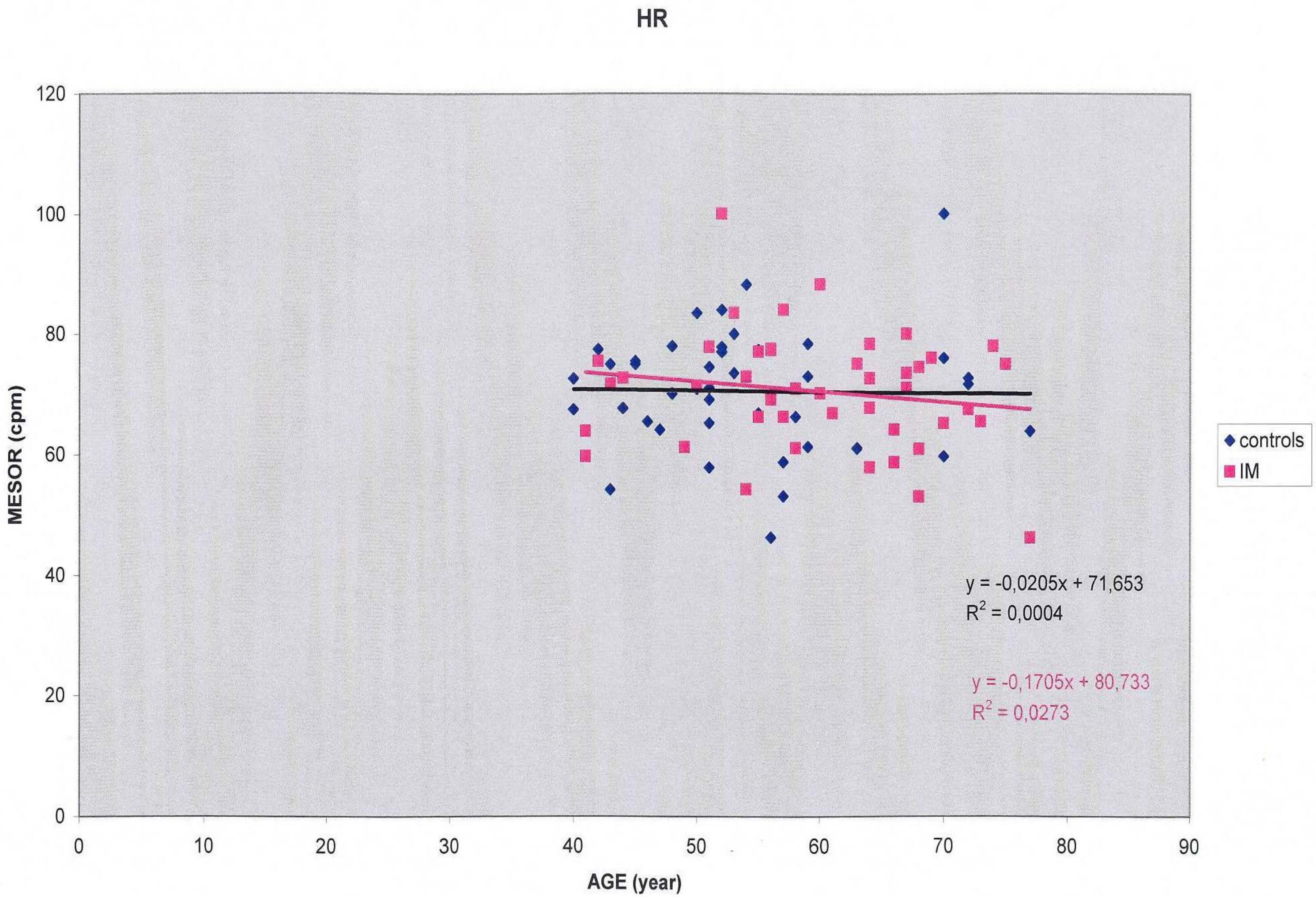

Fig. 3 Relationship between MESOR of heart rate (HR, bpm), measured by 7-day ambulatory blood pressure monitoring, and age (years) of the MI and C subjects

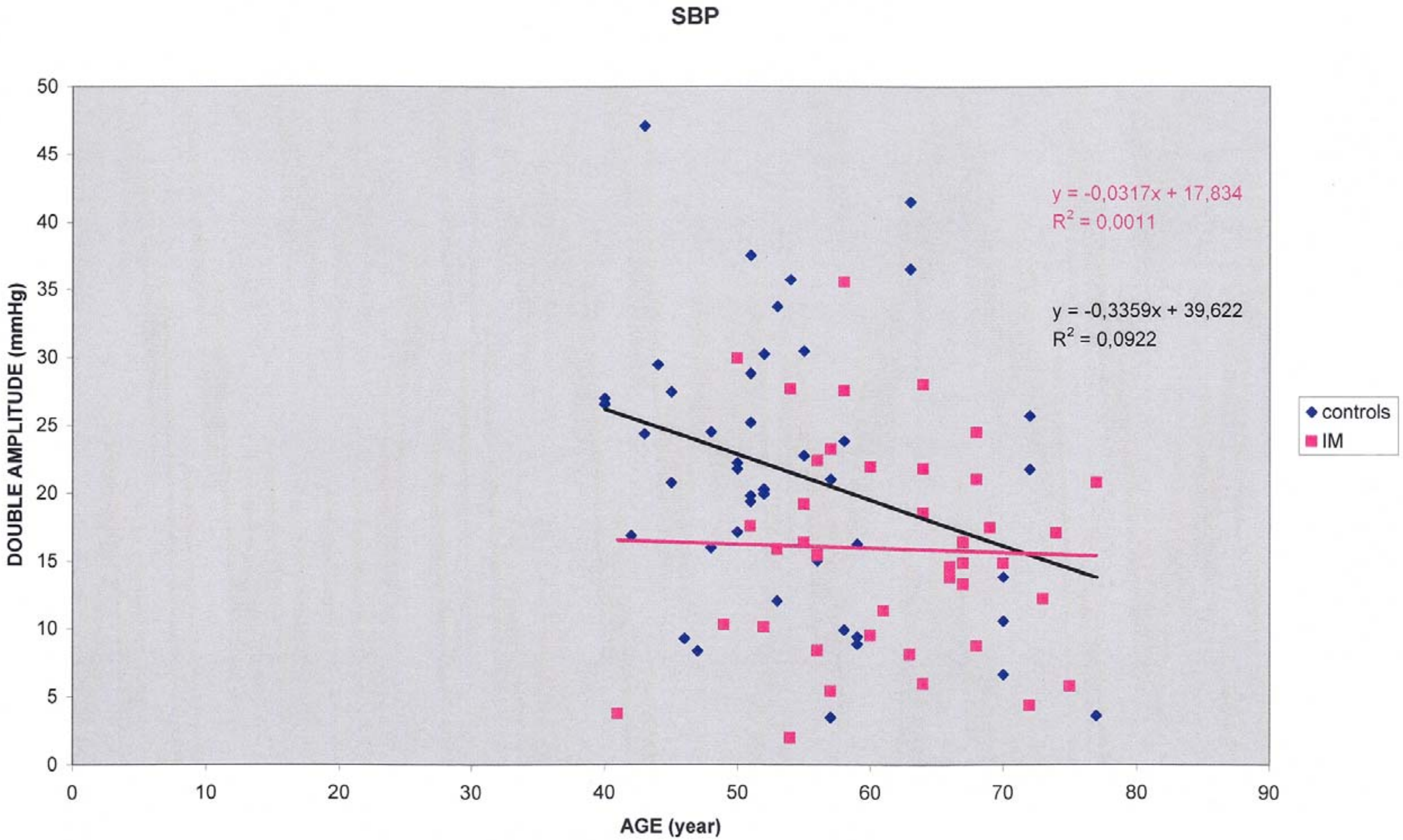

Fig. 4 Relationship between circadian amplitude of systolic blood pressure (SBP, mmHg), measured by 7-day ambulantory blood pressure monitoring, and age (years) of the MI and C subjects.

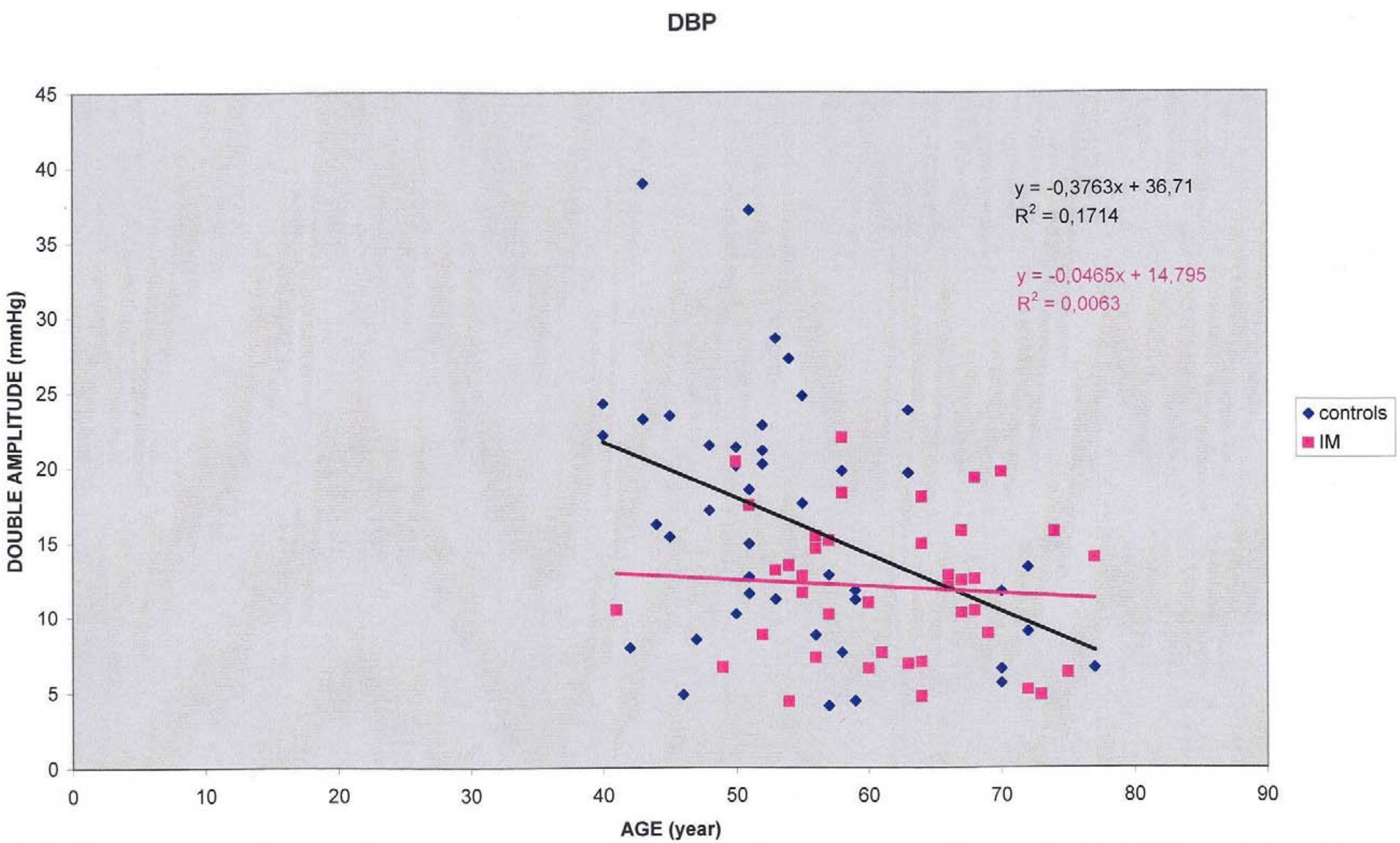

Fig. 5 Relationship between circadian amplitude of diastolic blood pressure (DBP, mmHg), measured by 7-day ambulatory blood pressure monitoring, and age (years) of the MI and C subjects.

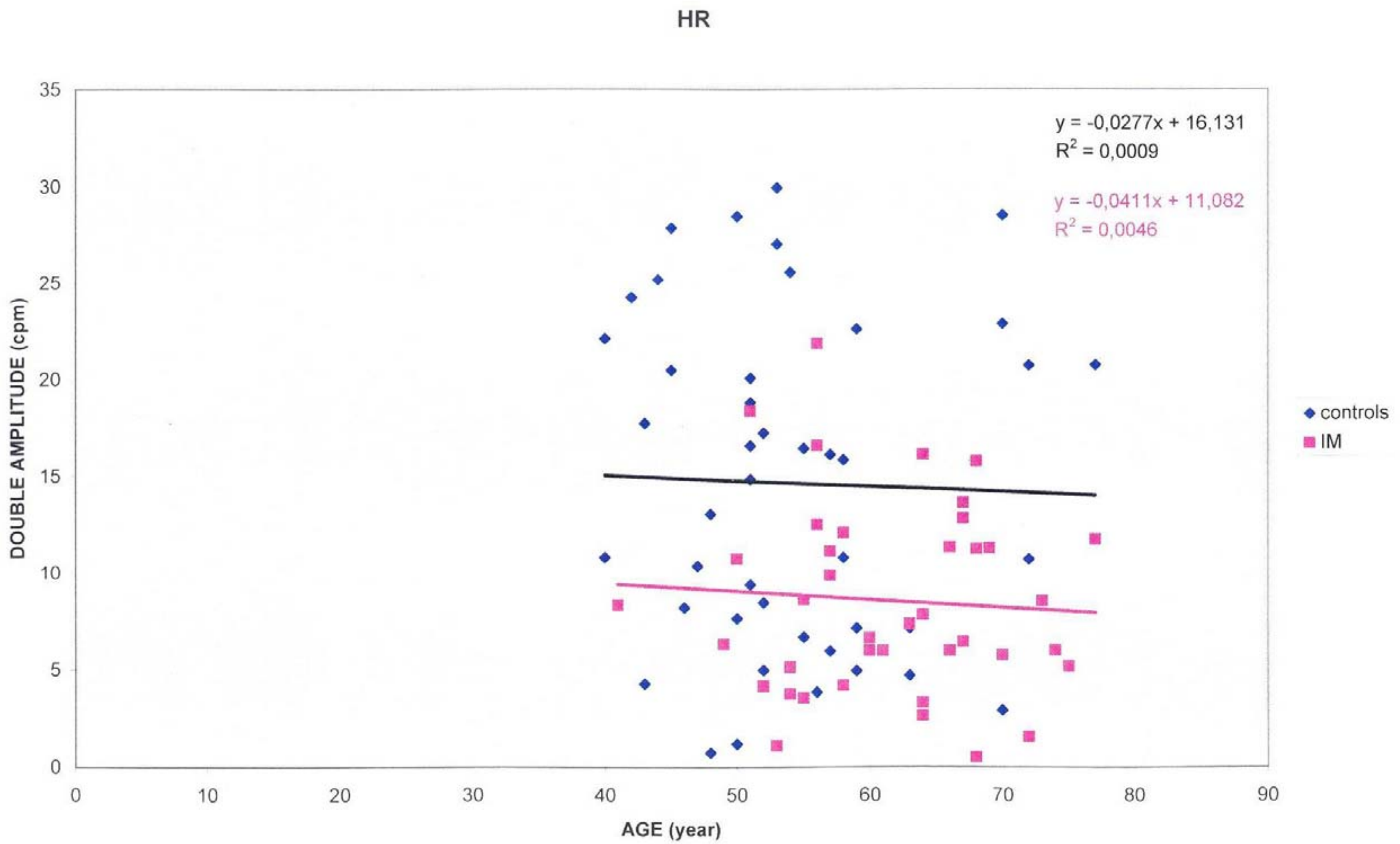

Fig. 6 Relationship between circadian amplitude of heart rate (b.p.m, HR), measured by 7-day ambulatory blood pressure monitoring, and age (years) of the MI and C subjects.

DISCUSSION

There is a growing body of evidence suggesting that time structures in us and around us are intricately interwoven. Most if not all components of variation found in biota are also found in the environment, and vice versa [10]. For instance, about daily changes are seen in almost every biological variable under 24-hour synchronized conditions. It has also long been known that the phase of circadian rhythms can be manipulated by changing the phase of the environmental cycles [11]. At least for the case of circadian rhythms, their genetic inheritance has been demonstrated on a molecular basis [12,13], suggesting that the influence from the environment has been acquired genetically during the course of evolution.

The mapping of chronomes should benefit our understanding of human health and disease in several ways. The study of human chronomes can serve the derivation of refined reference values to better define health and to identify pre-disease, so that prophylactic interventions can be instituted as early as possible, preferably before the disease sets in [14-16]. The focus is thus put on pre-habilitation, in the hope that the need for re-habilitation will thereby be reduced [17,18,19].

Several studies [20, 21] comparing the classification of patients based on single office measurements with that based on ambulatory monitoring for one to seven days suggest that the incidence of misdiagnosis is around 40%, in keeping with the 48% response to placebo in the Australian Therapeutic Trial [22,23]. Comparison of circadian characteristics from day to day in records spanning at least two days further indicates the shortcomings of monitoring limited to a single 24-hour span [24, 25, 26]. Prolonging the monitoring from one to two days reduces the uncertainty in the estimation of circadian parameters by about 35% [27], whereas further information on the biological week [28, 29, 30, 31] requires monitoring for at least 7 days, the current recommendation of BIOCOS for everybody at the outset [32]. It is now widely accepted that prognosis of target organ damage is by far superior when it is based on around the clock monitoring than on single office measurements [33,34,35].

The mistaken impression that the circadian variation in blood pressure and heart rate is sufficiently stable to be approximated by a single 24-hour profile stems in large part from the use of statistical methods on groups of subjects rather than focusing on the individual patient. Correlation analyses applied to large groups of subjects with a wide range of average values emphasize similarity. Statistical analyses focusing on individual differences observed from one profile to another, however, yield information more likely to help the patient in need of the treatment [24]. Several case reports document this point [16, 36, 37, 38, 39]. Continued monitoring is the most logical solution.

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

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

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

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Non-invasive Evaluation of Arterial Stiffness in Czech Adult Population using the device VaSera® 1500

Dedicated to Prof. Franz Halberg, Dr. M.D., Dr. h.c. multi

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Abstract

The traditional non-invasive method for the early detection of arteriosclerosis is the brachial-ankle pulse wave velocity (PWV), however, this method is significantly influenced by the changes of blood pressure (BP). Recently, a new non-invasive method for the arterial stiffness assessment was developed – the cardio-ankle vascular index (CAVI). This method has been shown to be not affected by the BP variations and so that it could be recommended for wide clinical use, including large population studies. The aim of this paper was to evaluate the CAVI in the population sample of Czech adult population. A group of 121 healthy subjects (aged from 20 to >70 years) was examined using the newest type of non-invasive monitoring system VaSera® 1500 (Fukuda Denshi Co., Tokyo, Japan). This control group was then compared with 3 groups of patients with selected lifestyle-related diseases: coronary artery disease (CAD; n = 74), diabetes mellitus (DM; n = 36) and hypertension (HT; n = 58). The statistical analysis showed a significant differences of the CAVI parameter between the healthy subjects and patients with coronary artery disease, diabetes and hypertension; the mean CAVI value in the control group (6.9) was significantly lower compared to the patients with CAD (CAVI = 9.2; $P < 0.001$ vs.control group), diabetes (CAVI = 8.5; $P < 0.001$ vs.control group) and hypertension (CAVI = 8.9; $P < 0.001$ vs. control group). These results demontrate that CAVI should be considered as an important clinical parameter independent of blood pressure changes, and should be recommended as a valuable indicator of the preventive evaluation of the arteriosclerotic risk in healthy subjects and patiens with life-style related diseases.

Keywords:

cardio-ankle vascular index - arterial stiffness – arteriosclerosis - blood pressure - cardiovascular diseases

Introduction

The World Health Organization (WHO) report estimates that around 20 million (32%) of total deaths are resulted from the various forms of life-related diseases (including CAD), many of which are preventable by action on the major primary risk factors. CAD and stroke are no longer only diseases of the developed world; some 70% of all CAD death worldwide took place in developing countries, while these countries also accounted for 80% of the global

CAD disease burden. The above mentioned WHO report estimates that CAD will be the leading cause of death in developing countries by 2010. Therefore, the early detection of the arteriosclerotic plaque development has a crucial importance. Up to the present the widely used method is the evaluation of the brachial-ankle pulse wave velocity (PWV). However, several studies reported the significant dependence of PWV on the blood pressure variations, so that the value of the measuremen is seriously compromised (1). Due to this limitation, a new and simple instrument for the early diagnosis of arteriosclerosis is of great interest. Recently, the device VaSera® was developed as a new non-invasive screening tool in fight against atherosclerosis that is a considerable cause of CAD. VaSera measures vascular compliance using sophisticated new oscillometric technology termed CAVI or Cardio Ankle Vascular Index, used for the quantitative assessment of the arterial wall stiffness. According to some recent studies, the parameter CAVI is less influenced by the blood pressure changes (2 and 3). The aim of this study was to investigate: 1) the influence of the changes of blood pressure on CAVI in Czech healthy adult subjects; and 2) the differences in the value of CAVI between the healthy subjects and patients with selected lifestyle-related diseases: coronary artery disease (CAD), diabetes mellitus (DM) and hypertension (HT) .

Patients and Methods

Patients' selection

A group of 121 healthy subjects (men and women) aged from 20 to >70 years was recruited in St.Anna Faculty Hospital in Brno (Czech Republic) and examined using the newest type of non-invasive monitoring system VaSera® 1500 (Fukuda Denshi Co., Tokyo, Japan). This control group was then compared with 3 groups of patients with selected lifestyle-related diseases: coronary artery disease (CAD; n = 74), diabetes mellitus (DM; n = 36) and hypertension (HT; n = 58).

Methods

Cardio-ankle brachial index (CAVI) – according to Yambe et al. (1)

CAVI reflects the stiffness of the artery from the heart to ankles. As arteriosclerosis progresses, the CAVI value becomes higher. CAVI is calculated based on the stiffness parameter β which is measured by carotid echography or the like and is not affected by blood pressure. Thus, it represents the natural vascular stiffness. The latest type of the device

VaSera, the VaSera 1500® adopts the oscillometric method for blood pressure measurement. In addition, it does not simultaneously measure blood pressure at 4 limbs but at first it measures blood pressure at the right brachial and ankle and then measures at the left brachial and ankle. Thus, arteries at the right and left sides are alternately pressurized with the other side open. This not only reduces burden to examinees but also enables more accurate measurement. CAVI calculation is based on the stiffness parameter β. It is an index to diagnose sclerotic degrees of the carotid artery, etc. from the diametrical variation and blood pressure measured by ultrasonic echography and represents the natural vascular stiffness independent of blood pressure. CAVI is calculated using the stiffness parameter β obtained with the Bramwell-Hill equation (4).

The stiffness parameter β

$$\beta = 【\ln Ps/Pd】 \cdot 【D/\Delta D】 \quad \cdots (1)$$

Ps : Systolic pressure
Pd : Diastolic pressure
D : Diameter
⊿D : Change of Diameter

From the Bramwell-Hill equation (here, the ratio of volumetric change, V/ΔV, is converted to ratio of luminal change, D/ΔD)

$$PWV^2 = \frac{\Delta P}{2\rho} \cdot \frac{D}{\Delta D} \quad \cdots (2)$$

$$\frac{D}{\Delta D} = \frac{2\rho}{\Delta P} \cdot PWV^2 \quad \cdots (2)'$$

CAVI is obtained by substituting the equation (2)' for D/ΔD in the equation (1).

The final equation of CAVI

$$CAVI = 【\ln Ps/Pd】 \cdot \frac{2\rho}{\Delta P} \cdot PWV^2 \quad \cdots (3)$$

Ps : Systolic pressure
Pd : Diastolic pressure
PWV : Pulase wave velocity between heart and ankle
ρ : Blood density
⊿P : Pulse pressure

The reference values of CAVI are as follows:

CAVI < 8.0 normal range
8.0 =or< CAVI < 9.0 borderline
9.0 =or< CAVI arteriosclerosis suspected

In order to limit as much as possible the influence of the diurnal variations all the subjects were examined during stable time period, between 7:00 AM to 10:00 AM. All the subjects were asked to avoid caffeine drinks in the morning. The examinations were conducted in a quiet room and at a stable temperature of 21-22°C. The influence of blood pressure changes on CAVI was evaluated only in the kontrol group (healthy subjects). The correlation between the R-CAVI and L-CAVI, as well as the correlations between CAVI and age, systolic and diastolic presssure were examined only in the control group.

Statistics

Visualisation of the data is based on comparative histograms and box-whisker plots. The descriptive summary of L (left) and R (right) values of CAVI is based on robust non-parametric statistics, i.e. median and 5^{th} – 95^{th} percentile range. The statistical significance of difference between L and R values was tested by Wilcoxon paired test. Statistical significance of differences in averaged values of CAVI among the different groups of examined subjects was evaluated using one-way ANOVA followed by Tukey post-hoc test; the variables were described using mean and its 95% confidence interval. Pearson correlation coefficient was applied for the analysis of relationship between CAVI and other descriptors (R and L side, age, systolic and diastolic blood pressures). The level of statistical significance was established at $P < 0.05$.

Results

Statistical analysis showed that there is no singificant difference between the right (R) and left (L) value of CAVI. The mean CAVI value in the control group without signs of atherosclerotic diseases) was 6.9 ± 0.5. CAVI in patients with CAD was 9.2 ± 0.3 (P < 0.001 vs.control group) and in the group of diabetic subejcts was 8.5 ± 0.3 (P < 0.001 vs. control group). Finally, in the group of patients with hypertension the CAVI was 8.9 ± 0.3 (P < 0.001 vs. control group). These results suggest that the mean CAVI value is significantly lower in the patiens with selected life-related diseases, and thus reflects quantitatively the extent of arteriosclerotic process. The results also revealed the presence of a strong correlation between R-CAVI and L-CAVI (r = 0.963; P < 0.001) and between mean CAVI (R and L) and the age (r = 0.756; P < 0.001). A weak correlation was found out between meanCAVI (R and L) and systolic blood pressure (r = 0.355; P < 0.001), and mean CAVI (R and L) and diastolic blood pressure (r=0.354; P < 0.001). These results indicate that CAVI is not dependent on the variations of the blood pressure.

Summary statistics of CAVI values

N=191	*Mean*	*95%CI*	*Median*	*5-95% quantile*
R-CAVI	7.64	(7.39; 7.88)	7.50	(5.20; 10.30)
L-CAVI	7.70	(7.46; 7.94)	7.50	(5.30; 10.24)
average CAVI	7.67	(7.43; 7.91)	7.45	(5.23; 10.22)

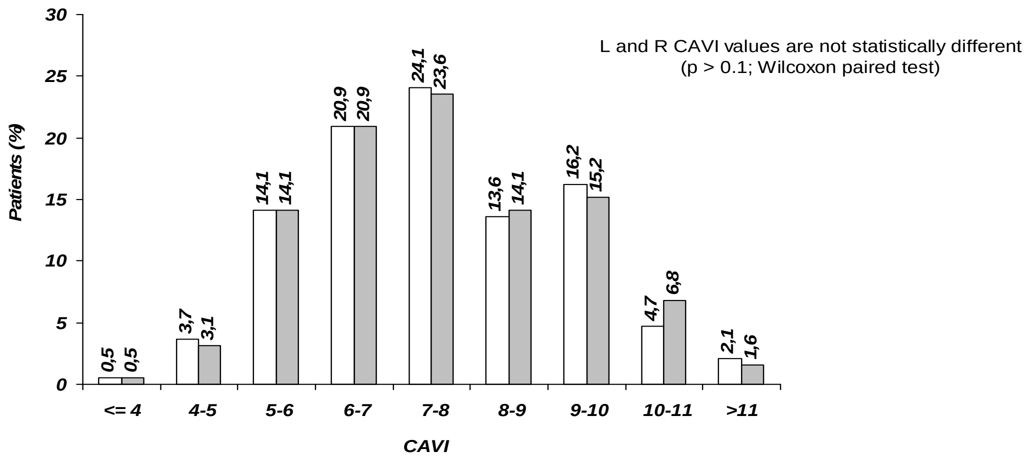

Fig 1 shows the summary statistics of the healthy subjects and average CAVI (± SD) for each age group.

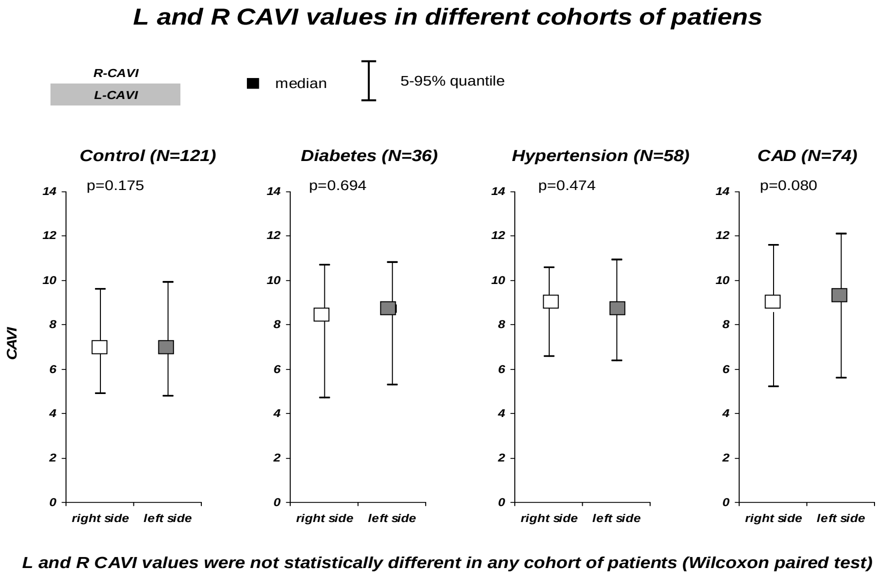

Fig 2 shows the results of the averaged R and L-CAVI values in the healthy subjects (controls) and in the groups of patients with diabetes, hypertension and CAD.

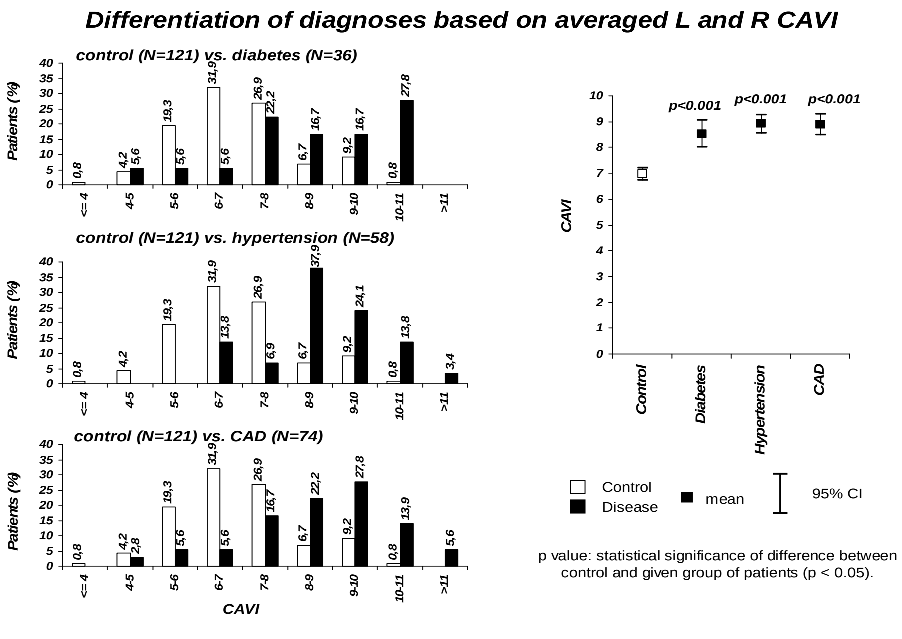

Fig 3 shows the significant differences of the averaged CAVI values in the control group and in the patients with diabetes, hypertension and CAD.

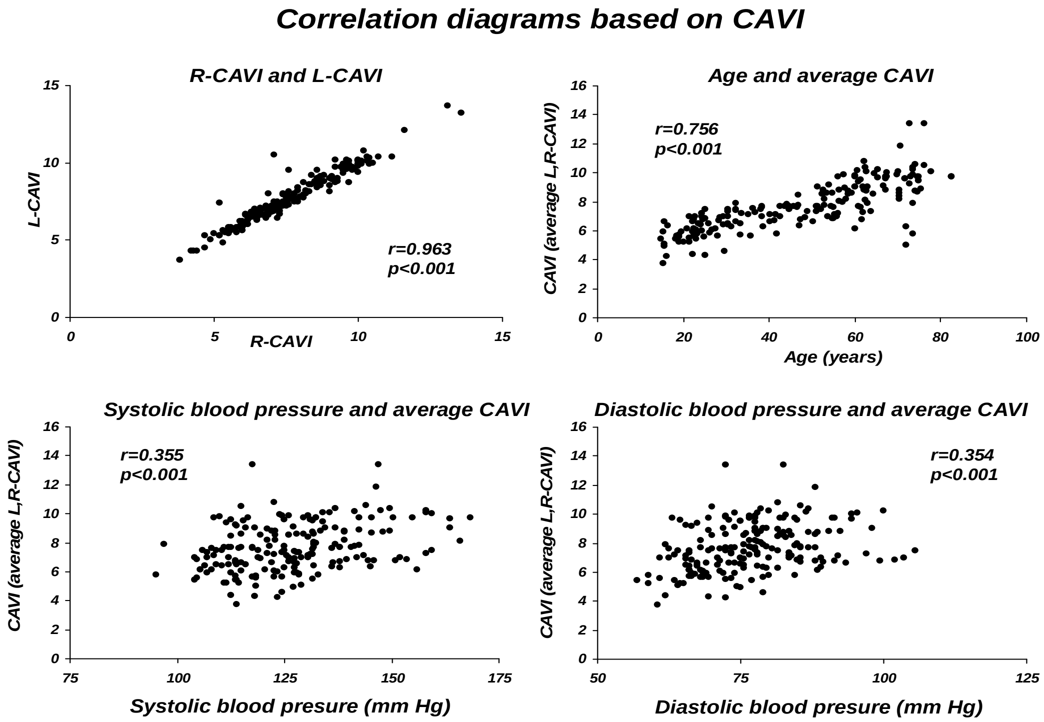

Fig 4 shows the correlation diagrams between the averaged values of L-CAVI and R-CAVI, between averaged CAVI and the age, and between averaged CAVI and systolic and diastolic BP.

Discussion

The mortality caused by the so-called life-related diseases in the developed countries has become the highest in the world. It has been shown that these diseases are strongly associated with the lifestyle and inactivity, favorizing plaque formation and atherosclerosis developent. Social needs for quantitative measurement of atherosclerosis were rapidly increasing because the arteriosclerotic process is considered as an independent risk factor for the cardiovascular diseases. The vesell wall arteriosclerotic changes represent the main risk for the onset of myocardial infarction and stroke; both complications vitally worsen the prognosis and the quality of life in the populations of developed countries (5 and 6). For these reasons, a preventive and simple quantitative method for early diagnosis of arteriosclerosis is required.

The measurement of the aortic pulse wave velocity (PWV) is calculated by measuring the pulse transit time and the distance traveled between two selected sites (ie, arterial distance over transit time), which is inversely related to the distensibility of the arterial walls. PWV is still popularly practiced and its usefulness in early diagnosis of arteriosclerosis was demonstrated (7 and 8) but it had a inherent limitation of blood-pressure dependency (1). Aortic PWV is pressure dependent, and PWV must be corrected for diastolic blood pressure (9) and carotid and femoral pulse waves are often difficult to detect, thus limiting use in daily clinical practice. Hayashi et al. proposed the concept of an arterial stiffness β index (10), however, stiffness β reflects only the regional (local) arterial stiffness, is expensive and requires specialized ultrasonic equipment. Intima-media thickness (IMT), also called intimal medial thickness, was also becoming popular. IMT is a measurement of the thickness of artery walls, usually by external ultrasound, occasionally by internal, invasive ultrasound catheters, to both detect the presence and to track the progression of atherosclerotic disease in humans (11). IMT has increasingly been used in medical research since the mid 1990's and its key advantages are the lower cost (compared with most other methods), relative comfort for the patient and lack of need of invasive methods or any X-ray radiation. IMT can be used repeatedly, over years, without compromising the patient's short or long term health status. However IMT is limited to the morphological local regional measurement, and not to obtain a representative image of functional aspect in arterial stiffness. Radiographic IMT using advanced computed tomography (CAT) scanners is more approximated due to its ability to use software to more slowly and carefully process the images and the examination of the artery segments from whatever angle appears most appropriate (12) However, the major limitation of all CAT scanners is the dose of X-ray delivered to the patient’s body and there are also concerns about the safety of repeated doses of X-rays to track disease status over time.

It is known that lowered extensibility of the aorta causes onset of the heart disease and so determines the prognosis. Arteriosclerosis generally progresses from the aorta to both carotid arteries and then the cerebral and coronary arteries (13). For the accurate non-invasive evaluation of the stiffness of the aorta, femoral artery and tibial artery, the cardio-ankle vascular index (CAVI) which is independent of blood pressure was developed. CAVI is a simple test, similar to PWV but the main unique diference is that CAVI is not influenced by blood pressure fluctuations during the measurement and CAVI could be used as a reliable index of arterial stiffness even in subjects with labile blood pressure. Also our results indicated that CAVI is not dependent on the variations of the blood pressure and this is an important finding opening the possibility to evaluate f.e. the proper effects of antihypertensive drugs on the blood pressure and the arterial stiffness (2) The variation coefficient for CAVI is 3.8%, and the reproducibility seems to be enough sufficient for clinical application (2). The regions measured by both CAVI and PWV include elastic and muscular vessels (aorta and femoral–tibial arteries) and the calculation formula for CAVI is fully compatible with the aortic PWV measured by conventional methods. Coronary artery ischemic disease, diabetes mellitus and hypertension induce severe arteriosclerotic changes resulting in increased arterial stiffness, and represent a major risk factor of arteriosclerosis development (14). The significant diference of the mean CAVI values between healthy subjects and the patients with above mentioned 3 life-related diseases in this study seems to support this fundamental idea. It is also well known that arteriosclerosis increases with age (15) and our results showed that CAVI increases with age too, and thus age should be regarded as a strong risk factor. In other words, the higher value of CAVI reflects the extent of the plaque formation and this further hihglights the predictive value of CAVI of arteriosclerotic risk (16).

Conclusion

In conclusion, CAVI assessed by the device VaSera® 1500 is simple and valuable clinical test for the estimation of the arterial stiffness. CAVI is not influenced by blood pressure variations, and therefore very useful for the early detection of the plaque formation in healthy subjects and for monitoring of the arteriosclerosis progression in patients with life-related diseases. However, the number of subjects included in this study was not sufficient (121 healthy volunteers only) and further large population studies are needed.

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Respiratory exchange ratio at maximum load before and after termination of controlled ambulatory rehabilitation program in patients after acute myocardial infarction

Dedicated to Prof. Franz Halberg, Dr. M.D., Dr. h.c. multi

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INTRODUCTION

To be able to evaluate correctly peak values of oxygen intake (VO_{2peak}) and working capacity, we must know whether in exercise test a sufficient metabolic load (full metabolic capacity utilization) was achieved. The peak value of respiratory exchange ratio (RER_{peak}; ratio of CO_2 output to O_2, intake, indicated also as respiratory quotient), correlating with the increased lactate value and acidosis degree, is the criterion of the achieved level of metabolic load (full metabolic capacity utilization) at submaximal and maximal load.

According to the Statement of the Working Group on Cardiac Rehabilitation and Prevention of the European Society of Cardiology the full metabolic loading is achieved at $RER_{peak} \geq 1{,}15$ and the exercise testing is valid (1).

AIMS

To assess the influence of respiratory exchange ratio RER_{peak} on VO_{2peak} validity in evaluation of the measure of improvement of maximal aerobic capacity of patients who suffered an acute myocardial infarction after 12-week controlled ambulatory rehabilitation program.

MATERIAL AND METHODS

Study population

We evaluated 49 men incorporated into 12-week controlled ambulatory rehabilitation program. All patients suffered an myocardial infarction (AIM) and started rehabilitation program within three months after AIM (Table 1). The acute myocardial infarction was diagnosed at 1st Department of Cardioangiology in St. Anna University Hospital in Brno.

The patients were divided into two groups according to the achieved RER_{peak}. Group A reached $RER_{peak} \geq 1{,}05$, in group N $RER_{peak} < 1{,}05$ (Table 1) was achieved in one or both exercise tests.

In the course of the rehabilitation program all patients were symptomatically stable and their medication treatment was unchanged.

The whole study was carried out in accordance with ethic principles of Helsinki convention from 1975 in the revision from 1983. All patients signed their informed approval.

Table 1 Characteristic of the examined set of patients with myocardial infarction

	Age (years) ($\overline{X}$ ± SD)	RER_{peak} ($\overline{X}$ ± SD) input	output
Group A (n = 25)	61.3 ± 9.9	1.12 ± 0.04	1.15 ± 0.07
Group N (n = 24)	57.8 ± 10.9	1.01 ± 0.06	1.10 ± 0.13

Rehabilitation program

All patients went through the supervised exercise training with combined load three times a week for three months. The training unit consisted of warm-up phase (10 min), aerobic phase (25 min), resistance training phase (15 min) and relaxation phase (10 min).

Aerobic phase on bicycle ergometers (Ergoline REHA E900) consisted of warm-up phase lasting 3 to 4 minutes at a low load, of 25-min training with the intensity at the anaerobic threshold level given by spiroergometric examination, and 2-min cool-down phase during which the load intensity was gradually decreasing (2). The resistance exercises made on multifunctional machines TK-HC COMPACT included benchpress, pull down of the pulley and leg extension, out of the machine sitting-lying was performed. The load intensity was determined by the method 1-RM (one repetition maximum, i.e. one repetition of the given exercise made in the full extent of the movement with maximal load) (3). Individual exercises were made in 3 to 5 series, at 10 repetitions. During the whole training unit there were monitored heart rate, blood pressure, degree of subjective perception of the load intensity according to Borg scale, during the aerobic and resistance training phases also ECG was monitored.

Methods of examination

Symptom limited spiroergometric examination with ventilator gas analysis was performed before the starting and after the finishing of the cardiovascular rehabilitation program (98 examinations altogether). It was started by ECG monitoring at rest in lying and sitting position (Schiller CS 100). It was followed by 3-min adaptation in the sitting position on ergometer. The workload was increased in one minute intervals. The rate of the workload increase was chosen according to the supposed fitness in such a way that the total workload duration was 8 to 12 minutes. In the course of the exercise test ECG was monitored continuously, heart rate was recorded every minute according to ECG, manual blood pressure measurement and determination of the degree of subjective perception of the load according to Borg scale were made every 2 minutes. The test can be terminated because of dyspnoea, exhaustion, reaching of the limit heart rate value (220-age), abnormal hypertension reaction (≥ 230/115), decrease of systolic blood pressure (> 10 mmHg), indications of ischemia on ECG, pectoris angina, substantial dysrhythmia, loss of motion coordination, disturbances of consciousness, pains, orthopedical or neurological reasons, technical causes, etc.

Oxygen uptake, CO_2 output and ventilation were measured in each breath (breath-by-breath analysis) and averaged values for 30 s were recorded in the printed report (device Pulmonary Function System 1070 - MedGraphics, USA). The device determined automatically the anaerobic threshold according to the changes of ventilation-respiratory values and, moreover, in all of them the determined anaerobic threshold was checked according to V-slope, by comparing the curves of ventilation equivalent VE/O_2 a VE/CO_2 and the curve of CO_2 excess $[ExCO_2=((VCO_2)^2 / VO_2) – VCO_2]$.

The anaerobic threshold value was expressed as VO_2 and for the need of physical training in watts with the corresponding heart rate and degrees of Borg scale of subjective perception of the load intensity.

Statistical processing

Statistical processing was made by using the program Microsoft Excel for Windows and the program Statistica, version 6.1.

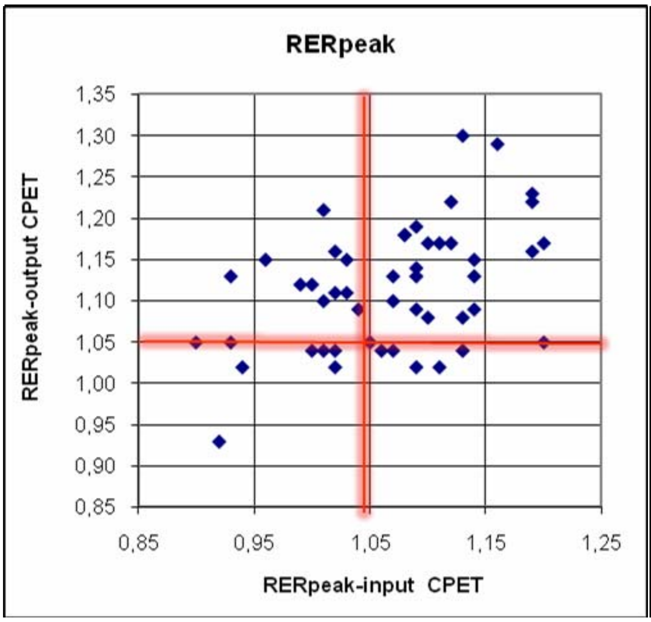
The distribution was evaluated by *Lillefors modification of Kolmogorov-Smirnov test of normality* in the program Statistica. With regard to normal distribution, parametric tests were used. In comparing two dependent variables *two-sample paired t-test to mean value* (in program Microsoft Excel) was performed. In comparing two independent variables first of all it was found out by *two-sample F-test for variances* whether the variances differ or not, and, as the case may be, either *two-sample t-test with equality of variances* or *two-sample t-test with inequality of variances* was used (all in the program Microsoft Excel).

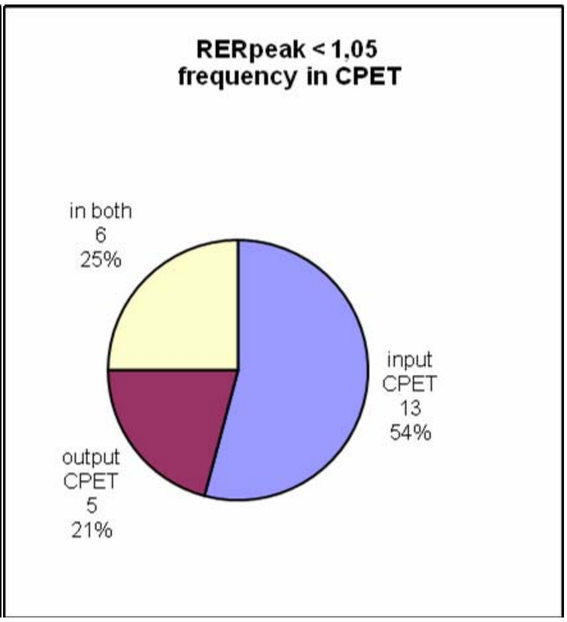
In all tests the significance level was primarily set to 0.05. If the result on this level was statistically significant, testing was made also on the significance level 0.01, possibly 0.001. Always double-sided testing was used. The results are presented in the form of means ($\overline{x}$) and standard deviations (SD).

RESULTS

Graph 1 shows the survey of 98 spiroergometric examinations according to the value of RER_{peak}. In 25 patients $RER_{peak} \geq 1.05$ was achieved in both tests (right upper quadrant of graph 1). In 5 patients only $RER_{peak} \geq 1.15$ was achieved and the value of VO_{2peak} can be therefore considered to be valid according to the Statement (1). In 30 examinations RER_{peak} < 1,05, from that in 13 patients in entrance examination (left upper quadrant of graph 1), in 5 patients in final examination (right lower quadrant of graph 1) and in 6 patients in both examinations (left lower quadrant of graph 1). In the group with $RER_{peak} < 1.05$ low RER_{peak} predominated significantly in entrance examinations (graph 2).

In these 30 exercise tests that were terminated prematurely (RER_{peak} < 1,05) only in one third the symptoms indicating possible limitation of the transport system (exhaustion, dyspnoea, pectoris angina) were the cause of the test termination.





Graph 1 Spiroergometric examinations according to the value of RER_{peak} Graph 2

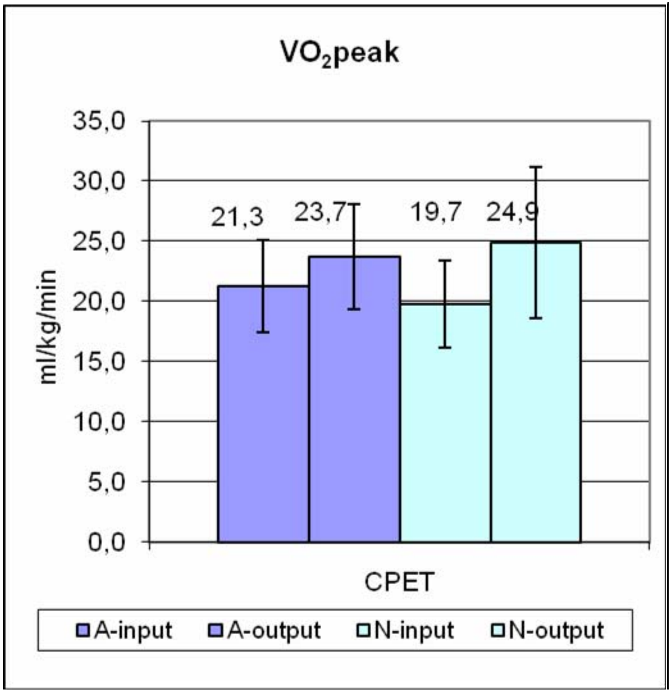
In the group A the value of VO_{2peak} increased by 2.4 $ml.kg^{-1}.min^{-1}$ ($p < 0.01$) after 12-week rehabilitation program and in the group N the value of VO_{2peak} increased by 5,1 $ml.kg^{-1}.min^{-1}$ after the completion of the rehabilitation program (table 2, graph 3). The value of the total achieved load (W_{peak}) increased in the group A by 0.24 $W.kg^{-1}$ ($p < 0.001$) and in the group N by 0.51 $W.kg^{-1}$ ($p < 0.001$) (table 2, graph 4). Comparison of differences between the groups A and N is in table 3 and graphs 4,6.

Table 2 Comparison of input and output values of VO_{2peak} and W_{peak} in individual groups of patients with IM

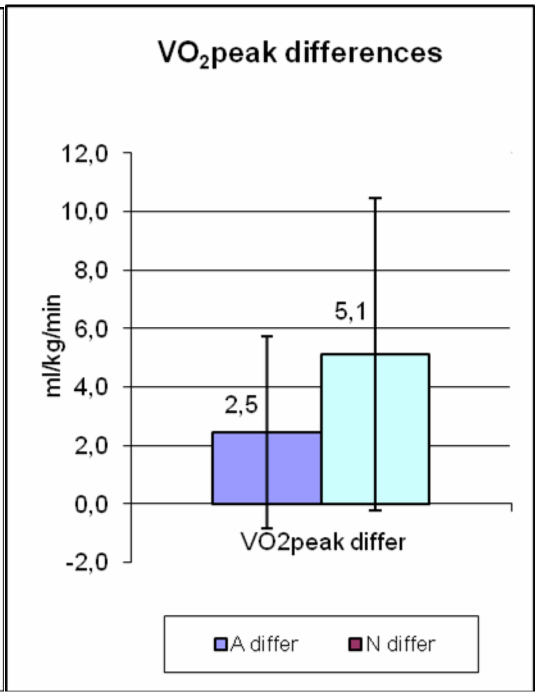
	VO_{2peak} ($ml.kg^{-1}.min^{-1}$)			**W_{peak} ($W.kg^{-1}$)**		
	Input	Output	Statist.	Input	Output	Statist. sign.
Group A	21.3 ± 3.9	23.7 ± 4.4	$p < 0.01$	1.40 ±	1.64 ± 0.36	$p < 0.001$
Group N	19.6 ± 3.6	24.9 ± 6.3	$p < 0.001$	1.21 ±	1.72 ± 0.46	$p < 0.001$

Table 3 Comparison of differences of VO_{2peak} and W_{peak} between the groups A and N of patients with IM

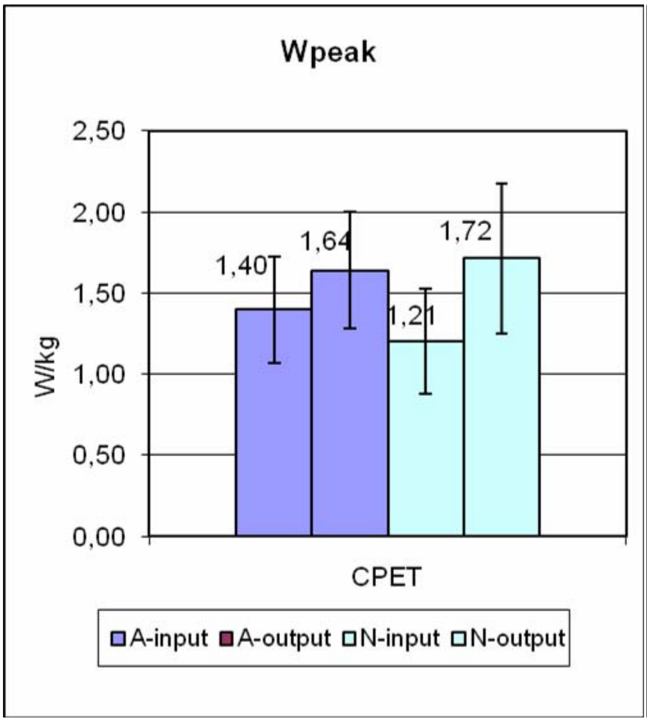
	Group A	Group N	Statist. sign.
VO_{2peak} ($ml.kg^{-1}.min^{-}$	2.4 ± 3.3	5.1 ± 5.3	$p < 0.05$
W_{peak} ($W.kg^{-1}$)	0.24 ± 0.24	0.51 ± 0.36	$p < 0.01$



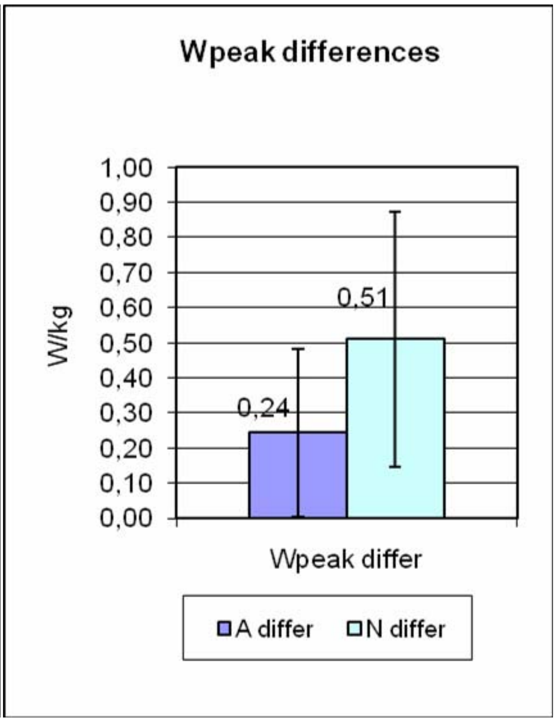
Graph 3



Graph 4



Graph 5



Graph 6

DISCUSSION

The results of our preceding studies of men and women with ICHS, included in the controlled rehabilitation program within the framework of cardiovascular rehabilitation, showed that from the value of $RER_{peak} \geq 1.05$ the values of VO_{2peak} can be considered to be acceptably valid for the purpose of comparison of exercise tests (4,5). That is why we divided this set of men after AIM in advance into groups A and N. If the achieved value of $RER_{peak} < 1,05$, then VO_{2peak} will be underestimated and thus a mistaken assessment of VO_{2peak} differences and distorted results in evaluation of dynamics of the changes can occur. It turned out also in the results of this study; lower input values of VO_{2peak} had a significant share in more than double increase of VO_{2peak} in the group N in comparison with the group A in the premature termination of the exercise test with subsequent increase of the difference between the entrance and final test. Similar changes were found out also in the analysis of W_{peak} both in the group A and in the group N.

It is apparent that the knowledge of RER_{peak} value is necessary for the correct interpretation of peak values (VO_{2peak}, W_{peak}, etc.). RER_{peak} value is important also for the correct classification into functional classes according to VO_{2peak} (e.g. according to Weber). With regard to the fact that the study is not a mortality one, we cannot express our opinion of VO_{2peak} validity for assessment of the prognosis (at RER_{peak} in the range of 1.05 to 1.14). The values of VO_{2peak} achieved at $RER_{peak} < 1.00$ have not a prognostic significance any more (6).

CONCLUSION

When comparing two and more exercise tests, achieving of the sufficient and comparable metabolic loading in both tests is the condition of the correct evaluation of the dynamics of changes; RER_{peak} value in both tests should be at least 1.05. The low value of RER_{peak} indicates premature termination of the exercise test and, consecutively, the low, underestimated value of $VO_{2peak.}$ In comparing two exercise tests with considerably different RER_{peak}, the values of VO_{2peak} and thus also the difference of peak values of oxygen intake are significantly influenced. At the low input RER_{peak} the difference of VO_{2paek} increases (apparently considerable improvement), at the low output RER_{peak} the difference, to the contrary, decreases (apparently small or no improvement of VO_{2peak}). According to the results of our study, premature termination of the symptom-limited exercise test is relatively frequent. In men with ICHS RER_{peak} is lower than 1.05 (4,5) in as many as 40 %.

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CARDIOVASCULAR EXERCISE TRAINING IN MEN AFTER ACUTE MYOCARDIAL INFARCTION

Dedicated to Prof. Franz Halberg, Dr. M.D., Dr. h.c. multi

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INTRODUCTION

Cardiovascular exercise trainining is very important in the complex care of patients with cardiovascular disease. It starts already during hospitalization and after the discharge to home care it continues in the form of controlled out-patient rehabilitation program individual training at home (1). It increases physical fitness, improves quality of life (2-4) and decreases cardiovascular mortality (5,6). Dynamical endurance aerobic activities are the basis of each training unit (7-9,13,14). The best known and most widespread type of aerobic training is the training with continuous work load. Interval training (1,10) can be an alternative training method for persons with a low tolerance of load, with a lower contractility of left ventricle, or for elderly people.

AIM OF THE STUDY

The aim of the present study was to evaluate the effect of 12-week controlled out-patient rehabilitation program with continuous and interval work load on aerobic capacity and performance on the level of anaerobic threshold in men after acute myocardial infarction (AIM) treated by percutaneous thoracoplasty of coronary artery (PTCI with stent implantation).

SET OF PATIENTS

44 men patients after AIM were included into the study. They were divided into two groups. The first group with ejection fraction (EF) 52 ±7 %, group K, n=22, went in aerobic phase

through the training with continuous work load, the second group with EF 49 ±12 %, group I, n=22 went in aerobic phase with the interval training.

Controlled out-patient rehabilitation was started within 12 weeks after AIM. AIM diagnosis was identified at 1st internal cardioangiological clinic of Faculty of Medicine, Masaryk University, St. Anna Teaching Hospital in Brno (treated by PTCI with stent implantation). During rehabilitation all patients were symptomatically stable and their medication was not changed.

The groups did not differ in age and ejection fraction, their characteristic is given in Table 1.

Table 1 Characteristic of the set

	Group K	**Group I**
Number (n)	22	22
Age (years)	57 ± 12	60 ± 7
Ejection fraction (%)	52 ± 7	49 ± 12
Starting RHB (weeks after AIM)	6 ± 2.5	5 ± 3.4

METHODOLOGY

Methods of examination

Before the beginning of rehabilitation (RHB) program and after its completion we made spiroergometric examination to symptom-limited maximum (Pulmonary Function System 1070, MedGraphics, USA). The examination was started by monitoring resting EKG in lying and sitting position (Schiller CS 100), followed by 3-minute adaptation in sitting position on ergometer. The work load was increased every 2 minutes by 20 W to symptom-limited maximum. Anaerobic threshold was determined from the course of changes of ventilatory-respiratory parameters. For the use of RHB it was expressed in watts, heart rate and degrees of RPE (Borg scale).

Before the beginning of resistance training (i.e. in the 3rd week of RHB program) we made isometric test („handgrip“, DHG-SY3, Recens) to verify blood pressure response to isometric load. In the case of a normal response the entrance 1-RM test (one repetition maximum test) was made in three exercises of resistance training. The test was repeated in the 6th week and in the 12th week of RHB program.

Rehabilitation program

The controlled out-patient RHB program lasted 12 weeks altogether with frequency three times a week. The training unit lasted 60 minutes and consisted of warm-up phase (10 min), aerobic phase (1^{st} to 2^{nd} week 40 min; 3^{rd} to 12^{th} week 25 min), toning phase (3^{rd} to 12^{th} week 15 min) and relaxation phase (10 min). The patients in „K“ group went in aerobic phase through continuous training, in „I“ group they went through interval training. For the interval training the following modification was chosen: 30 s of working phase with intensity on the level of anaerobic threshold and 60 s of relaxation phase with the minimum work load 5 watts.

The interval training was indicated by residual ischemia, low ejection fraction of left ventricle, generally low tolerance of work load.

The warm-up phase was aimed at preparing cardiovascular and motor system to further load, prevention of muscular-skeletal lesion. The warm-up phase was composed from dynamical endurance exercises (simple floor gymnastic exercises, exercises with gymnastic apparatus) and stretching of muscle groups with a tendency to shortening.

The aerobic phase was effected on a bicycle ergometer (Ergoline REHA E900) controlled by the program ErgoSoft+ for Windows. The aerobic training intensity was determined on the anaerobic threshold level.

The resistance training was realized on multifunctional muscle conditioning machines TK-HC COMPACT. Four exercises were done (bench press, pull down, leg extension on the machine and sitting-lying positions). The resistance training intensity was determined by the method 1-RM and training loads were determined in percents of maximum: 30-60 % 1-RM each week increases by 10 %). The number of sequences was 3 - 5 with ten repetitions. Before starting the resistance training, the patients were thoroughly informed about proper breathing and technique of doing exercises.

Modified Schultz autogenic training was used for relaxation.

In the course of the whole training monitoring of heart rate, blood pressure and degree of RPE, during the aerobic phase also EKG was carried out.

Statistical processing

Statistical processing was made in the programs Microsoft Excel and Statistica, version 8. Distribution was tested by Lillefors modification of Kolmogorov-Smirnov test of normality. According to the result either paired t-test or Wilcoxon test for dependent specimens were used. The significance level was determined to 0,05, at the statistical significance on this level the testing was made on the level 0,01 (0,001). The results are presented as means with standard deviations.

RESULTS

After the completion of the program a statistically significant increase of the oxygen intake on the level of anaerobic threshold in both groups was recorded (table 2). VO_2ANP increased in „K“ group by 13 %, VO_2ANP/kg by 11 %. VO_2ANP increased in „I“ group by 20 %, VO_2ANP/kg also by 20 %.

Table 2 Parameters of aerobic capacity on the level of anaerobic threshold

	Group K		p	Group I		p
	Before RHB	After RHB		Before RHB	After RHB	
VO_2ANP ($ml.min^{-1}$)	1086±190	1225±291	0.001	995±209	1194±242	0.05
VO_2ANP/kg($ml.min^{-1}.kg^{-1}$)	12.9 ± 1.7	14.3 ± 2.5	0.01	11.6 ± 3.30	13.9 ± 3.71	0.05

VO_2ANP = oxygen intake on the level of anaerobic threshold

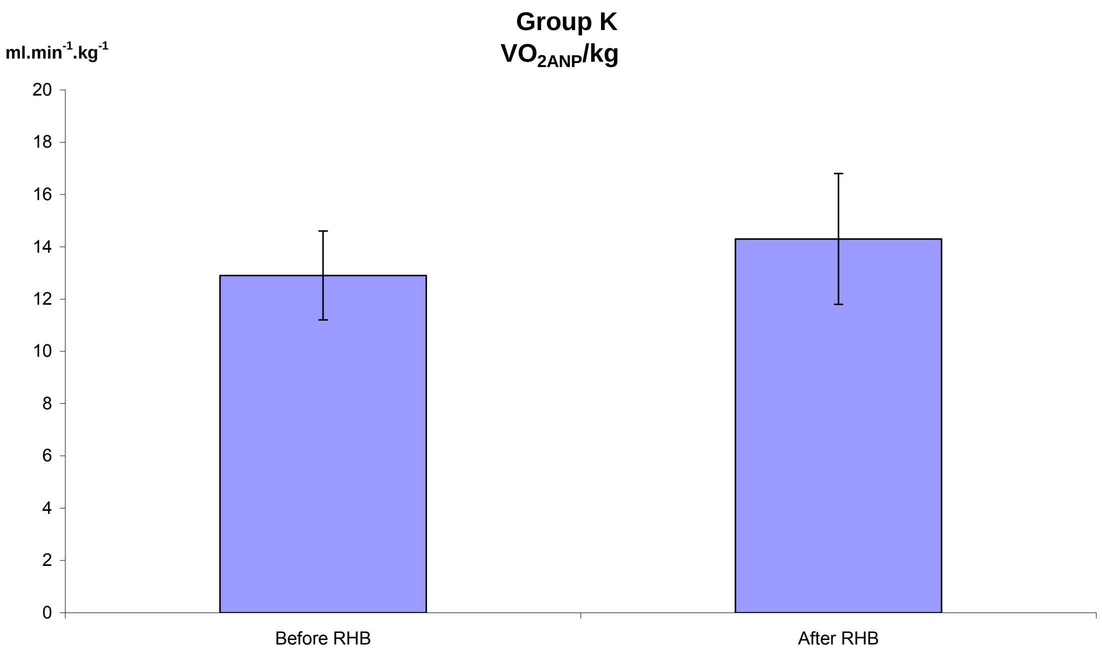

Fig. 1 Oxygen consumption before and after cardiovascular exercise training at the level of anaerobic threshold in group K ($p < 0.01$)

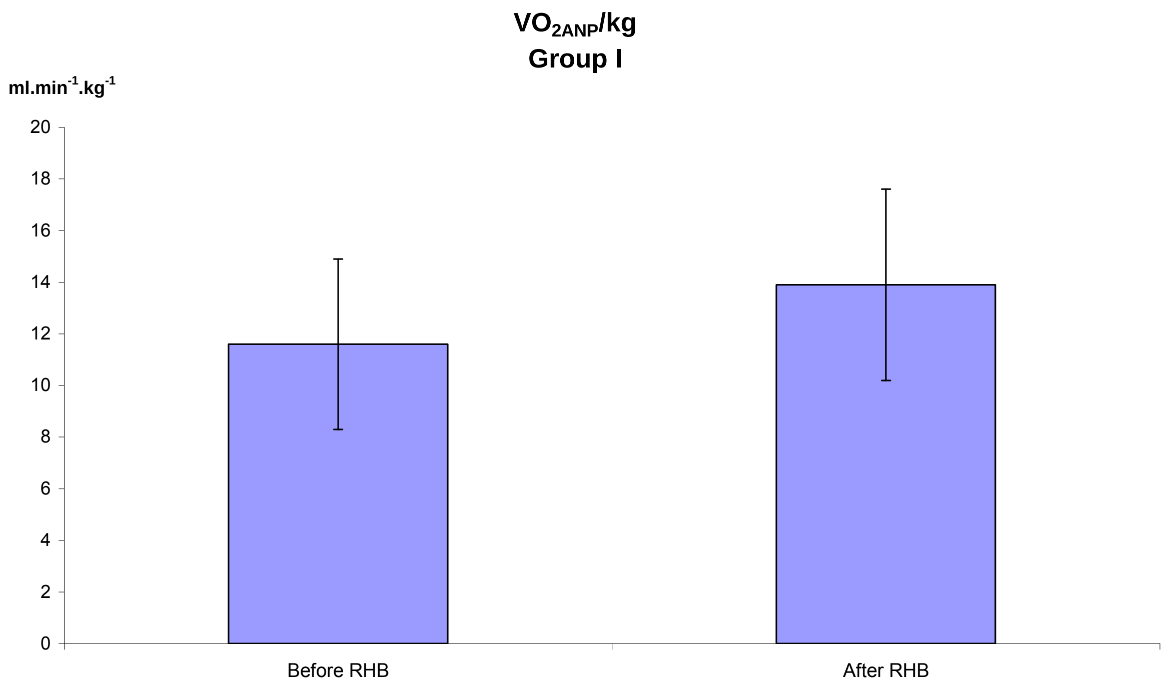

Fig. 2 Oxygen consumption before and after cardiovascular exercise training at the level of anaerobic threshold in group I ($p < 0.01$)

Tolerance of work load on the level of anaerobic threshold also improved statistically significantly in both groups (table 3). WANP in „K“ group increased by 15 % and WANP/kg by 17 %. In „I“ group WANP increased by 35 % and WANP/kg by 37 %.

Table 3 Performance parameters on the level of anaerobic threshold

	Group K		P	Group I		p
	Before RHB	After RHB		Before RHB	After RHB	
WANP (W)	62 ± 14.2	71 ± 19.4	0.01	52 ± 10.2	70 ± 16.1	0.001
WANP/kg(W.kg^{-1})	0.7 ± 0.17	0.8 ± 0.19	0.01	0.6±0.17	0.8 ± 0.26	0.001

WANP = performance on the level of anaerobic threshold

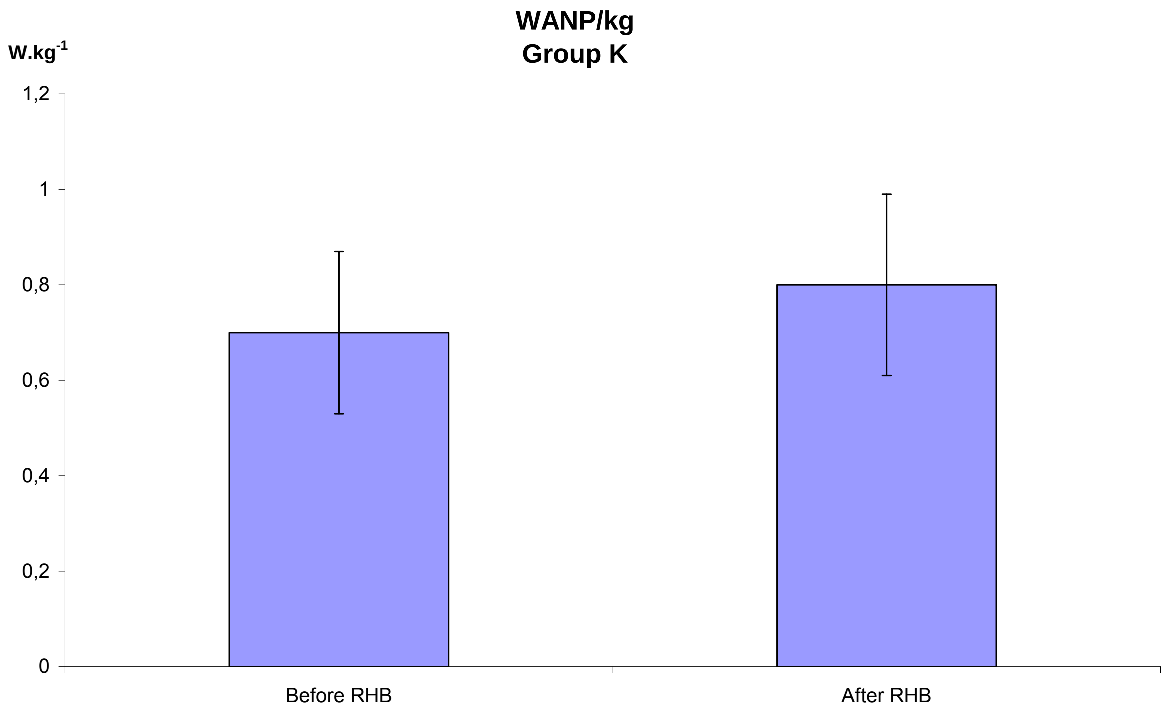

Fig. 3 Work load before and after cardiovascular exercise training at the level of anaerobic threshold in group K (p < 0.01)

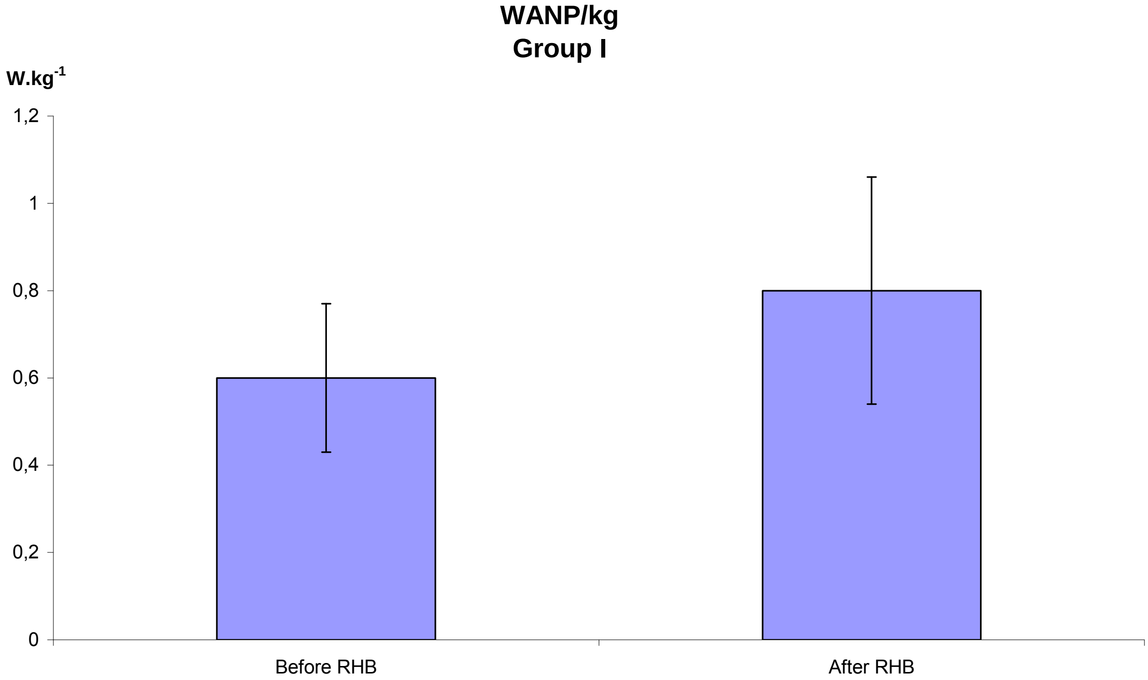

Fig. 4 Work load before and after cardiovascular exercise training at the level of anaerobic threshold in group I ($p < 0.01$)

DISCUSSION

The training with continuous work load and the interval training are used widely not only in sports activities, but also in rehabilitation. The interval training in cardiovascular rehabilitation is often recommended and conducted individually with regard to the health and functional state, to the age and gender of the patient. Work load intensity, duration of working and relaxation phases in interval training and the total number of exercise intervals differ according to the orientation of the training (10-12). Mífková et al. (11) used in her study the following modification of interval training: 30 s of working phase on the level of anaerobic threshold and 60 s of relaxation phase on the level of 5 watts. 38 men with ischemic heart disease were monitored in the study. Both groups differed in age and ejection fraction. The total work done by the patients in this interval training modification was 2,5 to 3 times lower than in the group of patients for which the continuous training was prescribed. In the final spiroergometric examination there was no statistically significant difference between the groups with interval and continuous training either in performance parameters or in parameters of aerobic capacity (evaluated on the level of the highest values achieved). Both in interval and continuous type of the training similar results were obtained at the same training work load intensity.

In our study we used the same modification of interval training: (30 s of working phase with intensity on the level of anaerobic threshold and 60 s on the level of 5 W). We evaluated selected parameters on the level of anaerobic threshold. The patients in our group did not differ in age and in ejection fraction. The benefit of interval training lies in the possibility of obtaining improvement even in risk patients (11).

CONCLUSION

The group with interval training (I) had already before the starting of the program a lower oxygen intake and a lower tolerance of work load than the group with continuous training (K). After the completion of the program the oxygen intake on the level of anaerobic threshold increased statistically significantly in both groups (VO_2ANP increased in „K“ group by 13 %, VO_2ANP/kg by 11 % . VO_2ANP increased in „I“ group by 20 %, VO_2ANP/kg also by 20 %). The tolerance of work load increased statistically significantly on the level of anaerobic threshold in both groups. (WANP increased in „K“ group by 15 % and WANP/kg by 17 %. In „I“ group WANP increased by 35 % and WANP/kg by 37 %.) In both groups we recorded statistically significant improvement of the monitored parameters after 12-week rehabilitation program. Both types of the training were well tolerated.

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THE EFFECT OF 8-WEEK REHABILITATION PROGRAM IN MULTIPLE SCLEROSIS: COMBINATION OF AEROBIC AND RESISTANT TRAINING

Dedicated to Prof. Franz Halberg, Dr. M.D., Dr. h.c. multi

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INTRODUCTION

Multiple sclerosis (MS) is chronic system auto-immune disease that causes functional neurological deficit on the basis of dissemination of demyelinisation focuses in central nervous system (CNS) area (1). Probable cause of persisting neurological deficit is the axon involvement that appears at the beginning of the disease. Maximum axon loss occurs in the first years of the disease (period with minimal disability and clinical finding). As a result of depletion of functional reserves of CNS, substantial deceleration in conduction of nerve impulse develops. Further axon loss brings on an irreversible disability (2). Demyelinisation and axon involvement are localized particularly in periventricular area, brain-stem, cerebellum, lateral and posterior cords of spinal chord. Predominant manifestations include therefore central pyramidal symptoms, cerebral, stem and sensitive symptoms, disorders of autonomic regulation, urinary continence etc. (3). By demyelinisation processes, MS also attacks basic physiological response to work load. Functional changes in skeletal muscles, particularly reduction of the number of fibres of the type I, reduction of oxidative abilities and prevailing anaerobic activity of skeletal extrafusal fibres, are ranked among other pathophysiological processes (4). Increasing disability leads to secondary signs - lost of physical condition with a gradual reduction of muscular mass, reduction of cardiorespiratory fitness including autonomic nervous system dysfunction and finally lost of functional independence (5, 6, 8, 9). Controlled exercise activity represents a significant element with impact on physical condition and course of MS disease.

PURPOSE

The aim of this study was to analyze the effect of 8-week rehabilitation program consisted of aerobic and resistant training form on the parameters of functional fitness, muscle strength, cardiovascular autonomic functions, fatigue and functional independence in a group of patients with Multiple Sclerosis (MS).

METHODOLOGY

Forty patients with verified MS disease, members of „Unie ROSKA Brno“ treated at the 1st Clinic of Neurology, St. Anna Faculty Hospital in Brno, were recruited to the study. Twenty of them fulfilled the entrance criteria for the study: ability of the patient to undergo entrance and final examination, aerobic training on bicycle ergometer and resistant training on multifunctional strenghtening machines. The patients with internal, metabolic and other diseases which could influence validity of the exercise test were excluded. Clinically unstable state of disease, active autonomic nervous system (ANS) dysfunction and medication with influence of cardiorespiratory system or ANS was also a criterion of exclusion.

The study was approved by Masaryk University Ethical Comittee and all the MS patients who participated in the study confirmed "Informed approval of the patient".

Twenty patients were included to the examined group of patients. 2 of them were not able to finish complete program, 3 of them were excluded because of arrhythmias. Final group of patients consisted of 15 patients (12 women, 3 men). General characteristic of the group of MS patients with the evaluation of disease activity (Kurtzke's Expanded Disability Status Scale; EDSS) are given in the table below (Table 1).

Table 1 Basic anthropometric data and MS disease activity description of the examined group of MS patients (mean ± SD)

Women / men	12 / 3
Age (years)	50.7 ± 13.1
Height (m)	1.7 ± 0.1
Weight (kg)	69.1 ± 8.9
Body mass index (BMI)	24.9 ± 3.3
Clinical disability (EDSS)	2.8 ± 0.7
MS duration (years)	15.7 ± 14.4
Primary progressive form of MS (n)	1 (6.7%)
Secondary progressive form of MS (n)	5 (33.3%)
Relabs-remittent form of MS (n)	9 (60.0%)
Walking without aid (n)	11 (73.3%)
Walking with 1 or 2 crutches (n)	4 (26.7%)
Spastic paraparesis (Ashwoth ≤ 2; n)	2 (13.3%)
Without MS specific pharmacotherapy (n)	6 (40.0%)
Imunomodulancia (Interferon, Betaferon, Copaxon, Rebif; n)	7 (46.7%)
Cortico-therapy (Medrol, Solumedrol, Imuran, Prednison; n)	2 (13.3%)

The effect of 8-week rehabilitation program on the parameters of functional fitness, muscle strength, cardiovascular autonomic functions, fatigue and functional independence in a group of patients with MS was evaluated by comparison of the results of entrance examination before starting rehabilitation program and final examination after completion of rehabilitation program.

Entrance and final examination consisted of:

Kurtzke's Expanded Disability Status Scale (EDSS) - a standard scale for evaluation of clinical disability in patients with MS (10). It is a neurological examination that evaluates the impact of MS on 8 basic functional systems. The scale is divided into 20 levels in the interval from 0 (no functional disorder or impairment) to 10 (death due to MS).

Functional Independence Measure (FIM) - a scale for evaluation of independence in basic daily activities (11). Locomotor skills, mental functions and general degree of independence are evaluated in the range from 18 (full dependence) – 126 (full independence) points.

Modified Fatigue Impact Scale (MFIS; 12) is a questionnaire (21 items) expressing subjective assessment of fatigue impact on physical condition (MFISp), cognitive functions (MFISc) and psychosocial functions (MFISps). Answer to each item can score 0 (no fatigue present) to 4 points (almost permanent fatigue). Results of evaluated scales and questionnaires of the examined group of MS patients are given in the table below (Table 2).

Table 2 Results of evaluated scales and questionnaires of the group of patients (mean ± SD)

Scale	Value	Min. - max. value
Clinical disability (EDSS)	2.8 ± 0.7	0 – 10
Fatigue (MFIS)	28.5 ± 17.6	0 – 84
MFISp - physical	14. ± 8.3	0 – 36
MFISc – cognitive	11.7 ± 8.6	0 – 40
MFISps – psychosocial	2.3 ± 1.9	0 – 8
Independence (FIM)	118.5 ± 10.4	18 – 126

Symptom limited spiroergometry was carried out in standard conditions (13) on bicycle ergometer. The twelve-lead electrocardiogram was recorded (Cardiovit CS 100 – Schiller). Ventilation-respiration values were determined by a gas analyzer (Pulmonary Function System 1070 – MedGraphics CPX/D, USA). The work load during exercise test was increased every 2 minutes by 20 W to the symptom-limited maximum. The anaerobic threshold was determined from the course of changes of ventilatory-respiratory parameters. For the use of rehabilitation it was expressed in watts, heart rate, and degrees of RPE (Borg's Rate of Perceived Exertion).

Heart rate variability (HRV) was examined by TASK FORCE MONITOR (CNSystem, Graz, Austria; 14). The examination was carried out by means of non-invasive continuous recording of heart rate and beat-by-beat measurement of blood pressure. 5-minute recording was made at rest in supine position with metronome controlled breathing (f = 0.33 Hz). The data were processed using spectral analysis in the low-frequency component of HRV (0.05 - 0.15 Hz; LF; [ms^2]), high-frequency component of HRV (0.15 - 0.50 Hz; HF; [ms^2]), total spectral power (TP; [ms^2]), index of sympatho-vagal balance (LF/HF). Examination was carried out in standard conditions (exclusion of physical activity 24 hours before examination, more than 4 hours after last meal, 8 hours without smoking and coffee or alcohol drinking, examination between 9 and 12 a.m.).

The controlled outpatient RHB program was designed for 8 weeks with the frequency of twice a week. The training unit lasted 60 to 90 minutes and consisted of a warm-up phase (10 min), an aerobic phase (1^{st} to 2^{nd} week 20-40 min; 3^{rd} to 8^{th} week 25 min) and a relaxation phase (10 min). Resistant training was added to the training unit in the 3^{rd} week of RHB program (3^{rd} to 8^{th} week 15-20 min). ECG, blood pressure and RPE were monitored during the aerobic phase for safety reasons.

The warm-up phase was aimed at preparing the cardiovascular and locomotor system for further work load, prevention of musculoskeletal lesions. It consisted of dynamic endurance exercises, basic gymnastic exercises and stretching of muscle groups with a tendency to shortening.

The aerobic phase was realized on a bicycle ergometer (Ergoline REHA E900) controlled by the program ErgoSoft+ for Windows. Interval or continuous work load training used for the aerobic phase was chosen according to entrance spiroergometry examination (interval training was used in cases of generally low tolerance of work-load intensity). The intensity of training was set at the anaerobic threshold level. The interval training consisted of 30 s of working phase with the intensity at the level of anaerobic threshold and 60 s with a minimum work-load of 5 watts.

The resistant training was added after isometric exercise test ("handgrip", DHG-SY3, Recens) to verify physiological blood pressure response to isometric work load. In cases of normal response, the entrance one repetition maximum test (1-RM test; [kg]**)** was made for three exercises of resistant training (bench-press, pull-down, leg extension). The resistant training was provided on multifunctional strenghtening machines (TK-HC COMPACT). Three exercises were performed: bench-press, pull-down, leg extension. The intensity of resistant training was determined by the 1-RM method. The patients started resistance exercises at 30–60 % 1-RM with weekly increase of 10 %. All three exercises were repeated 10 times in 3 to 5 sets. Proper breathing and technique of exercises was checked by physiotherapist.

Modified autogenic training was used for relaxation at the end of the training unit.

Statistical processing was made using the software Statistica (STATISTICA, StatSoft, Inc. 2008, v. 8.0). Normality of distribution was tested by the Lilliefors modification of the Kolmogorov-Smirnov test. Wilcoxon test for dependent samples was used to compare the entrance and final examination results. The results are presented as means ± standard deviations (SD).

RESULTS

Comparison of mean antropometric values, clinical disability, functional independence and self-perceived fatigue before and after training program completion is given in the table below (Table 3). Significantly lower values of MFIS and MFISp are demonstrated.

Table 3 Comparison of antropometric values, functional independence, self-perceived fatigue before and after training program (mean ± SD)

Parameter	Before training	After training	P
Weight (kg)	69.1 ± 8.9	68.2 ± 8.6	NS
Body mass index (BMI)	24.9 ± 3.3	24.5 ± 3.2	NS
Clinical disability (EDSS)	2.8 ± 0.7	2.7 ± 0.7	NS
Fatigue (MFIS)	28.5 ± 17.6	26.0 ± 14.9	* 0.018
MFISp – physical	14.6 ± 8.3	13.3 ± 6.9	* 0.043
MFISc – cognitive	11.7 ± 8.6	10.8 ± 7.4	NS
MFISps – psychosocial	2.3 ± 1.9	2.1 ± 1.6	NS
Independence (FIM)	118.5 ± 10.4	119.2 ± 8.4	NS

* $P < 0.05$, NS – without statistical relevance

Comparison of mean values of cardio-respiratory tolerance before and after training program completion is given in the table below (Table 4). Significantly higher values of maximal symptom-limited work load and oxygen consumption are demonstrated.

Table 4 Comparison of cardio-respiratory values before and after training program (mean ± SD)

Parameter	Before training	After training	P
W_{SL} (W)	94.4 ± 25.0	102.7 ± 27.9	* 0.042
W_{SL}. kg^{-1} (Watt. kg^{-1})	1.4 ± 0.3	1.5 ± 0.4	* 0.026
W_{ANP} (Watt)	53.5 ± 14.0	57.2 ± 13.6	NS
W_{ANP}. kg^{-1} (Watt.kg^{-1})	0.8 ± 0.2	0.8 ± 0.2	NS
VO_{2SL} (ml O_2)	1463.1 ± 359.2	1578.4 ± 390.3	* 0.015
VO_{2SL} . kg^{-1} (ml O_2.kg^{-1})	21.1 ± 4.4	22.8 ± 4.9	NS
VO_{2SL} . SF^{-1} (ml O_2.tep^{-1})	10.7 ± 3.0	11.2 ± 2.5	NS
MET_{SL}	6.0 ± 1.3	6.5 ± 1.4	NS

* P < 0.05, NS – without statistical relevance

Comparison of mean values of 1-RM before and after training program completion is given in the table below (Table 5). Significant improvement in all of the exercises is demonstrated.

Table 5 1-RM test values before and after training program (mean ± SD)

1- RM test	Before training	After training	P
Bench-press (kg)	22.3 ± 9.3	28.1 ± 9.7	*** 0.0001
Pull-down (kg)	22.1 ± 11.3	28.3 ± 11.3	*** 0.0001
Leg extension (kg)	26.5 ± 8.3	30.9 ± 9.0	*** 0.001

*** P < 0.001

Evaluated values of HRV were logarithmically transformated because for the purposes of data distribution. Comparison of mean values before and after program completion is given in the table below (Table 6).

Table 6 HRV results (logarithmically transformed, mean ± SD)

HRV parameter (controlled breathing 0.33Hz)	Before training	After training	P
Log LF	1,98 ± 0,44	2,07 ± 0,40	NS
Log HF	2,04 ± 0,46	2,03 ± 0,51	NS
Log TP	2,39 ± 0,36	2,45 ± 0,39	NS

LF – low frequency band, HF – high frequency band, TP - total power, NS – without statistical relevance

DISCUSSION

Obtained results of our study concern a sample of MS patients with mild to moderate (16) clinical disability (2.8 ± 0.7, interval 1 to 4) and with a majority of a relaps – remittent form of disease (9 patients, 60%). The rehabilitation program influenced neither clinical status nor functional independence measure. These findings could be caused by various factors. Only 20% of patients had major motor dysfunctions. The majority of causes of disability were sphincter, sensitive, visual and cerebellar dysfunctions. These dysfunctions could not be effectively improved by our program. The results of our training program could also be influenced by the insufficient length of the program. The high level of functional independence in the tested group of MS patients at the beginning of the program approximates the maximal FIM test values (118.5 ± 10.4; max. 126 points). We suppose the decrease from the maximal values to be caused mainly by sphincter, sensitive, visual and cerebellar dysfunctions. These dysfunctions could be influenced by exercise training only in a minimal extent (118.5 ± 10.4 FIM entrance examination values vs. 119.2 ± 8.4 FIM final examination values; 17, 18).

Very important finding was a significant decrease in self-perceived fatigue questionnaire MFIS (28.5 ± 17.6 vs. 26.0 ± 14.9, * 0.018) and its subscale evaluating physical impact of fatigue on health condition MFISp (14.6 ± 8.3 vs. 13.3 ± 6.9, * 0.043). On the basis of presented results we consider that fatigue could be primarily influenced by the physical training as described in recent literature (19, 20, 21). Up to now, there are no relevant and consistent results available concerning combined rehabilitation program for MS patients (22).

Physical fitness and cardio-respiratory tolerance

The comparison of mean values of cardio-respiratory tolerance before and after training program demonstrated 8.7% improvement in symptom limited maximum work load and 7.8% improvement in symptom limited oxygen consumption. Our former pilot studies (23, 24, 25) demonstrated only 4% improvement of $VO_{2SL}.kg^{-1}$ (6 MS patients, EDSS 4.3 ± 1). Other parameters were not influenced statistically significantly. It is surprising that Bjarnadottir et al. (26) demonstrated in a group of 16 MS patients (EDSS ≤ 4) 14.7% improvement of peak oxygen consumption, 18.2% improvement of peak work load and 27.3% improvement of peak work load on the anaerobic threshold level. The training program (60 min) was designed for 5 weeks (3 times per week). It consisted of warm up phase (3min, 33% VO_{2max}), aerobic phase on bicycle ergometer (15-20 min, 55-70% VO_{2max}), resistant phase with 13 exercises (upper, lower extremities, trunk muscles, 15 to 20 repetitions) and 5 minutes of stretching with relaxation. The evident difference in physical fitness results could be probably explained by different weekly frequency of the training. Similarly Petajan et al. (27) found in a group of 21 MS patients (EDSS ≤ 6) 9.1% improvement of peak work load after 5 weeks and 18.6% improvement after 10 weeks of aerobic training (15 weeks program, 3 times/week). A similar rehabilitation program was designed by Rampello et al. (28). They achieved 10% improvement of W_{max} (82 ± 43 W vs. 103 ± 48 W) and 20% improvement of $VO_{2max}.kg^{-1}$

(17,1 ± 7,1 vs. 20 ± 6,6 $ml.min^{-1}. kg^{-1}$) after 8 weeks (3 times / week) of training (11 MS patients, EDSS 3,5). Mostert and Kesserling (29) refer 12% improvement of VO_{2max} after 4 weeks of training intervention (5 times / week, 30 min bicycle ergometr).

Possible explanation of different results between lower values of our study and above mentioned may probably be in different design of aerobic training on bicycle ergometer. We used interval training form in 70% of patients. The interval training form is generally considered rather an alternative form of training and is preferred in patients with lower work load tolerance. In this kind of training, work load phase alternates with a phase without any load or a lower intensity load. In our study, 30 seconds of the work load with the intensity at the level of anaerobic threshold alternated with 60 seconds with the intensity at the level of 5 to 10 Watts. This type of training produces only a minimum amount of lactate. At our dept., continuous training is usually used for patients with higher cardiorespiratory capacity. Differences of the results (W_{ANP}, $W_{ANP}.kg^{-1}$) of above mentioned training programs could also be caused by the use of different exercise protocols (interval vs. continuous training).

Muscle force

The comparison of entrance and final 1-RM test values showed significant improvement in all of the tested exercises after program completion. The highest strength was noticed in pull-down (21.9%) and bench-press (20.6%) exercises which are predominantly focused on shoulder muscle groups. Schwidt et al. (30) demonstrated greater effect in upper extremity strength than in lower extremity in MS patients. Similarly in our study we found only 14% increase of lower extremity muscle strength in comparison to upper extremity muscle strength (pull-down 21.9%, bench-press 20.6%). In our previously reported pilot studies (23, 24, 25) in a group of 6 MS patients (EDSS 4.3 ± 1.0) we noticed statistically significant increase of muscle strength only in upper extremities. We suppose that MS patients should profit from a specific lower extremity resistant training program more. This type of exercise training should have a priority in designing a rehabilitation program. White et al. (31) even recommend incorporating of the resistant training before an aerobic training.

In our group of patients, only 2 of them patients were able to follow the scheme of 10 % weekly increase of 30–60 % 1-RM. The majority of them did not achieve even 60% level of resistant training intensity increase. It probably indicates low tolerance and low capacity of MS patients to progression in resistant training. A period of rehabilitation programs focused on lower extremities resistant training should therefore be prolonged.

Autonomic cardiovascular control

There were not found any signs of autonomic nervous system dysfunctions in the life history of examined group of patients. The comparison of HRV results with normative values of healthy population showed a significant decrease in all of the spectral bands (14). Nevertheless we registered statistically insignificant increase in LF and HF spectral powers and in Total Power in comparison to the initial values. Spectral analysis of heart rate variability is often used for monitoring and evaluation of rehabilitation therapy effect. On the basis of our experience with similar types of training programs in patients with Ischemic Heart Disease (32), Myocardium Infarction (34) or Hypertension (33) we consider increase in HRV spectral powers a sign of improving adaptability of autonomic cardiovascular regulation.

Program safety, negative symptoms and program duration

We noticed only a slight exacerbation of neurological signs (hemiparesthesis, visual worsening) in two cases because of light asymptomatic viral infection in combination with the exercise training load. One week of home rest without any specific pharmacotherapy was recommended by supervising neurologist. One patient (spastic paraparesis, 2 point of Asworth scale) reported a temporary increasing of lower extremity spasticity. It was expressed as acral clonus and worsening of tibialis anterior muscle spasticity. No other patient was emergently forced to interrupt the program. On contrary Rampello et al. (28) presented in their 8 weeks study 26% loss of included patients (MS exacerbation, social status change etc.). We did not notice any discomfort during training on ergometers but nearly 70% of patients reported myofascial or light postural disturbances requiring simple chiropractic interventions caused by the exercises for muscle strengthening. The similar findings reported Dodd et al. (32). The maximal fatigue increase was reported between the 2nd and 3rd week of the program probably due to adaptative physiological response to exercise work load. There were not noticed any signs of overtraining. We decided to choose 8 weeks of training program on the basis of our experiences with the same training design in cases of Ischemic Heart Disease, Diabetes Mellitus, Myocardium Infarction and Obesity (36, 37). 8 weeks of exercise training program with combination of aerobic and resistant training form realized twice a week is according to previously reported articles (27, 29, 31, 38, 39, 41, 42, 43) the shortest rehabilitation program to record improvement in a physical fitness of MS patients.

CONCLUSION

The results of our study demonstrate a possibility to influence some of the physical fitness parameters after 8 weeks of rehabilitation program realized twice a week with combination of aerobic and resistant training form in group of MS patients with mild to moderate clinical disability (EDSS 2.8 ± 0.7). Selected design of exercise training load significantly improved parameters of physical capacity (W_{SL}, $W_{SL} \cdot kg^{-1}$), aerometabolic parameters (VO_{2SL}), extremity muscle strength (1-RM bench-press, pull-down, leg extension) and self-perceived fatigue (MFIS, MFISp). We did not notice significant changes in clinical disability (EDSS) and functional independence. We consider increase in HRV spectral powers after exercise training as a sign of improving adaptability of autonomic cardiovascular regulation.

We also consider 8-week of rehabilitation program with combination of aerobic and resistant training form should be safe for the MS patients with mild to moderate clinical disability. It is essentially important to prescribe an individual intensity of training work load with a respect of an actual medical condition. The combined training program seems to be safe for the MS patients with this level of disability.

ABSTRACT

The aim of this study was to analyze the effect of 8-week rehabilitation program consisted of aerobic and resistant training form on the parameters of functional fitness, muscle strength, cardiovascular autonomic functions, fatigue and functional independence in a group of patients with Multiple Sclerosis (MS).

At the beginning and at the end of the study we examined 15 MS patients with clinically active form of MS (age 50.7 ± 13.1 years, 12 women, 3 men, mean duration of MS 15.4 ± 14.4 years, EDSS 2.8 ± 0.7) who participated in the rehabilitation program. The diagnosis was made in the 1st Dept of Neurology. The patients underwent a clinical examination, MS activity rating (EDSS), symptom-limited bicycle spiroergometry (MedGraphics), spectral analysis of heart rate variability by Task Force Monitor (frequency band LF, HF, TP and sympatho-vagal balance LF/HF) and the extremity muscle strength evaluation (1-RM). The patients were also tested for fatigue (questionnaire MFIS) and functional independence (FIM).

The controlled outpatient RHB program was designed for 8 weeks with the frequency of twice a week. The training unit lasted 60 to 90 minutes and consisted of a warm-up phase (10 min), an aerobic phase (1st to 2nd week 20-40 min; 3rd to 8th week 25 min) and a relaxation phase (10 min). Resistant training was added to the training unit in the 3rd week of RHB

program (3rd to 8th week 15-20 min). ECG, blood pressure and RPE were monitored during the aerobic phase for safety reasons. Three exercises were performed: bench-press, pull-down, leg extension. The intensity of resistant training was determined by the 1-RM method. The patients started resistance exercises at 30–60 % 1-RM with weekly increase of 10 %. All three exercises were repeated 10 times in 3 to 5 sets.

The comparison of entrance and final values showed a significant improvement of functional capacity, namely in the values of spiroergometry parameters ($P<0.05$, Wilcoxon paired test) W_{SL} (94.4 ± 25.0 vs. 102.7 ± 27.9 W, p = 0.042),$W_{SL}.kg^{-1}$ (1.4 ± 0.3 vs.1.5 ± 0.4 $W.kg^{-1}$, p = 0.026), VO_{2SL} (1463.1 ± 359.2 vs. 1578.4 ± 390.3 mlO_2, p = 0.015) and also in the values of muscle strength in Bench-press (22.3 ± 9.3 vs. 28.1 ± 9.7 kg, p = 0.0001), Pull-down (22.1 ± 11.3 vs. 28.3 ± 11.3 kg, p = 0.0001) and Leg extension (26.5 ± 8.3 vs. 30.9 ± 9.0 kg, p = 0.001). We found out the positive significant impact of rehabilitation program on self-perception fatigue scale MFIS (28.5 ± 17.6 vs. 26.0 ± 14.9, p = 0.018; MFISp 14.6 ± 8.3 vs.13.3 ± 6.9, p = 0.043). The other studied parameters did not achieve the statistical relevance. We consider increase in HRV spectral powers a sign of improving adaptability of autonomic cardiovascular regulation. Clinical status (EDSS) and functional independence (FIM) were not influenced by exercise training load and length of the rehabilitation program.

We can conclude that the results of our study demonstrate a possibility to influence some of the physical fitness parameters, muscle strength and self-perceived fatigue after 8 weeks of rehabilitation program realized twice a week with combination of aerobic and resistant training form in group of MS patients with mild to moderate clinical disability (EDSS 2.8 ± 0.7.

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BAROREFLEX SENSITIVITY IN PARKINSON'S DISEASE

Dedicated to Prof. Franz Halberg, Dr. M.D., Dr. h.c. multi

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INTRODUCTION

Symptoms of autonomic nervous system (ANS) dysfunction are inseparable part of Parkinson's disease (PD). These non-motor syptoms are increasingly recognized as a significant cause of morbidity in later stages of PD (49). Recently ANS dysfunctions are extensively studied by many authors. Most of them, in relation to the method used, declare progression of ANS dysfunction proportionally to the progression of other motor symptoms of PD or to the disease duration (13, 34, 35, 41, 51, 66). Some of them declare autonomic failure even before the occurence of first motor symptoms (20, 48, 55). However hardly any double-blind, randomized, controlled studies are available (59).

Clinical studies evaluate ANS function by standard tests which are often based on examination of cardiovascular functions. It is substantiated by the fact that impairment of these functions accompanies all the course of the disease and cardiovascular failure is one of the most common causes of death in PD patients (18).

The most common ANS tests include orthostatic test (15, 35, 43, 51, 63, 70); Valsalva maneuver (13, 15, 18, 66), isometric work load test (66); 30:15 ratio - the ratio between the increase of heart rate (HR) at the 15^{th} heart action and the decrease of HR at the 30^{th} heart action after standing up from supine position (8); E:I ratio - the ratio between the longest RR interval during expiration and the shortest RR interval during inspiration (18); evaluation of the HR and blood pressure (BP) response to a deep breathing (13, 18, 47, 66); tilt table test (8, 15, 35, 52), test of hyperventilation (11, 15, 47); cold pressor test (15), sympathetic skin response (6, 8, 15, 19, 77), test of skin wrinkling (16) etc.

The evaluation of the degree of ANS dysfunctions is still in the forefront of research interest (1, 8, 13, 16, 34, 42, 73). Preceding studies however do not deal with the differences in factors like the severity of PD disability, type of dopaminergic and other pharmacotherapy (56, 57, 66, 67). Examination of heart rate variability (HRV) and baroreflex sensitivity (BRS) lies among non-invasive methods with high sensitivity, validity and reproducibility (29) that can declare ANS dysfunction in early stages of the disease (13, 18, 20, 22, 34, 39, 54, 60). Baroreflex is one of the most powerful short-term control mechanisms of arterial blood pressure.

Some authors also recommend the examination of BRS for differential diagnostics of PD and other extrapyramidal syndromes (6, 12, 15, 18).

The decrease of autonomic control of heart activity is a natural process caused by aging. However, age is not the only factor to cause this decrease of ANS activity (21, 65). Correlation of ANS dysfunction with the duration and especially progression of PD was declared repeatedly in many former studies (13, 66, 18, 45, 74). On contrary, the most recent studies based on iodine-131-meta-iodobenzylguanidine (MIBG) uptake in myocardial scintigraphy do not support this hypothesis and find no correlation between age, disease duration and progression (62). Furthermore, recent study by Haensch et al. (25) with the use of MIBG give the evidence that cardiac denervation occurs also in cases of absent orthostatic hypotension and impaired heart rate variability in PD.

The theory of antiparkinsonian pharmacotherapy as the other main factor of ANS dysfunction cause was also disproved. ANS dysregulation was also declared in studies with de novo PD patients before the first use of antiparkinsonian pharmacotherapy (5, 21, 25, 31, 39, 47). Nevertheless, the type of treatment should be analysed in respect to the aim of study and interpreted correctly. There is wide evidence about modification of cardiovascular responses by levodopa, bromocriptine, selegiline etc. (10, 14, 23, 33, 40, 56, 57, 66, 67, 72).

Another important factor with great impact on ANS function is psychosocial status and cognitive impairment, especially depression (11, 38), dementia (30), apathy, anhedonia etc. (53, 78).

AIM

The aim of the present paper was to study BRS and to analyze the relation between progression of clinical impairment of PD and changes of blood presssure control by baroreflex mechanism.

DESIGN AND METHODS

45 patients with idiopathic PD were recruited to the study from the Czech society „Společnost Parkinson o. s.“ that organizes for its members regular exercise therapy with the frequency 1-2 times a week. Their diagnosis of idiopathic Parkinson’s disease was confirmed at the Ist Clinic of Neurology, St. Anna Faculty Hospital in Brno according to United Kingdom Parkinson's Disease Society Brain Bank diagnostic criteria for Parkinson’s disease (16).

25 out of 45 patients that were recruited to the study did not fullfil the entrance criteria for serious comorbidities (st.p. acute myocardium infarction, hypertension, diabetes mellitus), medication (antiparkinsonian pharmacotherapy with proved affect on cardiovascular function, antidepressives), depression or the presence of any other exclusion criteria listed above.

20 patients (12 men, 8 women) were included into the study. We evaluated Body Math Index (BMI).

They fullfilled the entrance criteria: confirmed diagnosis of idiopathic PD according to above mentioned criteria; stable medication without change at least 4 weeks before BRS examination; no pharmacotherapy with proved effect on ANS or circulatory functions (4, 7, 10, 14, 23, 27, 28, 33, 40, 56, 57, 66, 67, 72); no serious comorbidities with impact on cardiorespiratory and ANS function; non -smokers; no history of any cardiovascular diseases or abnormal ECG; no depression according to Montgomery Asberg Depression Rating Scale (44).

Clinical examination of Unified Parkinson’s disease rating scale (UPDRS) was used for evaluation of motor status - UPDRS III (range from 0 points – no motor complications to 56 points maximum motor complications), late motor complications - UPDRS IV (range from 0 points – no late motor complications to 23 points maximum late motor complications) and clinical impairment - UPDRS V (stadium from 0 – no impairment to 5 maximum impairment). Questionnaire method was used to assess the ANS status - SCOPA AUT. BRS was examined non-invasively as described in detail below. Basic characteristics of examined group of patients are given in the table below ($\bar{x}$ ± SD; Table 1):

Table 1: Basic characteristics of PD patients

PD (n = 20)	**AGE (years)**	**DURATION OF DISEASE (years)**	**BMI**
$\bar{x}$	70.9	6.0	26.4
SD	6.3	3.0	2.3

Group of age and sex matched control subjects (CONTROL) was examined to enable comparison of the absolute values of BRS. All the patients in this group fulfilled the entrance criteria specified above for PD patients. Basic characteristics of the CONTROL group is given in the table below ($\bar{x}$ ± SD; Table 2):

Table 2: Basic characteristics of healthy patients – controls (C)

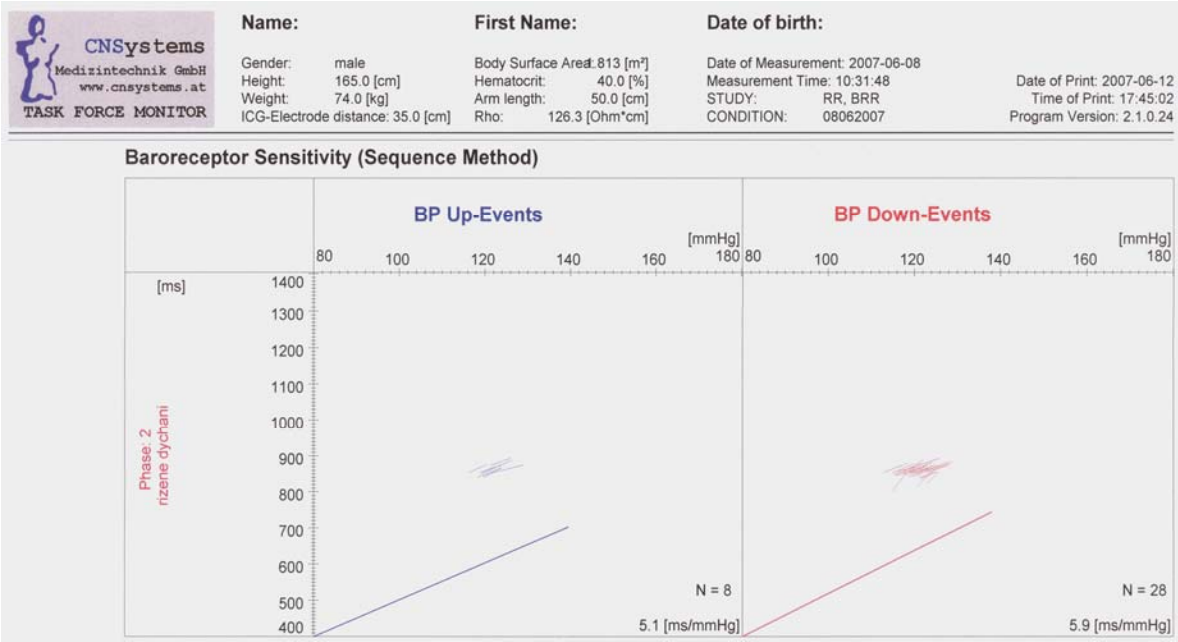
C (n = 11)	**AGE (years)**	**BMI**
$\bar{x}$	69.9	28.0
SD	9.9	3.3

Assessment of BRS was based on non-invasive short term examination (5 minutes) in the supine position at rest using sequence method of analysis by the system Task Force Monitor, CNSystems Medizintechnic GmbH. Fallowing criteria were fulfilled: No abnormal physical activity the day before examination; at least 6 hours of sleep during the night before examination; good quality of sleep (score 6 or higher on the quality of sleep scale from the worst sleep „0“ to the best sleep „10“), observance of typical schedule of daily tasks including medication; only a light breakfast before examination without coffee, tea, alcohol (58) taking into account the age of patients - at least 2 hours before the examination; the ideal “on“ state during examination (18); examination on work day between 9 and 11 a.m. to minimize the effect of circadian variations (37).

The data for the analysis are obtained from beat to beat measurement of blood pressure and heart rate. BRS is assessed from sequences of examination where there was an increase or decrease of systolic blood pressure (SBP) at least in 3 successive RR intervals. The treshold value for including measured beat to beat SBP and RR interval changes in a sequence is set at 1 mmHg for SBP changes and 6 ms for RR interval changes. The slope of regressive curve based on the relation between SBP and RR interval expresses the baroreflex heart rate, shortly baroreflex sensitivity ([ms/mmHg]; 9, 36, 37).

Metronome controlled breathing with frequency f = 0.33 Hz (13, 24, 41, 47, 50, 54, 64, 66, 75) was used to increase reproducibility of BRS examination. Graphic example of BRS sequence analysis examined in supine position at rest with metronome controlled breathing (f = 0.33 Hz) is given in the graph below (Graph 1).

The measurement took place in a quite room. The subjects were examined after at least 10 minutes of resting in supine position with spontaneous breathing.



Graph 1: Graphic example of BRS examination results

The absolute values of baroreflex (ms/mmHg) were considered the indicator of the extent of cardiovascular ANS regulation impairment in all the cases where the number of sequencies was sufficient (down events ≥ 7 and up events ≥ 7) (the group of patients PD I). The patients with insufficient number of sequencies (down events ≤ 7 and up events ≤ 7) were grouped in the PD II.

The differences in all examined parameters were evaluated statistically. The normality of data distribution was tested by the Kolmogorov-Smirnov test and the differences between groups PD I. and PD II. by the T-test for independent samples (STATISTICA, StatSoft, Inc. 2008, v. 8.0).

The study was approved by the Ethical Comittee of Masaryk University. All the patients were informed about the examination method used and their rights in relation to this study.

RESULTS

The results of the comparison of both groups of PD patients (PD I. vs. PD II.) are given in the tables below ($\bar{x} \pm$ SD, statistical significance). In the table 3 there are values of age, duration of the disease, BMI and frequency of spontaneous breathing ($\bar{x} \pm$ SD, statistical significance; Table 3):

Table 3: Characteristics of patients PD I., PD II. and healthy subjects C

	AGE (years)	**DURATION OF DISEASE (years)**	**BMI**	**SPONTANEOUS BREATHING FREQ. (Hz)**
C (n=11)	69.9±9.9	--	28.0±3.3	0.28±0.05
PD I. (n=11)	70.7±7.2	5.1±2.7	26.8±2.7	0.32±0.03
PD II. (n=9)	71.0±4.9	7.2±3.0	26.0±1.4	0.32±0.04
	n. s.	**n. s.**	**n. s.**	**n. s.**

In the table 4 there are values of motor status UPDRS III, late motor complications UPDRS IV, basic measure of clinical impairment UPDRS V and a questionnaire enquiry for ANS dysfunctions status SCOPA-AUT ($\bar{x}$ ± SD, statistical significance; Table 4):

Table 4: Results of Unified Parkinson's disease rating scale (UPDRS): motor status - UPDRS III, late motor complications - UPDRS IV, clinical impairment - UPDRS V, and a questionnaire enquiry for ANS dysfunctions status SCOPA-AUT

	UPDRS III	**UPDRS IV**	**UPDRS V**	**SCOPA-AUT**
PD I. (n=11)	19.8±10.0	3.7±3.2	1.7±0.5	15.0±8.1
PD II. (n=9)	25.0±8.8	4.0±2.4	2.3±0.5	21.4±6.6
	n. s.	**n. s.**	**** p ≤0.01**	**n. s.**

Statistical comparison of values of the UPDRS V reveals significant increase in PD II. group defined as a group with insufficient number of sequencies in BRS examination. Comparison of the values of other parameters - UPDRS III, UPDRS IV and SCOPA-AUT shows only insignificant increase in PD II. group.

In the following table mean values of RR interval, systolic blood pressure (SBP), diastolic blood pressure (DBP) and BRS are presented ($\bar{x}$ ± SD, statistical significance; Table 5):

Table 5: Examination results: hemodynamic parameters and BRS

	Heart rate (b.p.m.)	**SBP (mmHg)**	**DBP (mmHg)**	**BRS ms/mmHg**
CONTROL (n=11)	72.6±13.0	127.7±11.1	78.3±9.5	7.7±3.6
PD I. (n=11)	69.0±9.5	127.7±10.6	83.2±8.3	4.7±1.4
PD II. (n=9)	64.8±8.7	118.3±7.5	76.2±8.6	--
	n. s.	**n. s.**	**n. s.**	**** p ≤0.01**

Statistical comparison of chosen parameters: RR interval, SBP, DBP and BRS between groups PD I., PD II and CONTROL revealed insignificant differences in the values of RR interval, SBP and DBP. BRS was significantly lower in PD I. group defined as a group with sufficient number of sequencies in BRS examination in comparison to CONTROL group.

DISCUSSION

Baroreflexes are continuously activated by small deviations of arterial pressure around the set point. Spontaneous fluctuations of arterial pressure and RR interval can therefore express the quality of cardiovascular control mechanism (37).

BRS measurement plays an important role in the evaluation of cardiac ANS neuropathies in cardiovascular diseases as well as in neurodegenerative diseases. The mechanism of baroreflex is active during sudden changes of blood pressure and as well in the steady-state. For that reason BRS activity can be evaluated also by analysis of spontaneous fluctuation of arterial SBP and RR interval under various determined conditions in steady state (18, 36, 37).

Current research studies declare sympathetic noradrenergic dysfunction in PD patients. Its clinical importance is based on the fact, that this dysfunction is considered to lead to orthostatic hypotension. The incidence of orthostatic hypotension is among 20-50% of PD patients and is of major interest for substantial participation on falls and accidental injuries (20, 42, 63). There was 25% incidence of orthostatic hypotension among our group of PD patients.

There are other factors besides baroreflex that have an impact on heart rate variability during breathing. These factors influence correlation between RR interval fluctuations and oscilations of SBP that is not caused only by baroreflex but also by respiration itself (4). Nerve links in CNS cause excessive transfer of signal from the centre of respiration to medullar vagal efferent neurons which results in inhibition of vagal activity during inspiration

(47). HR fluctuations are also dependent on local intracardial or sinnodial stretch reflex (32). Another reflexes with the impact on HRV are Hering-Breuer reflex (stimulated by lung and thoracic wall expansion during inspiration) and Bainbridge reflex (increase of central venous volume causes changes in cardial filling). Both stimulate cardiopulmonary structures mechanically and so increase HR (47). Humoral substances (e.g. angiotensin) play also an important role in central modification of baroreceptor responses. All these factors can be influenced by different patterns of breathing, exercise, psychological stress etc. (37). We consider BRS examination with metronome controlled breathing at the frequency 0.33 Hz a method that decreases the impact of above mentioned factors and increases reproducibility of BRS examination.

The results of the present paper support the theory of progression of ANS dysfunction on the basis of BRS examination from 5 minute recording during metronome controlled breathing with the frequency 0.33 Hz. Decreased number of UP and DOWN events was found in cases of advanced PD.

The same results were reported by Oka et al. (46) and Friedrich et al. (18) on the basis of BRS examination of larger groups of PD patients (spontaneous breathing). Friedrich et al. conclude the same results with the use of trigonometric spectral analysis of BRS.

BRS score 4.7±0.5 ms/mmHg in case of our group PD II. with initial PD with UPDRS V 1.7±0.5 is significantly lower than that of CONTROL group. The same values of BRS for healthy controls were published by Tank et al. (94) for spontaneous breathing in supine position and age category 60-69 years (8±3 ms/mmHg). Szili Török et al. (68) published similar data on the basis of a study with 23 PD patients of mean age 65±9.3 years, UPDRS V 2.1±0.8, BRS 4.3±3.5 ms/mmHg and control group of age and sex matched healthy individuals of mean age 70±6.6 years and BRS 8.9±6.9ms/mmHg.

No correlation was found in our study between any of the UPDRS subscales, SCOPA AUT and symptoms of autonomic dysfunction. Correlation between orthostatic hypotension and decreased values of BRS was presented by other authors (15, 18, 47). Idiaquez (30) suggest independent involvement and variability among PD patients. The same opinion is supported by latest studies by Shibata (62) based on MIBG myocardial scintigraphy.

ANS impairment is often less appreciated than motor impairment but is important source of disability and handicap for many PD patients (71, 76). Management of non-motor symptoms should definitely be a part of comprihensive rehabilitation approach to the treatment of PD.

BRS examination plays an important role also in relation to the most common cause of death in PD. Increased mortality in PD patients is mainly due to respiratory and cardiovascular complications (2, 3). The ATRAMI study in patients after myocardium infarction showed that depressed BRS can be considered an independent predictor for sudden cardiac death (61).

We consider examination of BRS a valid tool for non-invasive assessment of ANS dysfunction in PD.

CONCLUSION

Advanced stages of PD are accompanied by more pronounced ANS dysfunction that leads to a decrease of a number of sequencies in BRS examination and to a decrease of absolute values of BRS (4.7±1.4 ms/mmHg in PD patients vs. 7.7±3.6 ms/mmHg in healthy controls).

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