Faculty of Medicine • Masaryk University • Brno • Czech Republic

Department of Physiotherapy and Rehabilitation
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PROCEEDINGS

SYMPOSIUM

NONINVASIVE METHODS IN CARDIOLOGY

Edited by: Halberg F., Kenner T., Fišer B., Siegelová J.

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The Symposium takes place under the auspices of

Prof. PhDr. Petr Fiala, Ph.D., Rector of Masaryk University Brno

Prof. MUDr. Jan Žaloudík, CSc., Dean of Faculty of Medicine Masaryk University Brno

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CONTENTS

ROLE AND CLINICAL IMPORTANCE OF THE EVALUATION OF ARTERIAL PULSES

Thomas Kenner

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Dedication

This short and incomplete review of some own interests and some outlooks is dedicated to

Bohumil Fiser

who, together with all members of the "Brno-team" organized and stimulated so many interesting ideas and meetings, and who together with all friends in this city made Brno to a meeting point, where all of us love to come together.

It seems to me that many ideas and plans, on which all of us sometime started to work and which then were forgotten or neglected, suddenly come up again, so that even some historical parameters recently receive a kind of scientific medical OSCAR, which is titled " GOLD STANDARD".

I would say, that exclusively Bohumil and all members of the "Brno Team" deserve such a "Gold Standard" title.

Below I will try to present my opinion that I have doubts about the validity of all other "gold standard" titles in medical science.

Remarks

The choice of words, which are used in order to express certain thoughts, gives insight into unconscious trends of brain activity.

I am astonished about the increasing abundance of expressions like „gold standard" in medicine and medical research. One interesting explanation of using such an expression can be found in Sigmund Freud's book on "jokes and their relation to the unconscious".

There appear to me two main considerations for an analysis. At first the jealous association of medicine with gold and money may play a role. In fact, this is in agreement with the observation of a present trend in clinical medicine towards business-like industrialization (Lüscher, 2008). On the other hand it seems surprising that in the current time of financial and banking crisis, the rather slippery and variable gold value is chosen for the description of biological norms and standards. Perhaps unconsciously the word gold expresses the wish that life should not be associated with the uncertainties of international oil corruption.

One such “gold standard” supposedly is the value of the pulse wave velocity for the estimation of the stiffness along the aorta as measured between carotid and femoral artery (see T. Weber 2008).

Introduction

The time course of functional processes in a dynamic system – like the CV-system - depends on the structure of the system. Therefore, one can state that the observation of functional processes can be used to extract diagnostic information about structure and function.

The functional processes of the CV-system are related to flow and pressure in the vascular channels.

This trivial introduction aims to the question how to extract relevant diagnostic information, and how to analyze and present this information.

Any time-dependent signal – like arterial pulses – can be analyzed and described in terms of time domain or in terms of frequency domain.

The time sequences of arterial pressure and flow are described mathematically by a pair of transmission equations. These equations have been used already in the 19 th century by E.H. Weber, by A.I. Moens and by J. v. Kries.

When I read about hemodynamic recordings, interpretations and calculations I have the feeling that experiments and descriptions should be revisited, which Wetterer and Kenner have published in 1968 in a book, which had the disadvantage to be written in German and which in addition is unavailable since many years. These experiments and explanations were easy to understand and were intended to present some basic knowledge about developments in analysis of arterial pulses in a simple form.
The following is the attempt to review and to explain some fundamental facts, which seem to me essential for application in diagnostic procedures.

TIME DOMAIN

Pulse wave velocity

The pulse wave velocity is an essential term in these equations. The equation, which describes the pulse wave velocity as a function of the physical properties of an elastic tube and the contained fluid bears the name Moens' equation:

$$c = \sqrt{Eh/2r\rho}$$

c: pulse wave velocity, E: elastic modulus, h: wall thickness, r: radius of the tube,
ρ: density of the fluid

The pulse wave velocity in a tube increases with increasing elastic modulus (a measure of stiffness) and with wall thickness. c decreases with increasing radius and increasing density of fluid (blood).
Due to the tissue properties, distension of arteries – by increasing blood pressure – inceases the elastic modulus and consequently the pulse wave velocity.

Characteristic impedance

For illustration of the behavior of pulse waves in an artery Wetterer and Kenner used a model system consisting of a pump and an elastic tube, which on its distal end is adjusted with an outflow resistance. In the example of Fig. 1 the pump generates a flow pulse. The pressure reacts with a pressure pulse. As will be shown below, such a pump like a normal ventricle may be called a "hard" pump. During the diastole the outflow valve is closed, consequently no central flow can be seen during this period.

The relation between the amplitude of the pressure pulse (dp) and the flow pulse (dq) is described by the so called characteristic impedance

$$Z = dp/dq$$

Z can be determined by the following relation:

$$Z = c\rho/r^2\pi$$

The stiffer the artery and the higher the pulse wave velocity, the higher is the pressure amplitude – in relation to a given flow amplitude.

Pulse wave reflection

Pressure and flow waves run along a fluid filled tube with velocity c. On a location where the characteristic impedance increases or decreases or where a resistance is located, wave reflection takes place. The reflected part of a wave then runs into the reverse direction. In the arterial system the main peripheral reflections are positive, thus the pressure wave returns without changing sign, as in the simple example of fig. 1 (from Wetterer and Kenner p. 28).
If a reflected wave reaches the closed outflow (e.g. aortic) valves, then total reflection takes place – as can be seen in fig. 1. As long as the valve is open through systole, the reflection factor may be reduced. The reflection factor k indicates the sign and magnitude of the reflected part of the wave as related to the incoming magnitude. The following equation describes the reflection factor at the location of resistance.

$$k = (R - Z)/(R + Z)$$

The equations include the description of the reflection of both, pressure and flow waves. It was Ph. Broemser who recognized the fact, that the returning reflected pressure wave may influence the ejection of the corresponding ventricle. He was the first to discuss the possibility of an optimal matching between heartbeat and the structure of the vascular system.

Pressure-flow relation and wave reflection

A resistance R is defined as the quotient of pressure gradient and flow gradient. From the observation of a typical pressure-flow relation it can be concluded that at any point of the function shown in fig. 2 (from Wetterer and Kenner p. 316), that – according to the given definition – R may have a different value for different pressure values. It was to my knowledge R. Ronniger (1955) who recognized that for the peripheral reflection of a wave the steepness of the pressure-flow relation in the range of the pressure amplitude is essential:

$$R_{diff} = dp/dq$$

The fact that the pressure-flow relation is not proportional, but may be nonlinear and may be described by a non-proportional line, is important for the actual values of systolic and diastolic pressure as indicated in fig. 2. It can be concluded that the reflection factor and the magnitude of peripheral reflection is not necessarily related to the value of the total peripheral resistance.

Negative reflection

There are two interesting conditions where negative reflection takes place.

One condition is present when – e.g. in the upper extremity – a reflected wave runs towards the branching point at the aorta. At this point the reflected wave finds – entering the aorta - a marked decrease of the characteristic impedance. Therefore, this wave is negatively reflected. – It returns in distal direction after changing sign.

Another condition is artificially produced by the inflation of a cuff during the classical measurement of blood pressure. The location of the artery, which is occluded by the inflated cuff, has an effect as a positive reflection site. During the following reduction of the cuff pressure, the arterial pressure wave may suddenly open the occluded artery, thus generating an effect which corresponds to a sudden shift from positive to negative reflection at this location (see Kenner 1979). In any location and/or condition of the body where arteries are compressed by outside pressure, similar phenomena may be present.

Hard (flow) and soft (pressure) pump

Fig. 3 (from Wetterer and Kenner p. 185) explains the difference between extreme types of pumps. A normal strong ventricle generates flow pulses even against increasing outflow resistance. It rather corresponds to a "hard pump". In contrast, a ventricle in a state of decompensation reacts markedly towards changes of outflow resistance. It rather can be compared to a soft pressure pump. In the case of a hard pump retrograde incoming waves, which arrive at the root of the aorta during systole are reflected positively. In the case of a soft pump, during systole the reflection factor is reduced or even a negative central reflection can be expected.
These considerations explain the fact that the properties of the heart muscle have a characteristic effect on the central aortic pulse contour.

FREQUENCY DOMAIN

Resonance and transfer function

If, into the elastic-tube model, instead of periodic pulses of a certain frequency, sinusoidal flow oscillations of variable frequency are generated by the pump then, resonance phenomena can be observed as shown in fig. 4 (from Wetterer and Kenner p. 60).

It is evident, that a peripheral pressure contour has a different shape a central (aortic) pressure pulse.
In the case of sinusoidal pressure variations, the shapes of flow and pressure are always and everywhere sinusoidal. Besides by the frequency, central as well as peripheral oscillations can be characterized 1. by amplitude and 2. by phase.
In fig. 4 only amplitudes can be recognized, which vary in characteristic manner as function of the frequency.
The importance of calculations in terms of frequency domain can be explained by the fact – mentioned above – that any signal can be transformed from time domain into frequency domain by so called Fourier transform. An example in Fig. 5 (from Wetterer and Kenner p. 258) will be explained below.

The relation, which permits to determine the connection between two pulses describes the frequency dependence of the relation between amplitudes and phases, and thence between the pulse contours, is called transfer function. Recently the transfer function between radial and aortic pressure pulses is quite often mentioned. This transfer function supposedly permits to calculate the shape of the aortic pressure pulse from recorded pressure pulses at the radial artery (O'Rourke 1996).

Input impedance and extended analysis of cardiovascular control

The relation between pressure and flow pulses can – in the frequency domain – be described by a transfer function. The amplitudes ("modulus") of this function, which depends on the frequency has the dimension of a resistance. In order to illustrate this function, fig. 5 shows the frequency dependence of this function from measurements by O'Rourke and Taylor in a dog (taken from an illustration in Wetterer and Kenner 1968). Dogs have a marked respiratory arrhythmia, which is shown as an insert; this simplifies the estimation of the data shown in fig. 5. The function which describes the frequency dependence of the input impedance is characterized by a U-shape with a marked minimum.

In a study published nearly 40 years ago (Kenner 1972) it was shown, that there are two components of information in the input impedance. The part above the heart rate contains information about the arterial system as discussed above. The second part of lower frequencies, which can not easily be measured, contains information about cardiovascular control; e.g. baroreceptor reflex and autoregulatory control of blood flow and blood pressure.

The observation of input impedance in the region of frequencies below the heart rate, depends on the presence of slow pressure-, flow-, or heart rate- variations. In the example of fig. 5 the spontaneous arrhythmia was useful. Also, experimentally generated variations, which influence blood pressure and flow like e.g. tilting may be used.

In the paper mentioned (Kenner 1972), a simple method for the description and examination of the overall control properties of the circulatory system was derived and discussed. The objective of the study was, to present an overlook over the behavior of the whole circulation in response to disturbances in the low frequency region. Therefore, approximated transfer functions were used to describe the circulatory control properties.

The low frequency input impedance (frequency region between about 0.0005 Hz and heart rate) is shown to be a very useful magnitude to examine the closed loop behavior of the system.

The term closed loop condition indicates the presence of feedback within the system. In contrast, open loop is an experimental condition if the sensors (e.g. baroreceptors) can be stimulated isolated without feedback.

It is found that the basic control mechanisms in local arterial beds as well as in the whole circulation can be described by pressure and flow control loops, both having first order transfer properties. Considering the circulation as a whole, the fact has to be taken into account, that the system, including the heart as an amplifier, is a mechanical feedback system. Onto this system the autoregulatory and neural (baroreceptor) control loops exert their influence.

A set of equations was established which permits to describe the dynamic properties of the circulatory system under closed loop condition and under a variety of open loop conditions. The effect of blood volume variation, infusion of vasoactive drugs, and the role of a time delay into a control circuit can be demonstrated. The equations in addition yield a simple and powerful stability criterion, which permits to predict under which conditions instability and pathologic oscillations of blood pressure, blood flow and also of respiration may be generated.

Summary

Quite some time after the periods of Otto Frank, Philipp Broemser and Erik Wetterer – whom I can call my teacher and who wrote a book on the arterial pulse together with me – the interest in arterial hemodynamics appeared not really of importance in medicine.

Recently fluid dynamics of the cardiovascular system and in particular, the generation of arterial pressure and flow pulses gain more and more interest. Parameters and mathematical variables were rediscovered or reinvented and several types of indices were constructed. The computerization finally permitted easily to estimate and calculate parameters and indices. And of course, competition between different types of instrumentation plays a role, even as far as normal values of parameters and indices are concerned. Funny enough, as a consequence, certain parameters and measurement techniques are being revalued as "gold standard".

In this short study it is attempted to summarize some basic facts of cardiovascular fluid dynamics. Furthermore it is attempted, as short as possible to explain the two ways to describe signals: in the way of time domain and in the way of frequency domain.

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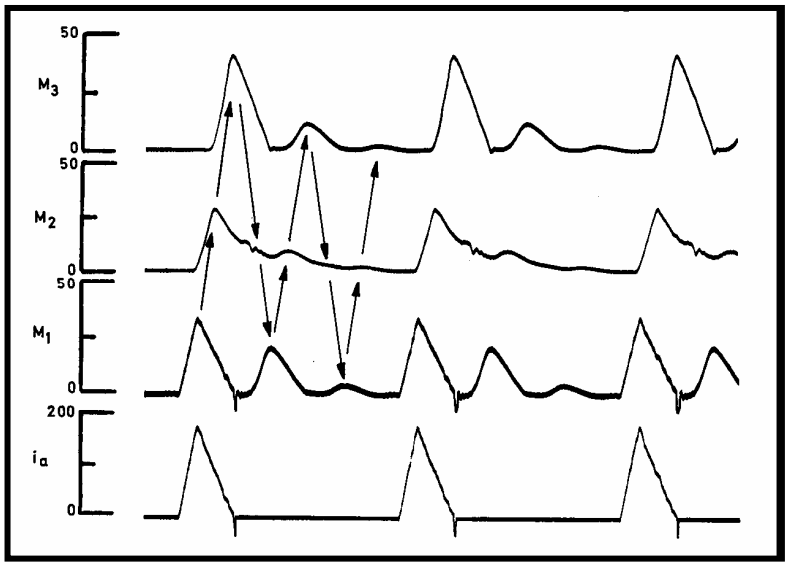

Fig, 1
Central flow pulse (bottom) and positive end-reflection of pressure pulses i flow, M pressure (central, middle, end of tube).

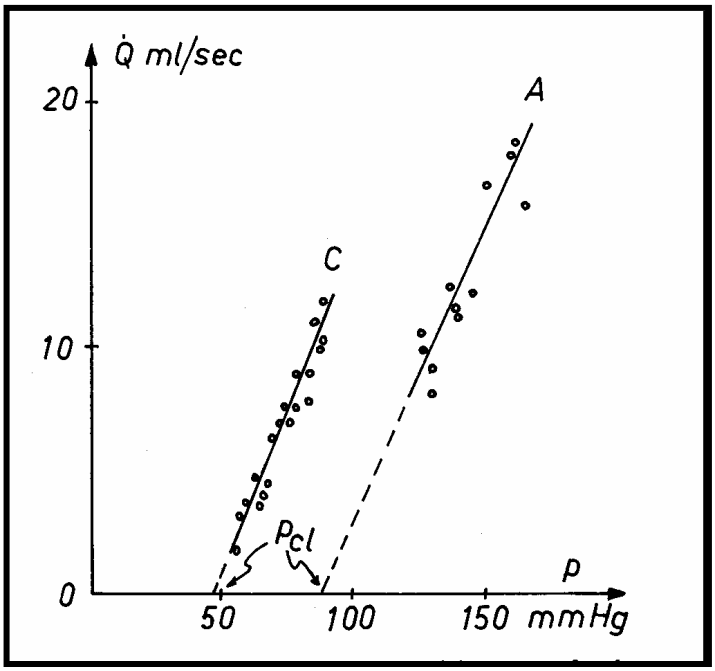

Fig. 2
Non-proportional pressure (p) – flow (Q) – relation In an anesthetized dog. C control, A after Adrenalin-infusion

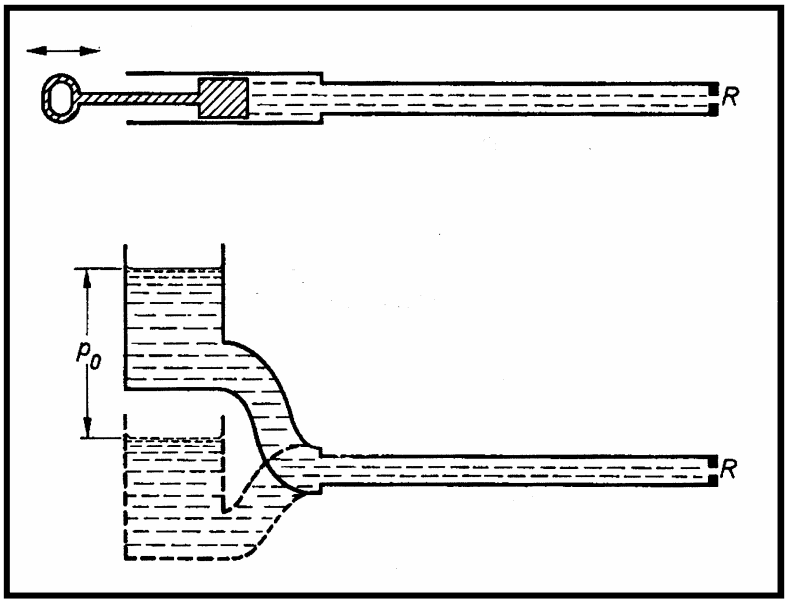

Fig. 3
"hard" flow pump
"soft" pressure pump

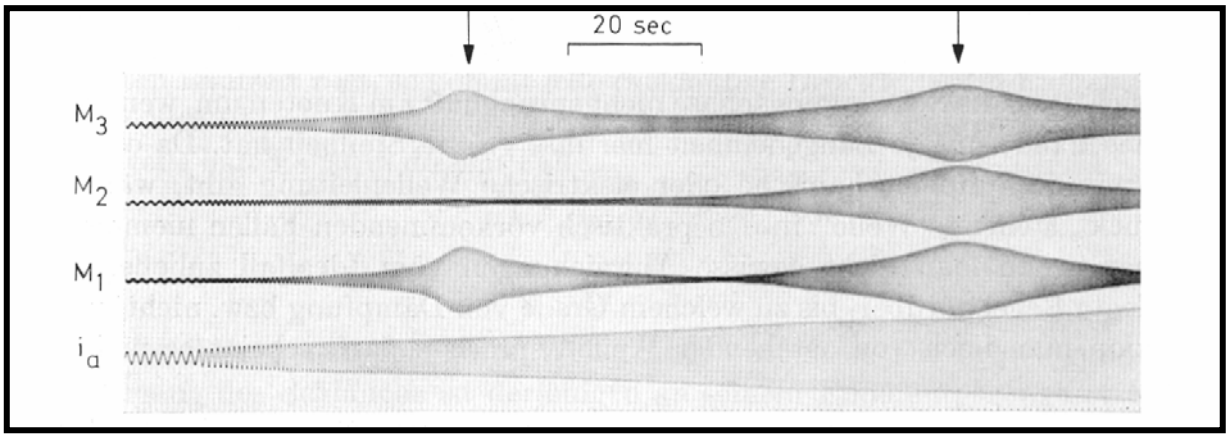

Fig. 4
Resonance of pressure oscillations. From left to right the frequency of the flow-input increases from 0.7 Hz to 6 Hz.
Arrows: resonance frequencies at 2.22 Hz and 4.44 Hz.
i flow, M pressure (central, middle, end of tube)

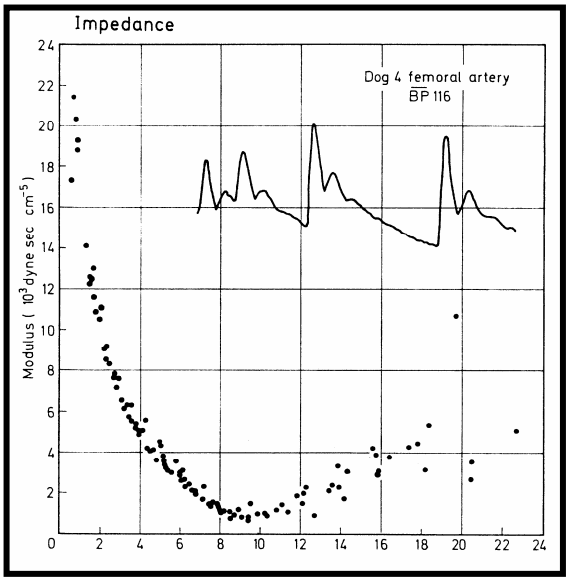

Fig. 5
Input-impedance of a dog-aorta.
(after O'Rourke and Taylor 1966).
See text.

All figures are taken from Wetterer and Kenner (1968)

Quo vadis chronomics 2008:
Measuring variability in us, among us and around us

Franz Halberg, Germaine Cornélissen and Othild Schwartzkopff

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The project on The BIOsphere and the COSmos (BIOCOS) works toward change from a health care based on spotchecks in care providers' offices to a more thorough cost-effective self-surveillance based on monitoring. For instance, the chronomics of blood pressure (BP) and heart rate (HR) detect **v**ascular **v**ariability **d**isorders (VVDs) and their combinations in **v**ascular **v**ariability **s**yndromes (VVSs). 7-day/24-hour chronobiologically interpreted ambulatory monitoring has been ongoing at Masaryk University, the leading European academic institution for chronobiology, in Brno. The time series thus obtained lend themselves to monitoring the sun, specifically space weather, unseen but important, accounting for novel differences between life and death.

1. VARIABILITY ACCOUNTS FOR THE DIFFERENCE BETWEEN LIFE AND DEATH

Genetics, the study of diversity in space, in inbred mice enabled the development of chronobiology, the study of diversity in time.

Both are important since:

In response to the same stimulus such as noise,

- one *audiogenically susceptible* inbred strain of mice may respond with convulsions and death; *but*
- another *audiogenically resistant* strain may not respond to the same noise and will survive

as studied by genetics (not shown)

In response to the same stimulus such as noise,

- one group of audiogenically susceptible mice may respond with convulsions and death when exposed at a *vulnerable time;* but
- another group of the same audiogenically susceptible mice can be *prevented* from convulsions and death and will survive, when exposure is targeted at a *resistant time;* i.e., by *shielding in time*

as studied by chronobiology

Next, nonphotic cycles were found to characterize

- sudden cardiac death, suicide, crime, war and terrorism,

as studied by chronomics

2. ORIGINS:

- Study of the quantitative rules of plant hybridization began in a pea patch in **Brno,** now in the Czech Republic, and developed into *genetics*
- Study of the quantitative and inferential rules of variability in blood eosinophil counts in inbred mice began in **Minneapolis,** USA, and developed into *chronobiology*
- These sciences study **diversity:**
  - **genetics** in *space*
  - **chronobiology** in *time*

The diversity of the cosmos embedded in us led to **chronomics**, the study of aeolian yet congruent transdisciplinary time series around us, e.g., by chronobiologically interpreted 7-day/24-hour and much longer multidecadal, physiological and archival monitoring implemented in Brno, Minneapolis and the broader project on The BIOsphere and the COSmos, BIOCOS

These differences, first encountered in chronobiology, then extended to chronomics, complement genetics, led to the recognition that our genes have coded the information not only ~24-hour rhythms but also about infradians with periods, τ, ranging from 0.5 week to τs shorter and longer than 0.5 year and to τs beyond 1, 2, 3 or 5 decades. Some of these cycles discussed long ago, forgotten and surfacing again because of biological counterparts, are detected for HR and/or mental function (1, 2).

BIOCOS contributes papers to this volume dealing with BP (4-6) as a densely sampled variable in order to avoid "flying blind" with respect to diagnostics, therapeutics and space weather (7-12). A truly individualized health care starts when, in addition to a reference standard derived from peers of the same gender and age, a sequential test also provides a reference refined for the given subject at the given time (3). Monitoring is not a luxury when, as shown in Figure 1, the same currently popular drug Hyzaar can do harm in a patient (Su) in the morning, but is very beneficial when taken in the same dose by the same person in the evening some weeks later. In Su, Figure 1, described in detail in these proceedings by Prof. Watanabe (3), medication was changed systematically, on a usual routine of living with diurnal activity and nocturnal rest. In the morning the medication raised the circadian amplitude of BP to an extent of exacerbating or inducing a circadian overswing or CHAT, whereas at another time it lowered both the circadian amplitude and MESOR, and offered benefit, Figure 1.

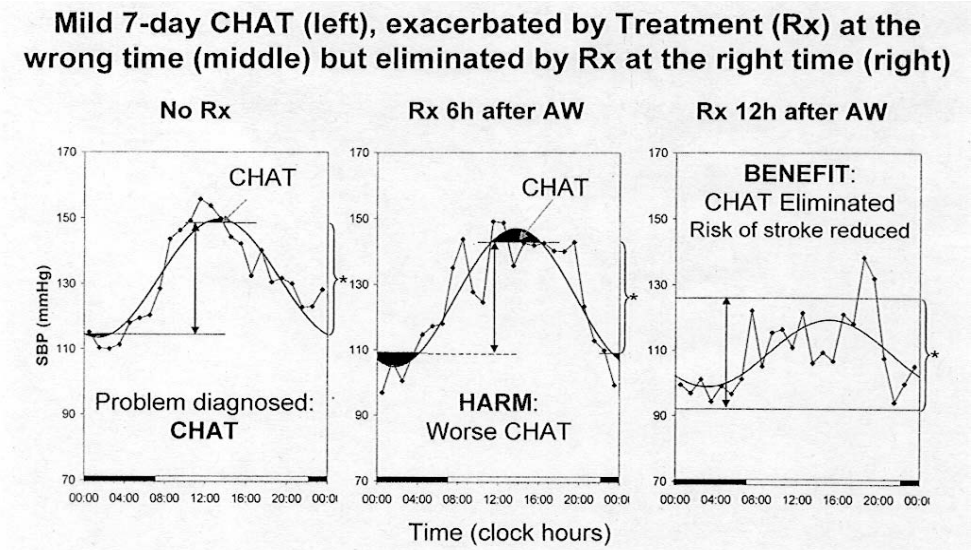

Figure 1 © Halberg

Earlier, Figures 2 and 3, a student (TT), in whom a high BP was just diagnosed and in whom the administration time, as in Su, had also been systematically varied around the clock to find the optimal treatment time, we found differences as a function of time. The optimal time differed between patients Su and TT. More specifically, we show in Figure 2 how medication was changed in one and the same newly diagnosed patient: the same dose of the same treatment at certain times, such as at 12:00, did not lower the BP MESOR further (fifth column headed "ΔRx 12"). When we tried the same treatment time again, (11th column), we found that it failed. In Figure 3, we also find that at certain times, such as at 20:00, the treatment raises the circadian amplitude of BP in TT.

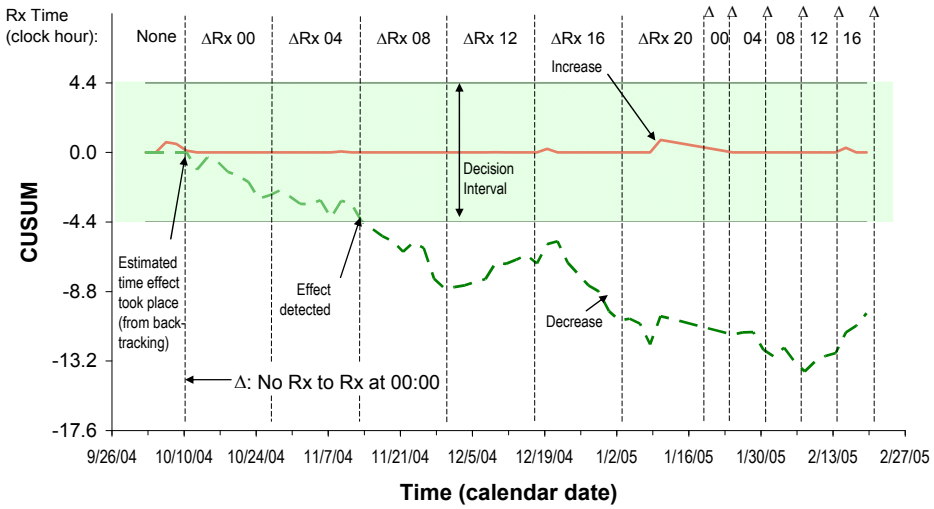

Figure 2. Changing timing of medication (ΔRx) during consecutive spans shows efficacy of treatment. An empirical approach to chronotherapy: immediately after diagnosis, one should ascertain that the treatment is effective. Optimization of treatment effects by timing can be achieved for the individual patient by systematically changing, e.g., advancing the time of treatment. Successful treatment of MESOR-hypertension assessed by a self-starting cumulative sum control chart (Cornélissen et al. 1997). To optimize his hypotensive treatment (Rx), a just-diagnosed 24-year-old individual (TT) switched his Rx first every 17 days by 4 hours and then mostly at shorter intervals. Note statistically significant decrease in MESOR, evidenced by the breakout outside the decision interval of the negative CUSUM line. With continued Rx, the blood pressure MESOR leaves the decision interval, indicating a statistically significant decrease in overall blood pressure. © Halberg

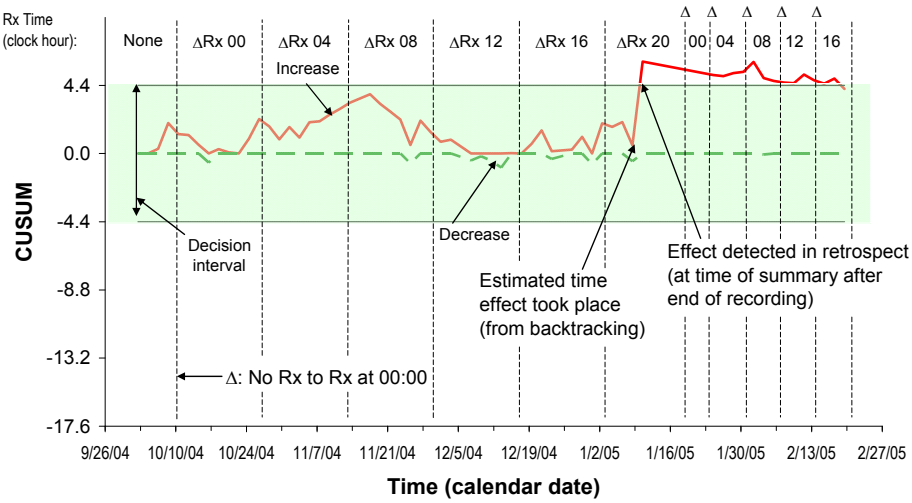

Figure 3. Changing timing of medication (ΔRx) during consecutive spans shows risk of iatrogenic CHAT. An empirical approach to chronotherapy: immediately after diagnosis, one should ascertain that one does not induce circadian hyper-amplitude-tension (CHAT) by inappropriate timing of anti-hypertensive medication. In this 24-year old man (TT) who advanced the time of treatment by 4 hours every 17 days initially and at shorter intervals thereafter, treatment in the evening was associated with iatrogenic CHAT, raising the question whether the risk of MESOR-hypertension may not have been traded for the even higher risk of stroke that CHAT represents (see p. 30 of Halberg et al. 1995). Iatrogenic circadian CHAT, induced by treatment at 20:00 daily, was silent to office visits. TT may have traded benefit (lowering of the MESOR of blood pressure, Fig. 2) for something worse (circadian overswinging of BP). This danger applies to some hypertensives (who tend to have a large circadian amplitude of BP) to whom treatment time is not specified by the care provider, as was the case for TT (or is specified for bedtime). A few others who took hypertensive medication at bedtime were also found to have CHAT. The figure also shows the assessability of otherwise undetected harm by as-one-goes sequential analysis. © Halberg

Clearly, we need continued surveillance since we cannot predict when the lesson of Figure 1 may apply; the monitors are still slightly obtrusive and costly, but are affordable in BIOCOS with an 80% price reduction for use on a family-and-friends basis. We have the software to analyze treatment and other effects objectively, but we need computer routines to bridge gaps for special problems of research. To get this job done in a temporal microscopy and telescopy, when often the data present themselves with gaps; these problems are overcome by least-squares up to a point. Hence, methods to deal with unequally spaced data are of special concern to Prof. Jerzy Czaplicki (13), and we are glad to have his contribution included herein.

The task remaining is that of the education of the public first and foremost, and of medical students upstream and of care providers, of course, to the extent possible. To cite a historical example, surgeons found it a terrible burden when it was suggested that they scrub before surgery. It will take more cases, such as that of fulminating CHAT (Figure 11 in [4]), to convince the public of the necessity to diagnose and treat vascular variability disorders, VVDs, notably when two or more VVDs coexist in vascular variability syndromes, VVSs, Figure 1.

In this volume, we deal further with cancer, which also poses the task of marker rhythms monitoring so as to individualize the timed treatment, but as a compromise to practicality, a simple protocol is advocated (14) to convince the profession that the results already in hand in terms of circadian optimization need extension. In another paper, at the level of the eukaryotic unicell (15), we find again, as in the circulation, signatures of the cosmos, as we do when chronomics aligns suicides with the terrestrial and solar environment (16). Prof. George Katinas finds two of the solar beat periods in his diastolic BP (5), and we find that same ~0.42-year period in the 17-KS excretion and in urine volume of a late friend who monitored his steroid excretion for 15 years, Figure 4, whether he stayed at home in Copenhagen, visited Haile Selassie, the emperor of Abyssinia (now Ethiopia), or lectured at the Royal Society (he always took a volumetric along and saved a sample of his 24-hour urine) for determining the breakdown products of steroids, hormones essential for survival and reproduction. Moreover, the time course of 17-KS at the ~0.42-year period mimics that of the planetary geomagnetic index Kp, Figure 5 (17), and we find that the same ~5-month solar period is globally congruent in period also with the volume of urine in which the steroids were determined, Figure 6, but the time course of urine volume (not shown) mimics that in the cycle of Zürich numbers, a measure of solar activity also gauged by proxies such as aurorae (18). BIOCOS and the broader chronomics welcome the cooperation of Prof. Jarmila Siegelova in the spirit of Mendel and hope that her initiative in BP and HR monitoring will not have to wait (as long as Mendel had to) to see the fruits of her endeavors. This hope is justified since by contrast to Mendel, who was denied the right to teach, Jarmila is teaching us even as emerita. With her, we reanalyze the original data of Brückner and Lockyer, and follow-up information that became available in the interim (19) validating by chronomics the pioneers' time-macroscopic scholarship.

In summary, we have tools for monitoring BP and HR that are somewhat cumbersome and costly, but are cost-effective and will be further improved as the demand for them increases. We have computer programs for a chronobiologic diagnosis and, what seems critical, for a chronobiologic optimization of the timing of treatment and for surveillance of its maintained efficacy. What is needed most is the recognition by the public and the medical student that a good drug at the wrong time can do harm, whereas at the right time it serves well. If a system with a website now being built becomes a reality, it can serve not only the user's individualized health care, but will also monitor the sun and its associations that include sudden cardiac death, suicide and the greatest societal ills affected by the cosmos, crime, war and terrorism, and thus the course of history. Figures 7 and 8 should emphasize the need to store, analyze and use data; Figure 9 shows a plan for doing so.

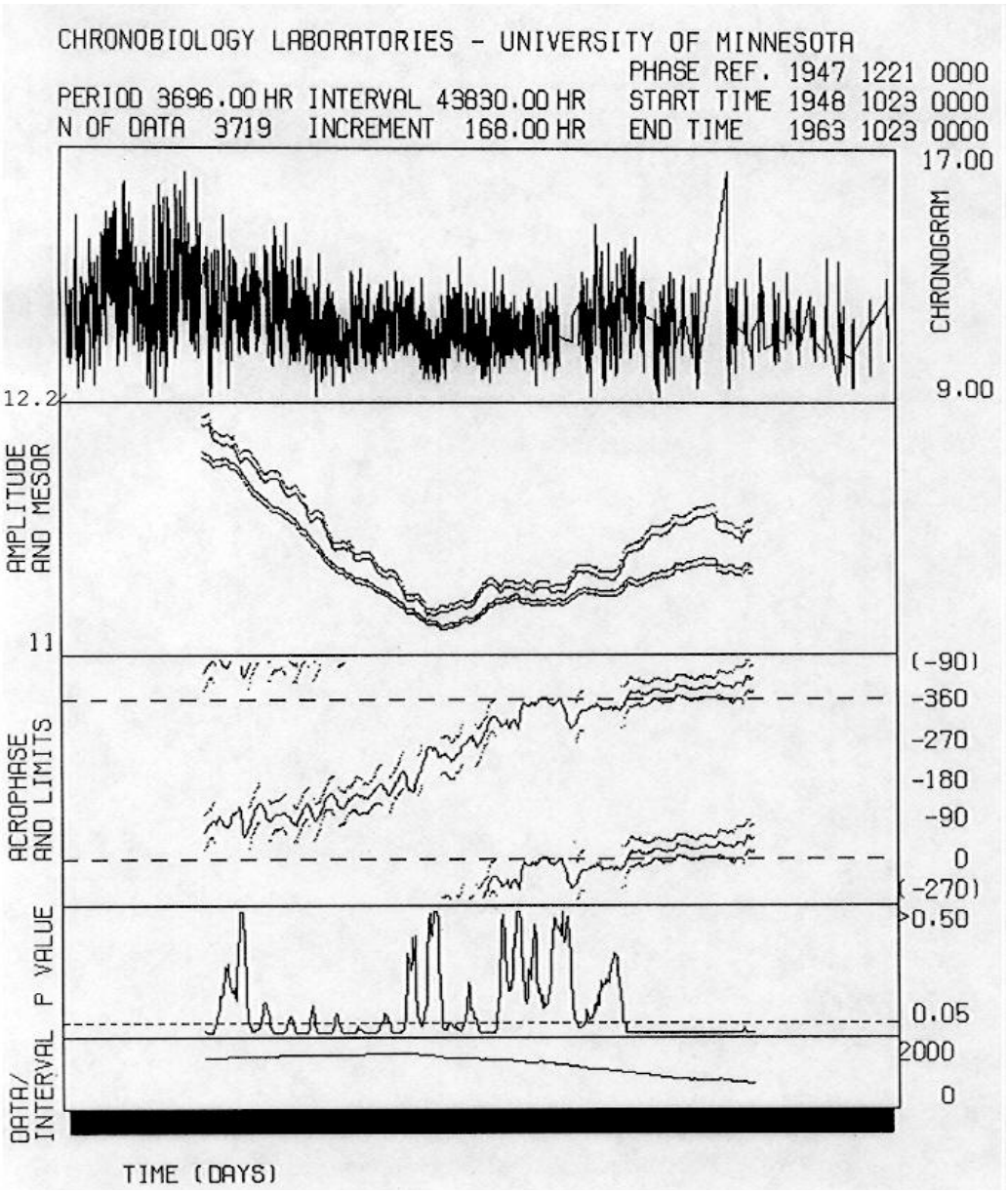

Figure 4. Urinary 17-ketosteroid recorded over 15 years in CH, a clinically healthy male scientist 49 years of age at start of study. Chronobiologic serial section showing, on top, the daily excretion of 17-ketosteroids; in the next row the MESOR, M, as the lower curve and the cis-half-year (0.42-year) amplitude, A, as the distance between the two curves in the second row; dots below the lower and above the upper curves indicate the standard deviations of the Ms and As. Acrophases in the third row are shown with dots, corresponding to their CIs (95% confidence intervals) when results are statistically significant, P-values for the rejection of the "no 0.42-year" amplitude are shown in the fourth row and are mostly below the dashed horizontal line indicating the 5% level. The time course of cis-half-year acrophases in this figure mimics when the no 0.42-year amplitude assumption can be rejected the time course in Figure 5 of the acrophases of the cis-half-year of the planetary geomagnetic index, Kp. Urine volume is congruent overall in period globally with the former two variables, but its phase behavior is transiently congruent only with relative sunspot (Zürich) numbers differing in its time course from that of the phase of 17-KS and Kp (not shown). The two biospheric variables differ in terms of their environmental phase synchronization. © Halberg.

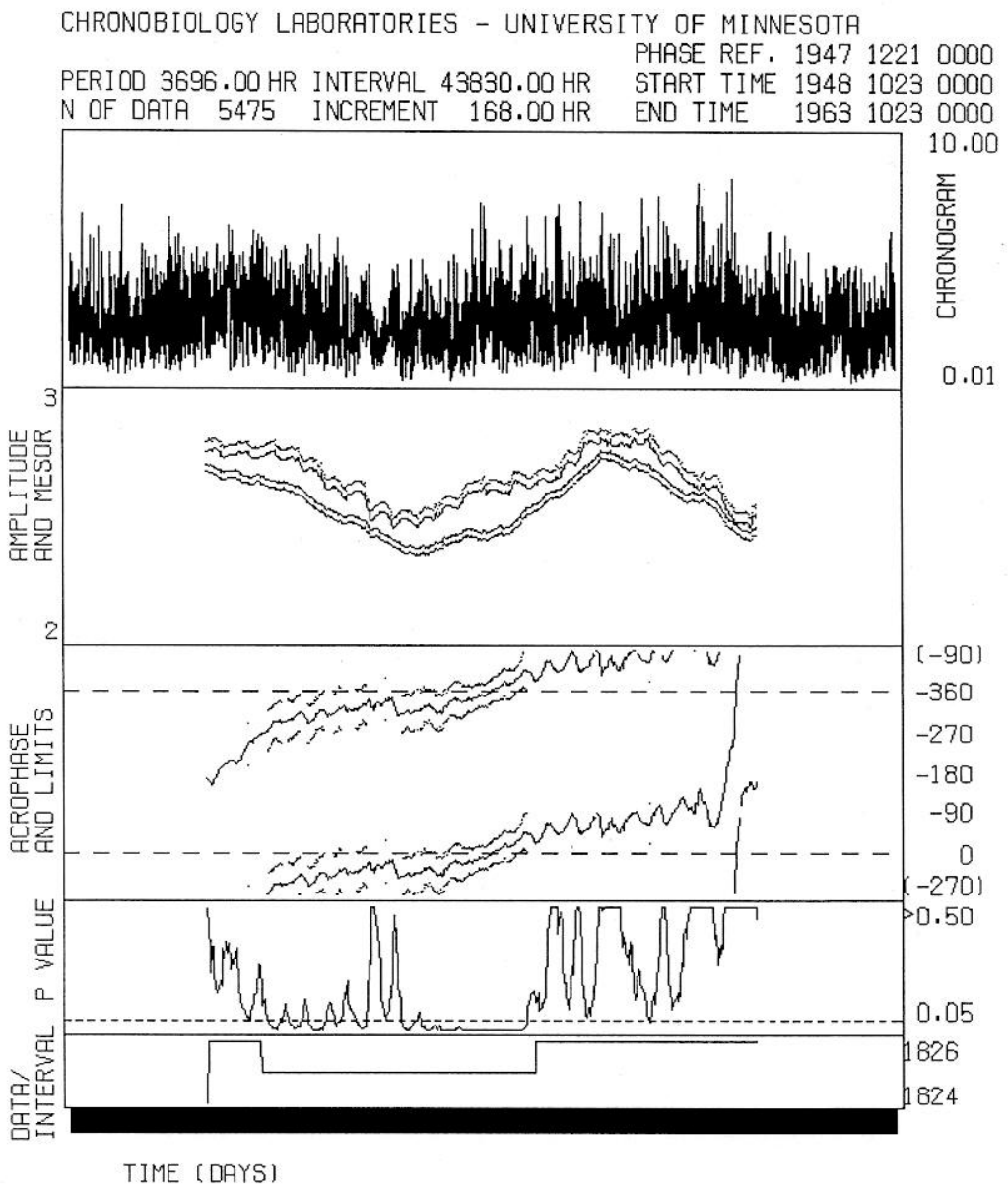

Figure 5. A chronomic serial section of the planetary geomagnetic index Kp from October 23, 1948, to October 29, 1963, with the fit of a 0.42-year cosine curve shows a similar time course of acrophases as that of the 17-KS in Figure 4. Note that statistical significance is lost toward the end of the record for Kp in this figure, but not for 17-KS in Figure 4. Note further at the beginning the lack of statistical significance in Kp, but not in 17-KS may be driven by Kp, but this is not suggested by the behavior of the As that are quite large for 17-KS at the end of the record in Figure 4, while the cis-half-year is not statistically significant in Kp and its amplitude decreases with time. Time courses of intermittently congruent environmental periods concurrent with the persistence of a previously or subsequently congruent period in the biosphere (when the previously congruent environmental period is not detected) serve to resolve partial endogenicity in cosmic-biospheric associations, preferably when all data series are equidistant and are the longest available matching data series at a given time. Problems arise when at least one series is unequidistant because of artifacts that can simulate a periodicity when none exists and vice versa can obscure a real periodicity to the point that it is no longer detected. © Halberg.

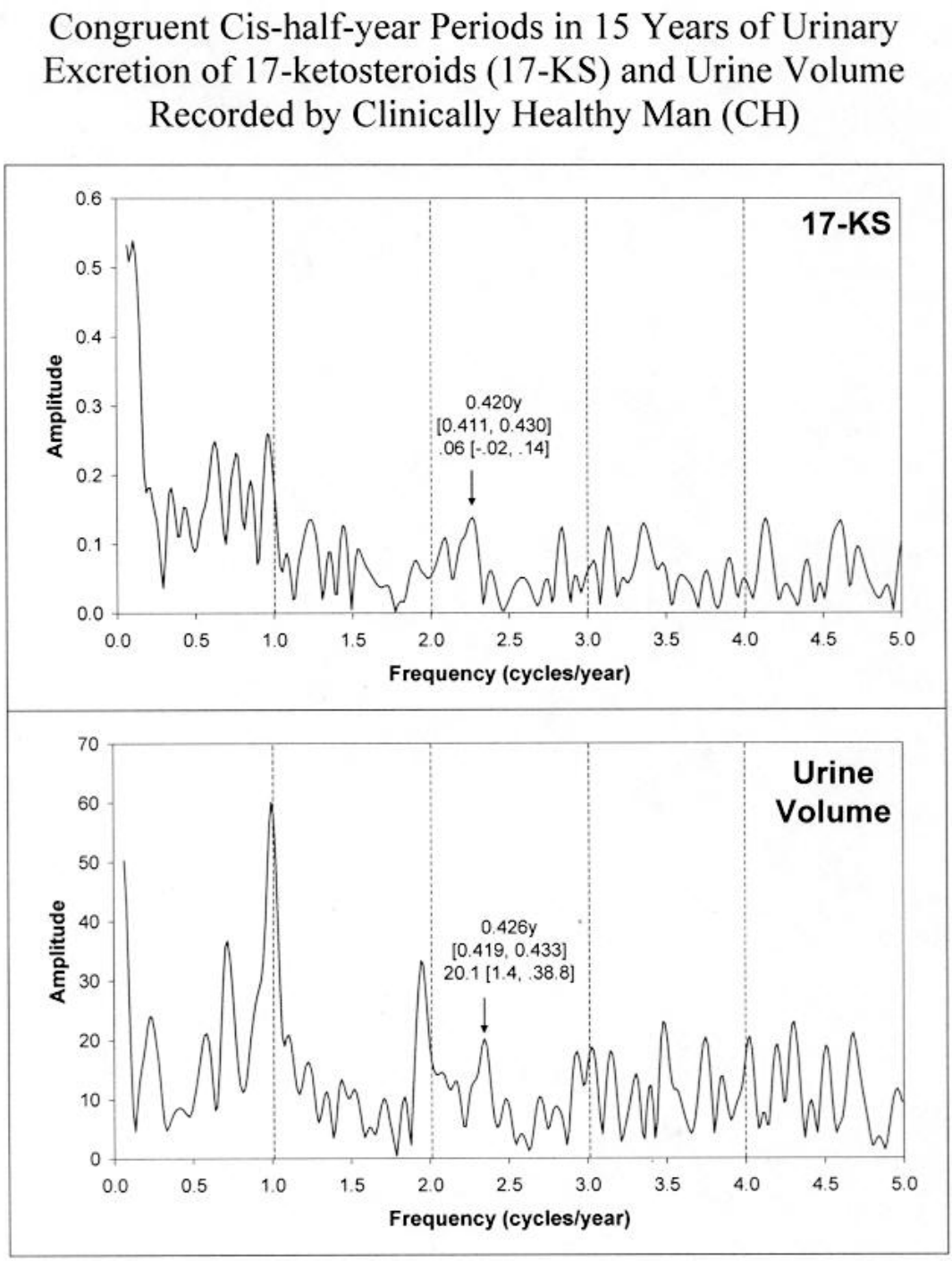

Figure 6. Global spectral window with a predicted ~154-day (0.42-year) component in both the excretion of certain breakdown products of steroidal hormones (the 17-ketosteroids, 17-KS) (top) and in the volume of urine excreted by a clinically healthy man (CH) (bottom). The ~0.42-year component is also found in two related but not identical environmental variables, the geomagnetic index (Kp) (Figure 5) and solar activity (Zürich relative sunspot numbers, not shown). © Halberg.

Figure 7. Failure to store, analyze and use routine cardiovascular, e.g., blood pressure, heart rate or other ECG monitoring for both further medical research in the light of long-term outcomes and the transdisciplinary study of solar variations recall the tall tale of Baron Münchhausen's horse, which was cut in two by the town gate as it closed: when the head of the horse subsequently drank at the well, the water poured of its severed midsection onto the ground. Similarly, much information from within the physiologic range (the indispensable water in our analogy) is lost today but may be usefully recycled tomorrow. Illustration by Martin and Ruth Koser-Michaels from Münchhausen: Des Freiherrn Wunderbare Reisen und Abenteuer, Droemersche Verlagsanstalt, Munich, © 1952, facing p. 32. Reproduced with permission of the publisher.

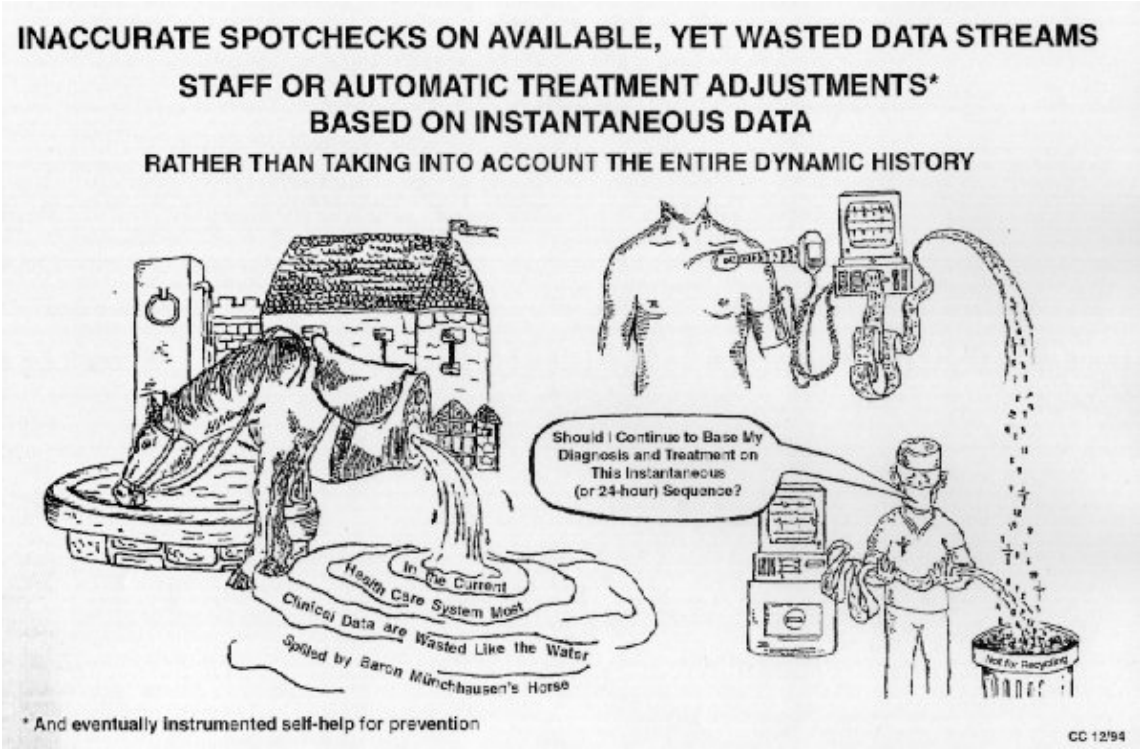

Figure 8. The alternative to the status quo is recycling, in a website in Figure 9. © Halberg.

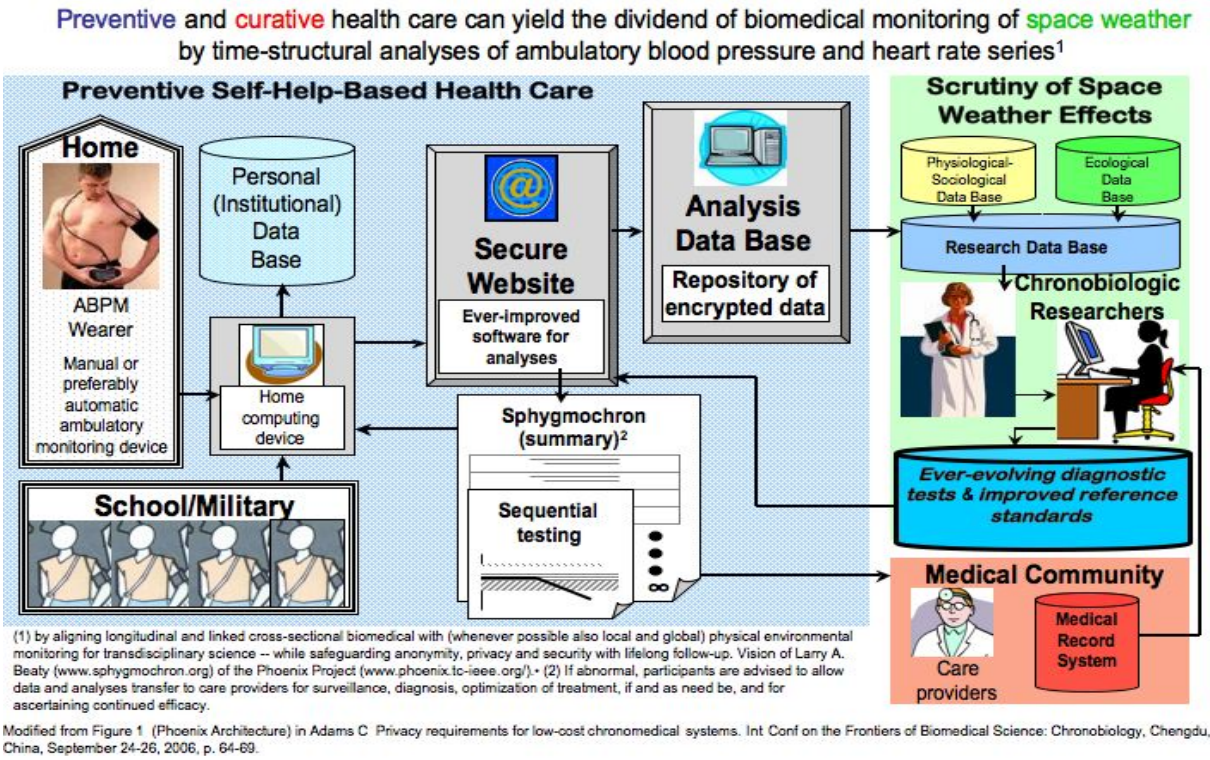

Figure 9. The Phoenix Group of volunteering electrical and electronic engineers from the Twin Cities chapter of the Institute of Electrical and Electronics Engineers (http://www.phoenix.tcieee. org) is planning on developing an inexpensive, cuffless automatic monitor of blood pressure and on implementing the concept of a website (www.sphygmochron.org) for collection and analysis of data collected with these instruments. © Halberg.

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Circadian stage-dependent infradian-modulated changes in a mental function during aging

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RBS, a clinically healthy man, started estimating 1 minute by counting at 25 years of age: he continued such estimations 2-7 times/day on the average 5 times/day, until the age of 60, with very few interruptions. The data are here separated into 3-hourly bins, providing 8 data sets for 8 fractions of the 24-hour day, i.e., 00:00-03:00, 03:00-06:00, 06:00-09:00 ..., 21:00-00:00. The mean and standard error (SE) were determined for each daily fraction on a yearly basis. Changes as a function of age were assessed by linear regression of yearly means for each of the 8 3-hour circadian stages. Results are shown in Figure 1.

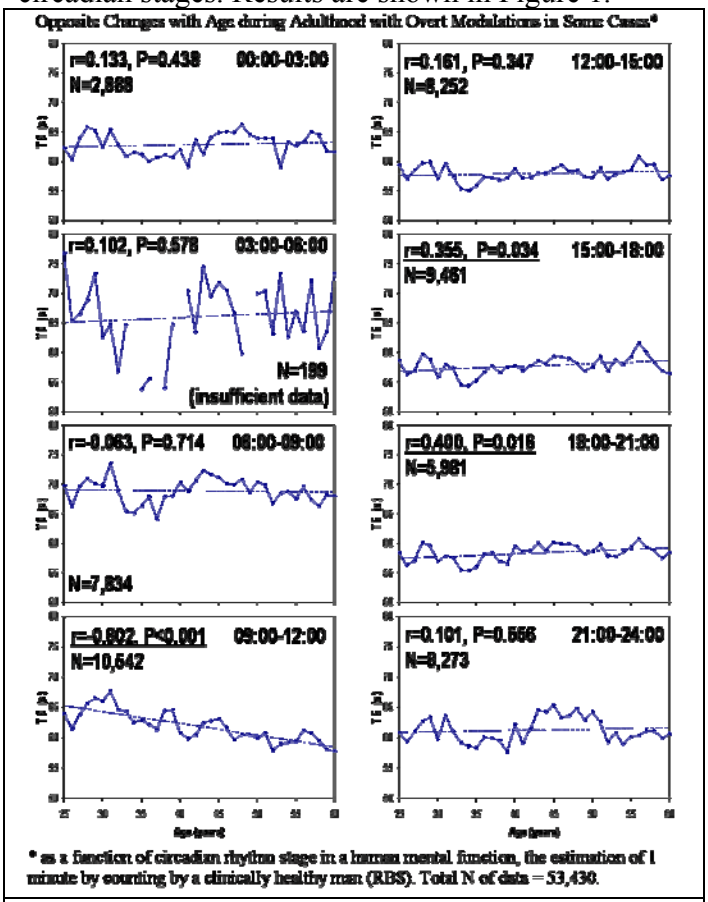

Figure 1. Different time course of aging in data collected during various 3-hour spans of the day, during 36 years of around-the-clock estimations of 1 minute. RBS, clinically healthy man, 25 years of age at start of 1-minute estimations ~5 times a day for 36 years. © Halberg.

Between 09:00 and 12:00, counting to 60 takes statistically significantly less time at 60 than at 25 years of age ($r=-0.802$, $P<0.001$), whereas between 18:00 and 21:00, the opposite is true ($r=+0.400$, $P=0.016$). The bin from 03:00-06:00 is the least documented, by only 199 measurements; it is most irregular to eyeballing, presumably due to the relatively small number of tests. In the 7 other well-documented bins (N=2888-10542), the data between 00:00 and 03:00 allow the naked eye to discern a modulation by cycles with relatively long periods, but any impression of one or the other longer cycle is subjective. Table 1 is objective and qualifies impressions.

Testing the estimation of one minute for decades around the clock at different times of the day corresponding to different circadian stages (on a routine of diurnal activity and nocturnal rest) thus reveals diverse changes as a function of age. To the unaided eye, these occur at some circadian times, seemingly more or less linearly, albeit in different, even opposite directions, and/or at other times are overtly modulated by infradian cycles. When analyzed time-microscopically, such modulations are not the same, Table 1.

If we conceive of a time structure with a spectral element and an element of trends, the latter including one with age, we find in Table 1 that the spectral element of a mental function has several components, contributing in different ways to aging (1, 2). Above all, the

circadian rhythm's stage determines opposite effects that in their turn can be modulated further by components that also differ with circadian stage, Table 1. Most surprising is that between 12:00 and 21:00, an about 34-year component is statistically significant as a putative signature of the Brückner/Egeson/Lockyer cycle (3-6), also recently documented by Maravilla et al. (7) (35.6 years). Table 1 shows a few other periodicities as well in the same mental function, including about 15-year and about 9-year cycles, if not a circadecadal component, the former corresponding perhaps to a global cycle (8), the latter perhaps a signature of the solar wind, both validated by these analyses.

Table 1: Spectral components, including a Brückner/Egeson/Lockyer cycle of ~34 years, modulating aging of a mental function revealed by separate analyses according to circadian stage*

3-Hour Bins of time	Initial Trial period (y)	Convergent NLLS Period [95% CI] (y)	Amplitude [95% CI]
00-03	35	17.27 [13.65, 20.88]	1.55 [0.21, 2.89]
03-06	"	27.07 [17.50, 36.63]	4.54 NS
06-09	"	19.49 [14.64, 24.35]	1.73 [0.42, 3.04]
12-15	"	30.94 [16.37, 45.50]	0.87 [-.09, 1.82] BSS
15-18	"	33.53 [20.24, 46.81]	1.19 [0.11, 2.27]
18-21	"	33.63 [20.69, 46.58]	1.12 [0.16, 2.08]
21-24	"	18.66 [14.88, 22.44]	1.87 [0.62, 3.12]
03-06	15	19.31 [12.70, 25.92]	4.08 NS
09-12	"	17.57 [11.67, 23.46]	1.45 NS
12-15	"	14.29 [11.40, 17.17]	0.95 [0.04, 1.86]
15-18	"	13.95 [10.75, 17.15]	0.98 NS
18-21	"	14.27 [9.70, 18.84]	0.70 NS
12-15	10	9.09 [7.75, 10.43]	0.87 [-.05, 1.78] BSS
15-18	"	8.93 [7.49, 10.36]	0.96 [-.12, 2.05] BSS
18-21	"	8.92 [6.95, 10.89]	0.67 NS
Weekly means	35, 25 or 11 y	25.92 [23.68, 28.16]	1.17 [0.90, 1.44]

*Results converge to nonlinear least-squares (NLLS) analyses of different clock-hour bins approximating various circadian stages in RBS, a clinically healthy man 25 years of age at start of estimations continued to the age of 60 years (and beyond). BSS = borderline statistically significant, NS = not significant.

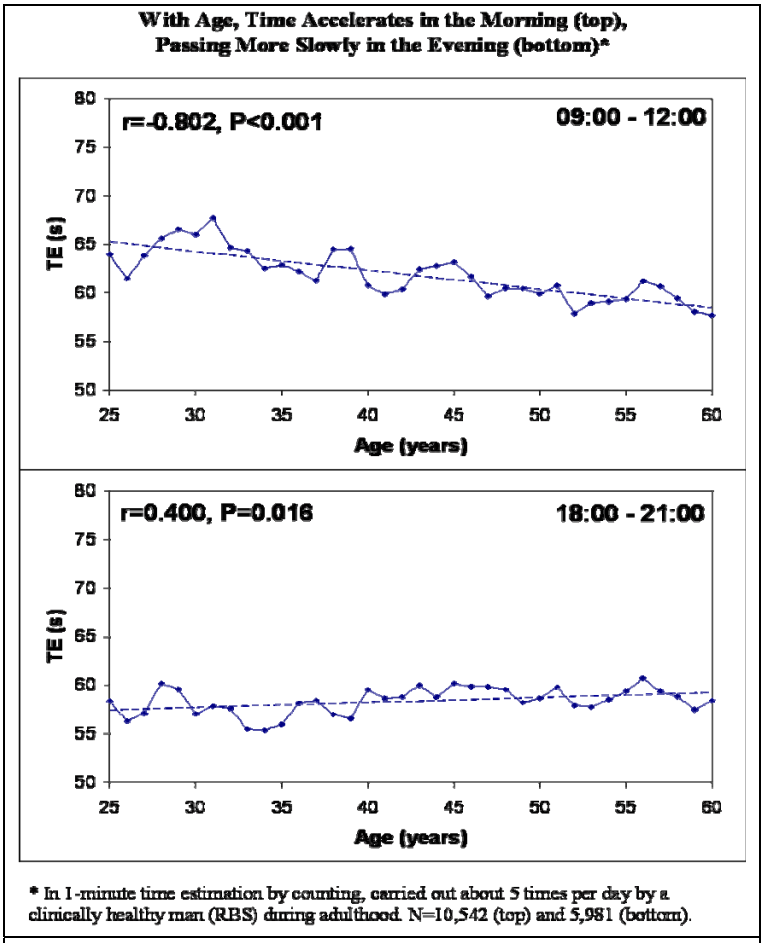

Figure 2. Opposite time course of aging during several decades as a function of clock-hour of testing the estimation of 1 minute. RBS, clinically healthy man, 25 years of age at start of 1-minute estimations ~5 times a day for 36 years. © Halberg.

It is methodologically noteworthy that opposite effects can be seen at different circadian stages, to a point that in the morning, time passes faster at age 60 than at the age of 25 years and the opposite is true in the evening, Figure 2. Figure 1 and Table 1 also document that possible solar infradians deserve consideration as circadian stage-dependent modulating entities. These conclusions are in keeping with the detection (in SBS, the father of the subject here investigated), of a prominent half-yearly spectral component in the evening, but not in the morning in his self-measurements of blood pressure during 22 years (9). Melatonin concentrations tend to be higher in the evening than in the morning. This may render a person more sensitive to geomagnetics in the evening than in the morning. Geomagnetics that display a prominent component with a period of 6 months (10, 11) can actually be tested by follow-up analyses of the time courses of the solar and biospheric variables involved to see whether subtraction and addition in waxing and waning amplitudes of the half-year component in geomagnetics (or any other pertinent frequency more generally) may have any coincident associations in the biosphere (12, 13).

Mental aging, dealt with by the axiom "use it or lose it" (14), may actually be qualified as "improve it", perhaps more so by timing, i.e., by using any mental exercise at the best time for optimization, a task for the future. For all students of aging, however, it seems clear that studies

done on a variable that changes its circadian amplitude with age such as a number of hormones do (1, 15), will have to be repeated with a view of different circadian stages contributing differently to the results (at circadian maxima and minima in opposite ways).

The reason can be readily understood: If the amplitude increases with age, there will be an increase with age at the time of peak and a decrease at the time of trough, unless there is also a change in daily mean (MESOR) and/or phase. Vice versa, again assuming no change in phase if the circadian amplitude decreases with age, as in the case of circulating DHEA-S (15), there will be a decrease at peak time and an increase at trough time, unless there is also a change in MESOR and/or phase. As to Figure 1, the 09:00-12:00 span is probably associated with maximal cortisol concentration in blood, which is considerably decreased in the evening hours: the hormone may contribute to mental function. The span from 00:00 to 03:00 may be characterized by maximal melatonin concentration.

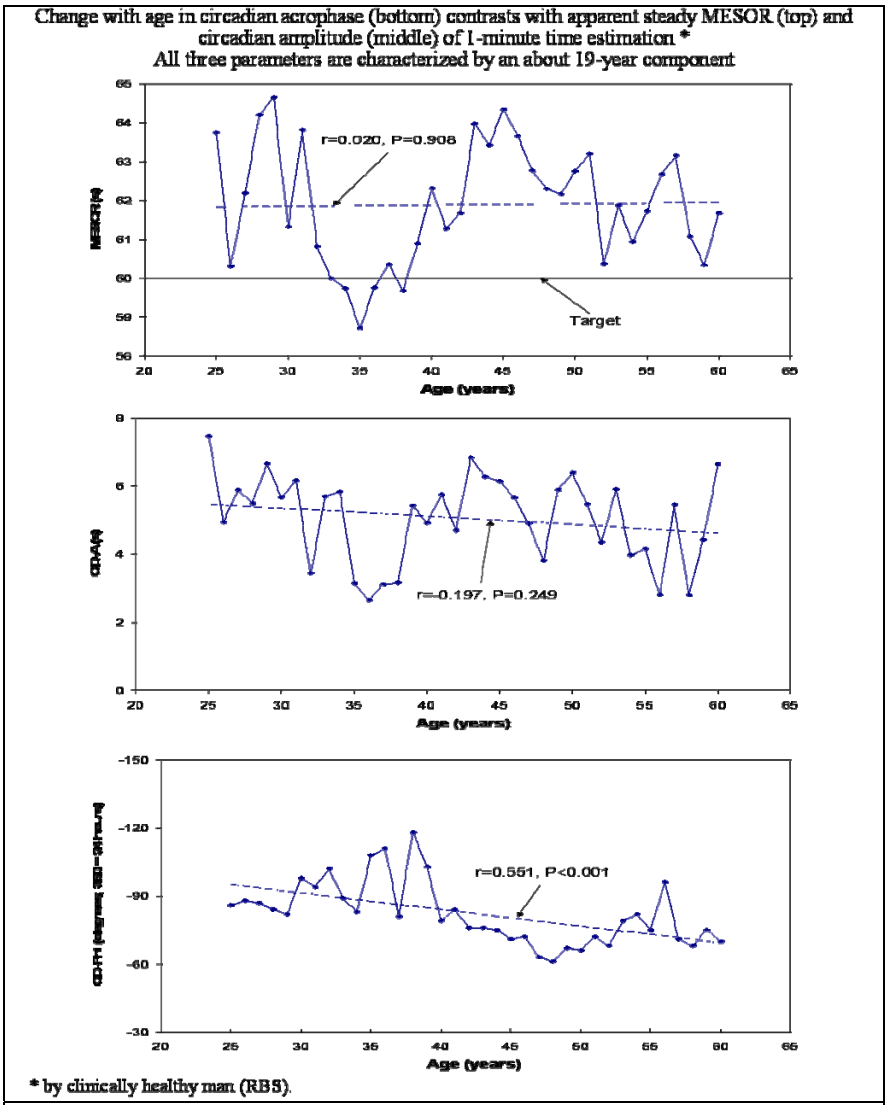

Figure 3. While effects in opposite directions may contribute to canceling any effect of aging on MESOR, the acrophase advance is statistically highly significant, in keeping with similar findings for other variables such as blood pressure and heart rate. RBS, clinically healthy man, 25 years of age at start of 1-minute estimations ~5 times a day for 36 years. © Halberg.

Using the 8 3-hourly means computed for each year from 1971 to 2006, a 24-hour cosine curve was fitted by least squares to yield estimates of the circadian MESOR, amplitude and acrophase. These yearly imputations were linearly regressed as a function of age. Whereas no change in MESOR is observed ($r=0.020$, $P=0.908$), there is a slight tendency for the circadian amplitude to decrease with age, as anticipated ($r=-0.197$, $P=0.249$), and there is a marked circadian acrophase advance ($r=0.551$, $P<0.001$), Figure 3. All three parameters are also characterized by an about 19-year component, resolved nonlinearly. Period estimates (and 95% confidence intervals) are 19.20 (15.25, 23.15) years for the MESOR, 18.99 (13.95, 24.04) years for the circadian amplitude, and 19.91 (15.90, 23.93) years for the circadian acrophase, with respective amplitudes (and 95% confidence intervals) of 1.55 (0.49, 2.62) s, 1.08 (0.10, 2.06) s, and 12.45 (4.99, 19.91) degrees (with 360 degrees corresponding to 19.91 years), respectively.

In the presence of low-frequency cycles with periods of about 10 years or longer as found herein, it is premature to speculate until accrual of more cases like RBS, and these added subjects and RBS himself collect longer series, so that time series covering at least 2 replications/subject and preferably more can be analyzed.

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The cosmos in a eukaryotic unicell

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This paper is dedicated to the memory of Hans-Georg Schweiger, who with one of us (SB) maintained an artificial culture of unicellular giant cells of Dasycladales at the Max-Planck-Institut für Zellbiologie after 1977 in Ladenburg bei Heidelberg, Germany. Hans-Georg realized that there are more rhythms than circadians, focusing on about (~) 7-day cycles. We here add evidence of ~yearly and even longer spectral components as signatures of our cosmos at the unicellular level.

Abstract

Acetabularia (Ac) is a model for a broad spectrum of rhythms, some mapped in individual unicells, others based on serially-independent sampling over a span of 14 years. We here emphasize first and foremost, with the late Hans-Georg Schweiger, that ~7-day rhythms can free-run in a unicell just as circadians do, desynchronized from a precise weekly schedule. The photic circannual rhythm here mapped is shown to be neither the sole nor the largest peak in a spectral window by the extended cosinor, a near- and a far-transyear can be documented in Ac as well as circadecadals, suggesting that nonphotics have been coded in genes already ~500 million years ago.

Acetabularia acetabulum

Ac is a eukaryotic giant unicellular alga with a nucleus that can be easily removed, a first advantage. At least equally important, however, is that this atavistic organism has a spectral element in its chronome (time structure), including inferentially statistically mapped ~24-hour (circadian) (1), ~half-weekly (circasemiseptan) (2), ~7-day (circaseptan) (3), ~half-yearly (circasemiannual) (4), yearly (circannual), longer-than-yearly -- near-transyearly (1.00 year < [τ {period} - CI {95% confidence interval}] < [τ + CI] < 1.20 years} and far-transyearly (1.2 years $\leq$ [τ - CI] < [τ + CI] < 1.9 years) (5) -- and ~10-yearly (circadecadal) (4, 5) cycles. This combination of photic and nonphotic components in the spectral element of Ac's chronome makes this organism unique among unicells. Much work has focused on *Ac. acetabulum* (formerly *Ac. mediterranea),* but other species, including *Acicularia schenckii,* have also been cultivated and investigated under laboratory conditions.

The relative prominence of circadian and circaseptan rhythms as spectral components in *Ac. acetabulum* kept under conditions of light (L) and darkness (D) alternating at 12-hour intervals (LD) and in continuous light (LL) is shown for oxygen production in Figure 1. A prominent 24-hour component in LD is very much reduced in amplitude in LL. This figure shows further in LD a weekly (168-hour) component that is less prominent than the circadian and is likewise reduced in amplitude in LL, but to a lesser extent, as compared to the circadian amplitude reduction in LL. Accordingly, for oxygen production by *Ac. acetabulum* in LL, the circaseptan amplitude is larger than the circadian amplitude, Figure 2.

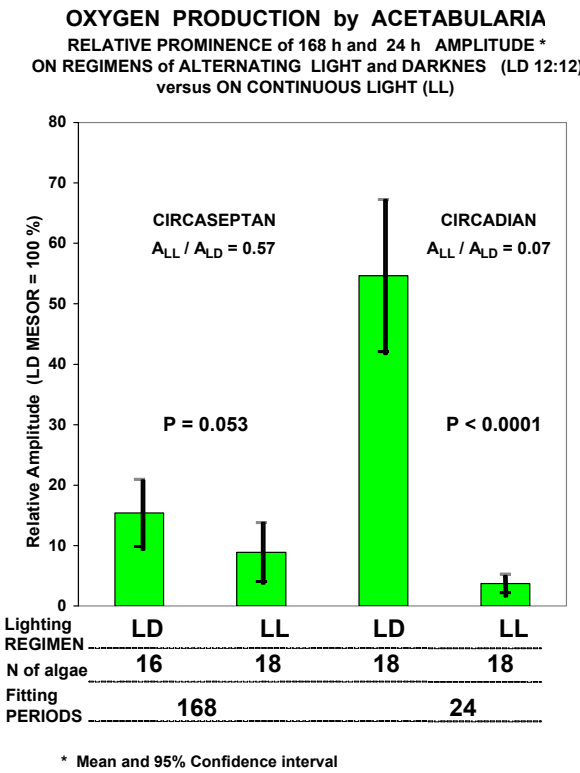


Figure 1. Inhibition by LL after transfer from LD is greater for a prominent circadian rhythm of *Acetabularia acetabulum* than that for a less prominent (in LD) circaseptan rhythm. © Halberg.

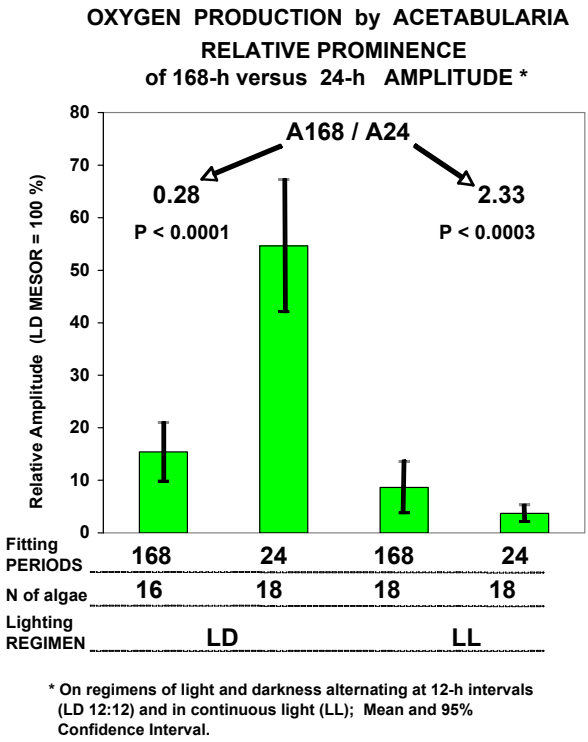


Figure 2. In keeping with Figure 1, a circaseptan rhythm is more prominent than the circadian in LL and less prominent in LD. © Halberg.

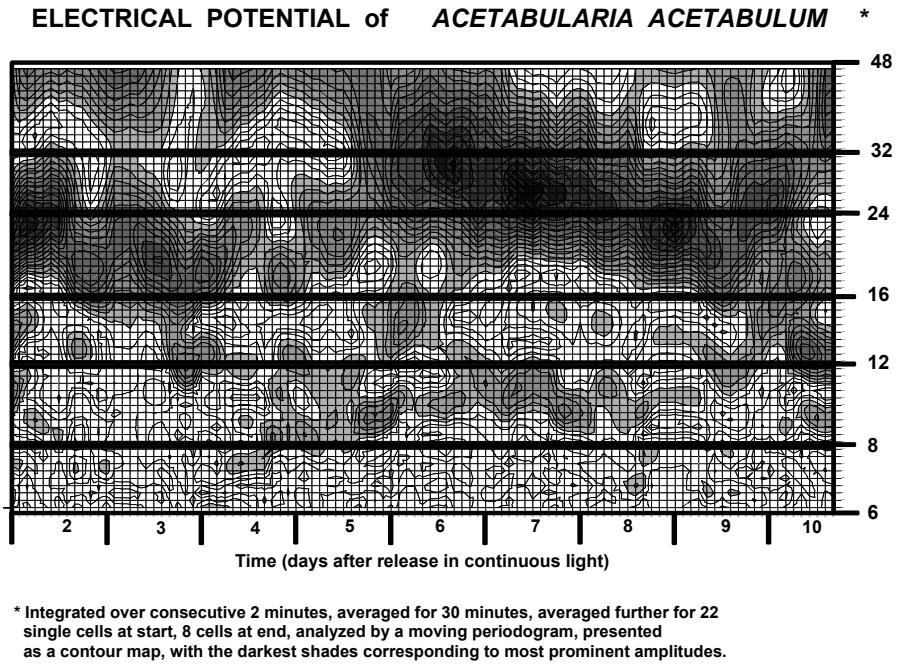


Figure 3. Gliding spectral window reveals nonstationary nature of circadian rhythm in LL, waxing and waning and drifting in frequency in LL. © Halberg.

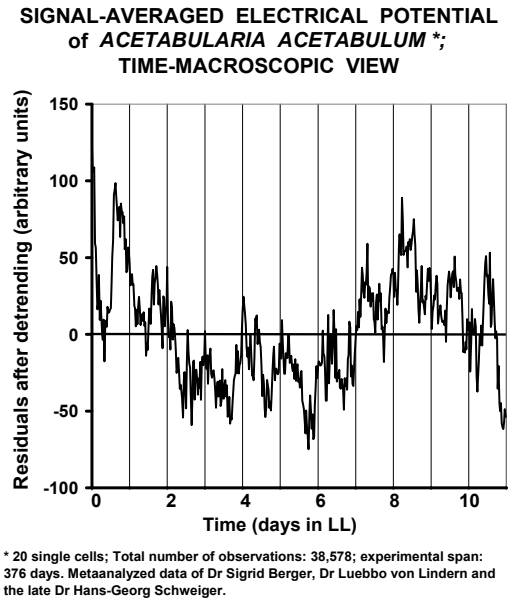
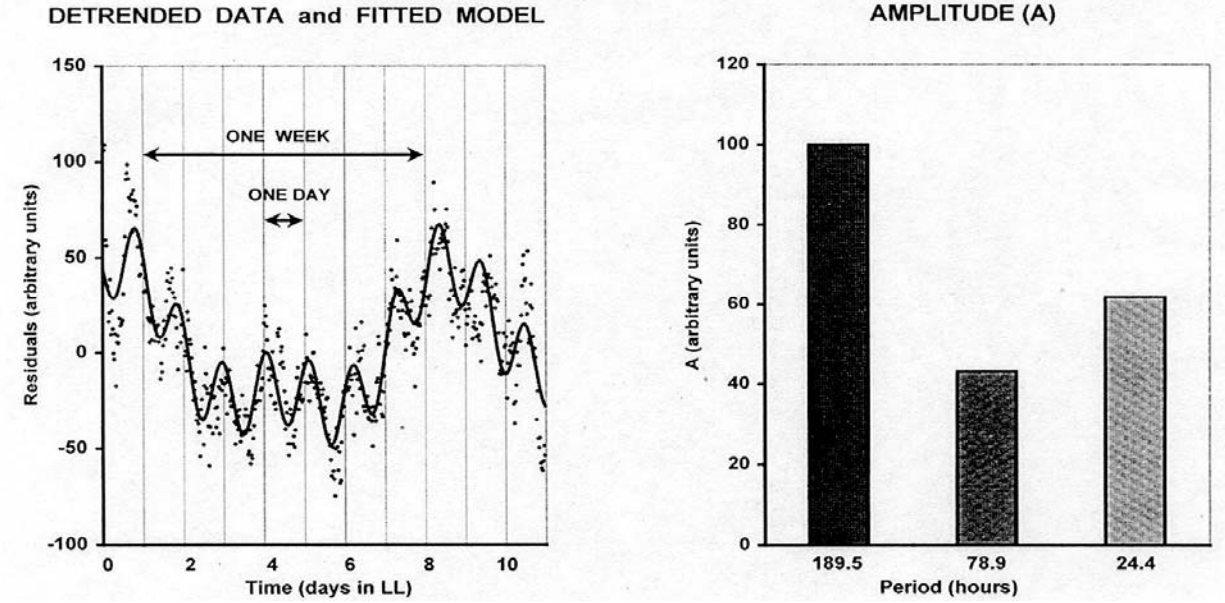


Figure 4. The naked eye sees the greater about-weekly as compared to the about-daily swing during the first 10 days in LL after prior synchronization in LD. © Halberg.

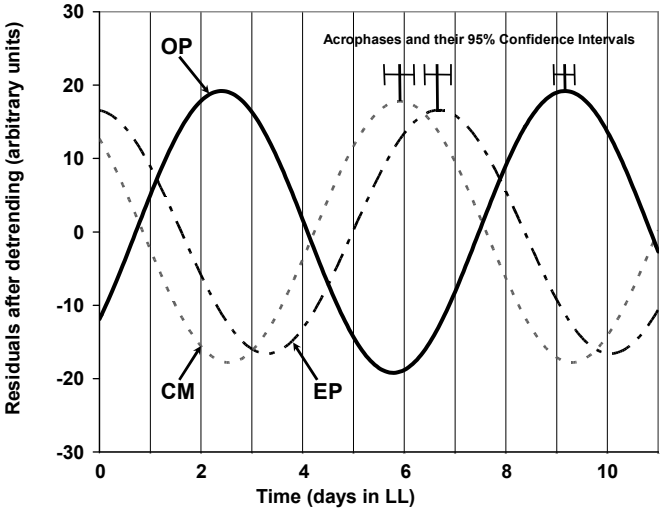
LARGER *ABOUT-WEEKLY* THAN *ABOUT-DAILY* CYCLE IN ELECTRICAL POTENTIAL OF A UNICELLULAR ALGA *ACETABULARIA ACETABULUM* EVOLVED 500 MILLION YEARS AGO*



* Nonlinear spectral analysis on signal-averaged data from 20 single cells, released (zero time) into continuous light (LL), After prior standardization in light and darkness alternating at 12-hour intervals (LD12:12) for up to one week. Total number of observations: 38,578; experimental span: 376 days. Note a more prominent amplitude (A) for a component with a period near a week, than tha As of the about daily and about half-weekly components (all free-running). The circaseptan A is equated to 100 and the other As are expressed as percentage of the circaseptan. Metaanalyzed data of Dr. Sigrid Berger, Dr. Luebbo von Lindern and the late Dr. Hans-Georg Schweiger.

Figure 5. Curve-fitting to data in Figure 4 shown as original values (dots) quantifies 3 spectral components (right) with circaseptan prominence. © Halberg.

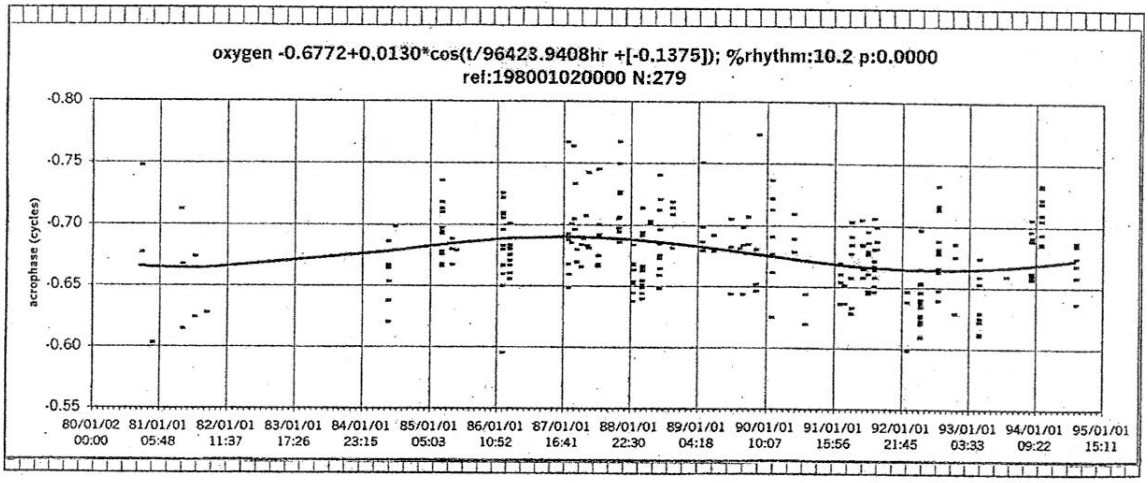
DIFFERENT TIMING
of FREERUNNING CIRCASEPTAN COMPONENT
in OXYGEN PRODUCTION (OP), CHLOROPLAST MIGRATION (CM) and ELECTRICAL POTENTIAL (EP)
in *ACETABULARIA ACETABULUM* *



*** Released into continuous light (LL) after prior standardization in light and darkness alternating at 12-hour intervals; period of 162.13 hours is average of presumably free-running periods of 160.7, 162.2 and 163.5 hours, for OP, CM and EP, respectively. Signal-averaged values of 20 - 24 single cells, each series detrended by 2nd or 3rd order polynomial, depending on length of series (< or > 14 days). Data from Dr. Sigrid Berger, Dr. Luebbo von Lindern and the late Dr. Hans-Georg Schweiger.**

Figure 6. Division of labor in time in LL in a eukaryotic unicell, as shown by non-overlapping 95% confidence intervals displayed by the width of bracketed horizontal lines on one of the peaks in each of the 3 approximating functions. © Halberg.

CIRCADECADAL RHYTHM IN CIRCADIAN ACROPHASE (FRACTION OF CYCLE) OF OXYGEN PRODUCTION OF *ACETABULARIA MEDITERRANEA**



*Approximated by -0.6772 + 0.013 cos (2πt/**11 y** - 0.1375); t_{ref} = 2 Jan 1980; PR=10.2%; P<0.001; measurements in LD12:12. Data kindly provided by Prof. Sigrid Berger.

Figure 7. Circadidecadal cycle in circadian acrophase in a population of unicells: putative signature of Schwabe's cycle (in relative sunspot numbers). © Halberg.

Figure 3 shows the time course of the nonstationary circadian behavior in electrical activity of a group of Ac cells (previously synchronized for up to a week with LD) for several days after release from LD into LL. Signal averaging reveals, to visual inspection, time-macroscopically in the first circaseptan cycle in LL, a circaseptan amplitude greater than that of the coexisting circadian component, Figure 4. Curve-fitting quantifies an about half-weekly (circasemiseptan) component as well (Figure 5), with an amplitude smaller than that of the circadian rhythm (6). Figure 6 shows differences in phase among three presumably free-running variables investigated in LL, oxygen production, electrical activity and chloroplast migration (7). Note from the non-overlapping CIs (horizontal lines around the peak) that the differences in timing of the 3 variables are statistically significant, documenting a division of labor in time in a unicell. Figure 7 introduces a circadecadal rhythm in the circadian acrophase of oxygen production with a period of ~11 years. First circadian parameters in LD were assessed, and among these the circadian acrophase was seen to exhibit a cycle associated with Zürich relative sunspot numbers.

Ac may have existed on earth ~500 million years ago (8). Hence it is a convenient object for comparisons of phylogeny, notably of nonphotic circaseptans with corresponding features in human ontogeny (9), demonstrating, at the unicellular level of chronomes (time structures) that spectral components like the near-week are prominent in both early phylogeny and in the multi-cellular human infant's early ontogeny, so that the latter can be modeled by the former (9). Several infradian rhythms which are cycles in individual humans have been mapped as population rhythms in Ac with serially-independent sampling as to individuals (4, 5) in Ac.

During the span of 1980-1991, 341 experiments were performed on the giant unicellular alga *Ac. acetabulum* at the then Max-Planck-Institute for Cell Biology in Ladenburg, Germany. These data are available online at http://www.mpizb-ldb.mpg.de/, linked to http://www.lvloldz.privat.t-online.de/deveppon.html, courtesy of Dr. Lübbo von Lindern. We here analyze a longer set obtained directly from Dr. Sigrid Berger, covering 14 years. Oxygen production, electrical potential and/or chloroplast migration were recorded at 30-minute intervals for spans ranging from 19 to 109 days. In most experiments, the cells were first maintained for up to 7 days in the initial span of light and darkness alternating at 12-hour intervals (LD12:12). When the circadian rhythm was well expressed *ad oculos,* the cells were exposed to LL. In many experiments, after 7 to 18 days, different pulses were applied to the cells, such as dark pulses (for 8-24 hours), or a drug was added to the medium (3-aminobenzamide, caffeine, geneticin, oligomycin, ouabain, pentanol, ethanol, etc.), for spans of up to 97 days.

Each stage of each experiment was examined for validity of protocol by the actual times originally recorded by computer in 341 experiments. Experiments ended as soon as the alga started to form gametangia (sign of maturation), or their cap diameter reached a size filling the diameter of the cuvette (sign of fast growth), or (less frequently) because of sudden cell death.

Two endpoints were examined herein, Table 1: the total duration of each study on a given cell, and the duration of the initial span during which the cell was kept in LD12:12 conditions. The duration of LD12:12 standardization spans was used as a primary check on algal behavior, since a subjectively satisfactory behavior (rhythm) in LD12:12 was the condition for release into LL. For comparison, data on two planetary indices of geomagnetic activity, Kp and Dst, were considered over matching spans. In order to check against influences of artifacts, 100 noise series were generated.

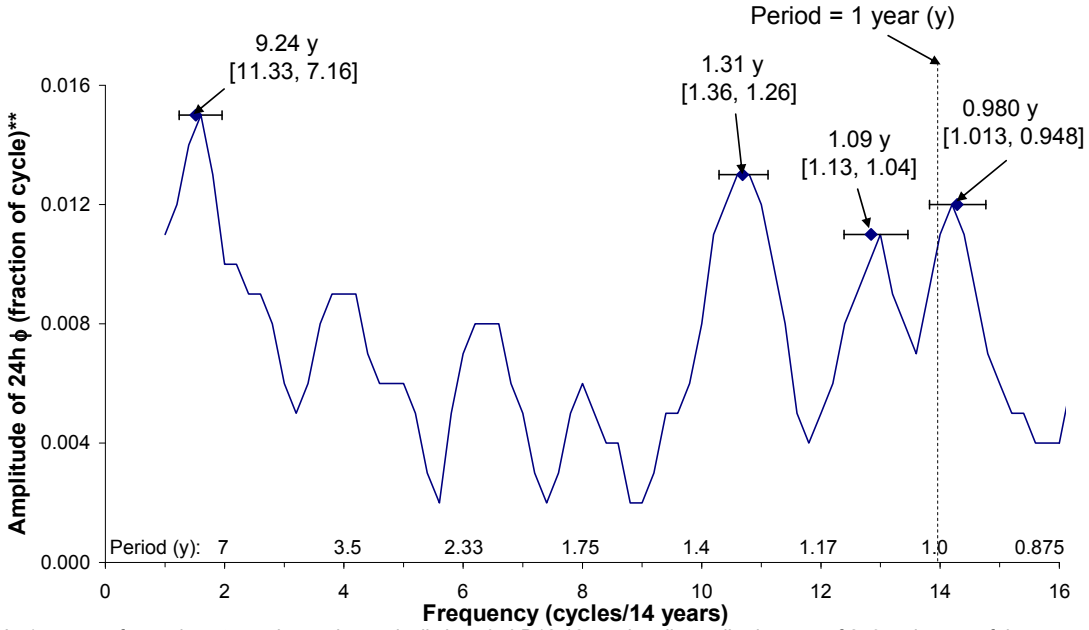
For each cell, the total study duration and the length of the LD12:12 span were assigned to the calendar date of the mid-time of the corresponding span. These data were analyzed by least-squares spectra with periods ranging from 10.5 years to 2.5 months, followed by a nonlinear least-squares scrutiny of the periods found linearly with ordering statistical significance (without

Table 1: Estimates and 95% confidence limits of spectral components characterizing the rhythms of two planetary indices of geomagnetic activity and the alga *Acetabularia*

Trial period, τ		Geomagnetic indices		*Acetabularia* (span duration, in days)	
(years)		Kp	Dst	Study span	LD12:12 spans
		(arbitrary units)			
10.5	τ	8.013 (7.523, 8.535)	7.780 (7.192, 8.494)	10.017 (8.003, 12.031)	10.469(7.680,13.258)
	A	0.43 (0.36, 0.50)	6.07 (4.50, 7.66)	5.75 (1.71, 9.79)	2.13 (0.73, 3.54)
5.25	τ	3.282 (3.148, 3.431)	3.374 (3.257, 3.502)	4.563 (3.549, 5.904)	4.265 (3.758, 4.918)
	A	0.20 (0.12, 0.27)	5.72 (4.16, 7.28)	3.56	2.10 (0.56, 3.65)
1.75	τ	1.750 (1.713, 1.789)	1.739 (1.711, 1.769)	1.585 (1.481, 1.711)	1.848 (1.698, 2.058)
	A	0.22 (0.14, 0.29)	5.79 (4.24, 7.35)	4.51 (0.93, 8.08)	1.30
1.0	τ	1.316 (1.294, 1.340)	1.019 (0.999, 1.038)	0.902 (0.864, 0.941)	1.032 (0.996, 1.091)
	A	0.19 (0.11, 0.27)	3.81 (2.22, 5.40)	5.10 (0.68, 9.53)	2.10 (0.54, 3.65)
0.5	τ	0.499 (0.494, 0.503)	0.502 (0.500, 0.505)	0.485 (0.475, 0.498)	0.498 (0.402, 0.504)
	A	0.21 (0.13, 0.28)	6.22 (4.66, 7.79)	5.07 (1.27, 8.88)	2.81 (1.28, 4.34)

A: amplitude. "Study span" and LD12:12 span are measures of vigor of the unicell in a total of 341 studies during 1980-1991.

An About-Yearly Component is Neither the Sole nor the Largest Infrannual Variation Characterizing *Acetabularia*'s Oxygen Evolution*



* In 14 years of experiments on these giant unicells kept in LD12:12, each cell contributing one of 279 estimates of the circadian acrophase based on up to a week's recording analyzed by cosinor. From Max Planck Institute for Cell Biology archives (HG Schweiger, director; courtesy of Sigrid Berger). Period lengths and 95% confidence intervals (CIs) assessed by nonlinear least squares. **Indicating prominence of change in circadian acrophase (ϕ) at frequency shown on abscissa.

Figure 8. Another demonstration, in the data underlying this figure, of a set of solar signatures, including transyears, as well as components with a CI (95% confidence interval, given in parentheses) overlapping the calendar year at one extreme (right) and the circadecadal Schwabe cycle at the other extreme (left) in a population of unicells sampled with serial independence as to the individual alga. © Halberg.

CIRCASEPTAN (TOP) AND CIRCASEPTAN (BOTTOM) GROWTH RESPONSE OF INTACT (TOP) OR ENUCLEATED (BOTTOM) *Acetabularia* WITH FITTED MODEL (LEFT) AND COSINOR (RIGHT)

Scheme of schedule shifts of the light-dark regimen

Interval between shifts, days	Experimental day																													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Control	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL
2	DL	DD	LD	LL	DL	DD	LD	LL	DL	DD	LD	LL	DL	DD	LD	LL	DL	DD	LD	LL	DL	DD	LD	LL	DL	DD	LD	LL	DL	DD
3	DL	DL	DD	LD	LD	LL	DL	DL	DD	LD	LD	LL	DL	DL	DD	LD	LD	LL	DL	DL	DD	LD	LD	LL	DL	DL	DD	LD	LD	LL
4	DL	DL	DL	DD	LD	LD	LD	LL	DL	DL	DL	DD	LD	LD	LD	LL	DL	DL	DL	DD	LD	LD	LD	LL	DL	DL	DL	DD	LD	LD
5	DL	DL	DL	DL	DD	LD	LD	LD	LD	LL	DL	DL	DL	DL	DD	LD	LD	LD	LD	LL	DL	DL	DL	DL	DD	LD	LD	LD	LD	LL
6	DL	DL	DL	DL	DL	DD	LD	LD	LD	LD	LD	LL	DL	DL	DL	DL	DL	DD	LD	LD	LD	LD	LD	LL	DL	DL	DL	DL	DL	DD
7	DL	DL	DL	DL	DL	DL	DD	LD	LD	LD	LD	LD	LD	LL	DL	DL	DL	DL	DL	DL	DD	LD	LD	LD	LD	LD	LD	LL	DL	DL
8	DL	DL	DL	DL	DL	DL	DL	DD	LD	LD	LD	LD	LD	LD	LD	LL	DL	DL	DL	DL	DL	DL	DL	DD	LD	LD	LD	LD	LD	LD
9	DL	DL	DL	DL	DL	DL	DL	DL	DD	LD	LD	LD	LD	LD	LD	LD	LD	LL	DL	DL	DL	DL	DL	DL	DL	DL	DD	LD	LD	LD
10	DL	DL	DL	DL	DL	DL	DL	DL	DL	DD	LD	LD	LD	LD	LD	LD	LD	LD	LD	LL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DD
11	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DD	LD	LD	LD	LD	LD	LD	LD	LD	LD	LL	DL	DL	DL	DL	DL	DL	DL	DL	DL
12	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DD	LD	LD	LD	LD	LD	LD	LD	LD	LD	LL	DL	DL	DL	DL	DL	DL	DL	DL
13	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DD	LD	LD	LD	LD	LD	LD	LD	LD	LD	LD	LD	LL	DL	DL	DL	DL	DL
14	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DD	LD	LD	LD	LD	LD	LD	LD	LD	LD	LD	LD	LD	LD	LL	DL	DL
15	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DL	DD	LD	LD	LD	LD	LD	LD	LD	LD	LD	LD	LD	LD	LD	LD	LL

D, 12 hr of dark. L, 12 hr of light.

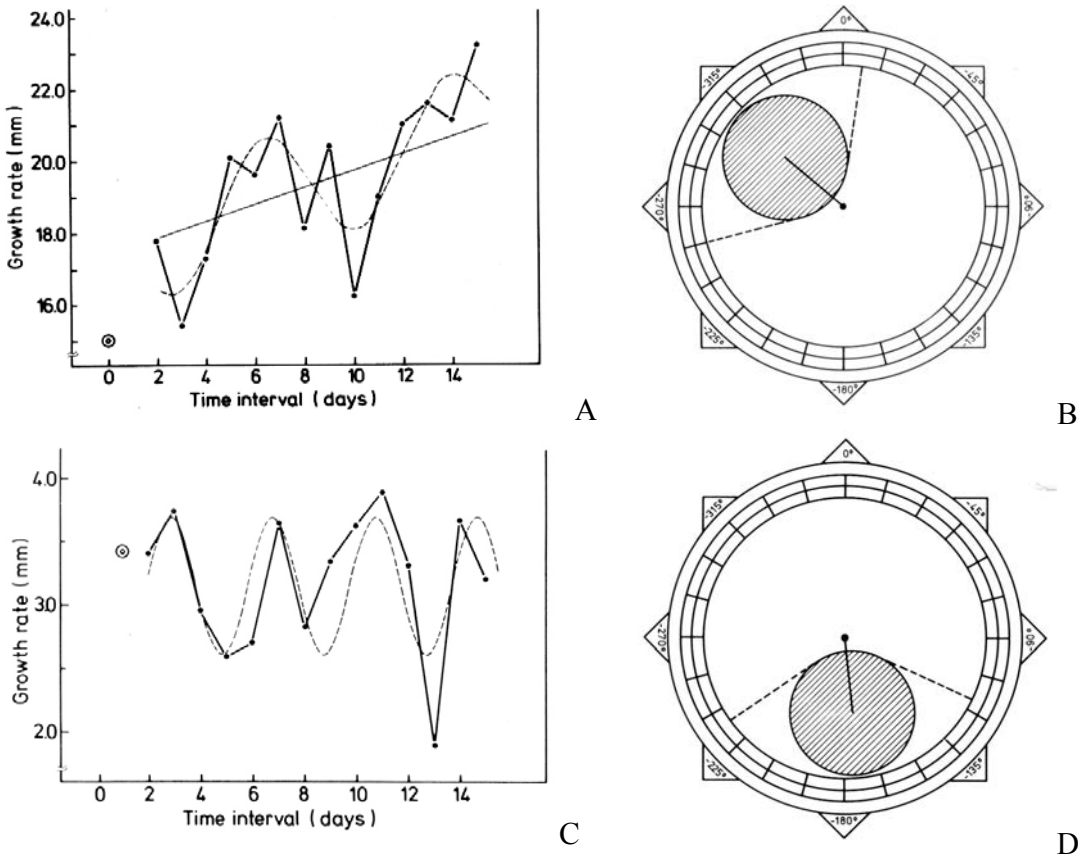


Figure 9. Shifts of a regimen of light (L) and darkness (D) alternating every 12 hours carried out at intervals ranging 2 to 15 days in unicells with and without a nucleus are associated with different patterns, allowing a glimpse into the role of the nucleus in the genesis of about-weekly vs. about half-weekly cycles. Original data from Schweiger et al. (3). © Halberg.

Table 2: Endpoints of linear-nonlinear rhythmometry of light transmission by *Acetabularia*

Nucleus present?	Estimates				
	—— Circadian ——		— Circaseptan —		$\frac{CS-A}{CD-A}$ (%)
	Period (h)	2A (AU)	Period (d)	2A (AU)	
1 (yes)	25.70	68.04	7.14†	26.34	38.71
2 (yes)	24.67	21.70	8.28	9.70	44.70
3 (no)	27.53	18.28	6.52	2.10	11.49
4 (no)	27.31	26.20	6.40	5.08	19.39
5 (no)	26.99	42.40	6.95	10.50	24.76
6 (no)	25.30	35.66	5.35	9.56	26.81
7 (yes)	24.84	10.34	8.13	5.54	53.58
8 (yes)	24.29	37.24	7.05	11.62	31.20
9 (yes)	24.48	7.20	7.25	10.94	151.94
10 (no)	26.09	53.78	6.44	6.22	11.57
11 (yes)	23.81	15.82	5.59	5.78	36.54
12 (no)	26.23	12.82	6.22	2.34	18.25
13 (yes)	22.47	27.28	8.88	17.42	63.86

2A=double amplitude. AU=arbitrary units. Estimates obtained by concomitant nonlinear fit of both circadian (CD) and circaseptan (CS) components and linear trend.
†No trend included in model (CS not resolved with inclusion of linear trend in model).

correction for multiple testing). The same procedures were applied to a planetary (Kp) and an equatorial (Dst) index of geomagnetic disturbance and to the 100 noise series matching the sampling of the biological data.

Table 1 reveals congruence, i.e., overlapping 95% confidence intervals at a period of 6 months between the biological and geomagnetic variables. Table 1 shows that Ac shares with terrestrial magnetism disturbance a precise half-yearly cycle, in two unusual endpoints that deal with the vigor of the cell, namely the duration of a total of 341 studies as a whole and the span that was required in LD. Figure 8 demonstrates, in addition to a yearly component, a near-transyear and a far-transyear, with τs of 1.09 (1.04, 1.13) and 1.31 (1.26, 1.36) years, respectively, in the circadian acrophase of oxygen production in LD in 279 separate studies.

Ac's circadian, circasemiseptan and circaseptan rhythms have also been studied after enucleation (3, 10, 11). Figure 9 shows that a circaseptan pattern can become circasemiseptan after enucleation in *Ac. acetabulum* (3). By removing the nucleus, a normally subtractive (or rather frequency-demultiplying) coupling in frequency of the circaseptan and circasemiseptan spectral components may be uncovered. Figures 10a and 10b and Table 2 show the effect of enucleation of Ac as a reduction of the circaseptan vs. circadian amplitude ratio, a hint of amplifying coupling between the two rhythms' mechanisms, a possibility requiring follow-up because of the relatively small number of cells involved, statistical significance notwithstanding.

There is the added finding in *Ac. acetabulum* that while enucleated cells are less vigorous than intact cells, insofar as more enucleated cells die during a study (as compared to nucleated ones) (3), the enucleated Ac's mortality can be greatly reduced by shifts of the lighting regimen (as compared to the mortality of unshifted cells without the rhizoid containing the nucleus). Figure 11 shows that among many other laboratory models of phase-shifting (of LD), the greatest effect upon the modification of lifespan, expressed as % of the mean, was found in *Ac. acetabulum,* as a prolongation rather than as a shortening of life, as a potentially favorable effect (12, 13). Models other than Ac are also useful (14). Changes with age are reported (15). The reader is further referred to studies on *Acicularia schenkii* (16) and more generally to (1) and (8). Apart from the opportunity to study enucleation effects, along with average trends, Ac has the thus-far broadest spectral element mapped in a unicell.

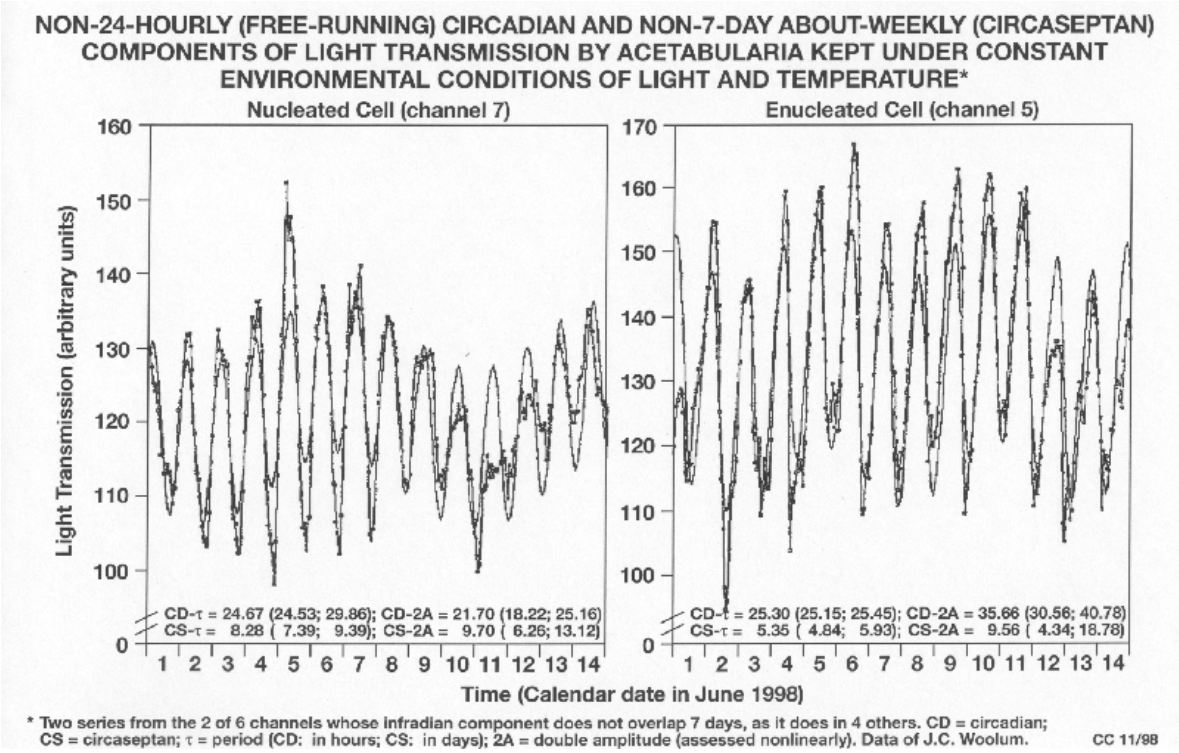


Figure 10a. Circaseptan-circadian relations in the presence and absence of a nucleus displayed for the unaided eye are analyzed in Table 2 and summarized in Figure 10b. © Halberg.

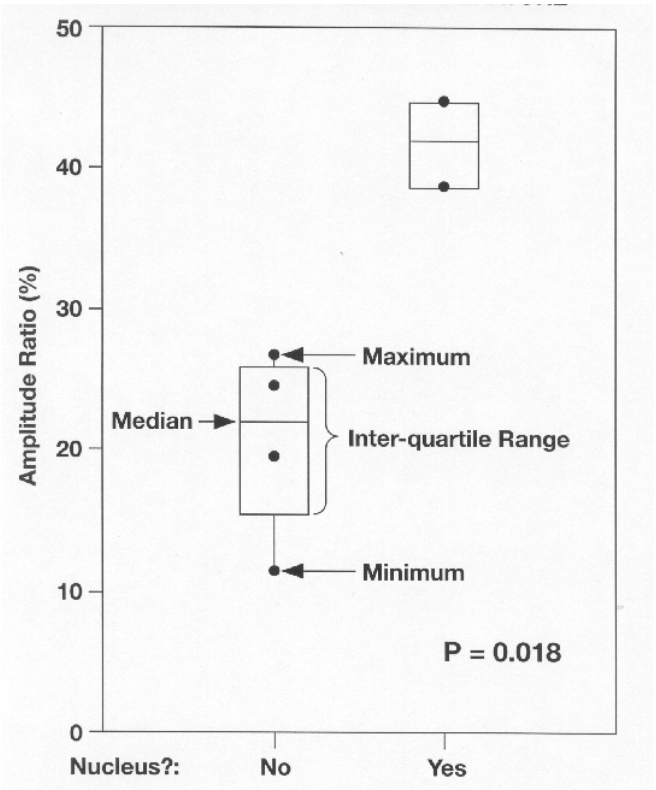


Figure 10b. Enucleation in Acetabularia acetabulum changes the circaseptan-to-circadian amplitude ratio of light transmission by Acetabularia kept under constant environmental conditions of light and temperature. The circaseptan prominence is reduced in a relatively small sample of individual unicells (dots) investigated (cf. Table 2 and Figure 11). * Data of J.C. Woolum. © Halberg.

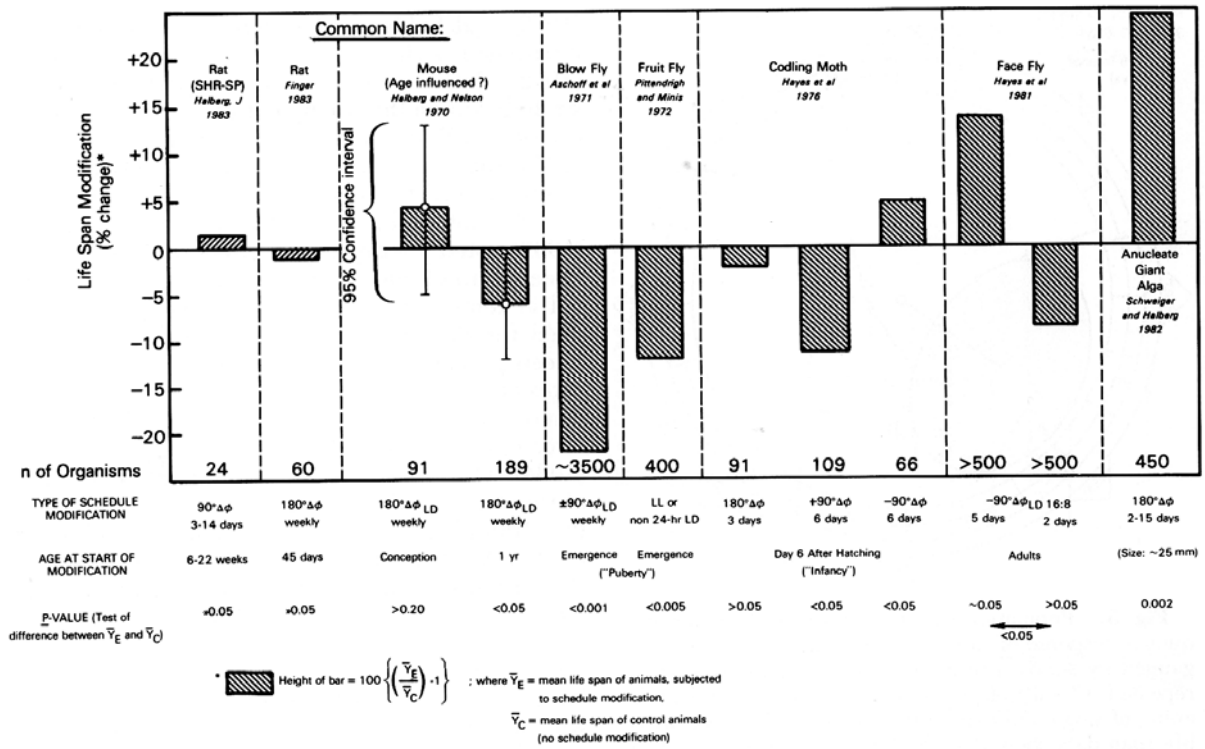


Figure 11. Manipulating the regimen of alternating light and darkness in *Acetabularia acetabulum* without vs. with a nucleus (last column) allows insight into the role of the nucleus as a useful putative synchronizer, replaced by the lighting regimen to the advantage of the enucleated cell. © Halberg.

1. Schweiger H-G, Hartwig R, Schweiger M. Cellular aspects of circadian rhythms. J Cell Sci Suppl 1986; 4: 181-200.
2. Schweiger H-G, Halberg F. Can a unicell measure the week and an isolated cytoplasm measure half a week? Notiz SIBioC 1982; 6: 525-526.
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Solar signatures in Australian suicide incidence:
gender differences in prominence of photic vs. nonphotic spectral components

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Abstract

Irrespective of gender in Australia, in a sample with many more males (50,169) than females (15,859) and much more prominently in the undiluted sample of males only, the photic calendar year is the largest component in spectra of the incidence of suicide. In the spectrum of suicide incidence of Australian females, a period, τ, of about (~) 0.563 year, of putative solar origin (insofar as it was identified as a beat period of solar rotation rates by one of us [CW]), happens to predominate in the para-annual, including parasemiannual spectral regions over much lower amplitudes at trial τs of 1.00 (and 0.50) year, with the latter being very prominent in the incidence spectrum of males committing suicide in Australia. The CI (95% confidence interval) of the ~0.56-year component (0.56-0.567 year) in the spectrum of women does not overlap the precise 0.50-year length, which in turn dominates the spectrum of suicide incidence in Minnesota, irrespective of gender. These geographic and gender differences among spectra with too many, albeit some predicted peaks should be complemented by more extensive data from many more locations.

Introduction

The built-in photic and societal signatures of the changes along the scales of 24 hours and of the seasons have been of consistent interest to psychiatry (1), including the topic of suicide, Figure 1 (2; cf. 3). Spectra of the incidence of suicide also reveal putative nonphotic effects, such as those of geomagnetics (4; cf. 5, 6). There are further nonphotic associations with (solar) weather in space, which influences geomagnetics. The sun can also act directly via particle emissions from it, the solar wind, which may in part penetrate the earth's magnetosphere. Any solar-terrestrial vs. human associations can be gauged in incidence spectra of environmental cycles vs. those of various epidemiological, psychophysiological and other biospheric time series (7-9).

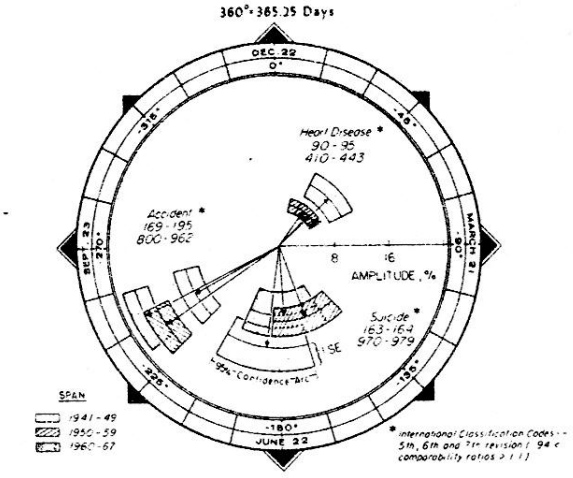


Figure 1. Cosinor summaries by fit of a 1-year cosine curve show circannual rhythms in the incidence pattern of mortality from suicide, cardiovascular diseases and accidents in Minnesota during 1941 to 1967. Note reproducibility of findings in consecutive spans. Deaths from heart diseases peak in the winter, suicides in June, and accidents somewhat later in the year. Focus upon the photic seasons must not detract from other nonphotic environmental contributions resolved by the extended cosinor in Figures 2, 5-7. © Halberg.

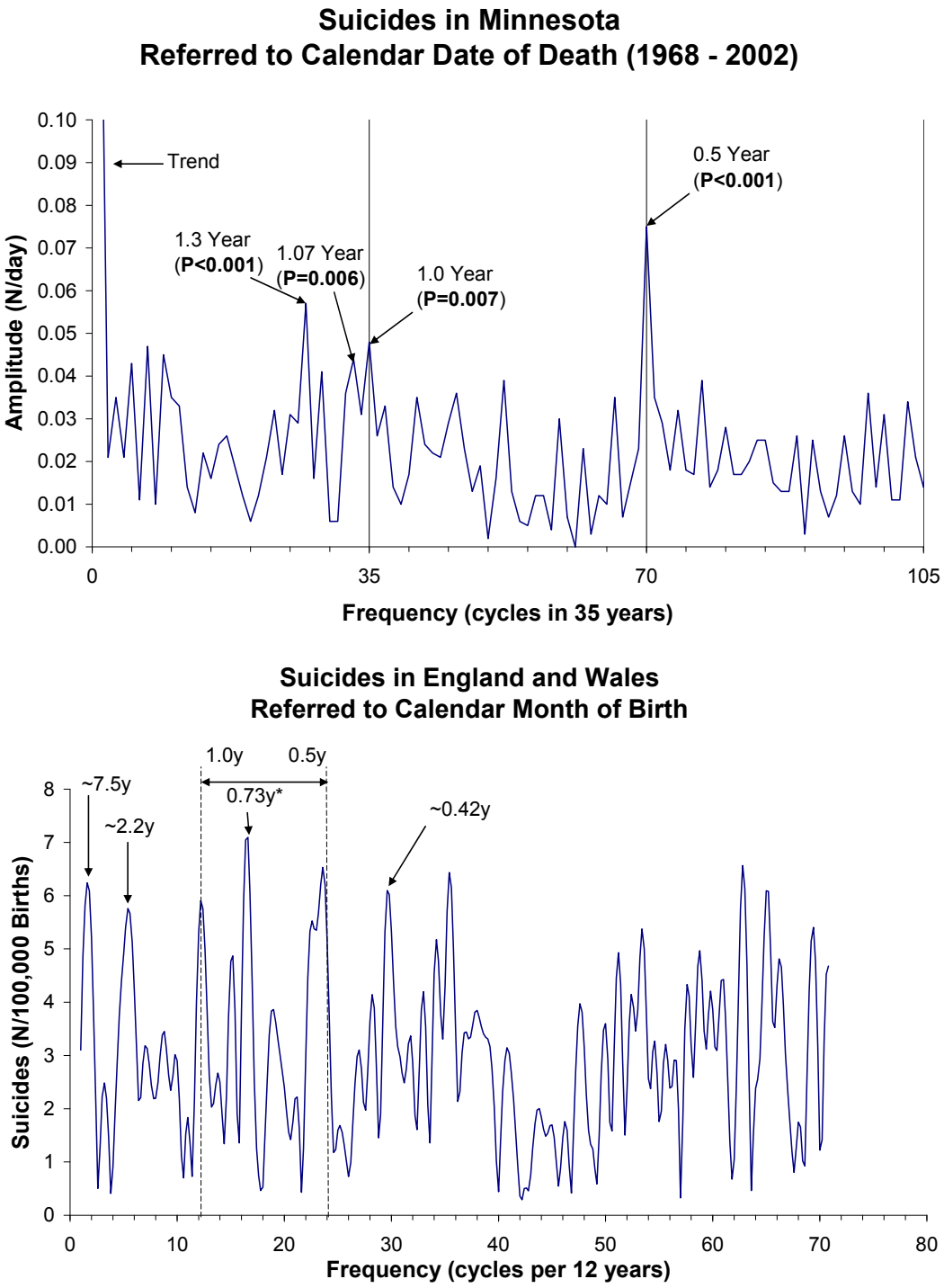


Figure 2. Spectrum of the incidence of suicide in Minnesota, by calendar date of death (1968-2002), irrespective of gender. Note prominent half-year component particularly related to geomagnetics (top); below, spectrum of the incidence of suicide in England and Wales, by calendar date of birth (1955-1966), irrespective of gender.
* Validated nonlinearly. Period = 0.727y (95% confidence limits: 0.703, 0.751y). © Halberg.

Congruence

Beyond the seasons (Figure 1) and associations of suicide with ambient electromagnetic fields (6) and geomagnetic storms (4, 7), there is a putative signature of the solar wind, namely an ~1.3-year cycle in Minnesotans in the USA committing suicide (8, 9), Figure 2 (top). This ~1.3-year component was theoretically identified by CW (10) as a beat frequency of solar rotation rates and was abundantly validated for diverse variables gauging solar activity (11-19). In the as-yet relatively short time series stemming from satellite measurements during about 40 years in the solar wind's speed, the sigma of its speed, and its proton density, the 1.3-year period is wobbly, drifting, bifurcating and joining in frequency and waxing and waning in amplitude to the point of being no longer detected, and in this sense of intermittency, spectral behavior in gliding spectra is described as aeolian and accordingly broader spectral regions were dubbed a far-transyear (1.2 years $\leq [\tau - CI] < [\tau + CI] <$ 1.9 years), and thus tentatively separated from a near-transyear (1.00 year $< [\tau - CI] < [\tau + CI] <$ 1.20 years). The latter was also found, among other variables (7), in spectra of time series of suicide in Minnesota (8, 9). The far-transyear also characterized sudden cardiac death in several locations (7, 20). In the incidence pattern of suicides in Minnesota (by the day of death), the solar wind's ~1.3-year far-transyear was second in prominence overall and had numerically the largest amplitude in the para-annual region, very slightly exceeding the prominence of the also statistically significant seasons, Figure 2 (top). A near-transyear of 1.07 years had a slightly smaller amplitude than that of the calendar year component.

The relative prominence of cycles in the visible range, such as a calendar-year component as a photic, thermic and social entity, vs. non-photic cycles has been taken as an approximate and tentative gauge of the importance of their relative roles played in human health and broader affairs. Thus, we assessed the roles of invisible weather in space and/or geomagnetic disturbance on the one hand vs. the associations of seasonal changes of weather on earth on the other hand. These associations of photic vs. nonphotic spectral prominence varied geographically for phenomena such as suicide (8, 9) or sudden cardiac death (7, 20). The 10th revision of the International Classification of Diseases separated the diagnosis of sudden cardiac death from cardiac arrests associated with myocardial infarctions, limiting it to electrical accidents of the heart, i.e., to cases with no history of heart disease and no findings at autopsy (when this latter examination was possible; 7). In this ICD-10, code I46.1, another prediction by CW, a spectral component of 0.42 year length has been found in several geographic locations (7). These conditions may be influenced not only through any link between helio- and geomagnetics, but also by other perhaps direct effects of particle emissions from the sun, ultraviolet flux and gravitation, all associations summarized as nonphotic (to contrast them with photic associations in the visible domain of the day and the calendar year).

A prominent half-yearly cycle in geomagnetics (4, 21-23), dominating the spectrum of suicides by the day of death irrespective of gender in Minnesota, based on data over 35 years, had the highest amplitude and the latter had thus been associated with geomagnetic activity. Obviously, similar periods validated by an inferential statistical comparison of their CIs of τs for congruence or similarity, Figure 3, do not prove causality; they constitute a first basis for a follow-up amplification or damping (addition or subtraction) remove-and-replace approach that examines any association with the biosphere of time-varying environmental behavior, e.g., of an environmental cycle, the subtraction including a failure to detect the cycle (removal). Thus far, the behavior of the biospheric cycles examined by this approach showed damped persistence after removal of the corresponding environmental spectral component (7, 24-26). This phenomenon, dubbed bioresonance, can last for long spans after the environmental counterpart is no longer detected.

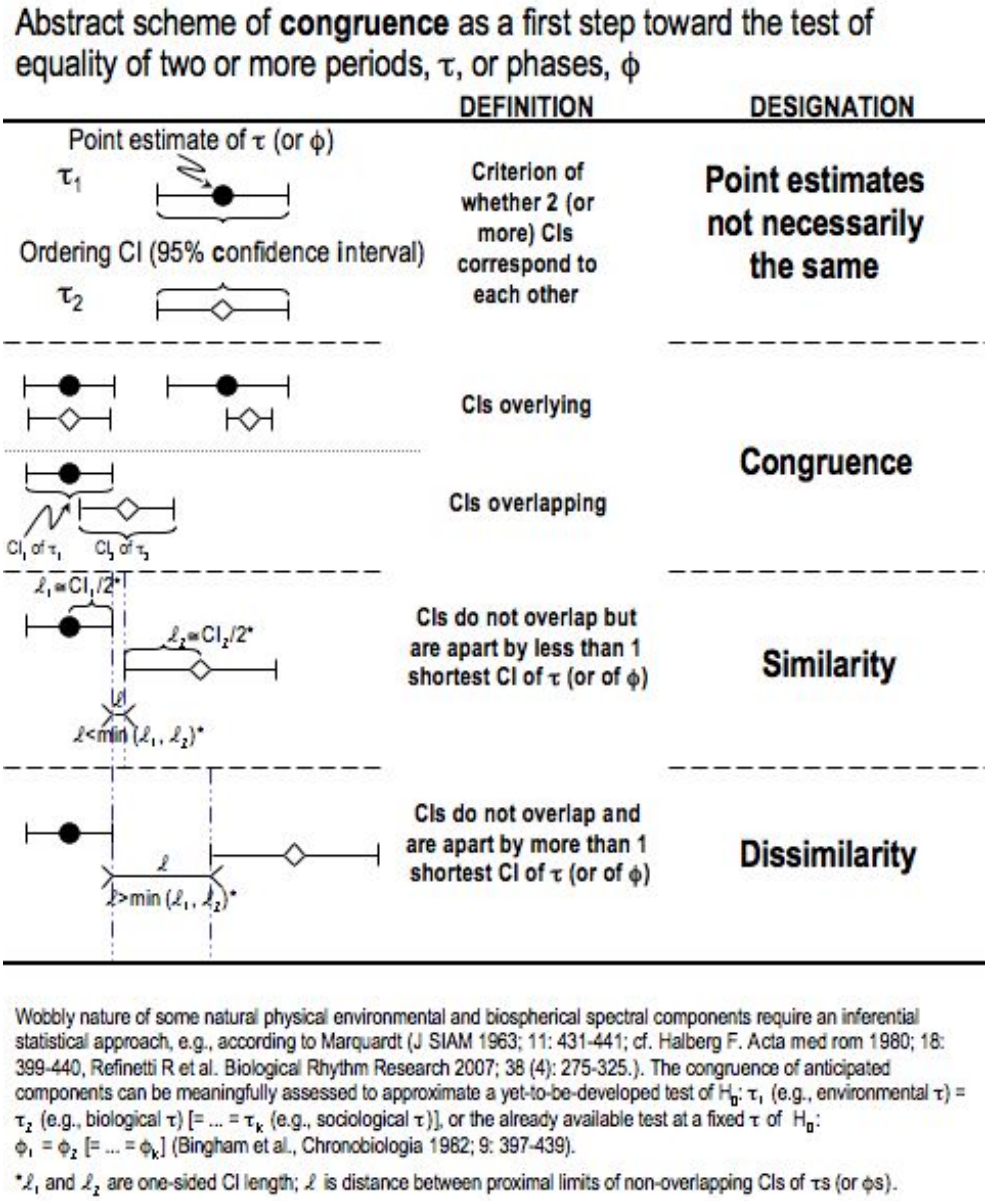


Figure 3. Congruence vs. similarity vs. dissimilarity can be gauged by CIs (95% confidence intervals) of characteristics such as the period or phase of a neighboring spectral component in two or more concomitantly sampled time series of the same variables or of different variables within tissues, organs, organ systems, individuals, populations, disciplines and, most interestingly, when they are transdisciplinary, as are transyears or trans- and cis-half-years. Congruence implies overlying CIs (100%) or overlapping ones (<100%), while similarity implies close CIs that do not overlap (0% congruence). The concept of % congruence awaits elaboration. © Halberg.

Nonphotic prominence in Minnesota, England and Wales

There was also a clear spectral peak at a trial τ of 0.5 year in the spectrum of suicides by the day of birth (rather than by that of death, the only kind of statistics analyzed from Minnesota and Australia) in England and Wales (9), but in the latter location the most prominent component was one with a period shorter than a year with a τ of ~0.73-year length, i.e., on this side (cis) of the

year, a cis-year. In the data from England and Wales, there was also a component of ~0.42 year which, as noted, corresponds to another beat period of solar rotations, predicted as a result of a decades-long modeling by CW (26-32). This cis-half-year is an abundantly documented (albeit in relatively short series), highly variable (33-40) feature of solar activity and is also reflected in increasing numbers of geographic locations in sudden cardiac death, Figure 4 (7, 20, 41-43).

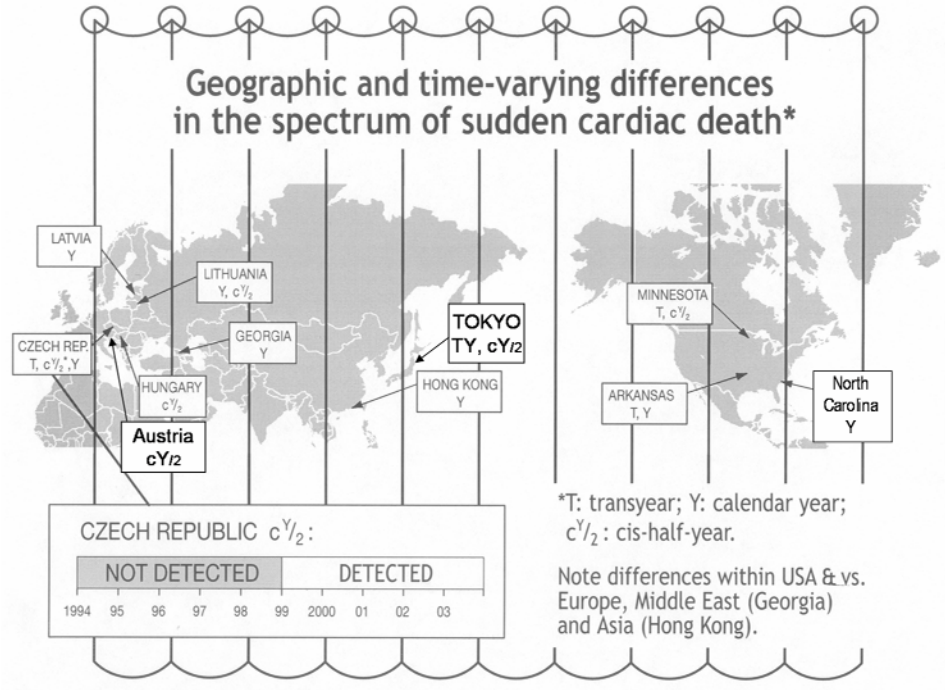


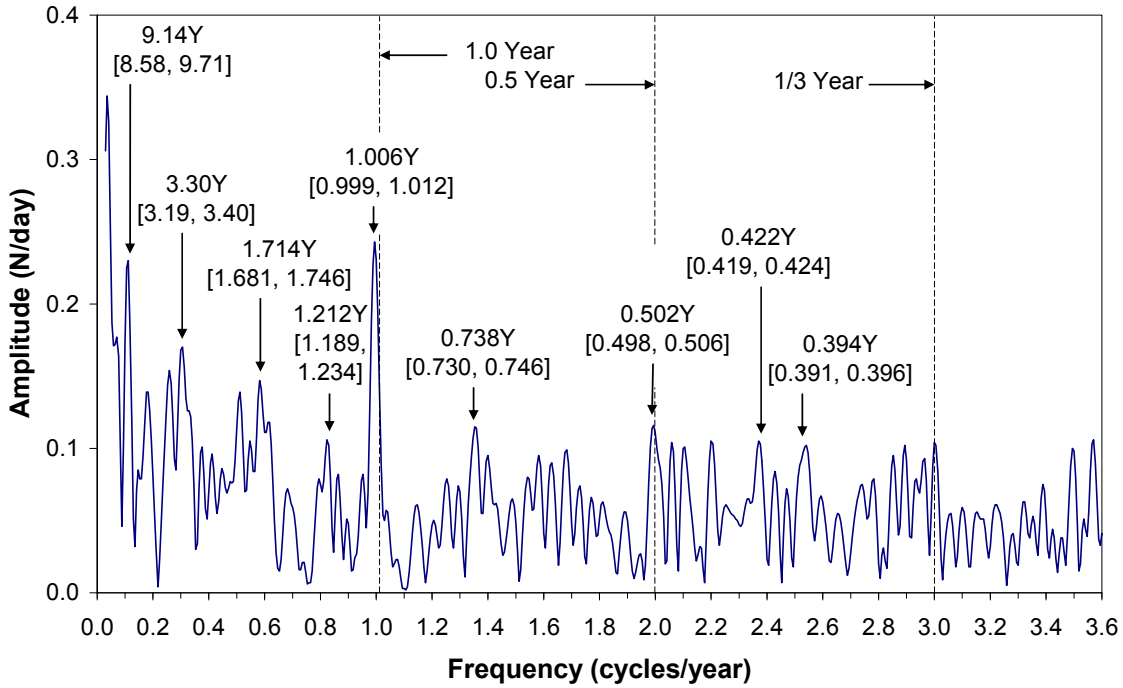
Figure 4. Because of limited available data and many other inaccessible data, a curtain of uncertainty hides any time- and geographic (geomagnetic or dip-magnetic) site-specificity of various spectral aspects in the incidence of sudden cardiac death in many locations, with some exceptions recorded herein. Thus, as compared to a far-transyear of about 16 months and with a cis-half-year of about 5 months (cY/2), but no calendar year in Minnesota and in Tokyo, we find both a calendar year and a far-transyear in Arkansas and in the Czech Republic. At the latter site a cis-half-year is detected after 1999, but not before. In some locations the calendar year and the 0.5 year are the sole peaks in the para-annual and para-semiannual region. © Halberg.

A 0.5 year peak dominating the spectrum of suicide incidence in Minnesota was also found in England and Wales in statistics by the day of birth of those committing suicide. Geomagnetic disturbance was thus putatively associated with suicide in all locations investigated, as were the seasons. The 0.5-year peaklet in suicide incidence in Australia characterizes notably males.

Non-photic signature in female and photic in male and overall suicides in Australia

In incidence statistics by the day of death, the calendar year dominates in Australia overall, Figure 5, and in males, Figure 6, but not in females, Figure 7. Transyears that were prominent in Minnesota are also found in Australia at ~1.21 years in females, Figure 7, and at ~1.71 years in males, Figure 6, that are both represented overall in Figure 5. When the data from Australia are separated into those of males that were the majority (and had a trend removed), the impression gained from all data in Figure 5 is supported by the prominence of the seasons in males, Figure 6, yet there is also a peak, among others, at the presumably solar signature of an ~0.42-year and at the putatively geomagnetic 0.5-year. In data from females in Figure 7, a (putatively solar) ~0.56-year

Coexisting Photic and Non-photic Components in the Incidence Pattern of Suicides in Australia (1968-2001)*



* Original data of Michael Berk. Data detrended (removal of linear trend). Number of cases: 66,028.

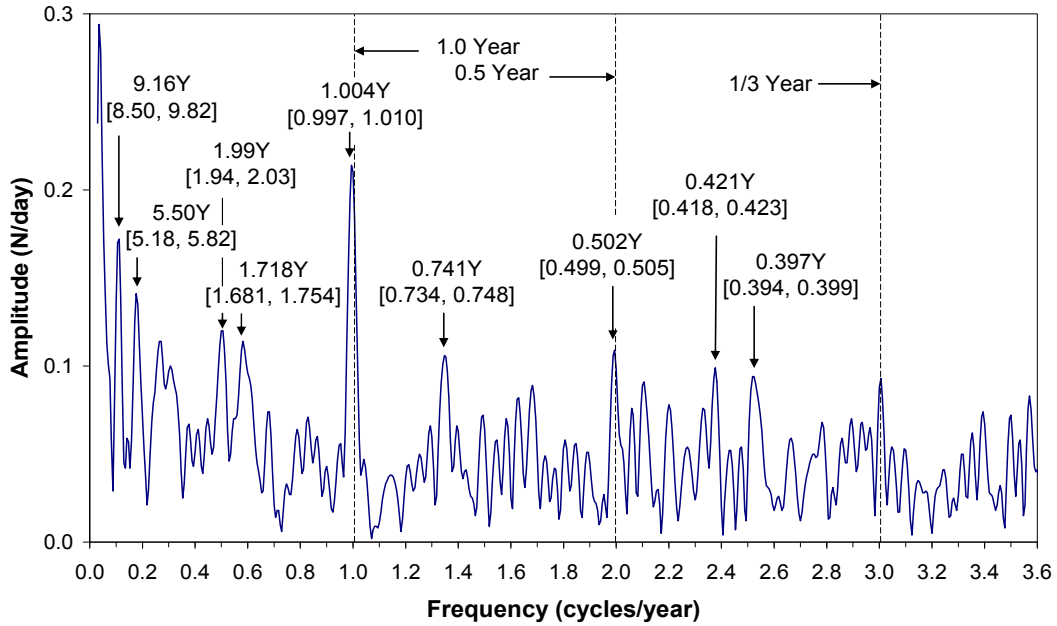
Figure 5. Suicide incidence (coded by day of death) in Australia shows a prominent photic year and non-photics such as a putative geomagnetic circasemiannual component and putative solar transyears and a cis-half-year. © Halberg.

component is found. As already noted, it has been reported as a beat frequency of solar dynamics (10), and is numerically more prominent than the yearly and half-yearly components.

The marked gender difference in Australia is based on a relatively smaller number of females as compared to males, and deserves further study in other geographic locations. Two sites were examined by the day of death (Australia and Minnesota) and one location by the day of birth: it can be suggested, as in the case of sudden cardiac death (7, 20, 43), that photic and non-photic components are present in all locations, irrespective of the kinds of statistics by day of death vs. of birth. The seasons dominate in Australian males and in Australians overall (because of the larger number of males), but not in Australian females and not in Minnesota, nor in England and Wales. Among non-photics, the ~1.3-, 0.56- and 0.42-year components may be primarily solar and the 0.5-year component, partly terrestrial in origin. It remains to be elucidated why and how three of the solar rotation's beat periods have biospheric signatures, but not the other seven thus far. How do 1.33, 0.56 and 0.42 differ from the other beat periods in terms of physics? In evidence accumulated thus far, the ~0.42-year component has a special place. With an also-present far- and near-transyear, the cis-halfyear characterizes breakdown products of steroidal hormones critical to survival and reproduction.

The broad-scale geographic mapping of factors underlying mood by focus on the extreme of depression in the form of suicide remains a challenge. It is already known that negative affect has both a solar and a geomagnetic component with a (non-photic) τ of 7 days, while positive affect is predominantly circadian (44). With the new information on hand, the role played by the cosmos

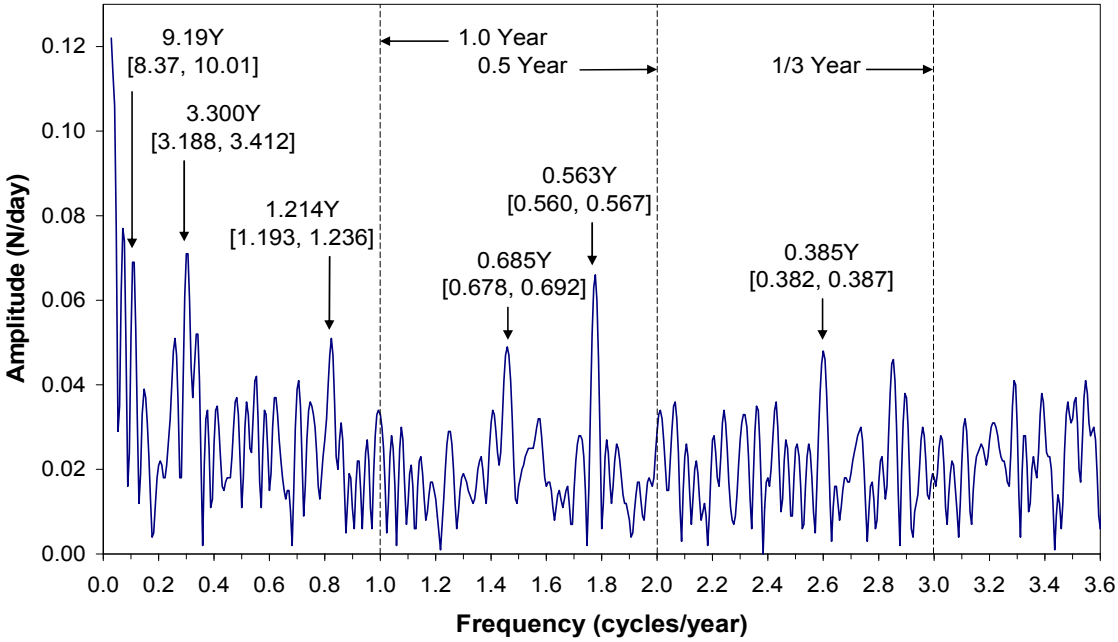
Dominant Seasons in the Incidence Pattern of Suicides by Males in Australia (1968-2001)*



* Original data of Michael Berk. Data detrended (removal of linear trend). Number of cases: 50,169.

Figure 6. Coexisting photic and nonphotic components in suicides by males in Australia. © Halberg.

Dominant Solar about 0.56-year Component in the Incidence Pattern of Suicides by Females in Australia (1968-2001)*



* Original data of Michael Berk. Number of cases: 15,859.

Figure 7. Nonphotic prominence in the incidence spectrum of suicides by females in Australia. © Halberg.

can be explored at likely built-in windows of new resonant frequencies to be investigated in populations and in the few documented individuals by addition and subtraction up to a remove-and-replace approach where the amplification and damping of one or the other of the intermittent environmental spectral components is done by the cosmos (7, 24, 25).

Certain frequency windows are identified for further study in the para-annual region of spectra of the incidence patterns of suicide, such as the ~1.3-year far-transyear (7, 45) and three windows that are very narrow in the parasemiannual region, since the τs are close to each other. A precise half-yearly component in circulating melatonin at middle latitudes by night (46) relates putatively to geomagnetics. It has been mapped as a distinctly different entity (as far as CIs of the τs are concerned) as compared to ~0.56- and 0.42-year cycles, predicted as solar beat periods (10) and found to have CIs not overlapping the precise half-year length.

To complicate the issue, when the circulating melatonin was determined with serial independence as to individuals in 172 patients in blood drawn from each of them at 6 consecutive 4-hour intervals was analyzed as six separate series, each series consisting of data from a given clock-hour, the CIs of the τs all overlapped the 0.42-year τ (47). The CIs of τs from analyses of two more (related) series of circulating melatonin MESORs and circadian amplitudes of the patients' set as a whole also overlapped the 0.42-year length (47). The resolution of the relative prominence of cycles with periods of ~0.42-, 0.50- and 0.56-year, should they coexist concurrently in some future study, will require very long series, notably if the time courses of these components in the environment and, among others, in suicide are to be compared, as was done for the biological week (25) and the far-transyear (7). Moreover, for the case of the same data on melatonin circulating in the blood of 172 patients studied during several years, in which a cis-half-year is found by extended (linear-nonlinear) cosinor (47), a precise half-yearly component was previously reported by a different (population-mean cosinor) approach (46).

Transdisciplinary discussions

It could be chance that in a 15-year series of daily 17-ketosteroid excretions, a predicted (10) 0.42-year period and transyears were found. Periods with CIs all covering the 0.42-year length found in the melatonin circulating in the blood of 172 patients in Florence (47) could also be due to random sampling error, yet somehow the 172 patients studied over several years had to be synchronized and solar activity comes to mind as the synchronizer. With so many peaks in the spectra demonstrated elsewhere and here in Figures 2 and 5-7, many if not all of them could come about by the ever-present chance. But if the needed much longer series should become amenable for analyses, the role of chance could be reduced. Also with respect to underlying mechanisms (46, 47), it seems pertinent that Monteleone et al. (48; cf. 49) found that bright light (2000 lux) applied between 02:00 and 04:00 to human subjects depressed circulating melatonin by 40% more in women as compared to men, in keeping with a stronger solar effect in females. This finding could not be confirmed with exposure at an earlier time of night (50, 51), nor was a gender difference relating to melatonin found by others (studying mean values only) (52-54). Melatonin reportedly responds to magnetic fields (55) or magnetic storms (56-58) and is latitude-dependent (59); studies of its chronome over years with serially-independent sampling as to many more individuals seem highly desirable and may allow scrutiny of the results herein.

As to the degree of generality apart from suicides and from sudden cardiac death, the far-transyear has been documented in terrorism (60-62), in Gallup Polls (63), in human natality in the Philippines (64) and Brazil (65) and in epilepsy (66) and strokes (67) in Slovakia, but not in natality in Japan (68) or Italy (69), another example of a geographic difference in the time structure of epidemiological variations.

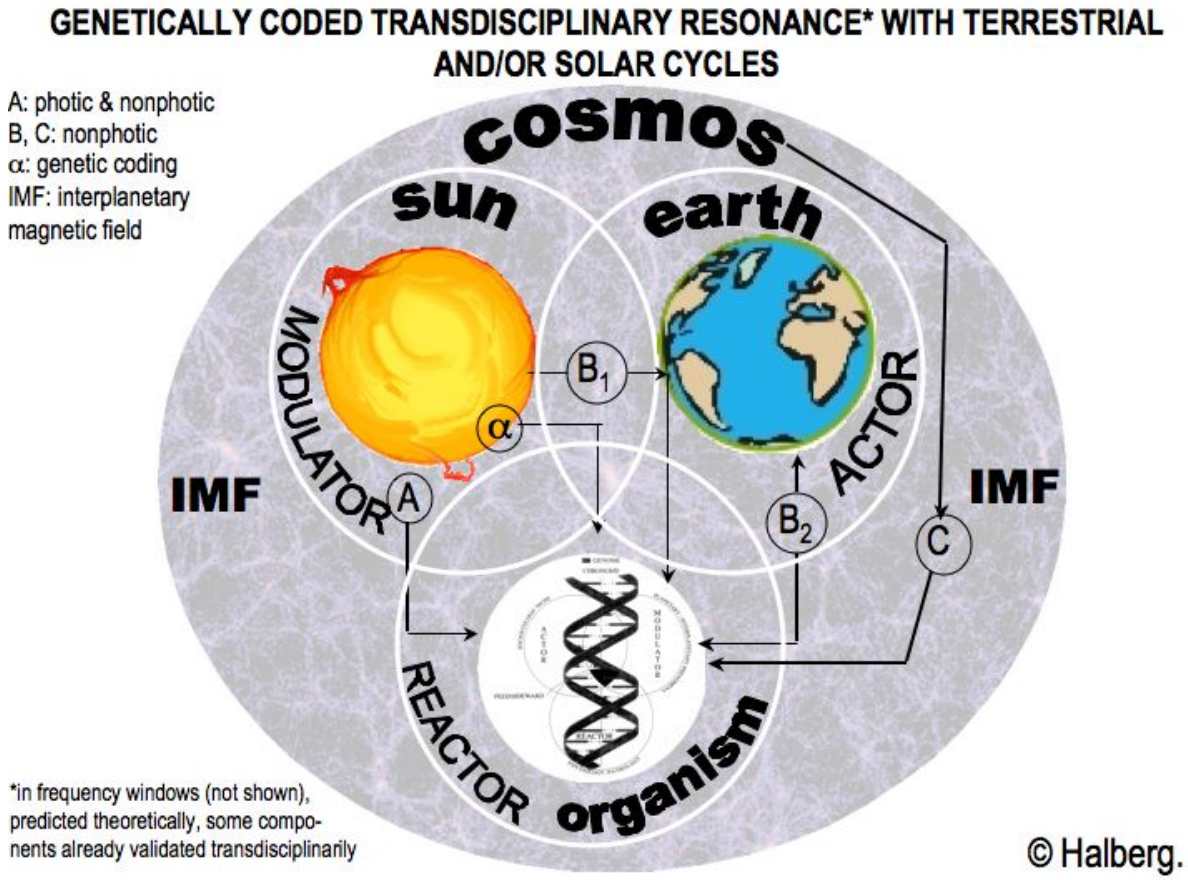


Figure 8. We need not ignore the many signatures of the cosmos with validated statistical significance of anticipated periods that characterize:
a. dozens of decades-long time series of blood pressure and heart rate;
b. other physiology and psychology, including mental functions;
c. religious proselytism;
d. suicide;
e. sudden cardiac death;
f. terrorist activity for the past 39 years;
g. 2,556 years of international battles compiled by Raymond Holder Wheeler;
h. military expenditures for training in non-medical science;
i. degrees earned;
j. Gallup Polls; and
k. political and military actions in nearly 200 years, meta-analyzed from the much broader treasure of data compiled by Alexander Leonidovich Chizhevsky.
While chance can never be ruled out, it would be further greatly reduced by systematic lifetime monitoring of physiology in health, of pathology and disease, notably in archives to separate effects of sun and earth, many of which are beneficial. Other effects such as extreme cold and heat or extreme light can be met by countermeasures such as housing, heating and air conditioning. The task remains to develop countermeasures to those nonphotic effects that can be documented as harmful. While the earth is the immediate actor, and for that action the sun is the modulator, with the biosphere reacts to both terrestrial and solar factors, the roles of actor, reactor and modulator are continuously changing. In the greenhouse effect, organisms are the actors, as shown by a double-headed arrow (B_2). There may be other more subtle effects of synchronized human action upon the earth. Original drawing by Mary Sampson. © Halberg.

Figure 8 attempts to describe the status quo of ignorance. The invisible (except, e.g., for northern lights) effects of space weather complement those of the visible light and of felt heat (and cold). They play a role in psychiatry and far beyond, as does the broader cosmos, gauged, e.g., by galactic cosmic rays (C, Fig. 8). The ~1.71-year far-transyear is also a characteristic of cosmic rays (70-72). When exposure to environmental cycles (their aeolian nonstationary nature notwithstanding) lasts for eons, they are eventually coded as bioresonance periods in the genes (α in Figure 8), yet are amplified or dampened by the continuing cosmic influences. But resonance may also be found in the relations of earth and sun. When the latter ceases to display a given period and then resumes it, such as an ~35-year cycle, the antipodal geomagnetic index aa may continue to exhibit that cycle in the interim. A bidirectional arrow in Figure 8 indicates that the biosphere changes the surface of the earth. The question whether the biosphere can substantially influence its cosmic as well as the physical earthly environment is beyond the scope of available evidence here summarized (73, 74). But the explanation of the status and of the origin of some cycles shorter than the Schwabe period can be considered in the following.

Introduction to the origin of solar *g*-mode periodicities < 11 years

A number of solar periodicities shorter than a dominant 11-year Schwabe cycle in time have been accepted as real at convincing probability levels, (for example, 40, 75, 76). But even these strong signals are not seen all the time. Their amplitudes occasionally are within the noise in the data, making them undetectable. Either they are still there, but weak, or they are gone and will be re-excited later. We describe a model that can explain the first case. The other case (gone and re-excited) may also be of interest to chronomics but it is more complicated and not discussed here.

a.) The Clockwork of Rotating g-Modes

This section summarizes the model (10, 31) operating deep inside the sun, Figure 9, which causes a small fraction of the upward moving energy to vary, as if controlled by a series of clocks. Although the clocks keep very good time, we shall see that the strength of each beat unavoidably changes from one beat to the next. Upward flowing energy is the ultimate cause of phenomena seen at the sun's surface and above (visible radiation, flares, mass ejections, solar wind, etc.). So when this energy flow varies on some schedule, it should be detectable in many solar observables and many biospheric variables influenced directly or indirectly by the sun.

The physical elements that can cause this are global oscillations of the sun called g-modes (77, 78). Each mode involves about 90% of the solar mass in its motion; thus it has tremendous stability even though its amplitude is small. The oscillation periods are of the order of hours but that is not what regulates the solar clocks. Instead it is the rotation rates of the modes when particular groups of them couple to form what is called a set (l), where l is an integer. Figure 9 shows how a set distorts the sun (highly magnified) as it oscillates. On the surface you can see that the strongest oscillation amplitudes concentrate near the equator in a limited range of longitudes. This is called a hot spot because that is where the set deposits the greatest amount of heat per unit area, which it supplies from its own kinetic energy. A second hot spot is located symmetrically on the other side of the sun. The hot spot extends to all depths inside the sun but its strength peaks at the two radii shown in the cutaway section and then it declines exponentially toward the center and toward the surface. Many more details on these sets are available in reference (31).

All sets rotate slightly slower than the solar mass in which they oscillate. There is a unique rate for each value of l. For the lowest degree sets for which there is observational evidence, Table 1 shows the rotation periods apparent to an earthbound observer. Also, the rotation rate relative to the fixed stars is given in nanohertz. These rates stand on three observational legs: A study of more than two centuries of sunspot numbers (10), the internal solar rotation curve from helioseismology (79), and a half century of 10.7 cm solar radio flux records (28).

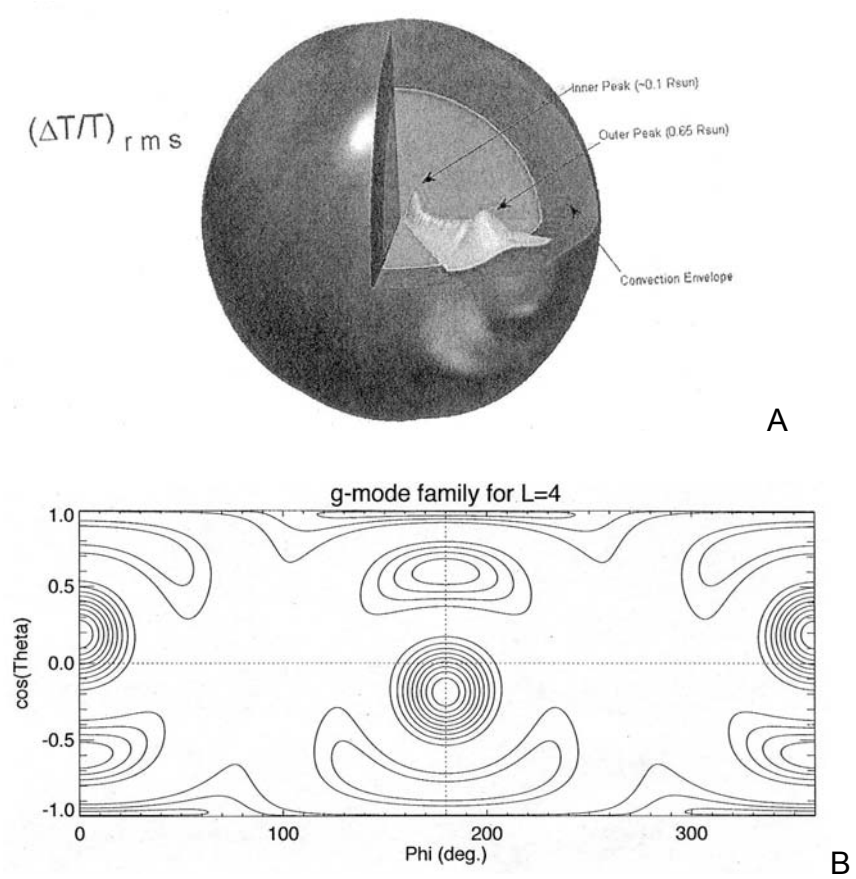


Figure 9. This cutaway sketch illustrates the set of g-modes for l = 4 oscillating inside the sun. Oscillatory power is concentrated along a straight line passing through the origin and intersecting the surface near the equator but not on it. We see only half of the power concentration since it extends to the opposite side of the sun. This structure rotates like a rigid body about the Sun's spin axis at a rate depending on l. When its rotation causes its hot spot to overlap with that of another set, extra energy is released, which affects observables at the sun's surface. Contour maps of these power distributions are available (31).

Table 1: Rotation rates of g-mode sets and their beat periods (28)

	Rotation		Beat Period (years)			
L	Apparent Period (days)	Absolute Rate (nHz)	L' = 3	4	5	G
2	35.05	361.87	0.425	0.335	0.295	0.242
3	31.50	399.12		1.58	0.967	0.562
4	30.66	409.15			2.50	0.873
5	30.16	415.50				1.34
G	29.26	427.29				

In addition to the low l values, the sunspot data also showed evidence for a strong feature at considerably higher l. Since rotation rates for high l are too close to be resolved by existing data, it is treated as one feature and called set(G). It had more impact on the sunspot data than any other set and is presumably the strongest of them (10). On time scales shorter than the Sun's 11 year cycle, the sets in Table 1 are those that would most prominently affect events on the Sun.

b.) Rotational Beat Periods and their Heat Pulses

When the hot spot of a set such as Figure 9 rotates past the spot of another set, extra heat is deposited at that place and time. The amount of heat is more than the simple sum of their separate effects because the hot spots interact nonlinearly. This gives great significance to the frequency at which two particular spots will overlap. In symbols, the beat period between two rotating sets is

$$P = [\ (f_1 - f_2)k\ ]^{-1}$$

where f1 and f2 are the rotation frequencies of the sets (e. g., Table 1). The factor k = 2 takes account of the fact that each set has two hot spots per rotation. (For certain phenomena most sensitive to latitude distributions, k =1.) The last few columns in the table show these beat periods. They impose themselves on various events at the sun's surface and beyond because the sun can utilize the extra energy made available at period P to magnify all the forms of solar activity (flares, sunspots, radiation, etc.) and even the solar wind.

All beat periods in Table 1 have been calibrated with over two centuries of monthly mean sunspot numbers and a half century of solar radio flux as mentioned above. Extra decimal places in rotation frequencies are carried over from the theory to protect the difference frequencies (beats). But the rotation frequencies contain an additive constant that is still uncertain to perhaps 2%. Beat periods in the table are accurate to about 1%.

If two rotating sets were the only ones in the sun, then a beat would release the same amount of heat every time. But there are other sets and sometimes they happen to be close to the region where the hot spots of f_1 and f_2 are interacting. Thus the total amount of heat released at a certain beat period will vary depending on what other hot spots happen to be nearby at that time. This explains why these periodicities are strong some of the time and at other times are too weak to be detected at the sun's surface.

Of the ten solar beat periods in Table 1, only three seem to have been found in the earth's biosphere so far in the human circulation and other aspects of physiology, pathology and sociology, including suicide. Two of them (1.34 and 0.56 yr) involve the set(G) which is the strongest set, at least in its ability to influence the sunspot numbers (10). Since that set has the smallest horizontal size (i.e., in latitude and longitude) it is supplying a very concentrated dose of energy to small areas. That may be why it is observed so well in a highly local effect like a sunspot or solar active region. But the strength of set(G) rather than its size is more relevant to the biosphere where, e. g., a 1.34 yr period is detectible in each of 44 mostly decades long physiological time series from of the order of a dozen subjects.

The third biosphere period, the cis-half-year (0.42 yr) is associated with the beat between two solar sets with the lowest values of *l*. They are the sets that have the largest horizontal sizes. They may have more effect on a larger scale effect like the solar wind. The details of how the g-mode sets would affect a particular solar feature have never been worked out quantitatively. Many such physical details of the Sun remain to be studied. Even more unknown, then, would be how effective a solar beat period could be in affecting the biosphere and perhaps encoding itself into DNA on Earth. Extensive future observations are far more likely to answer such questions than theoretical modeling.

Conclusion and Epilogue

Systematically aligned physical and biospheric, in individuals lifelong monitoring is overdue to complement the foregoing analyses of suicide and other much more extensive archival studies. Individuals' monitoring must not be left to a very few highly motivated subjects, but should proceed, preferably as family monitoring. One scientist, RBS, who started monitoring blood pressure (BP) at 20 years of age, persuaded his father SBS to undertake BP monitoring when the latter was in his sixties. RBS now has 41 years of around-the-clock data that complement 23 years of data from SBS (80, 81). YW began monitoring his own BP at 35 years of age and now has 21 years of mostly half-hourly data; he monitored his son FW's BP from birth and has new data with gaps up to 15 years of age (82, 83). A lifetime study or two may eventually thus be pieced together by data from father and son.

Current spotcheck-based physiology and medicine will eventually include automatic womb-to-tomb monitoring in its scope, for which the technology is available in the experimental

laboratory, albeit not yet unobtrusively and noninvasively for the human. What Humboldt started with Gauss and Sabine made into a magnetic crusade (84), which has proceeded to a systematic monitoring of the environment near and far by satellite, should be complemented by surveillance in the biosphere prospectively. A thorough analysis of the few accumulated longitudinal series that cover around-the-clock up to 40 years retrospectively is equally overdue, and certainly the further retrospective and prospective analysis of archives is desirable. Reference cycles in human development and aging would then become available to replace imaginary baselines (85).

The planned extension of studies on suicides as a function of latitude and longitude is overdue, but we are dealing with the consequence of extreme depression that originates from lesser abnormalities in mood that need further scrutiny of their circadian-infradian cycles. Solar signatures are found not only by noninvasive cardiology in health and disease, but also in mental functions, such as the rating of mood and vigor and the estimation of 1 minute around the clock about 5 times/day over 36 years. The series of mood ratings is characterized by an ~0.56-year (a trans-half-year). In the series on time estimation, some spectral components are congruent only with corresponding counterparts in the spectrum of the solar wind's speed, while other spectral components of the same mental function are congruent only with periods in geomagnetics and still other spectral components in this human mental function are congruent with both sun and earth, Figure 8. Fewer components in the para-annual and para-semiannual spectral regions have no environmental counterpart. The chance of monitoring solar activity biospherically and prospectively is a challenge in particular in noninvasive cardiology because the same data that serve for immediate health care can also be used, if they are recorded via a website for medical investigation and further for transdisciplinary research, as will become apparent from the BIOCOS contribution to these same proceedings. Archival studies have to be complemented by longitudinal monitoring of human and other biospheric variables.

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Reasons for a protocol for radiation treatment aimed at exploiting weekly rhythms

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Abstract: Circadian timing's merits have been documented earlier, but the administration of treatment at optimal clock hours may be difficult to implement in the clinic from a practical viewpoint, since it may require service outside routine scheduling hours. Scheduling along the scale of the week, as here proposed, does not depend on irregular treatment hours. Circaseptan optimization is promising in the experimental laboratory but has not yet been tested systematically in the radiotherapeutic clinic. Our purpose herein is to advocate a practical protocol.

Aim: To assess any benefit from chronotherapy of lung cancer by using daily radiation doses varying along the scale of the week. In our time structure (chronome), an about-weekly schedule is partly built-in (1), while, like many other rhythms, it is also driven by society and the environment (1, 2), just as circadians are (3).

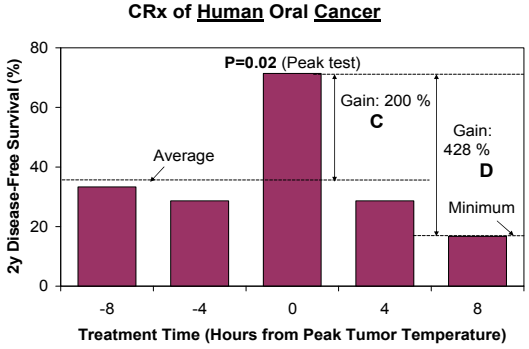

Figure 1a. Radiotherapy timed at peak tumor temperature leads to faster tumor regression (not shown) and to more than doubling of the 2-year disease-free survival rate, as compared to reference groups treated 4 or 8 hours before or after the tumor temperature peak. Data from Prof. emeritus B.D. Gupta and Dr. Akhil Deka. © *Halberg.*

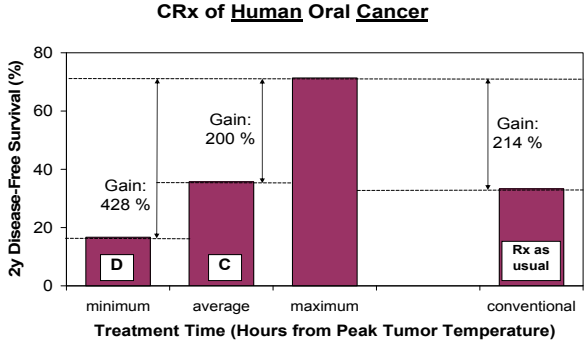

Figure 1b. Gain from radiotherapy timed at peak tumor temperature, gauged by the 2-year disease-free survival rate, is assessed by comparison with the average or lowest disease-free survival, when treatment is administered 4 or 8 hours before or after the tumor temperature peak, or when it is given "as usual" without consideration of circadian stage. © *Halberg.*

Circadian background: Disease-free survival was doubled in patients with tumors of the oral cavity by timing radiotherapy along the scale of the day, when treatment was administered at the circadian stage of highest tumor temperature, Figure 1a (4, 5). The gain at the best time by reference to the worst time was 428%; by reference to the average it was 200%. There was a gain of 214% by comparison with treatment as usual, Figure 1b (4, 5). These findings were empirical, yet supported by common sense, once it was realized that many tumors and most loads undergo a spectrum of rhythms.

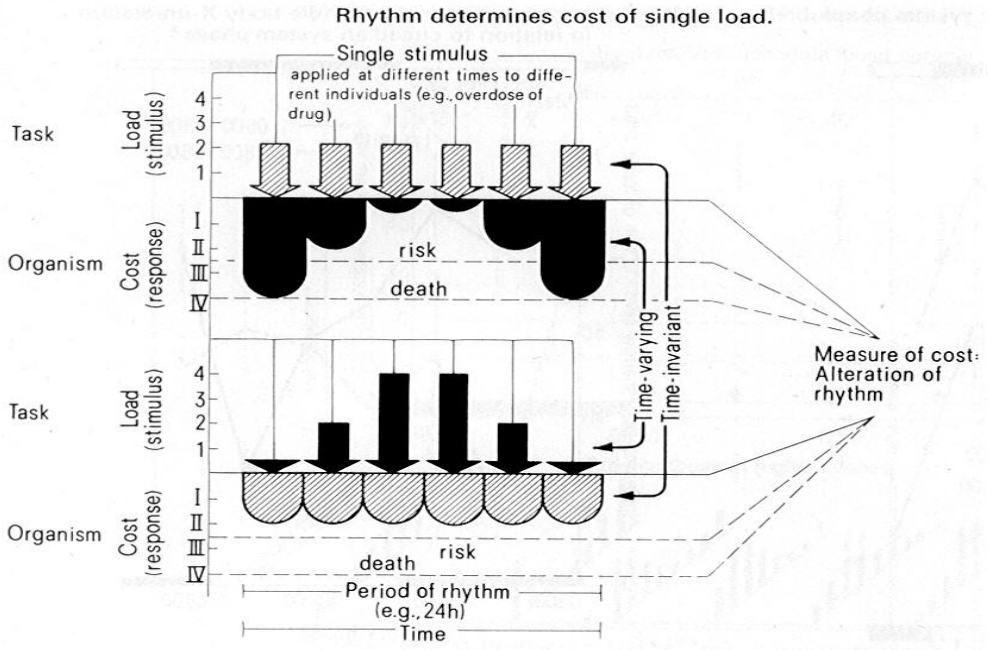

Figure 2. Rhythm determines cost of single load. Hours of changing resistance. As a function of the body's rhythms, a potentially harmful stimulus, such as a drug given in the same dose at different times to different yet compatible individuals (top) will have drastically different effects; not even risk is incurred at one time from a stimulus that is deadly at another time. It is thus common sense to give a potentially harmful drug at the time of highest resistance to it (bottom). See Figures 3 and 4 for scheduling a series of treatments (10). © Halberg.

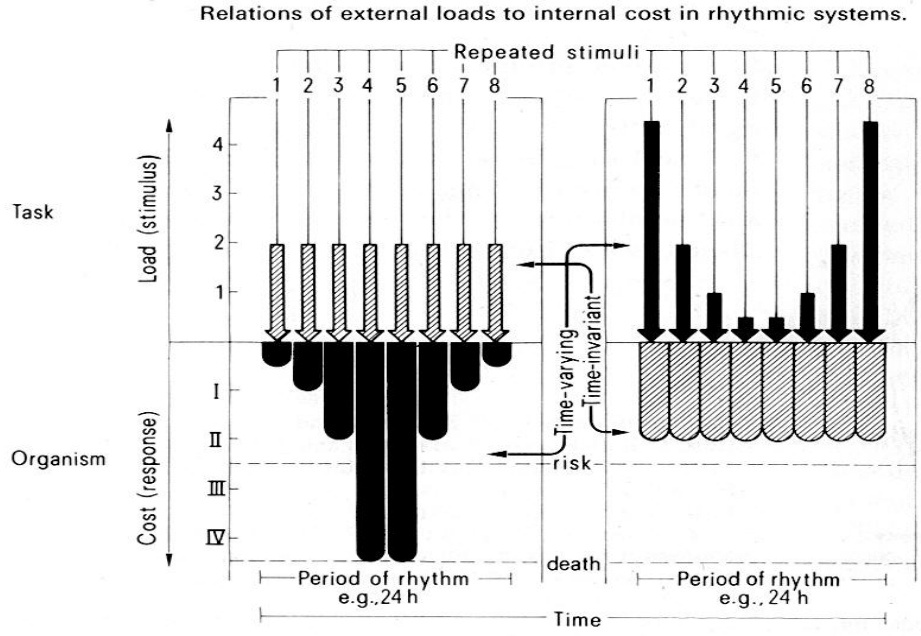

Figure 3. Relations of external loads to internal cost in rhythmic systems. The effects of repeated stimuli -- such as a course of drug or nutriceutical administration -- can be time-dependent; if so, a series of doses given in a time-invariant way might involve risk or result in death, whereas the same total dosage will be well tolerated when given in a way varying with due regard for the body's rhythms (10). By the same token, the desired beneficial effect will also be rhythm stage-dependent, and again dosing will have to be made dependent on timing. © Halberg.

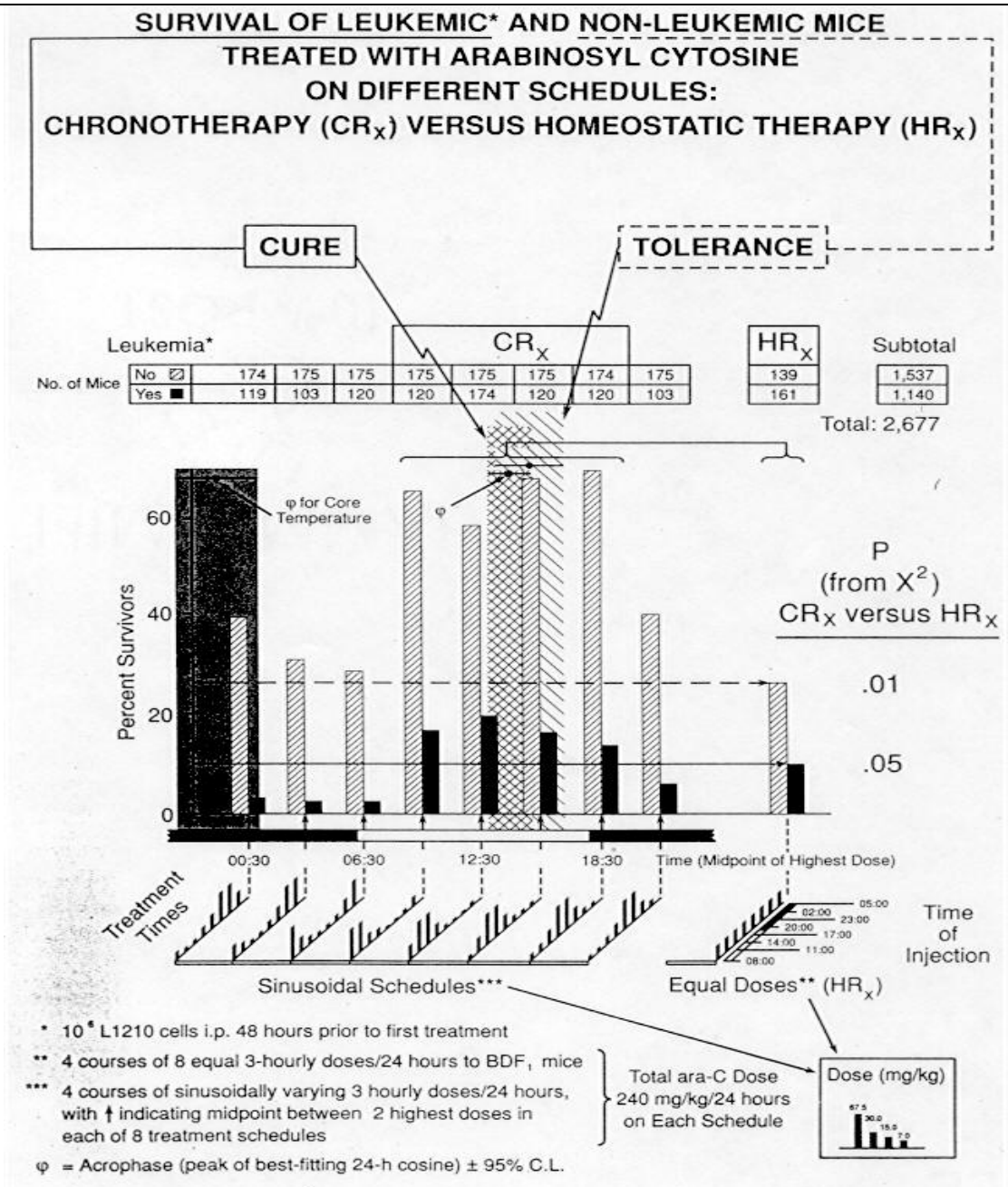

Figure 4. Murine tolerance of ara-C on different schedules. Study IV (L1210; inoc. 01.26.1972). Survival time of leukemic BDF_1 mice on different drug administration schedules (top) and timing of doses of ara-C (bottom) in sinusoidal and reference schedule consisting of 4 courses of 240 mg/kg/24 h each. When the same total dose of ara-C is given, certain sinusoidal drug administration schedules are definitely better tolerated by the mice than are other sinusoids or a currently conventional reference treatment of 8 equal doses over a 24-hour span (10). © Halberg.

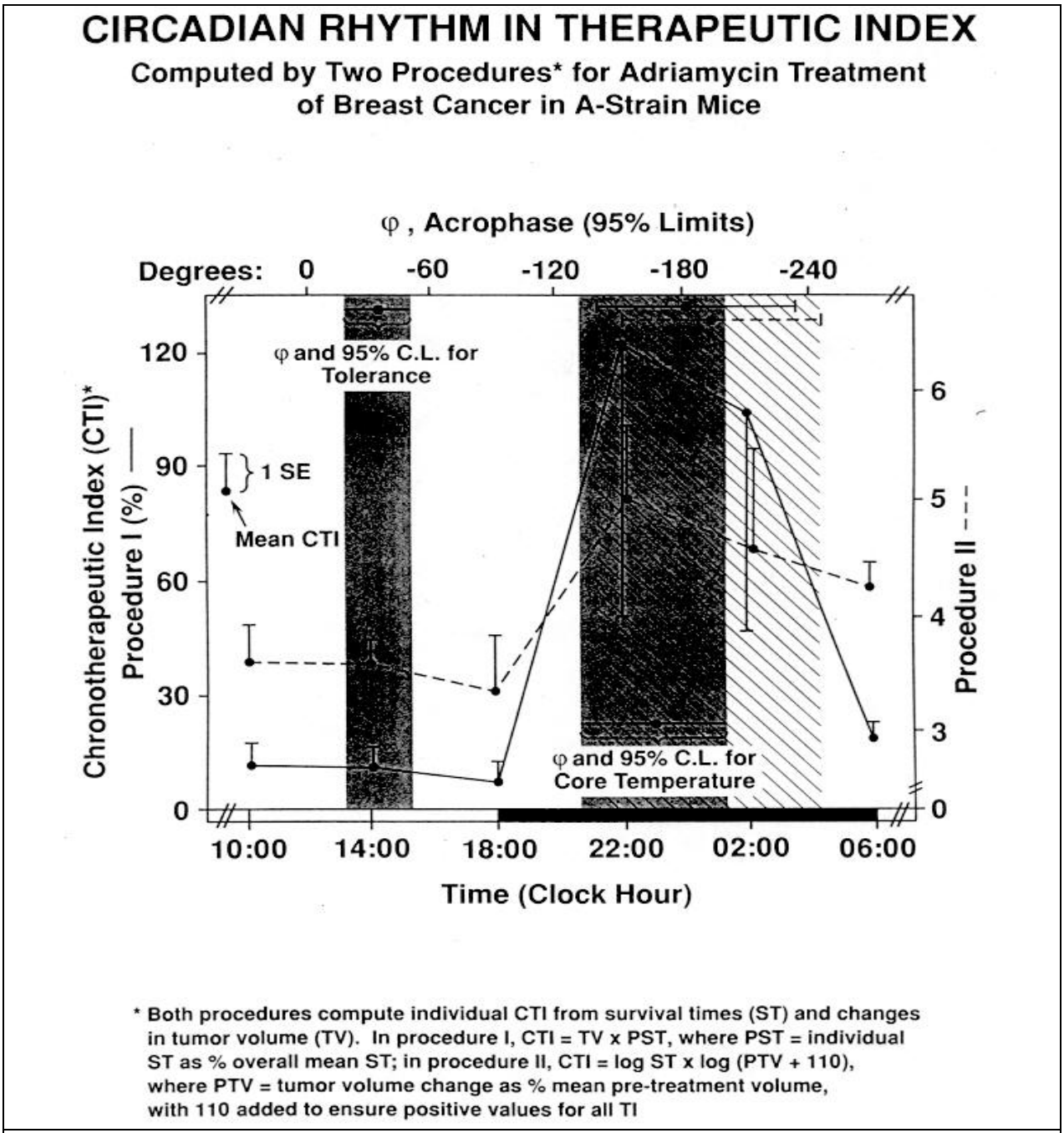

Figure 5. As a follow-up on a circadian rhythm in LD50 (20), a rhythm in therapeutic index was found by 1973 (10) and awaits use in the clinic, where it already doubled 2-year disease-free survival of patients with perioral cancers using the tumor temperature as a marker, Figure 1. © Halberg.

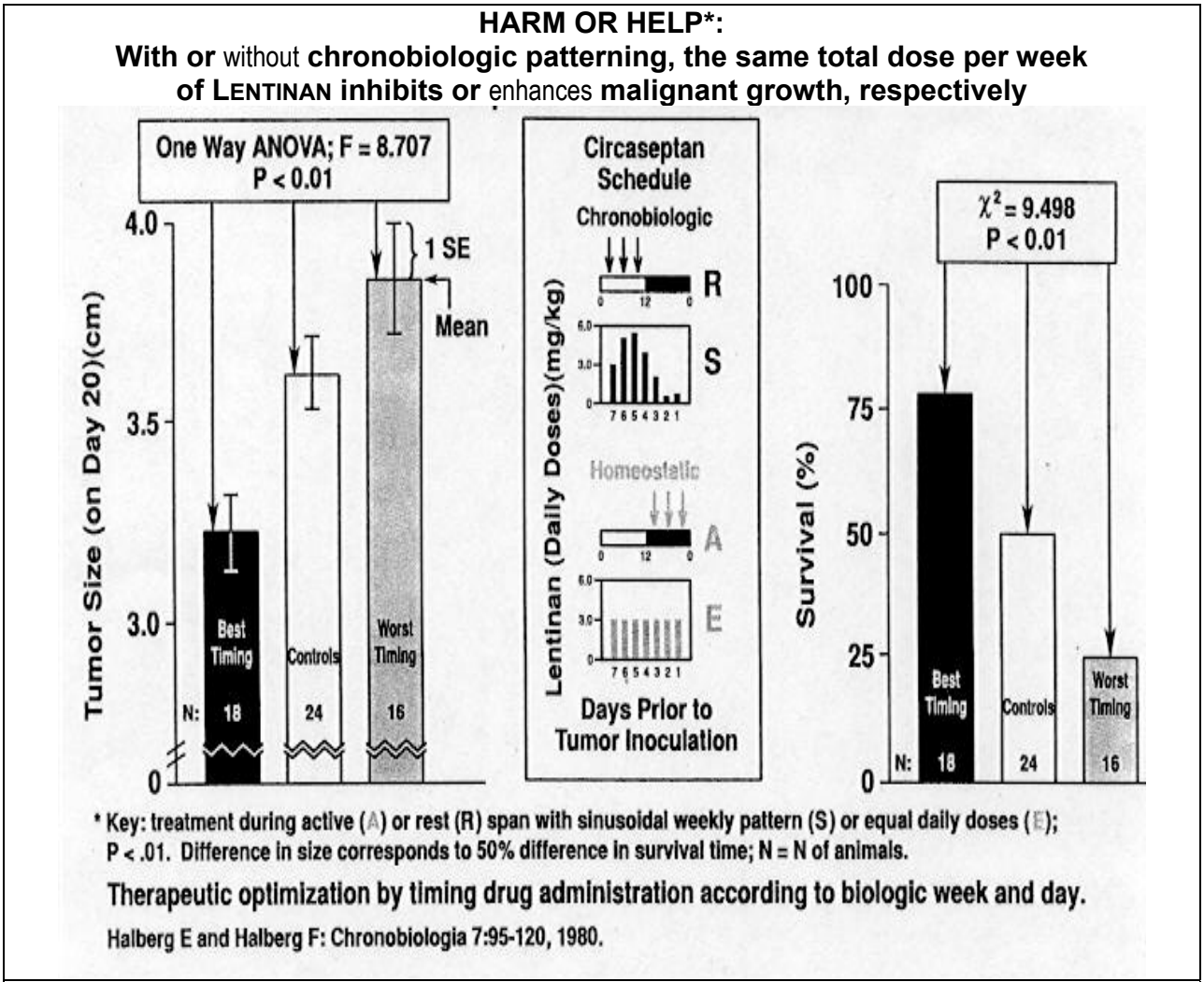

Figure 6. The same total dose of the same molecule, lentinan, depending on the circadian and circaseptan patterns of its administration, stimulates vs. inhibits the growth of a subsequently implemented malignancy (left) or shortens or lengthens survival (right). © Halberg.

Extension of timing to weekly optimization. In the laboratory, the importance of optimizing circadian and infradian timing (6, 7) was also documented for immunotherapies, Figures 6 and 7. Opposite effects are thus found, as shown in Figure 6, and a 30% gain in efficacy, above any gain from optimization according to the daily cycle, is documented in Figure 7 (8), while the optimization of radiotherapy by circadian and circaseptan timing in the laboratory is shown in Figure 8.

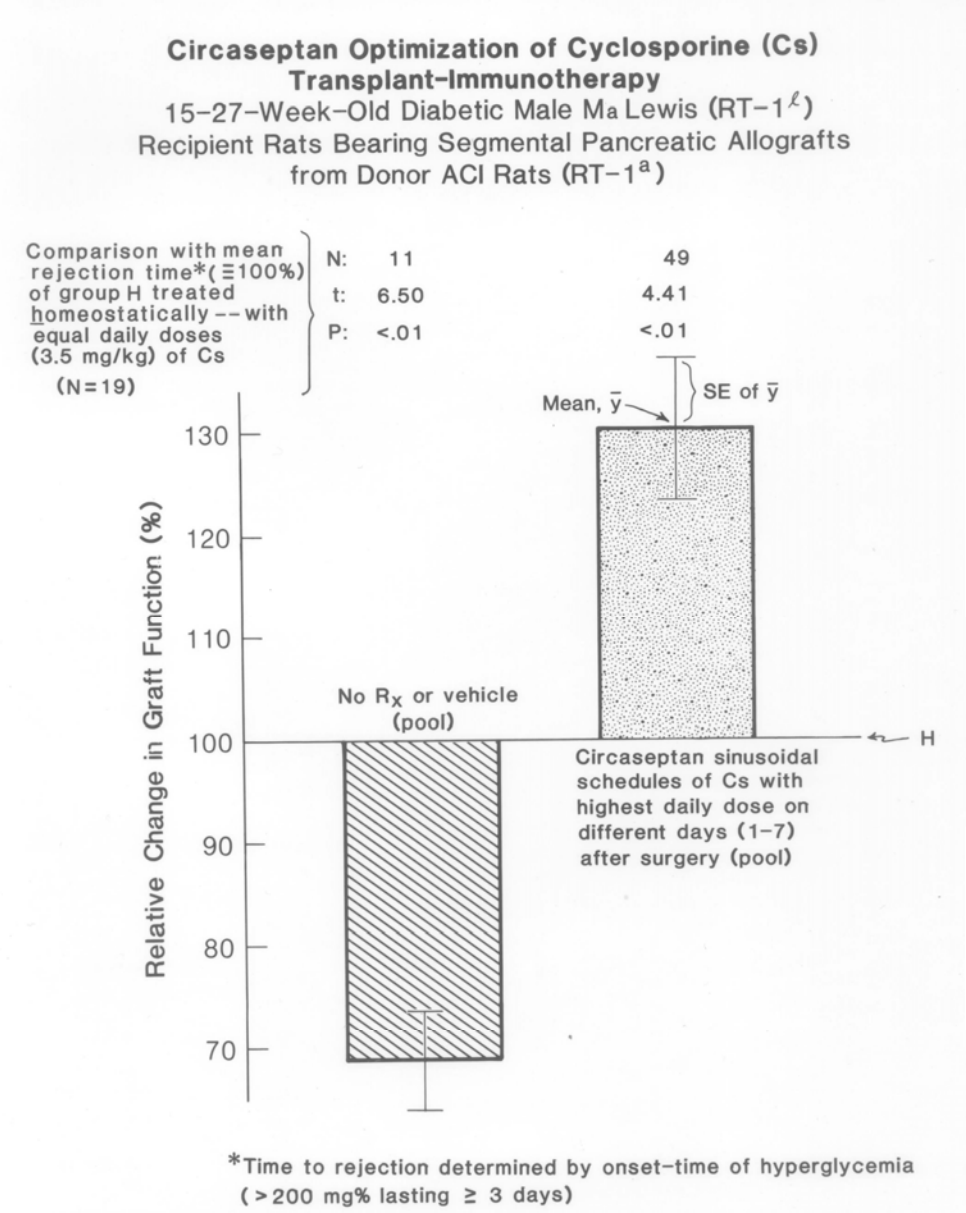

Figure 7. Cyclosporine chronotherapy of pancreas-allo-transplanted rats suggests further gain in graft function from doses varying from day to day according to a weekly periodicity, beyond the circadian stage-dependence of equal daily doses. Data of T Liu. © *Halberg.*

Combined circaseptan and circadian optimization of radiotherapy. Tumor cells of 4 different types of cancer were shown to grow not uniformly but according to rhythms with periods of 1 day and 1 week, the 1-week cycle being the most prominent (6, 7). Moreover, when radiation was applied at the time of highest cell division of these daily and weekly cycles, tumor kill by radiation was statistically significantly more effective than when it was given at the time of lowest cell division, Figure 8. Moreover, an about-weekly cycle may be amplified in surface temperature measured over a cancerous vs. a healthy breast (9).

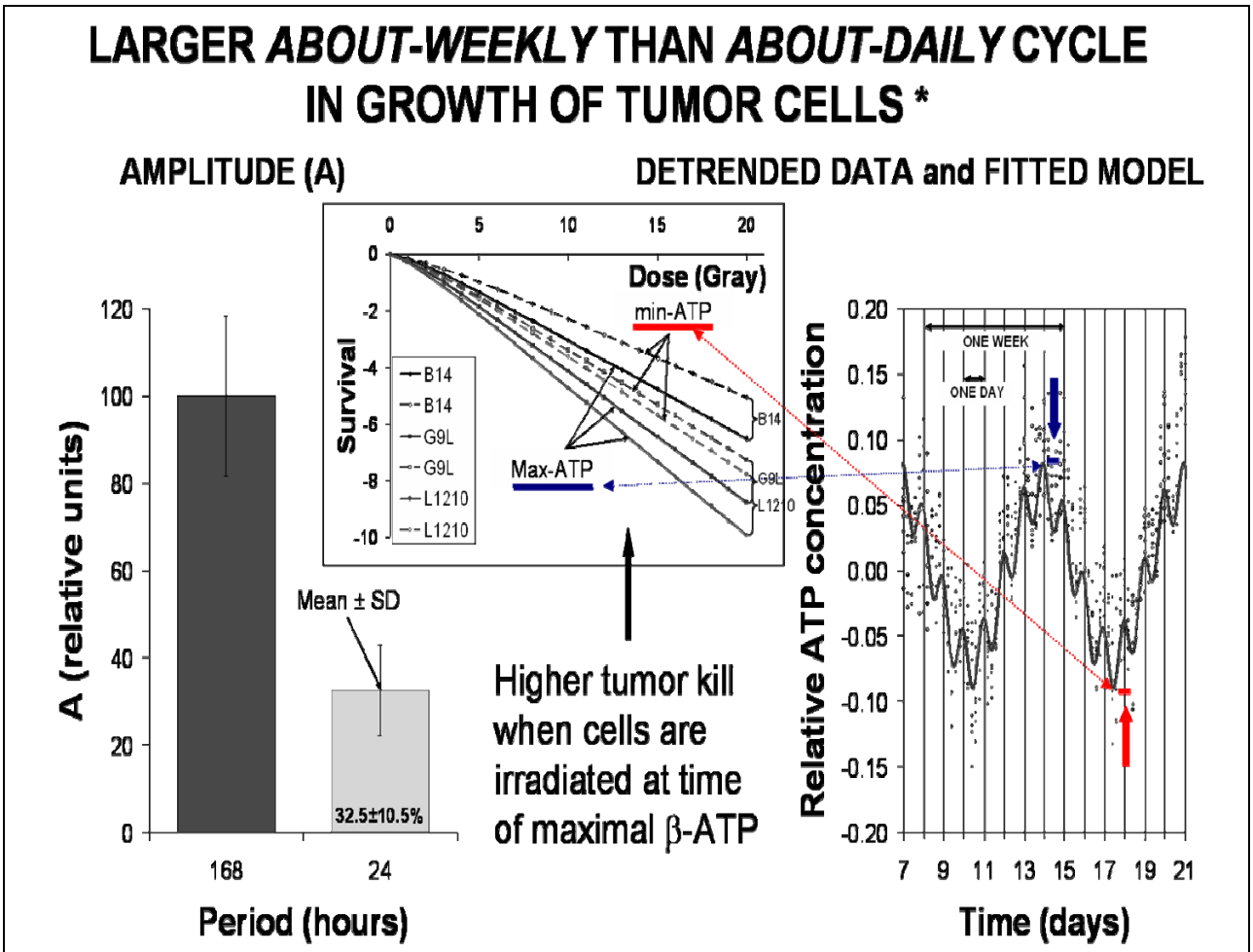

Figure 8. Time course of tumor cell growth pooled across all four kinds of tumor cells and both pH values shown after normalization for weeks 2 and 3 of study to illustrate circaseptan-over-circadian prominence. Irradiation shortly after the circaseptan-circadian maximum of β-ATP is associated with larger tumor cell kill (lesser survival) than irradiation shortly after the circaseptan-circadian minimum of β-ATP (middle). © *Halberg*.

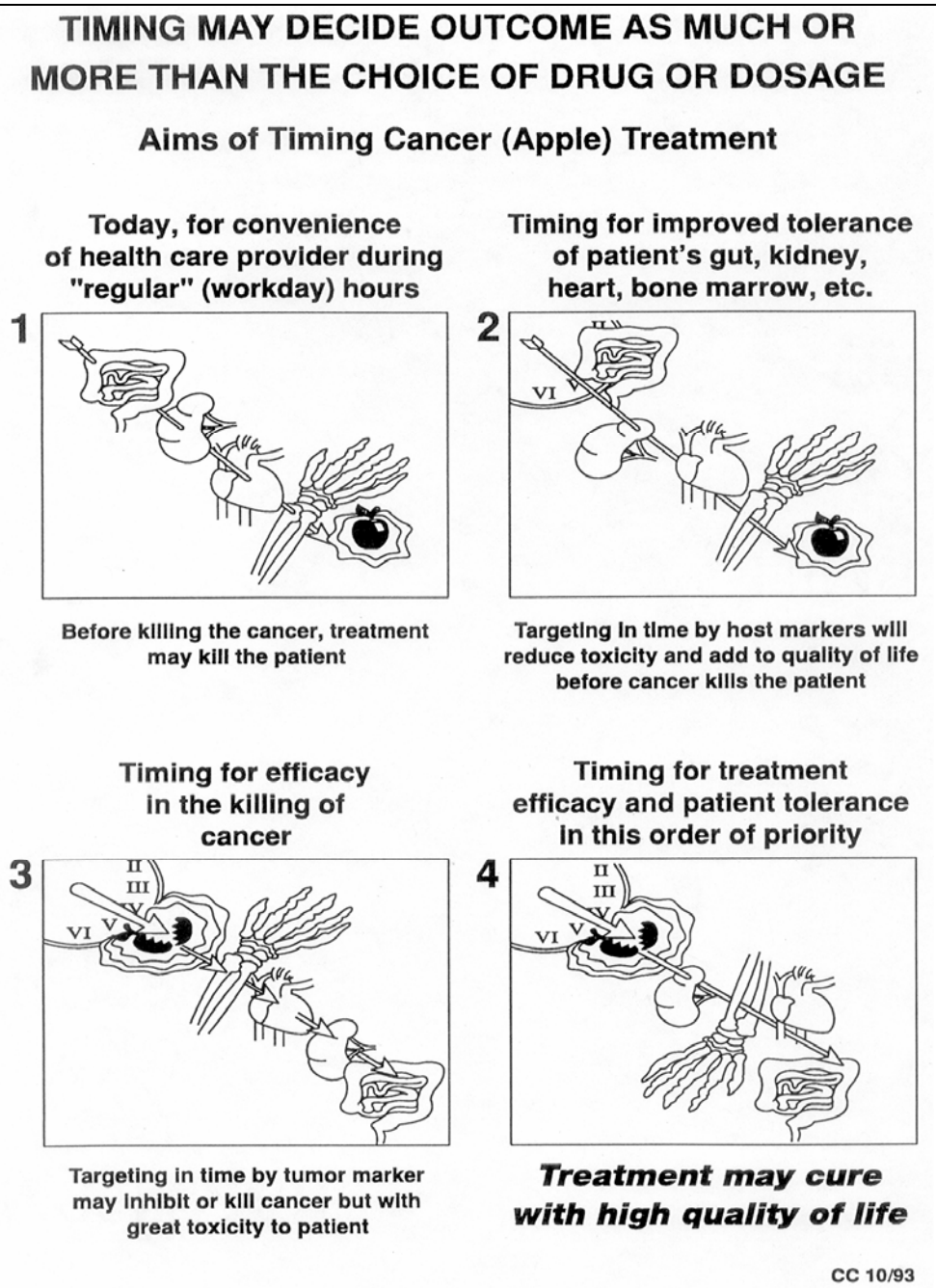

Figure 9. Task 3, illustrated in the left lower box, has been achieved in Figures 1 and 8 for radiation treatment. © Halberg.

More generally, a properly timed sinusoidal treatment pattern has been superior to an equal-dose schedule, Figures 4-9 (10). These results from the laboratory, Figures 2-6, and many others all suggest the possibility of increasing treatment efficacy and bettering outcomes by taking advantage of weekly cycles of gradually increasing and decreasing doses, as planned in the following protocol.

Suggested protocol for consideration or critique by all comers

Aim. To exploit for timed treatment any circaseptan schedules restricted to the five working days do not require activities during odd hours outside current schedules and hence are more readily implemented than the circadians.

Patients: Patients with newly diagnosed Stage I-III non-small cell lung cancer are eligible. They are to be stratified by stage, chemotherapy regimen, age group, and gender.

Outcomes: Before start of treatment and at 3-month intervals after initiation of treatment, maximal tumor diameter in two dimensions will be determined by CT scan. Tumor regression will be evaluated by the difference at each follow-up between maximal tumor diameter at that time and prior to treatment. Other outcome measures will be time to progression and overall survival. Toxicity will also be assessed during treatment and at each follow-up using the RTOG criteria (a six-point scale of bladder and bowel symptoms, produced by the Radiation Therapy Oncology Group).

Treatment: With or without concurrent chemotherapy, radiation therapy will consist of a total dose of 6000 cGy, to be administered over 6 weeks, 5 days a week (Monday-Friday). A given patient will be scheduled to always receive radiation therapy at the same time of day. Each daily treatment time will be recorded for each patient. Treatment will always start on a Monday. Patients on chemotherapy generally receive 12 mg of dexamethasone as part of their anti-emetic regimen. All patients in this study will receive the same dose on day 1 of treatment for potential synchronization of the weekly cycle.
There will be 6 groups.

- Group 1 will receive equal 200cGy doses per day.
- Groups 2-6 will receive the same weekly dose of 1000cGy that will be administered in different fraction sizes varying between 175 and 220cGy per day, according to a weekly cycle. The 5 groups will differ in terms of the start dose, as follows:

Week day	Group 2	Group 3	Group 4	Group 5	Group 6
Monday	175	193	220	220	193
Tuesday	193	220	220	193	175
Wednesday	220	220	193	175	193
Thursday	220	193	175	193	220
Friday	193	175	193	220	220

Sample size: This observational study will serve to determine uncertainties involved, to serve as a basis for sample size calculation. With the proposed design, patients can be accrued sequentially, so that as results accumulate, the required sample size can be determined and progressively refined, and patients can be recruited until the desired sample size is met. The major criterion will be the desirability to detect a 50% difference between best and worst outcome with 80% confidence. Statistical considerations have shown the superiority of the cosinor over the more usual one-way analysis of variance to achieve this goal (11, 12). Relatively small numbers of subjects evenly spread over the cycle to be investigated (such as a 24-hour cycle) have already served for determining the optimal treatment time (13, 14), including radiotherapy of perioral (15) and lung (16) cancer.

Marker rhythmometry: In the case of prior timed radiation treatment, tumor or oral temperature were used as organismic markers of treatment time (5, 17). Markers should indeed be used, the sooner the better, in follow-up investigations aimed at the other optimization of benefit from circaseptan timing of radiotherapy. They are here omitted in order to minimize the therapist's load and deviations from the current routine, so as to render the study practical without special support. Magnetic resonance spectroscopy has already been examined in clinically healthy subjects as a putative marker for circadian timing based on high-energy phosphate metabolism (18). This was also the approach taken in the experimental laboratory on cancer cells, yielding statistically significant differences in tumor cell kill as a function of circadian-circaseptan timing, Figure 8 (6, 7). Moreover, when there are no specific cancer markers for the kind of tumor to be treated, possibly even unspecific markers may serve as an index superior to an arbitrarily fixed clock hour or day of the week (19). One option being considered in this protocol is the possibility to synchronize the circaseptan component by the administration of a fixed dose of steroids, already given to patients undergoing complementary chemotherapy.

Conclusion: Chronotherapy started with the demonstration of a circadian rhythm in the response to whole-body X-ray irradiation (20). The importance of circaseptans soon was also seen (21). As compared to the cost of instrumentation for radiotherapy, timing is very cheap, and its benefits in the laboratory are duplicated for the case of circadian timing in the clinic. Circaseptans can also be considered for optimization in the clinic on the basis of evidence obtained in the laboratory. Marker rhythms remain to be sought for all aims in Figure 9, in keeping with common sense, Figures 2 and 3, and laboratory evidence, Figures 4-8, so that the gains made in the clinic, Figure 1, can be augmented by infradians.

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Brückner-Egeson-Lockyer (BEL) climate cycle in original Brückner's, Lockyer's and follow-up data

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Cycles of 30 to 40 years are dubbed BEL, after the initials of Eduard **B**rückner (1), Charles **E**geson (2) and W.J.S. **L**ockyer (3) and his father Norman Lockyer (4), who discovered (1-3) or discussed (4) about (~) 33-35-year cycles, the former two in terrestrial climate, the latter two aligning periodic changes in solar cycle length with climate, an association subsequently reported again without reference to an ~30-year cyclicity or its discoverers (5-7). The BEL findings, immediately (8) and later again (9, 10) questioned by some, confirmed by others (11), sensational a century ago (12), with notable exceptions (13, 14) forgotten, are here inferentially statistically validated as nonstationary (to the point of intermittency) and as transdisciplinary, extending from meteorology to societal affairs. Elsewhere in these proceedings, we report the BEL in a consumer price index over centuries, in over 2.5 millennia of international battles assembled by Raymond H. Wheeler, and military-political affairs presented rightly by Alexander Leonidovich Chizhevsky as setting the course of history. Elsewhere also, we report on the BEL in human heart rate, in a mental function, the estimation of 1 minute, and in the interplanetary magnetic field, findings suggesting a possible origin in heliogeomagnetics (15). The biosphere mirrors space weather, also in the circulation of blood. Solar variability may be monitored via several of its biospheric associations, notably as a dividend from individualized self-assessed preventive cardiologic health care.

Background

By contrast to the rapid development of an inferential statistical circadian physiology in the last 60 years (16-20), based on the relatively easy replicability of a 24-hour profile, infradians -- spectral components with a period, τ, longer than 28 hours -- are less extensively explored with uncertainties such as CIs (95% confidence intervals) of their parameters (15, 21-32). The longer the period of a cycle, the more time it takes to assess it, the fewer will be the numbers of documented cycles available for analysis, the greater will be the uncertainties of any prospective quantifications; and accordingly the broader have to be the tentative limits set for the range of a given cyclicity. Despite the great duration requirements for prospective approaches to infradians, immediate benefit may well be anticipated from focusing retrospectively (as well as prospectively) on infradians in archives and in already-accumulated, decades-long psychophysiological monitoring records, e.g., within the aims of a project on The BIOsphere and the COSmos, BIOCOS (22), which advocates eventually lifelong monitoring across generations.

With advice from Roederer (33), solar-terrestrial associations in the biosphere were classified as photic, when relating to electromagnetic radiation in the visible domain, whereas nonphotics were related to corpuscular emissions from the sun or from beyond and more broadly to heliogeomagnetics, ultraviolet flux, gravitation etc. Nonphotics such as transyears -- near-transyears ($1.00 \text{ year} < [\tau - CI] < [\tau + CI] < 1.20$ years) and far-transyears ($1.2 \text{ years} \leq [\tau - CI] < [\tau + CI] < 1.9$ years) (30) -- were broadly classified as spectral regions; components described in physics by adjectives such as "quasiperiodic", "quasipersistent" (34) or "mid-term", among other names, often drift in frequency, bifurcate, rejoin, and wax and wane in amplitude to the point of becoming transiently undetectable, be it because they are obscured by noise or they actually disappear from a given spectral line or band to reappear, e.g., to be re-excited later. The nonstationary behavior, particularly characteristic of the solar wind's speed (15, 23), has been

described as aeolian (after Aeolus, mythical ruler of the winds), in keeping with a consensus meeting of physicists and engineers with physicians and other biologists (35).

The transdisciplinary validation of aeolian biospheric behavior by corresponding cycles' length in physics and vice versa, was added as a desirable possibility to the definition. Aeolian transyears in some but not in other geographic locations characterize human natality (24, 25 vs. 36, 37), morbidity (27-29) and mortality from myocardial infarction (26), sudden cardiac death (26, 28, 38), suicide (30, 31) and violence (32, 39, 40). The further documentation, prospectively of 500-year cycles, not only in the concomitant emergence on different continents that did not communicate with each other of leading physicians, poets and historians (41, 42; cf. 15), but also in climate will take more than a few generations. Different cultures may prospectively reveal, along the scale of millions of years, myriadennian cycles already mapped on the ocean floor (43, 44).

Circatranstridecadals

Transtridecadal, aeolian cycles longer than (beyond = trans) 30 and shorter than 40 years, such as the BEL, are defined as having a CI of its τ overlapping the 30-40-year range, even when the point estimate of τ lies outside that range. These broad limits are proposed in view of the great variability and hence of the great extent of uncertainty associated with ~35-year cycles that have to be assessed often on the basis of data hardly covering more than a single cycle, notably in prospective biospheric studies. We dubbed this ~35-year cycle the **B**rückner-**E**geson-**L**ockyer, briefly BEL. Brückner documented it most extensively (1); Egeson's publication preceded Brückner's by a few months and covered a shorter span less densely (2); he had the audacity to refer to "sunspot causality" in the title and the scholarship to quote Lord (Francis) Bacon (1561-1626): "They say it is observed in the Low Countries [...] that every five and thirty years the same kind and suit of years and weathers comes about again; as great frosts, great wet, great droughts, warm winters, summers with little heat, and the like; and they call it the Prime" (LVIII. Of Vicissitude of Things, in Essays, Civil and Moral; 1597).

W.J.S. Lockyer's contribution was an ~35-year period in the changing length of the sunspot cycle, which he promptly related to climate (3), as did his father Sir Norman Lockyer, discoverer of helium and founder of the journal Nature, in a historical perspective written for the journal Science (4). To cite W.J.S. Lockyer verbatim: "There is an *alternate* increase and decrease in the length of a sunspot period reckoning from minimum to minimum. ... The total spotted area included between any two consecutive minima varies regularly. The cycle of this variation is about thirty-five years. ... The climate variations indicated by Professor Brückner are generally in accordance with the thirty-five-year period" (3). That the length of the solar cycle relates to environmental temperature was subsequently repeatedly reported (5-7), including a historical review (6), albeit without any citation of the Lockyers or of an ~35-year cycle in climate and in "the frequency of aurorae and magnetic storms" (3), for which a scholarly review by Samuel M. Silverman provided power spectral corroboration (45).

Procedures and scope. We here analyze Brückner's original summarizing chart, Figure 1 (1), and W.J.S. Lockyer's data in the light of information accumulated in the interim, Figure 2. The latter shows all Zürich relative sunspot (Wolf) numbers that became available in the interim bracketing those considered by the original investigators indicated by horizontal arrows. The variability of the solar cycle's length is shown in Figure 3 by two methods, one based on official cycle lengths, the other by chronomic serial sections, both computed from a longer series of Zürich numbers than Brückner and Lockyer had at their disposal. In Figure 4, we present results as global spectral windows computed from data taken off Brückner's chart as point estimates of the τs with CIs given in the middle, as well as by chronomic serial sections, left and right, the latter to see how the data vary as a function of time. For the latter purpose, in serial sections, we use intervals, each covering about 3 cycles (105 years).

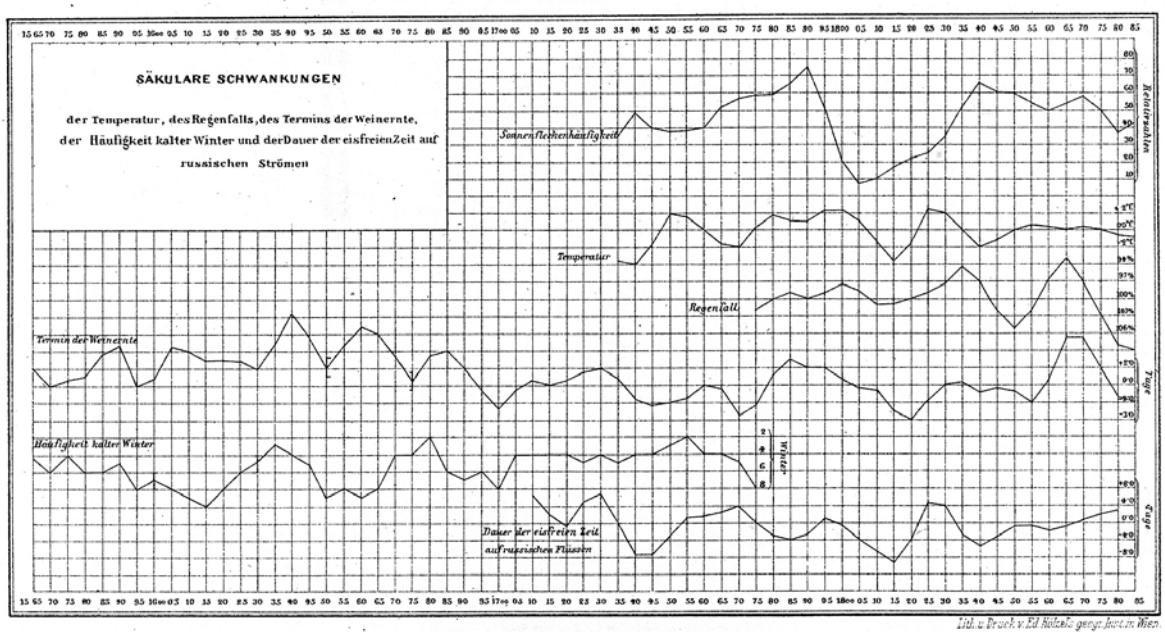

Figure 1. Brückner's chart summarizing his secular ~33.3-year variation (1) neither shows a regular cycle to the unaided eye, nor was it convincing in a mathematical analysis to Arthur Schuster (9), the opinion-leading analyst of his time, who introduced periodograms, for seeking hidden periods.

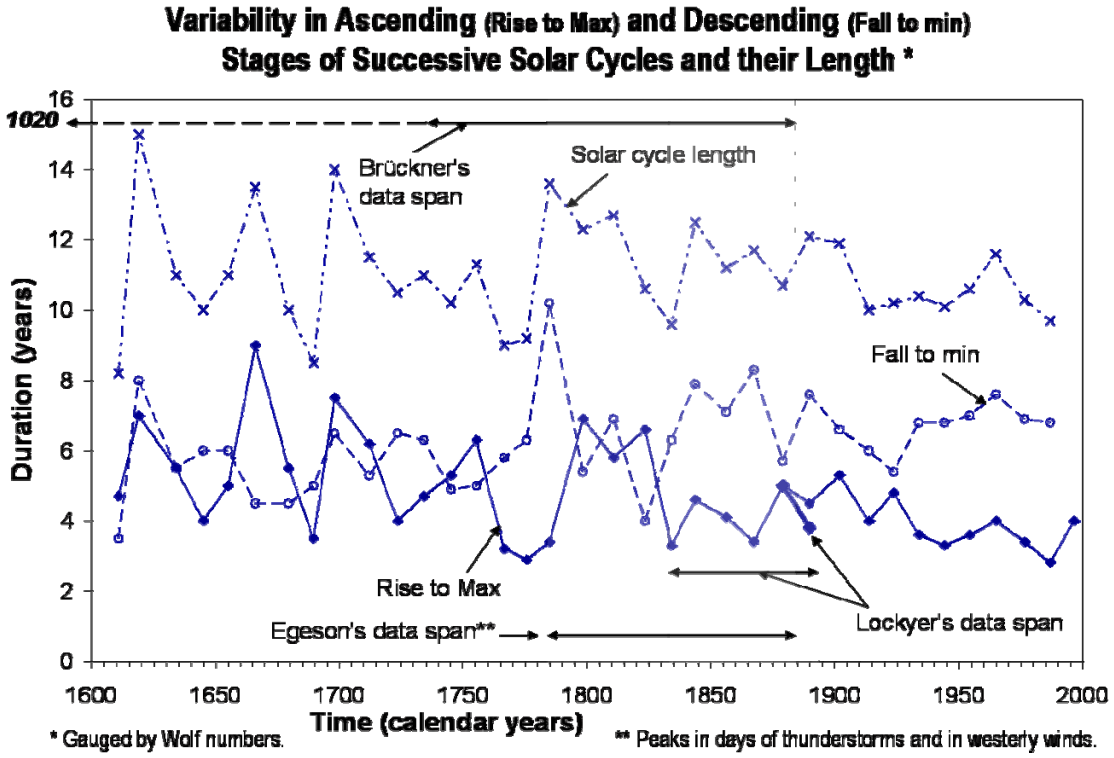

Figure 2. Displays of the durations of the ascending (Rise to Max), descending (Fall to min), and entire cycle length of consecutive solar activity cycles as reflected by sunspots between 1610.8 and 2000.3. Variability in overall solar cycle length is shown with its uncertainty. Variability in stages shows that the recently longer descending vs. the ascending stage of the solar cycle did not consistently prevail 200 or more years ago. The more limited spans of serial data available to Brückner, Egeson and the Lockyers are highlighted with double-headed horizontal arrows. © Halberg.

About 35-year cycles in climate are examined as part of a broad, partly novel spectrum of transdisciplinary periods. With geographic site- and time-dependence, nonphotic components not only coexist with photic ones such as the seasons, but can even replace the yearly component. Thus we arrive at biospheric associations with physical solar-terrestrial indices, steps toward breaking down disciplinary barriers, as suggested by Gregori (46) and Roederer (47). Biospheric studies then become tools of the physicist as well as vice versa.

The dangers of extrapolating from data limited to a few cycles, if not from hardly more than a single cycle, are noted at the outset. Thereby we also emphasize the urgent need for monitoring the many aspects of the biosphere and of aligning the results thus obtained with transdisciplinary ones. Lifelong physiological familial monitoring over generations should be investigated with much longer continuous systematic as-one-goes analyzed archival surveillance. This endeavor could match and enlarge the scope of the ongoing physical geomagnetic, solar and cosmic surveillance started by Humboldt with Gauss's (48) and Sabine's (49) magnetic "crusade", and extended by manned and in particular by unmanned satellites (50) in astrophysics complemented by telescope-based observations of solar magnetism.

The BEL constitutes critical control information for the foreseeable future and beyond, for those concerned with global warming and other problems of our civilization in health and disease. Methods for a transdisciplinary chronomic (time-structural) analysis (51-55) beyond those leading to the figures here presented seem desirable for an inferential statistical scrutiny not only of the forgotten BEL in the Figure 1 data originally interpreted only by Brückner's ingenious eyeballing but also for exploring the BEL's origins (56) and its signatures in the biosphere (57).

Results. Figure 4 quantifies the irregular cycles, i.e., the nonstationarity (sometimes intermittency) of Brückner's variables in Figure 1's time plots. Figures 2 and 3 show the variability in solar cycle length with the uncertainties added in a tabulation on top of Figure 3, which with Table 1 shows the CI of the amplitudes of each τ, including one of ~38 years, rather close to Lockyer's ~35-year variation. Table 2 summarizes some of the spectral components found in the time series taken off Brückner's chart. One glance suffices to show that a transtridecadal τ was the only statistically significant component in rainfall in the window examined and that a BEL was not found in the sunspot data considered by Brückner, shown with a horizontal double-headed arrow in Figure 2. The column entitled "PR" (percent rhythm, i.e., coefficient of determination, namely the percentage of the total variance contributed by a given spectral component) was biggest for a BEL not only in rainfall but also for environmental temperature, cold winters and ice-free rivers, but not for the wine harvest. For the latter variable, the CIs of the A slightly overlapped zero, as they did for the A of ice-free rivers. When the time course of the same variables is analyzed in separate chronomic serial sections of the span documented, Figure 4, sporadic intervals each of 105 years show statistical significance, indicated by dots bracketing the plotted acrophases, ϕ, for each of the variables and in the case of rainfall and the frequency of cold winters, statistical significance for a BEL prevailed in the majority of the intervals analyzed.

In the top row of Figure 4 on the left, the presence of dots indicates a nearly consistent statistical significance in environmental temperature. For several other variables, the intermittent presence of dots bracketing the acrophase indicates intermittent statistical significance. With the trial τ and interval used for analysis, BEL is statistically significant only part of the time in 4 variables other than the almost consistent periodicity in only one time series on the top left of Figure 4. The right section of Figure 4 again summarizes each series of Brückner's chart by a chronomic serial section with the fit of the precise period best fitting a given series, shown in the middle of Figure 4. This approach allows validation of the period indicated on the right of each row of at least some intervals of all time series, except for Zürich sunspot numbers in the bottom row of the chronomic serial sections of Figure 4.

Table 1: Durations characterizing the ~11-year cycle in Zürich (Wolf) numbers (WN) analyzed from 1600 to the present in 2008*

Endpoint	Period** (Best Fit) (y)	P-value (H_0: A=0)	M (y)	A (y)	ϕ (˚)	Nonlinear period (y)*** [95% CI]	A [95% CI] [1-parameter CI]
Rise to Max	44.44	0.051	4.76	0.81	-157˚	**43.15 [40.33, 45.98]**	0.91 [-0.14, 1.96] **[0.26, 1.57]**
Fall to Min	26.67	0.014	6.30	0.88	-315˚	**26.80 [25.71, 27.88]**	0.88 [-0.05, 1.82] **[0.30, 1.47]**
WN cycle length	38.10	0.037	11.06	0.93	-246˚	**38.05 [35.57, 40.54]**	0.93 [-0.22, 2.09] **[0.22, 1.65]**

*M: MESOR (**m**idline-**e**stimating **s**tatistic **o**f **r**hythm), a rhythm-adjusted mean

A: Amplitude (half the extent of predictable change within a cycle)

ϕ: Acrophase (time of overall high values recurring in each cycle), expressed in (negative) degrees, with 360˚ equated to trial period: t_{Ref} (0˚) = 1600.

CI: Confidence interval

**Linear in frequency analysis; fundamental period = 400 years (y); harmonic increment = 0.5 (18 harmonics).

***Nonlinear results qualified by the choice of trial period, selected as the period of the linearly-determined spectral peak; when the anticipated period of 35 years is used as trial period, results are not statistically significant and fail to converge to spectral peaks detected linearly. It seems important to always consider both the anticipated peak (here of 35 years, based on W.J.S. Lockyer's report, and thereafter any peaks that are not anticipated, and hence results are tentative). The CIs of the amplitude yielded by the conservative approach overlap zero, albeit only slightly (first set of CIs), while those of a 1-parameter approach (in bold) reject the zero-amplitude (no cycle) assumption.

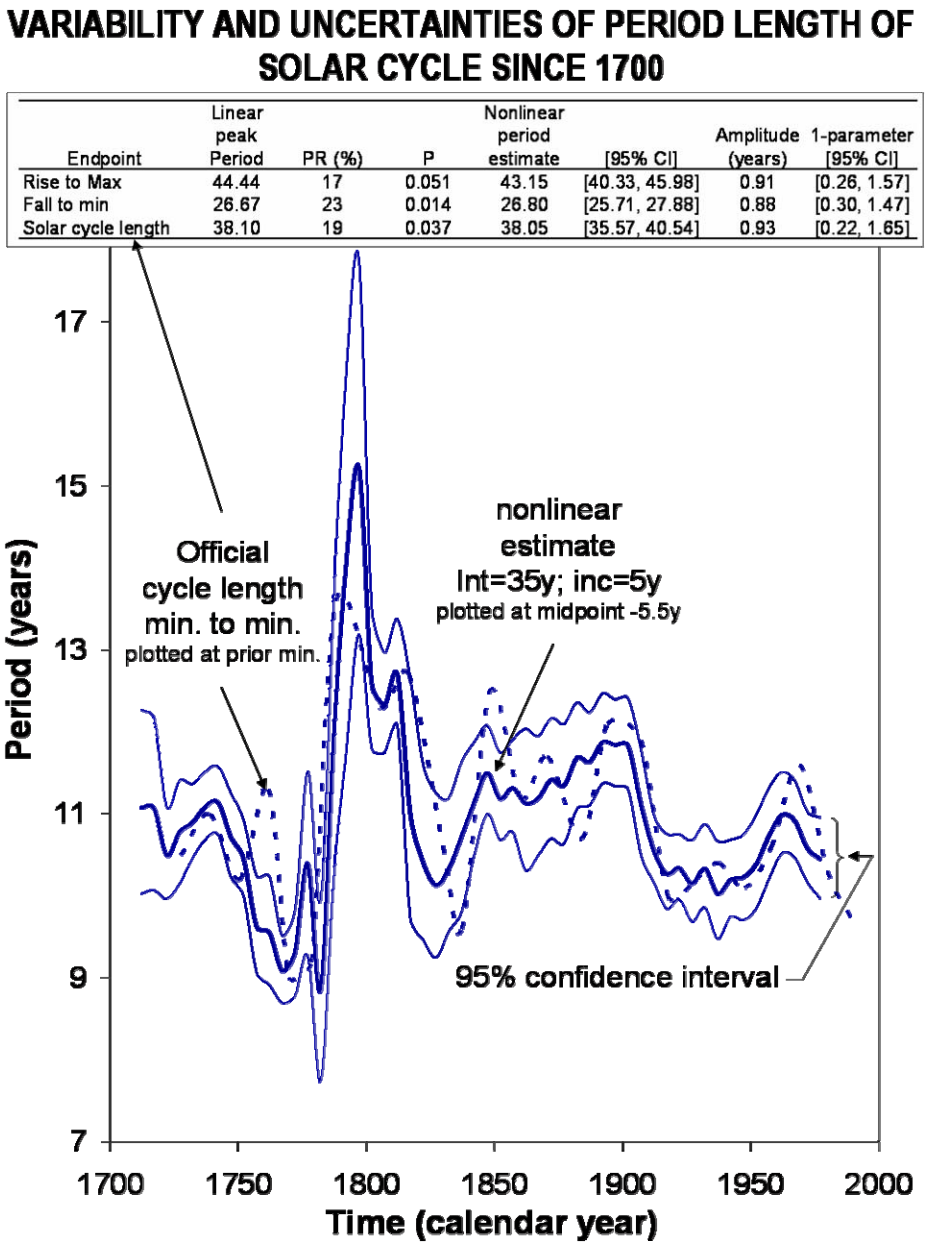

Figure 3. Variations of sunspot cycle length in Zürich relative sunspot (Wolf) numbers in a broader perspective than was available to Brückner, the Lockyers and Egeson. From a table listing dates of solar minimum and maximum since the minimum of 1610.8 until the estimated maximum of 2000.3, durations of consecutive solar cycle lengths were derived, as were durations from minimum to maximum ("Rise to Max") and from maximum to minimum ("Fall to min"), all assigned to the date of minimum (start of cycle). The data spanning about 400 years were analyzed by least squares spectra, in the frequency range of one cycle in 400 years to one cycle in about 22.2 years (18 harmonics, with a half harmonic increment). Components that accounted singly for most of the variation had periods of 44.4 (Rise to Max), 26.7 (Fall to min), and 38.1 (entire cycle length) years. When using as initial value the individual best-fitting periods found linearly, the conservative CIs for the amplitude overlapped zero, while the 1-parameter CIs did not (Table 1, and top of the graph). Period estimates and their CIs were 43.15 [40.33, 45.98], 26.80 [25.71, 27.88], and 38.05 [35.57, 40.54] years for Rise to Max, Fall to min, and cycle length, respectively, with corresponding amplitudes (and 1-parameter CIs) of 0.91 [0.26, 1.57], 0.88 [0.30, 1.47], and 0.93 [0.22, 1.65] years. © Halberg.

CHRONOMIC SERIAL SECTIONS OF BRÜCKNER's CHART (1565-1885)
AT FIXED 35-YEAR PERIOD (left) AND
AT NONLINEARLY ASSESSED BEST-FITTING PERIOD (right)

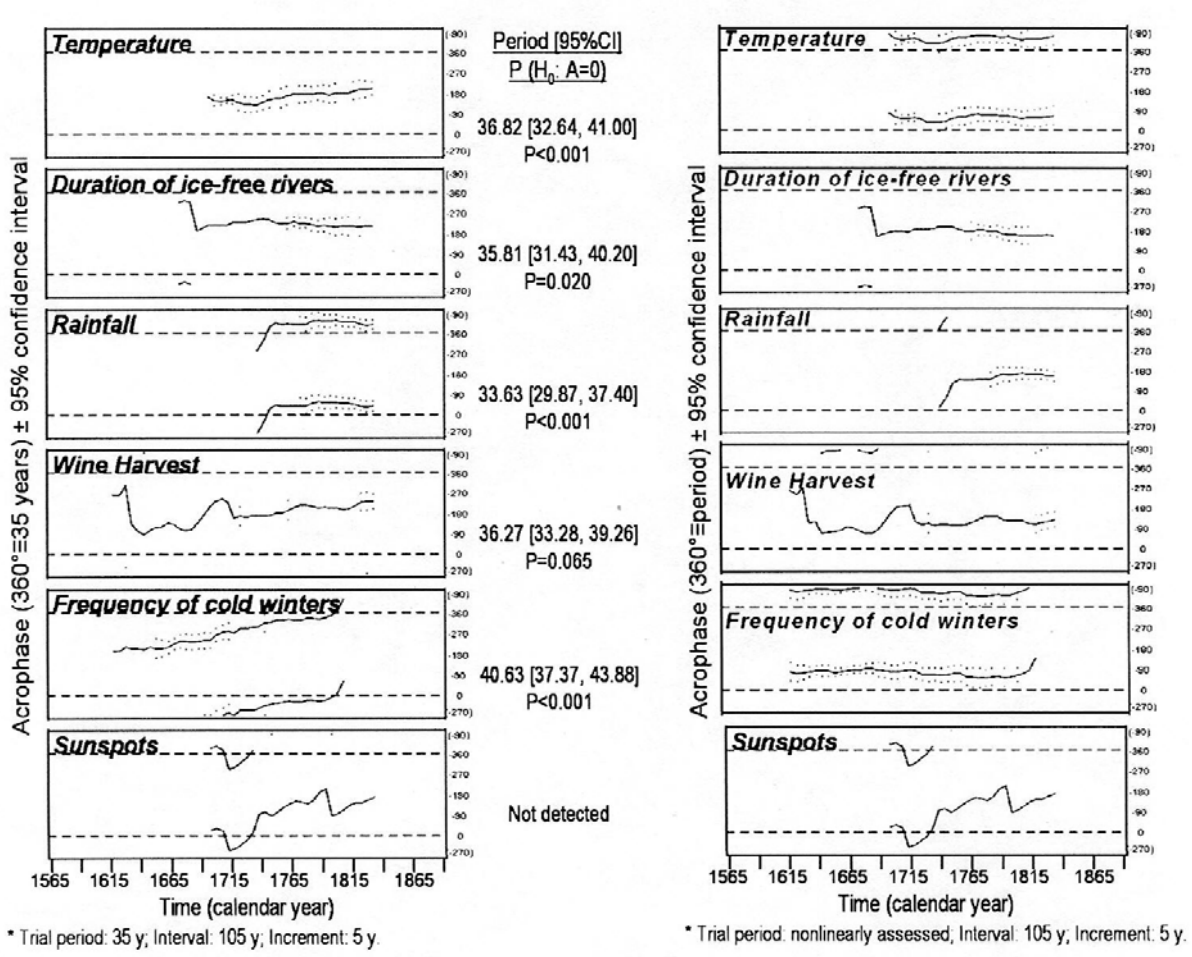

Figure 4. To study any time-varying behavior, Brückner's original series were each analyzed as a whole by the extended linear-nonlinear cosinor, and results are shown in the middle of this figure as periods with their CIs (95% confidence intervals) in parentheses. The global periods are bracketed by chronomic serial sections, carried out with intervals of 105-year length displaced with increments of 5 years for the fit of a period of precisely 35 years on the left side of this graph, whereas on the right, the serial sections are repeated with the period best-fitting a given series, differing slightly among the time series (shown in the middle section of the graph). Statistical significance is indicated by bracketing dots above and below the acrophase. Dots are consistently seen only for environmental temperature in the top rows on the left and right and for the frequency of cold winters in the penultimate row on the right. For rainfall, statistical significance is seen for over half of the available data span in the third row on the left and right, while a $P<0.05$ from the zero-amplitude test is more limited in rows 2, 4 and 5. A BEL cycle component in the spectrum of Zürich relative sunspot (Wolf) numbers during the spans here analyzed (bottom row) was not detected. This chronomic serial section, while showing the sometimes aeolian intermittent nature of BEL, validates and qualifies Brückner's intuition and accounts for Schuster's caution. The cycle is aeolian, including intermittency. © Halberg.

Irregular nonstationary behavior in the variables analyzed is characteristic of aeolian behavior; what is critical, the behavior is amenable not only to inferential statistical analyses but also to transdisciplinary validation, e.g., by the detection of beat and other periods found in solar dynamics as signatures in biospheric variables and vice versa for physical ones. The transdisciplinary covariation becomes informative when, upon removal and replacement of a spectral component in a physical variable (done by the cosmos), there is corresponding behavior in the biospheric variable (38, 58, 59). The evidence for a rhythm between the biosphere and the solar wind's speed becomes convincing when an amplification of the biospheric component by the presence of an environmental counterpart is accompanied by the damping of the biospheric component in the absence of the environmental counterpart (38, 58, 59).

The solar wind is certainly a major driver in the biosphere, revealing a BEL cycle in its speed and in proton density among other counterparts in the interplanetary magnetic field (56) and in the biosphere (57). As compared with the ~10.5-year Schwabe cycle in sunspots, we are dealing with much more irregular BEL cycles of smaller amplitudes, but not necessarily lacking importance, as noted elsewhere (14, 58, 59). Moreover, the power spectrum of a nearly 500-year series of 45,000 auroral observations analyzed by Samuel M. Silverman (45) globally in his Figure 5, based on monthly averages from 1500 to 1942, a sharp peak at ~33.3 years, as a follow-up on results from 1001-1900 (60, 61). Brückner deserves credit for including in his database the time of harvest in vineyards (1) along with that of cold winters. These variables allowed him in his climate research to backtrack to the year 1020. Analyzed globally, the no-35-year cycle assumption yields P=0.065. As to behavior in time in a chronomic serial section in Figure 4, only a few intervals are associated with a $P<0.05$, as apparent from dots bracketing the acrophase. But borderline significance globally and significance in some intervals of a predicted transtridecadal cycle is noteworthy and complements the thorough scholarship of Nico Stehr (14).

Brückner realized that the cycle he discovered has wide implications (62): in his monograph, he even presented statistics of an infectious disease, typhus (14; cf. 1). His legacy, in our climate-conscious era, is the systematic collection of long time series to check the far-reaching conclusions already drawn by Brückner in 1890 and by the Lockyers soon thereafter. On October 11, 1912, Brückner lectured at Columbia University in New York, suggesting that human migration to the USA and westward in the USA depended on his wet/dry cycles (12, 63). He also focused on rainfall. It is telling that in a picture he is shown with an umbrella. Rainfall and cloud cover remain important variables, being related to our cosmos (63, 64). More generally, nonphotic cycles coexist with and can override and replace seasonal effects, thus opening a broad chapter of biometeorology in space. We need to continue to map nonphotics systematically, with point-and-interval estimates of parameters, globally and as a function of time, as done for BEL in Figure 4 and Table 2.

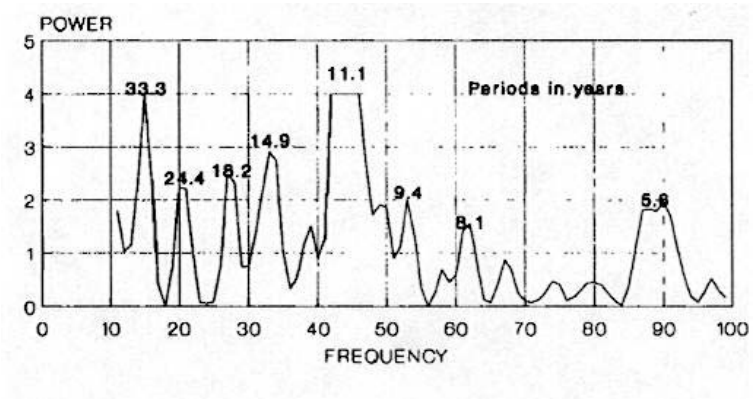

Figure 5. Power spectrum of monthly auroral occurrence for New England for the interval 1800-1948. Lag = 1200, truncated at 10; power at 11.1 = 32.2. Reproduced by permission of Samuel M. Silverman (45).

In the 21st century, Maravilla et al. (65) report on a "possible peak at around 30 years" in a time series of (solar) polar coronal hole evolution. A spectrogram of this time series, with frequency on the ordinate and time on the abscissa displaying peaks as contours, validates this spectral component only for a relatively small section of that time series, not globally in our hands, where the global peak's point estimate is at ~29.14 years.

In a 2006 publication in turn, we read: "The wavelet decomposition analysis also [among other cycles] exhibits the presence of a 33-year variation in all the solar terrestrial parameters with a minimum amplitude centered around 1997" (13). The much broader-than-circadian mapping of nonphotic as well as photic components in the spectral element of time structures is an overdue complement to Alexander von Humboldt's legacy, nearly 150 years after his death, and to the legacies of Raymond Holder Wheeler (66) and Alexander Leonidovich Chizhevsky (67).

Table 2. Extended cosinor analyses of Brückner's charted data (in Figure 2)*

	Linear analyses			Nonlinear analyses (trial period = 35 years)	
Variable	Period (y)	PR	P	Period (95% CI)	Amplitude (95% CI)
Rainfall	33.9	57.5	<0.001	33.63 (29.87, 37.40)**	3.99 (1.31, 6.68)
Temperature	85.5	11.6	0.179	36.82 (32.64, 41.00)**	1.54 (0.33, 2.75)
	36.9	39.5	<0.001		
	25.0	38.0	0.001		
Wine Harvest	67.7	11.8	0.020	36.27 (33.28, 39.26)**	1.09 (-.37, 2.56)
	36.1	8.4	0.066		
	25.4	10.3	0.035		
Cold Winters	95.6	10.5	0.109	40.63 (37.37, 43.88)**	1.60 (0.36, 2.84)
	58.0	15.3	0.036		
	40.6	31.0	<0.001		
Ice-Free Rivers	54.2	22.9	0.016	35.81 (31.43, 40.20)**	2.64 (-.31, 5.59)
	36.1	21.7	0.020		
	24.3	21.2	0.024		
Sunspots	81.2	59.3	<0.001	Not statistically significant‡¶	
	25.4	8.0	NS		

*The point-and-interval estimates for environmental temperature and rainfall prompt admiration for Brückner's intuition and success in eyeballing. Four point estimates of the period of 36.82, 33.63, 36.27 and 35.81 and three interval estimates of the amplitude are in keeping with his proposition of s(a)ecular variation in the sense of a variation corresponding to one human generation of 33.3 years. Note for wine harvest and ice-free rivers that the 95% confidence intervals given in () of the amplitude slightly overlap zero; those suggestive estimates remain inconclusive.

‡In denser monthly data starting in January 1749 (rather than 1735 in Brückner's chart) and ending in 1885 (as in Brückner's chart), the frequencies of one cycle in 33-35 years correspond to a trough. In a longer span, ending in July 2003, there is at most a tiny peak accounting for no more than 0.3% of the total variance.

¶The nearest peaklet detected in Wolf numbers with a period of 25.75 years has a confidence interval of (22.14, 29.36 years).

It is to the credit of the Lockyers in turn to have shown on relatively limited data, Figure 2, not only a periodicity of ~35 years in the length of the solar cycle, but also of having associated this periodicity with climate, referring to the agreement of their results with Brückner's findings. A. Wolfer in 1902 concluded "... from examination of the relative numbers and epochs from 1750 [to his time] that no regular periodicity exists and that 'the continued existence of a 35-year cycle is not yet demonstrated". Clough in 1905 was more positive (11). So are we, based on more than another century's evidence that validate W.J.S. Lockyer's contribution in 1901, Table 1 and Figure 3 (3).

By 1991, a number of physiological and pathological cycles were each validated in inferential statistical terms as biospheric signatures of solar frequencies (21). They were charted in 70 pages of figures, some of them complex, complementing an introduction to chronobiology (68). Further accumulating data will require complementary maps of chronomics, i.e., cycles around as well as in us and of their time course in the face of additions and subtractions (58, 59).

Discussion

The aligned mapping of time structure in and around us and the study of similarities and differences in their temporal behavior must go on not only for the sake of a better understanding of solar dynamics. It can start as a cost-effective dividend from a preventive noninvasive cardiology aiming to nip major severe debilitating vascular diseases in the bud. The same long-term monitoring that ushers in a new health care also extends modern technology to the recognition that cycles constitute life as it evolved and still depends on the cycles of our environment (59). Chronomics, by extending focus to infradians, provides critical information for any research in time, as already documented for aging, that in different circadian stages shows interactions of photic and nonphotic cycles, to the extent that time passes faster at 60 as compared to 25 years of age at one circadian stage (09:00-12:00), while the opposite is found at another stage in the evening. Moreover, the change with age at certain circadian stages is modulated by a BEL, as documented elsewhere in these Proceedings. Reference standards for BEL must accordingly be mapped at various circadian stages, since evidence is on hand to show that the detection of a half-yearly cycle in human blood pressure is possible in the evening but not in the morning (69). Maps of infradians may place all research in time, organic and inorganic, on a more solid basis. A website for both analyses of data for health care delivery and use of the same information for transdisciplinary research in chronomics is a step in the direction of systematic mapping. Legislation to support test pilots for lifetime physiologic monitoring in the family across generations, begun thus far only by two pairs of father and son (69-72), constitutes another important step; it does not, however, replace longitudinal mapping from womb to tomb.

Conclusion

Figure 3 and Table 1 validate, in inferential statistical lines, William J.S. Lockyer's report of an ~35-year period in solar cycle length, in the light of data accumulated from before and after those he examined. As to terrestrial variables, Eduard Brückner's scholarship also withstands inferential scrutiny in Figure 4, Wolfer's admonition and Schuster's and Kostin's concerns notwithstanding. Credit is also to be given (according to Norman Lockyer and to Rudolf Wolf) to Giovanni Battista Riccioli, who associated sunspots with weather on earth apparently soon after sunspots were discovered by Galileo, Scheinert and others. Figure 6 takes artistic license by depicting a meeting of individuals who in real life lived generations apart. It is apparently the only pictorial depiction of Riccioli, who in turn was preceded by Polybius (73) in relating climate to human affairs, including aggression, an important topic then and now.

Figure 6. Giovanni Battista Riccioli (1598-1671) is credited by Norman Lockyer (4) and Rudolf Wolf (74) with an early association of sunspots with weather on earth. Since no authentic images of Riccioli are known to exist, we include a fanciful artistic depiction of Riccioli with Tycho Brahe (1546-1601). "[This photo was taken] in a conference in Prague celebrating the 400th anniversary of the death of Tycho Brahe. It is a small detail of a larger ceiling mural in one of the rooms in the Clementinum, the old Jesuit college in downtown Prague, just off the Charles Bridge. ... The building today houses the Czech national library. ... [T]he likeness to Tycho Brahe's other known images is quite good ... Considering that Riccioli was only 3 at most when Tycho died, the 'conversation' depicted must be emblematic rather than historical." (Jole R. Shackelford, Adjunct Assistant Professor, History of Medicine, University of Minnesota, personal communication, 30 April 2008)

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Should 7-day/24-hour chronobiologically interpreted blood pressure monitoring replace single measurements before cataract surgery?

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Abstract. In an 89-year-old man (FH), who monitored his blood pressure (BP) and heart rate (HR) around-the-clock at half-hour intervals for decades (with interruptions) and continued to do so before, during and after cataract surgery, we seek any alterations in the time structure of BP and/or HR in relation to this intervention (even though FH recognized no anxiety himself). First, we look at BP and HR within the individualized range of the subject at the given time by a sequential test, and second by reference to broader standards derived from clinically healthy peers of the same gender and corresponding age. The sequential test applied to detect any abnormalities used an individualized reference standard and found changes hidden in the normal range of peers, while data remained within that range. In the week following successful mid-week surgery, the circadian amplitude of diastolic BP increased above peer limits, a reason for caution in the interpretation of the results during the week of intervention as possibly related to subconscious anxiety about the surgery. If they were so related at all, these abnormalities were exceeded by the pleasure (in retrospect "tension") associated with preparations of materials for publication at a conference, including this report. Apart from testing for physical or emotional loads (stress), we advocate, for any and all estimations of health more generally, a chronobiologically interpreted ambulatory automatic 7-day/24-hour BP and HR monitoring (C-ABPM) as soon as an appointment for a preoperative or any other health check is made, including cataract surgery.

Background. Concern about BP variability was emphasized in a doctoral thesis in 1880 (1; cf. 2), by Theodore C. Janeway (3) in 1904, by Frederic C. Bartter, head of the Hypertension-Endocrine Branch of the National Institutes of Health (NIH) in the 1970s (4), and subsequently by others (5). In 2008, we have tools to assess this variability (6), which has not yet been accounted for by official guidelines (7). Chronobiologic evidence in Table 1 (8) and Figures 1 and 2 (6, 8-10) has led to vascular variability disorders, VVDs. Several coexisting VVDs constitute vascular variability syndromes, VVSs, which cannot be detected without C-ABPM, Figure 2.

Opinion leaders already discourage in their recommendations (11) -- albeit not (yet) in official guidelines (7) -- reliance upon office BP measurements, as is now practiced for any health check. Consensus meetings (10) recommend a **c**hronobiologically interpreted 7-day/24-hour profile obtained by **a**utomatic ambulatory **BP** **m**onitoring (C-ABPM), which can detect prehypertension (8, 9), prediabetes (12, 13) and elevations of the circadian amplitude and MESOR of BP associated with minimal change retinopathy (14), another reason for monitoring BP in ophthalmology.

Outcomes in a 7-year follow-up could be predicted from 9 days of half-hourly around-the-clock ambulatory automatic monitoring, but not from 2-, 3- or 4-day profiles (15). The same study showed that the response to surgery detected an increase in BP and HR in the morning and a decrease in the afternoon (15; figure on lower inside cover of 10). Conceivably, a "white-coat hypertension" in the morning will be a "white-coat hypotension" in the afternoon. Terms such as "white-coat effect" or "masked hypertension", originating from justified concern to account for variability, prompt much investigation (16-38) to account for plain false positive and false negative diagnoses due to variability, but are no substitute for C-ABPM 7/24 for ruling out abnormality (8, 9,

12, 13) and much longer C-ABPM to evaluate VVDs and VVSs (Figures 1 and 2), that carry a risk larger than a high BP, and/or to study the development of high BP, also one of the VVDs.

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 5y)	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 28y	~every 4h 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	every 15min for 24h	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)	every 1h/48h in each trimester of pregnancy (336 profiles)	16,128 (16,128)	In addition to an 8 mmHg 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 6y	every 15min for 48h	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 24h	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 7y	every 15min 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	every 4h for 24h 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)	every 30min (≥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 (for healthy peers matched by gender and age). CHAT is a VVD, as is, among others, an excessive pulse pressure (PP), a deficient (below-threshold) HR variability (DHRV), an odd timing of the circadian BP but not of the HR rhythm (BP ecphasia), and a reliably diagnosed high BP, MESOR-hypertension or MH. LVMI: left ventricular mass index. By comparison with some classical studies, the number of measurements in chronobiological work completed thus far is likely to be larger, and confounding by inter-subject variability smaller.

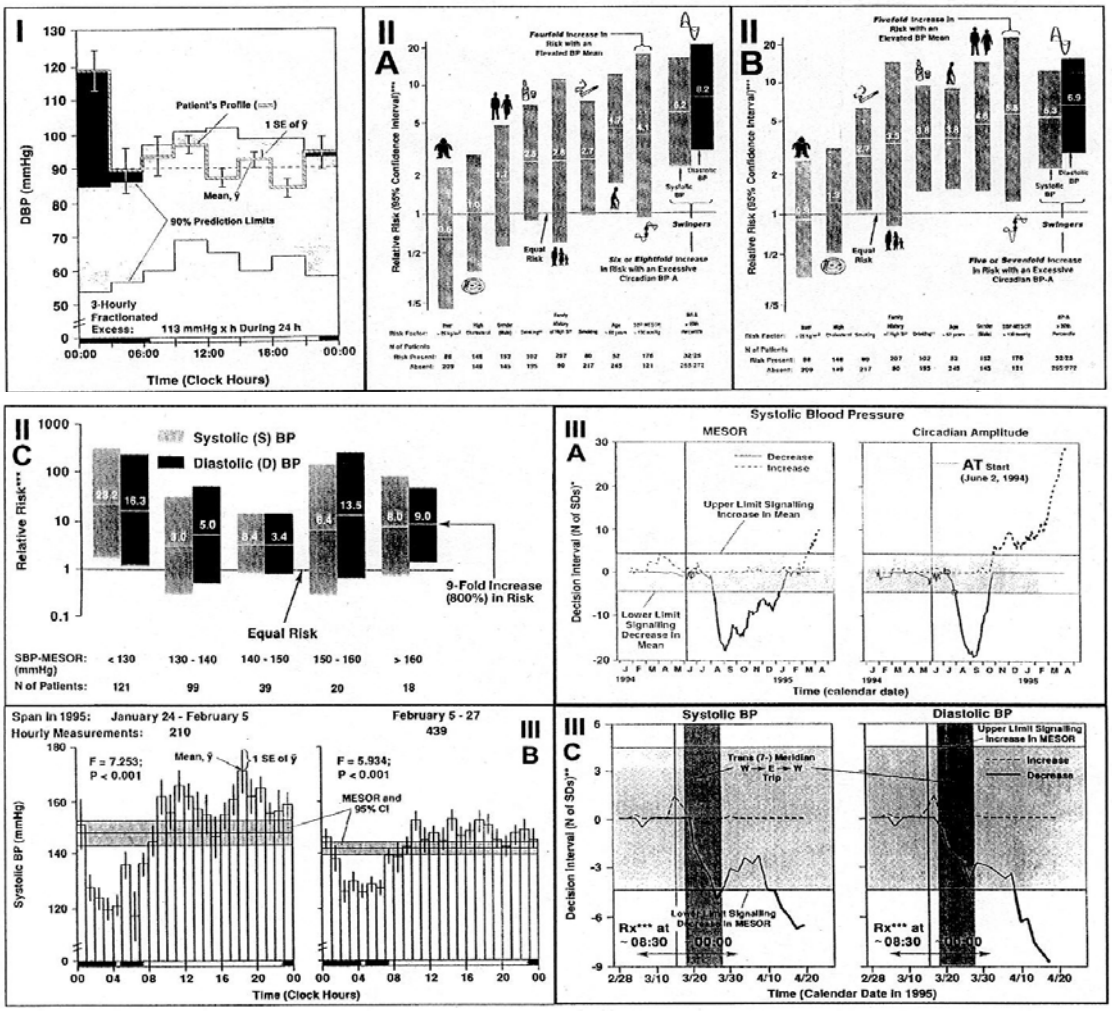

Figure 1. Illustrative results supporting the need for continued surveillance, and for a chronomic analysis of blood pressure series. I: Nocturnal hypertension: data stacked from 11 days of around-the-clock monitoring. Office spotchecks cannot detect nocturnal pathology. II A: Among risk factors, an excessive circadian blood pressure (BP) amplitude (A) raises the risk of ischemic stroke most. II B: Among risk factors, an excessive circadian blood pressure (BP) amplitude (A) raises the risk of nephropathy most. II C: An excessive circadian BP A is a risk factor for ischemic stroke independent from the 24-hour mean (MESOR). III A: Individualized assessment (by CUSUM) of a patient's initial response and subsequent failure to respond to autogenic training (AT) (EO, F, 59 y). III B: Individualized BP chronotherapy. Lower circadian double A (2A) and MESOR (M) after switching treatment time from 08:30 (left) to 04:30 (right)*. III C – Control chart assesses individualized anti-MESOR-hypertensive chronotherapy.

Chronomics detects nocturnal escape from hypotensive treatment taken in the morning (I above); a circadian overswing, CHAT; a risk of stroke and nephropathy, greater than hypertension (IIA-B), even in MESOR-normotension (IIC) and monitors transient and/or lasting success of treatment (IIIA-C). Merits are:

· Detection of abnormality during the night when the dose of medication taken in the morning may no longer be effective in certain patients, facts not seen during office visits in the afternoon but revealed as consistent abnormality by around-the-clock monitoring;

· Detection of abnormal circadian pattern of blood pressure (CHAT, "overswinging") associated with a risk of cerebral ischemia and nephropathy larger than other risks (including "hypertension") assessed concomitantly (IIA and B);

· Finding that CHAT carries a very high risk even among MESOR-normotensives who do not need anti-hypertensive drugs (IIC);

· Availability of statistical procedures such as a self-starting cumulative sum (CUSUM) applicable to the individual patient to determine whether an intervention such as autogenic training is effective and if so for how long it remains effective (IIIA);

· N-of-1 designs for the optimization of treatment timing: the same dose of the same medication can further lower the same subject's blood pressure MESOR and circadian amplitude when the timing of daily administration is changed (IIIB and C), as ascertained by as-one-goes (sequential) testing and parameter tests, procedures applicable to the given individual. © Halberg.

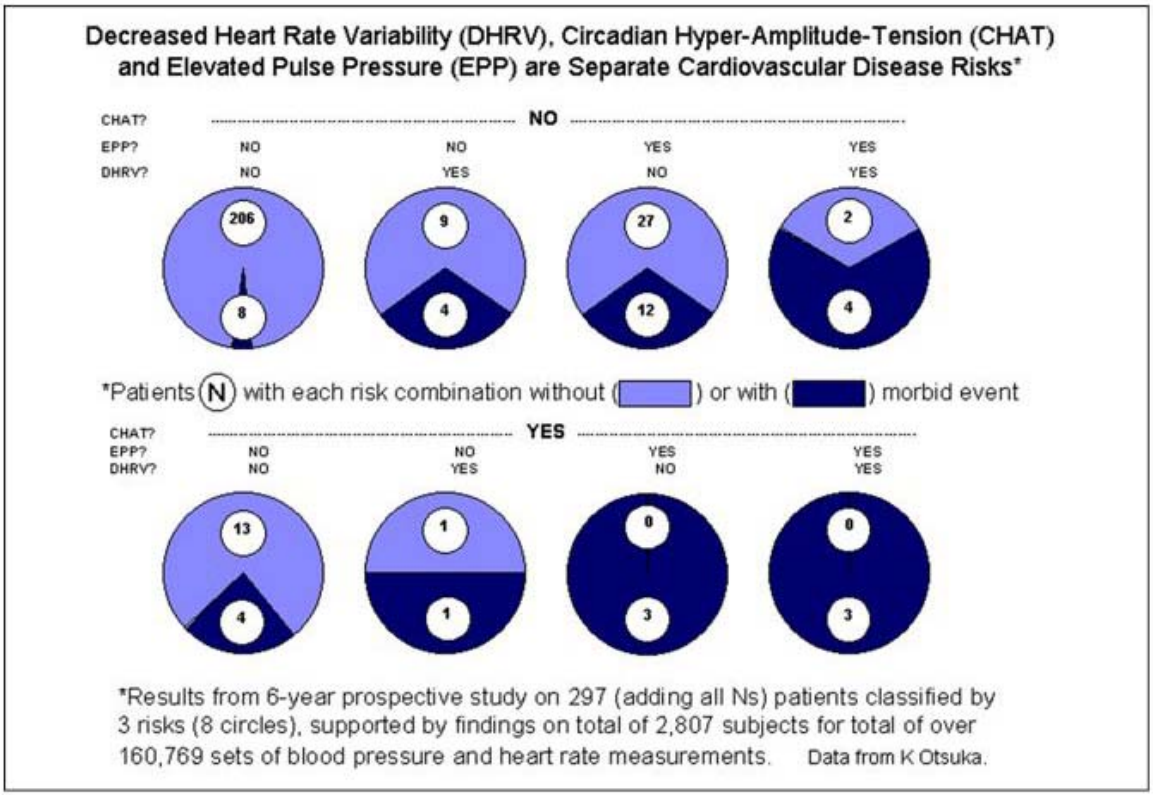

Figure 2. Based on C-ABPM 7/24, a **d**ecreased **h**eart **r**ate **v**ariability (DHRV), gauged by the standard deviation of HR, in relation to a threshold, preferably eventually assessed by reference to data from clinically healthy gender- and age-matched peers, a **c**ircadian **h**yper-**a**mplitude-**t**ension (CHAT) and an **e**levated **p**ulse **p**ressure (EPP) (the difference between systolic [S] and diastolic [D] blood pressure [BP], i.e., between the heart's contraction or relaxation, or the extent of change in pressure during a cardiac cycle) are separate **v**ascular **v**ariability **d**isorders (VVDs) that may coexist to form **v**ascular **v**ariability **s**yndromes (VVSs), along with other risk conditions such as an abnormal circadian timing of BP but not of HR, not shown, and of course with or without an abnormal, e.g., elevated BP average (MESOR), i.e., MESOR-hypertension. Vascular disease risk is elevated in the presence of any one of these VVDs and is elevated further when more than a single VVD or other risk factor is present, suggesting that these abnormalities in variability of BP and HR are mostly independent and additive. Abnormalities in the variability of BP and HR, impossible to find in a conventional office visit (the latter aiming at the fiction of a "true" blood pressure), can raise cardiovascular disease risk (gauged by the occurrence of a morbid event like a stroke in the next six years) from 4% to 100%. By comparison to subjects with acceptable BP and HR variability, the relative cardiovascular disease risk associated with a DHRV, an EPP and/or CHAT is greatly and statistically significantly increased. These VVDs and VVSs, silent to the person involved and to the care provider, notably the risk of CHAT, can usually be reversed by chronobiologic self-monitoring and thus self-help, also with a non-pharmacologic approach in the absence of MESOR-hypertension. © Halberg.

Methods. FH, an 89-year-old man planning to have cataract surgery on his right eye, was informed that his use of Flomax® (tamsulosin hydrochloride), an α-1 blocker for benign prostatic hypertrophy, may cause a condition known as intraoperative floppy iris syndrome (IFIS). IFIS results in prolapse of a billowing, floppy iris, causing progressive intraoperative miosis which increases the risk of intraoperative complications. Because of these increased surgical risks, the package insert for Flomax states that "If you are contemplating cataract surgery, make certain to advise your eye surgeon that you have taken Flomax".

On the day of surgery, FH was brought into the preoperative holding area, where a retrobulbar anesthetic was administered. The anesthetic consisted of a 50% mixture of 2% lidocaine and 50% mixture of 0.75% bupivicaine. After approximately 15 minutes, FH was transported to the operating room. He was given O_2 by nasal cannula while his BP, HR, respiratory rate and blood oxygenation

were monitored by anesthesia personnel. FH was prepped and draped in a sterile fashion, after which the surgery commenced. The iris demonstrated poor dilation, which was likely to be secondary to the use of Flomax. A Malyugin ring was placed to expand the pupil and stabilize the iris. The remainder of the cataract surgery progressed in a standard fashion. Upon completion, FH's operated eye was patched closed and he was taken to the recovery room.

FH had monitored his BP around-the-clock at half-hourly intervals for decades (with interruptions) with a TM-2421 monitor from A&D (Tokyo, Japan). He provided data for analyses by cosine fitting (top) and by stacking (bottom), summarized in a sphygmochron (39) in Figures 3 and 4. Cosinors were prepared on a daily basis (not shown) to examine characteristics of BP and HR variability on the day of surgery and during the days and weeks preceding and following the operation. Comparisons were made by parameter tests (40; cf. 39) and sequential testing (cusums) (41).

Results. The sphygmochron in Figure 3 summarizes the chronobiologically interpreted monitoring profile for the week bracketing surgery. On top, the upper half of parametric analyses yields measures of predictable extent of change, or double amplitude, 2A, and of timing of change, or acrophase, ϕ, as well as a midline-estimating statistic of rhythm, or MESOR, M, that are listed with reference ranges of acceptable values from clinically healthy peers matched by gender and age. The HR-M is below an age- and gender-matched peer-threshold HR-M; the timing of the circadian HR rhythm is odd, but these alterations were noted for the subject during the preceding years. Figure 4, another sphygmochron, summarizes results for the subsequent week. A diastolic BP overswing, CHAT, short for circadian hyper-amplitude-tension, is then diagnosed. A finding in the week of surgery of an elevation of the circadian DBP-2A, which was then still in the acceptable range, is exaggerated rather than damped in the week following successful uncomplicated surgery.

Figures 5a and 5b show the original data in the week bracketing the day of surgery and the following week, while the data of the day of surgery are seen in Figure 6, with dots representing measurements during the procedure and bracketing it by minutes rather than hours. Figures 7-9 show stacked data with a large circadian BP swing in the week bracketing surgery (left) and in the following week (right) after successful recovery. Figure 10 reveals that the sequential individualized test by cumulative sums led to a breakout from the decision interval for 3 of the 7 endpoints monitored, namely SBP-M and DBP-M and DBP-A, as indicated by an asterix on the abscissa. The sphygmochron in Figure 4 shows that this circadian amplitude alteration was more pronounced in the week following successful surgery.

Discussion. Chronobiologically interpreted ambulatory, automatic BP and HR monitoring has been suggested as a test of the emotional and physical load impinging upon an individual (42-45). In FH, unknown to him, changes in BP MESORs and in his diastolic but as yet not in the systolic circadian amplitude were detected in the week bracketing surgery. There were no detectable changes in HR or pulse pressure by cusum (41). The finding of an effect of the load (unconscious worry about the operation, if any), within the physiologic range of clinically healthy gender- and age-matched peers, is remarkable if one's attention is restricted to the week bracketing surgery, but is minor if compared to the greater alterations associated with the task of preparing this paper and a number of more complex reports for publication in a forthcoming conference volume.

SPHYGMOCHRON-TM

Monitoring Profile over Time;
Computer Comparison with Peer Group Limits

Blood Pressure (BP) and Related Cardiovascular Summary.

Name:---------- Patient #: FHal389
Age: 89 Sex: M
Monitoring From: 8/2/2008 16:30 To: 8/9/2008 11:32
Comments:

CHRONOBIOLOGIC CHARACTERISTICS

	SYSTOLIC BP (mmHg)		DIASTOLIC BP (mmHg)		HEART RATE (bpm)	
	Patient Value	Peer Group Reference Limits	Patient Value	Peer Group Reference Limits	Patient Value	Peer Group Reference Limits
ADJUSTED 24-h MEAN (MESOR)	137.9	109.3-141.6 Range	83.2	69.6-86.8 Range	***60.6***	65.9-87.9 Range
PREDICTABLE CHANGE (DOUBLE AMPLITUDE)	28.09	3.41-34.00 Range	23.34	0.00-27.55 Range	3.70	0.00-33.40 Range
TIMING OF OVERALL HIGH VALUES (ACROPHASE) (hr:min)	14:38	8:30-18:27 Range	14:41	8:54-16.58 Range	**23:47**	9:39-18:57 Range

	STD (MIN; MAX)*	STD (MIN; MAX)*	STD (MIN; MAX)*
PERCENT TIME OF ELEVATION	7.8%	7.4%	0.0%
TIMING OF EXCESS	20:55 (hr:min)	20:04 (hr:min)	0:00 (hr:min)
EXTENT OF EXCESS DURING 24 HOURS HBI*	22 (mmHg x hour)	3 (mmHg x hour)	0 (mmHg x hour)
10-YEAR CUMULATIVE EXCESS	79 (mmHg x hour)(in 1,000's units)	11 (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)

INTERVENTION NEEDED			**MORE MONITORING NEEDED**
No			Annually
Yes	Drug	Non-Drug	As soon as possible
			Other specify_____

Prepared By_____ Date____/____/_____

1) Unusually long standing or lying down during waking: unusual activity, such as exercise, emotional loads, or schedule changes, e.g. shiftwork; etc.; 2) Salt, calories, kind and amount, other, etc.

Figure 3. Sphygmochron of the data during the week bracketing the operation. Abnormality such as that for HR was present during prior years and does not seem pertinent to cataract surgery. Other abnormality in Figure 10 needs a personalized reference standard provided by cusums for FH on the basis of his accumulating data. © Halberg.

SPHYGMOCHRON-TM

Monitoring Profile over Time;
Computer Comparison with Peer Group Limits

Blood Pressure (BP) and Related Cardiovascular Summary.

Name:---------- Patient #: FHal390
Age: 89 Sex: M
Monitoring From: 8/9/2008 13:00 To: 8/16/2008 15:00
Comments:

CHRONOBIOLOGIC CHARACTERISTICS

	SYSTOLIC BP (mmHg)		DIASTOLIC BP (mmHg)		HEART RATE (bpm)	
	Patient Value	Peer Group Reference Limits	Patient Value	Peer Group Reference Limits	Patient Value	Peer Group Reference Limits
ADJUSTED 24-h MEAN (MESOR)	135.1	109.3-141.6 Range	82.5	69.6-86.8 Range	***61.1***	65.9-87.9 Range
PREDICTABLE CHANGE (DOUBLE AMPLITUDE)	27.84	3.41-34.00 Range	**27.95**	0.00-27.55 Range	2.83	0.00-33.40 Range
TIMING OF OVERALL HIGH VALUES (ACROPHASE) (hr:min)	14:54	8:30-18:27 Range	15:12	8:54-16.58 Range	**20:43**	9:39-18:57 Range

	STD (MIN; MAX)*	STD (MIN; MAX)*	STD (MIN; MAX)*
PERCENT TIME OF ELEVATION	9.9%	7.4%	0.0%
TIMING OF EXCESS	21:10 (hr:min)	20:52 (hr:min)	0:00 (hr:min)
EXTENT OF EXCESS DURING 24 HOURS HBI*	16 (mmHg x hour)	6 (mmHg x hour)	0 (mmHg x hour)
10-YEAR CUMULATIVE EXCESS	60 (mmHg x hour)(in 1,000's units)	22 (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)

INTERVENTION NEEDED			**MORE MONITORING NEEDED**
No			Annually
Yes	Drug	Non-Drug	As soon as possible
			Other specify_____

Prepared By_____ Date____/____/_____

1) Unusually long standing or lying down during waking: unusual activity, such as exercise, emotional loads, or schedule changes, e.g. shiftwork; etc.; 2) Salt, calories, kind and amount, other, etc.

Figure 4. Sphygmochron revealing (in bold) a diastolic circadian overswing, called **c**ircadian **h**yper-**a**mplitude-**t**ension, CHAT, associated, when persistent, with a risk of severe disease greater than a high blood pressure, but reversible in FH by relaxation or drugs (found on the basis of years of prior monitoring to be transient and amenable to treatment). The appearance of CHAT in the week following surgery, rather than in that of the intervention, prompts one to compare the lesser association with surgery of the breakout from the decision interval of the sequential test of the circadian DBP amplitude in Figure 10 with the appearance in Figure 4 of CHAT, the latter perhaps as a response to the pleasure of completing scientific papers. © Halberg.

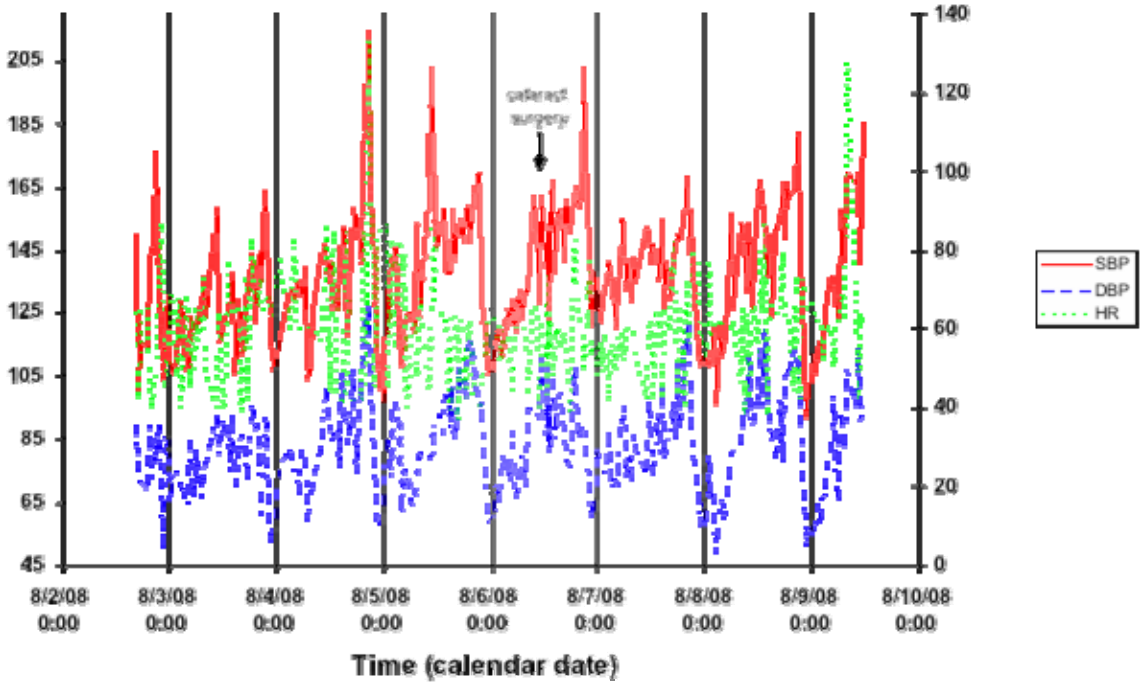

Figure 5a. Data bracketing cataract surgery on August 6, 2008, scheduled for 1:30 pm. The unaided eye sees an elevation of SBP and DBP on 2 days before surgery, but also sees elevations after surgery. Sequential tests in Figure 10 are more objective. © Halberg.

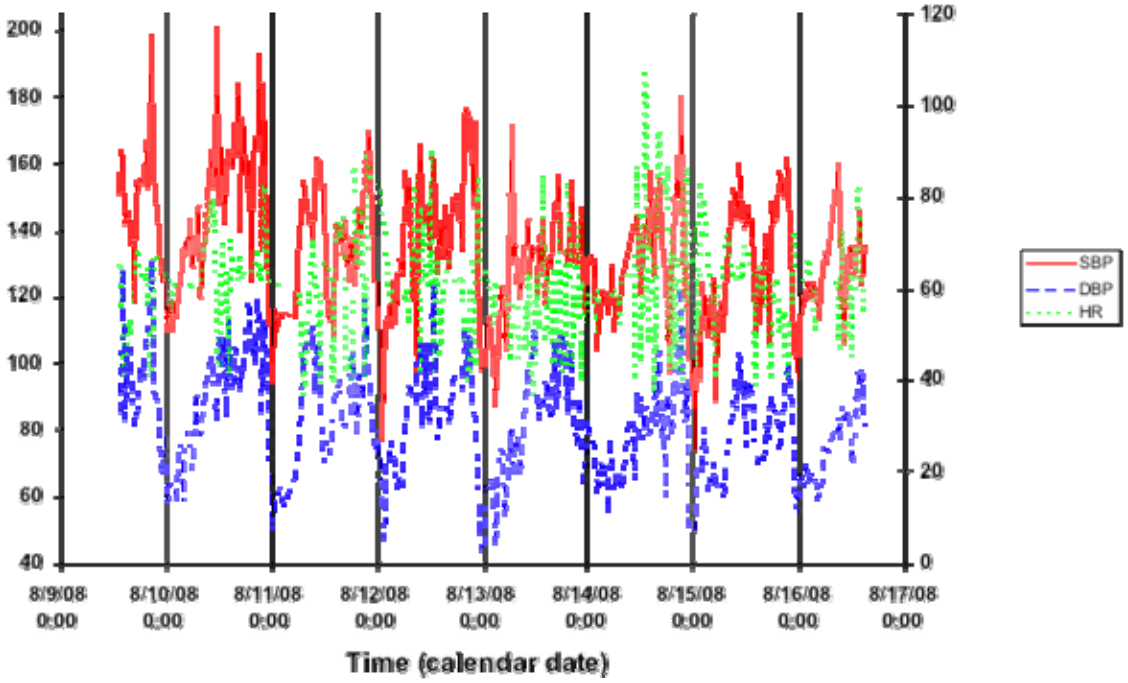

Figure 5b. Data from the week following that of mid-week surgery. © Halberg.

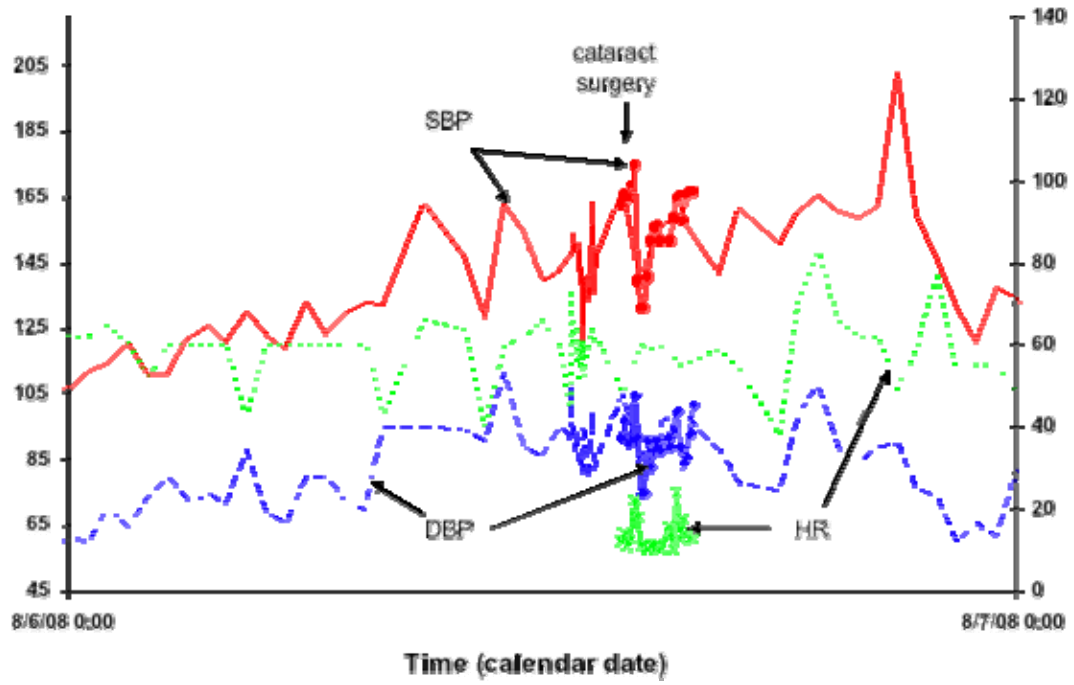

Figure 6. Original C-ABPM data of FH connected by lines on the day of monitoring with data of FH from the institute where surgery was performed, added as dots. © Halberg.

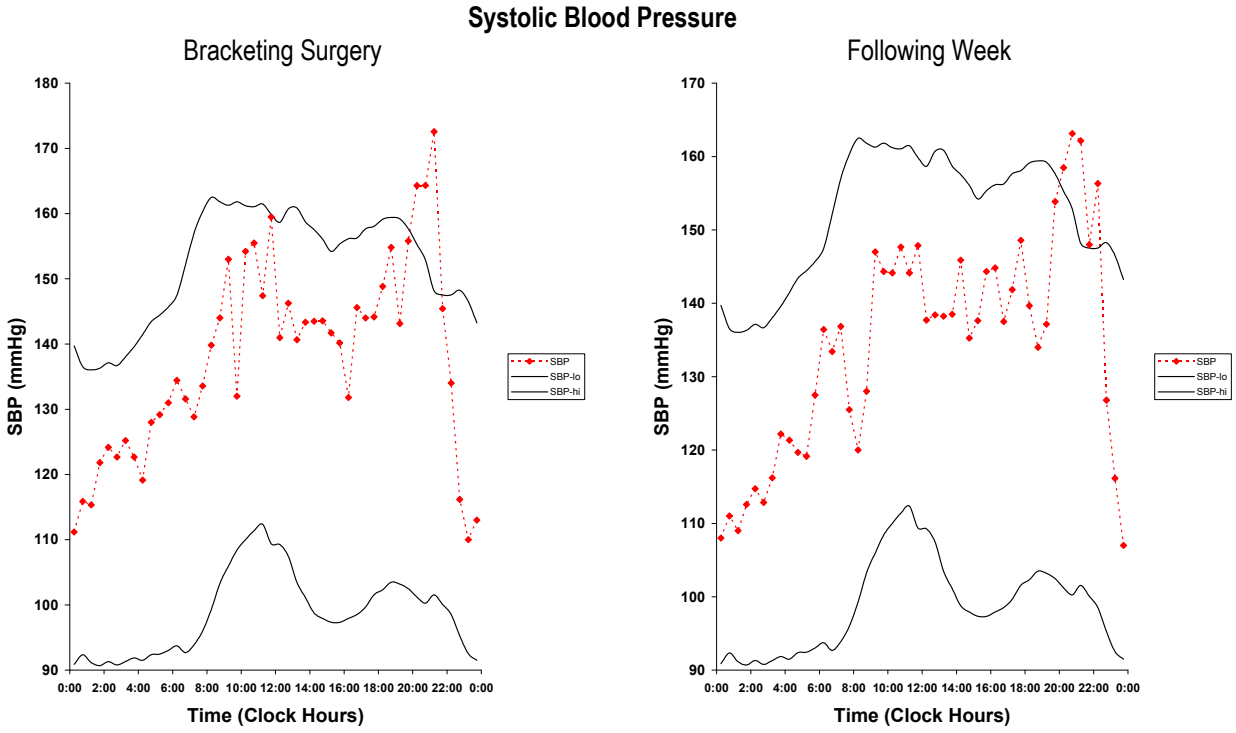

Figure 7. Systolic blood pressure plexogram of FH: data during the week bracketing surgery (left) and the following week (right), stacked along an idealized day at half-hour intervals, framed by time-varying reference limits from clinically healthy peers matched by gender and age. © Halberg.

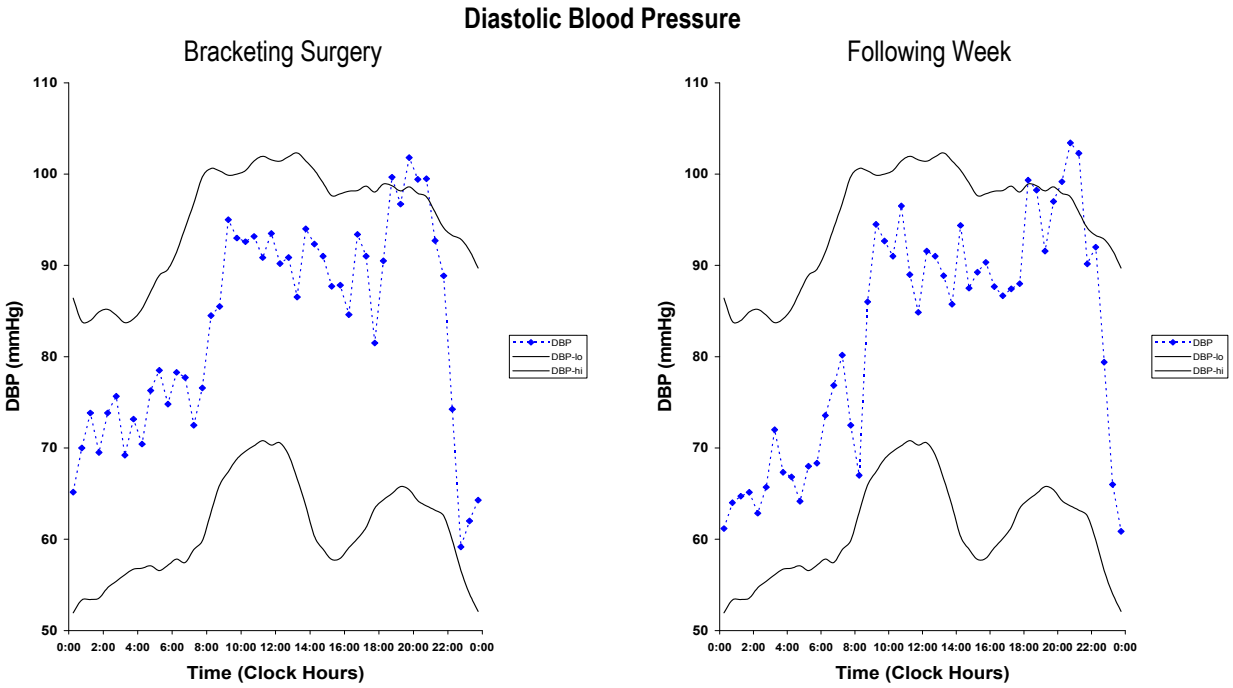

Figure 8. Diastolic blood pressure plexogram of data of FH during the week bracketing surgery (left) and the following week (right), stacked along an idealized day at half-hour intervals, framed by time-varying reference limits from clinically healthy peers matched by gender and age. © Halberg.

Figure 9. Heart rate plexogram of data of FH during week bracketing surgery (left) and the following week (right), stacked along an idealized day at half-hour intervals, framed by time-varying reference limits from peers matched by gender and age. © Halberg.

Date	SBP-M	DBP-M	HR-M	PP	SBP-2A	DBP-2A	HR-2A
19-Jul-08	112.1	67.7	62.1	44.4	21.40	5.23	7.64
20-Jul-08	119.3	70.1	60.2	49.2	20.51	17.21	10.89
21-Jul-08	129.7	73.6	64.2	56.1	33.12	8.35	3.97
22-Jul-08	115.8	69.4	65.7	46.4	13.90	11.56	27.55
23-Jul-08	125.7	72.4	60.9	53.3	6.27	11.03	5.66
24-Jul-08	122.2	69.5	61.4	52.7	27.76	20.07	6.51
2-Aug-08	125.8	77.6	58.5	48.2	11.05	12.23	2.15
3-Aug-08	131.0	79.3	63.4	51.7	11.99	20.93	9.60
4-Aug-08	143.6	84.9	64.1	58.7	37.29	24.73	18.20
5-Aug-08	137.4	86.3	56.2	51.1	36.62	30.04	5.49
6-Aug-08	145.6	82.5	57.5	63.1	23.79	15.08	6.46
7-Aug-08	135.3	84.1	61.0	51.2	32.80	33.27	9.01
8-Aug-08	143.5	87.0	63.9	56.5	40.83	33.04	7.82

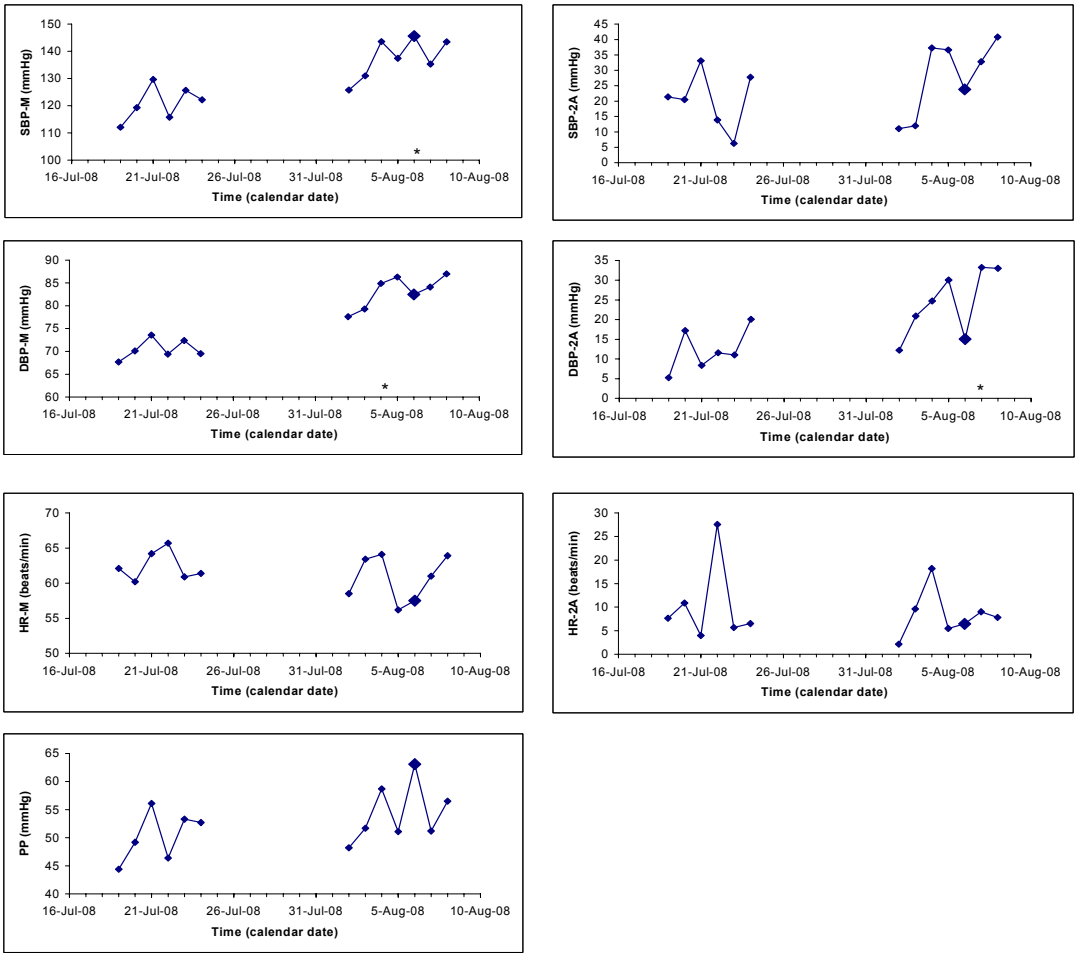

Figure 10. Cumulative sums serve for sequential testing. Asterix on abscissa of rows 1 and 2 (left) and row 2 (right) indicates detection of deviation from norm. © Halberg.

The elderly man here monitored (FH) is professionally active, usually 7 days a week, including the morning before surgery, scheduled for 13:30, and the hours after surgery and the continuance of his endeavors involving reading. Thus, his eyesight is important to him, but he was unaware of any anxiety and pursued his activities routinely. Hence the detection by cusum of an increase in the circadian DBP-A and of the SBP-M and DBP-M is noteworthy in the absence of conscious concern about the operation. These changes for a relatively brief span are almost certainly a physiologic response. But in other subjects, a CHAT of longer duration can be a useful warning even when the cardiologist's stress test is non-contributory, Figure 11 (46-48). Monitoring of BP for the week prior to surgery may be part of preoperative screening, yet the restriction of the monitoring

span to a week of recording holds only until automatic, unobtrusive and affordable devices become available.

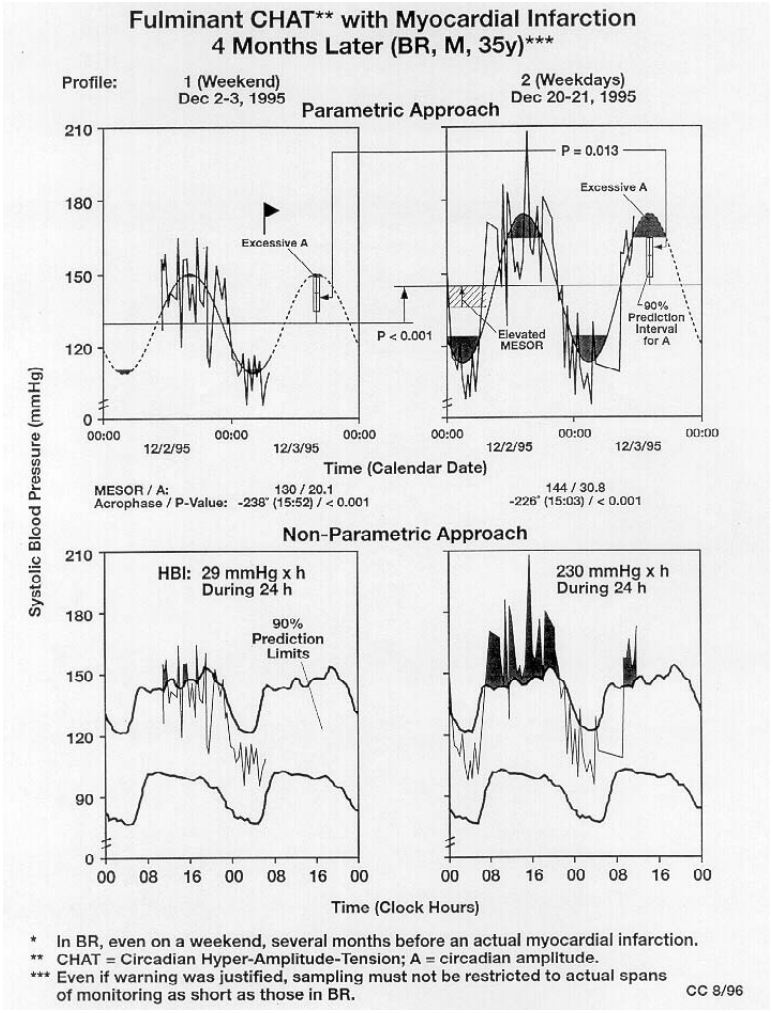

Figure 11. Excessive circadian BP-A is a more sensitive warning (flag) than a conventional "stress test"*. A myocardial infarction (MI) in April 1996, after an ignored chronobiologic warning of a fulminant CHAT, was necessary to convince a 35-year-old man (BR) of the need for C-ABPM. Four months before the MI, BR reluctantly agreed to be monitored for 7 days, but stopped after 1 day (of a weekend; Profile 1: 12/02/1995); 18 days later, he returned for another 7 days, but monitored only for 2 added days (midweek; Profile 2: 12/20-21/1995) 4 months before a myocardial infarction (MI) in April 1996:

Endpoint (units)*	SBP (mmHg)		DBP (mmHg)		HR (beats/min)	
Profiles	1	2	1	2	1	2
MESOR	130.3	**144.0****	81.0	86.5*	70.6	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	15.8	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 BP or HR above time-specified reference limit computed on 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; for BP; HBI: hyperbaric index in mmHg x h during 24h; for HR; TCI: tachycardic index, in beats/min x h during 24h. Values in **bold** are outside chronodesmic (time-varying and time-specified) reference limits. P: *0.05; **<0.01; ***<0.001. 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.

We routinely advocate a 1-week BP and HR profile at the outset, since there are cases where MESOR-hypertension was observed for up to 5 initial days of monitoring but not for a year thereafter, and since there can be large day-to-day differences in MESOR and 2A when monitoring is limited to 24 hours (in addition to any weekend vs. weekday difference, as part of multiseptan variation). With these qualifications, in BR, a **c**ircadian **h**yper-**a**mplitude-**t**ension, CHAT, with MESOR-normotension may have alternated with or preceded (as in the Okamoto rat and in human studies) the MESOR elevation of the second profile (see tabulation above), then associated with an elevated HBI of SBP and DBP. The recommended continued monitoring after the first profile and the urged immediate treatment after the second profile were not acted upon. The subject went to a care provider, who ordered a stress test which was acceptable. He started long-term monitoring 4 months later, after having had an MI.

BR and others could be isolated cases, but not 297 patients followed prospectively for 6 years, established first on a population basis in the hands of Kuniaki Otsuka (47, 48), the high relative vascular disease risk of CHAT, which can be fleeting or gradual as well as fulminant. With a proxy outcome, the left ventricular mass index, the risk of CHAT involving the heart, as well as the brain, kidney and eye, has been extended to a much larger number of patients, Table 1.

An increase of the human BP-2A can precede adverse vascular events at the time when as yet there is no change in other parametric or non-parametric chronobiologic or conventional indices for a deviant BP. Methods here used allow us to extend inferential statistical considerations from groups to the given patient. Preferably with more user-friendly instrumentation, yet with education in chronobiology irrespective of the kind of available tools, the monitoring of BP in time and its chronobiologic interpretation should prompt action for timely vascular disease prevention. © Halberg.

C-ABPM should constitute part of a preoperative screening routine and should further serve in research for a post-operative follow-up, so that the effects in spans bracketing the operation can be compared with those of other loads. Thus, an emotional load is detected by chronobiologically interpreted changes in the circadian amplitude of DBP and of changes in BP-MESORs coincident with cataract-related (or any other) surgery, yet their effect compares unfavorably with that of other loads. In FH, other presumably benetensive tasks (44), such as the (to him) pleasure of writing in preparation for a meeting abroad, involve more drastic changes than cataract surgery that exceeded the individualized limits set on the basis of his data prior to surgery but neither did the response exceed the limits of clinically healthy gender- and age-matched peers, nor did it equal changes associated with routine tasks.

Conclusion. The wear and tear of everyday life can be assessed by C-ABPM and is best interpreted on the basis of long-term monitoring of BP and HR. Objective findings that are statistically significant, made, e.g., in the context of cataract surgery, may then be identified as physiological transients and as minor by comparison to changes associated with other routine tasks.

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Brückner-Egeson-Lockyer (BEL) cycle in heliogeomagnetics

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Aim. In the foreseeable future, noninvasive cardiology may be based on dense if not continuous monitoring of variables such as beat-to-beat heart rate and related endpoints from the ECG. The ECG is already combined with blood pressure measurements around the clock in an automatic instrument for ambulatory use. Eventually, other variables such as the EEG will also be recorded automatically, ambulatorily, unobtrusively and affordably. Such monitoring has been started on a few "test pilots", but not yet from womb to tomb. Monitoring in schools could examine the merits of prehabilitation, i.e., of diagnosing and treating pre-hypertension (1, 2), pre-diabetes (3, 4) and other vascular variability disorders (VVDs), and if several VVDs coexist, the resulting vascular variability syndromes (VVSs). Thereby, incapacitation by morbid events such as strokes and the great cost of rehabilitation will be reduced by self-surveillance cost-free, for prehabilitation (5-7). With such records, it will become possible, as a dividend, to consider and analyze some of the already-known psychophysiological signatures of the cycles of the habitat near and far, including those of solar interplanetary and galactic as well as terrestrial variability (5, 8-19).

Background. Not only cycles with a period that fits, in length, within the lifetime of an individual organism, but also those with a longer period, detected on a population basis, are pertinent in an epidemiological context. Cycles with a period occupying decades and much longer ones, some exceeding by far several individuals' lifespan have already been found in populations as in nature (9, 10; cf. 19). A tridecadal cycle was described by Charles **E**geson, who wrote in 1889 that "we hear Lord Bacon say: '... every five and thirty years the same kind and suit of years and weathers come about again; as great frosts, great wet, great droughts, warm winters, summers with little heat and the like, and they call it the Prime'" (20). Shortly after Egeson, Eduard **B**rückner documented, more extensively albeit macroscopically, a 33-35-year variation (21), which was elaborated in relation to the length of the sunspot cycle by W.J.S. **L**ockyer (22), with comment in a historical context in the journal Science by his father Sir Norman Lockyer (23), discoverer of helium and founder of the journal Nature (24; cf. 25). Transtridecadals have been reported as a possible 35.6-year period by Dolores Maravilla et al. (26) in polar coronal holes, where this period is found in a spectrogram only transiently in the early 1990s, Figure 1. They are also cited by S.R. Prabhakaran Nayar (27) as a 33-year variation, the latter with an indication of a high degree of generality in solar-terrestrial associations.

Materials and methods. Against this background, a database consisting of 40 series (OMNI2; ftp://nssdcftp.gsfc.nasa.gov/spacecraft_data/omni/) was analyzed chronomically by the extended cosinor (28-30), to start with globally, as whole series.

Results. By the criterion of a positive lower limit of the CI (95% confidence interval) of the amplitude (i.e., by the rejection of the zero-33-year amplitude assumption), five of the OMNI2 series qualify as BEL, Table 1 (one of these variables, Na/Np, the alpha/proton ratio, is noted only in this table's footnote).

Table 1: Brückner-Egeson-Lockyer (BEL) cycle in heliogeomagnetics*

Variable	Period (years) [95% CI]	Amplitude (%M)** [95% CI]
Interplanetary magnetic field		
Proton Temperature	34.28 [26.99, 41.57]	13.62 [6.56, 20.68]
Sigma (Bx)	31.87 [24.70, 39.04]	6.81 [3.41, 10.71]
Plasma Speed	33.04 [20.10, 45.97]	2.47 [0.10, 4.83]
Planetary geomagnetic index		
Kp	32.65 [28.27, 37.03]	12.74 [8.58, 16.86]

*Monthly means from 1963 to 2003 (41 years), analyzed by the extended cosinor with nonlinear least squares, using 33.0 years as a trial period. By the criterion of a CI of the period overlapping the 30-40-year range and, if so, of a positive lower limit of the CI of the amplitude, 5 time series in the OMNI2 database qualify as compatible with a BEL cycle. Na/Np (alpha/proton ratio: http://nssdcftp.gsfc.nasa.gov/spacecraft_data/omni/omni2.text) also has a period of 36.84 years [29.97, 43.72]; 22 other variables converge to periods shorter than 30 years or longer than 40 years; 3 others do not reach statistical significance, and the remaining 10 do not converge, i.e., do not allow a period estimate with the trial period used. Zürich (Wolf) sunspot numbers for the span from 1745 to 2003 yield a period of 29.068 (27.92, 30.22) years.

**%M: percentage of MESOR

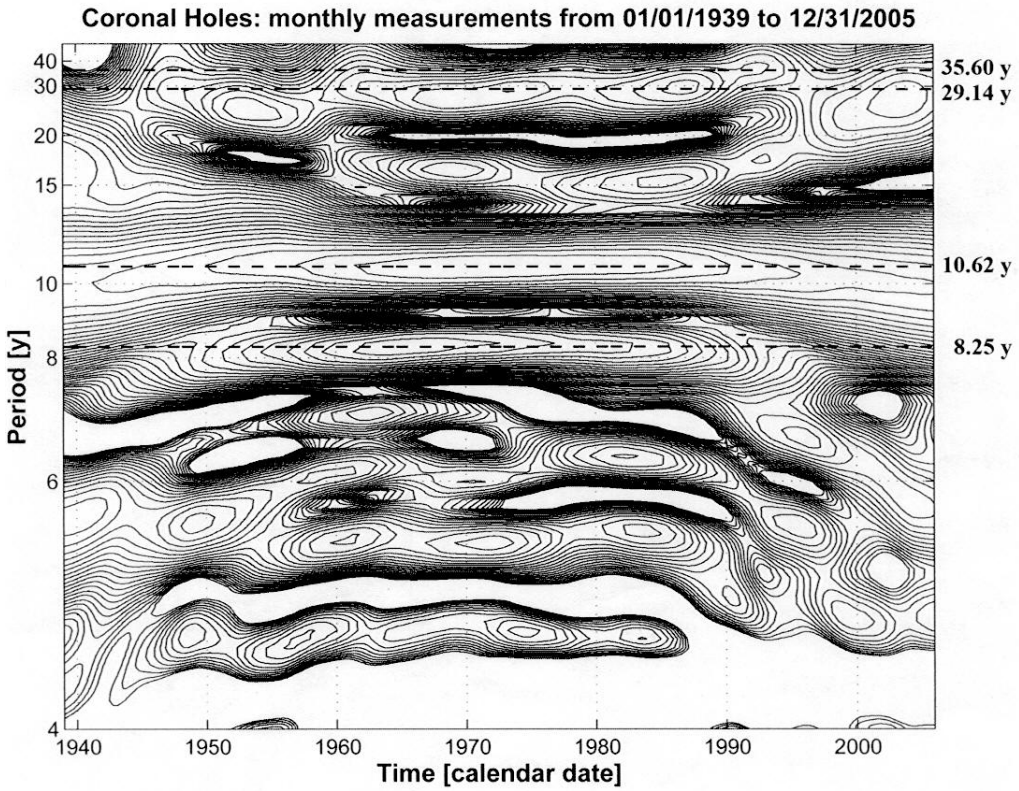
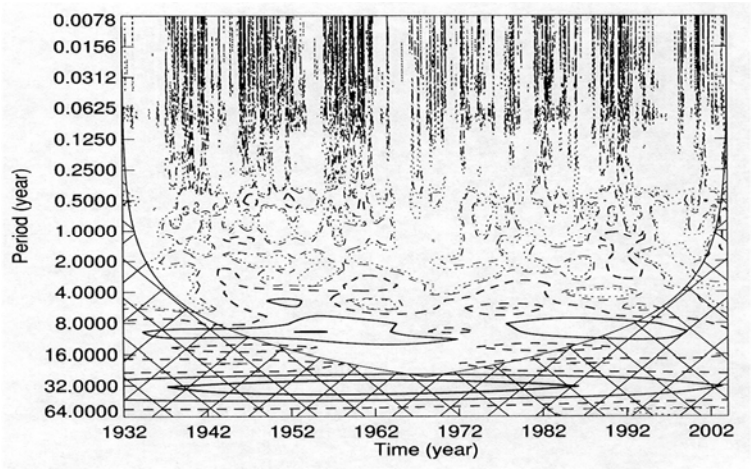


Figure 1. Spectrogram of coronal holes with calendar date on the abscissa and period in years on the ordinate reveal prominent, slightly longer than 10-year Schwabe cycles, other drifting components and a component around 29.14 years that for only a relatively short span, near the beginning of the last quarter of the display, shows a peak crossed by the upper horizontal line drawn at 35.6 years. © Halberg.

Note, at a 32-year trial period on the ordinate, a consistent spectral component in the geomagnetic index Ap (top) and an intermittent one in Zürich relative sunspot numbers (bottom)

Wavelet spectrum of geomagnetic disturbance



Wavelet spectrum of relative sunspot numbers, WN

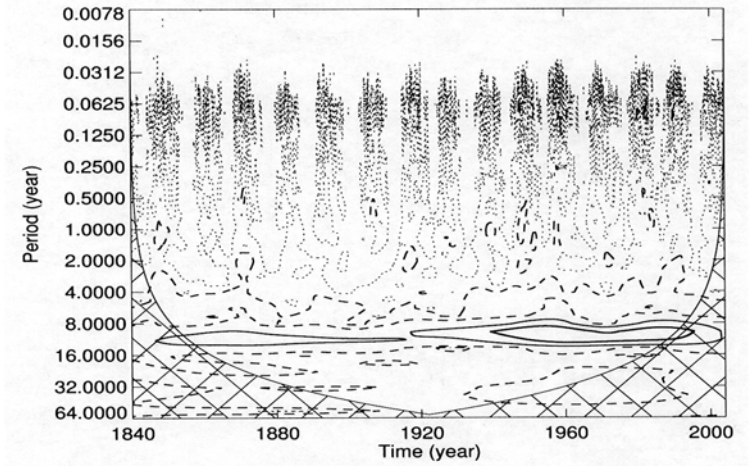


Figure 2: Top: Wavelet spectrum of the planetary geomagnetic index Ap, displaying the time course of this variable. Compared to other oscillations with a relatively short period, the semi-annual oscillation of the Ap index is very strong and is seen as a band present during most of the time, in keeping with results on the antipodal index aa in Figure 3. The strength of oscillations corresponding to about 1, 1.3, 3.3 and 5.5 years varies with time. The band in the 9- to 11-year range is very strong during the spans from 1934 to 1972 and from 1980 to 1996. Although the 33-year BEL-period is also strong, it is embedded in the cone of influence outside the paraboloidal curve.

Bottom: Wavelet spectrum of Zürich (Wolf) numbers showing a prominent about 11-year Schwabe cycle during 1850 to 2000, with maximal amplitude during 1944-1998, interrupted within the cone of resolution only during a minimum in that circadecadal cycle. The wavelet spectrum of Zürich numbers differs from the wavelet spectrum of Ap (top), also in keeping with the results of the extended cosinor. Solar effects may bring about the about 33-year variation by solar wind speed rather than by phenomena mediated by the number of sunspots. A transtridecadal period BEL cycle is intermittent in the wavelet spectrum of Zürich sunspot numbers.

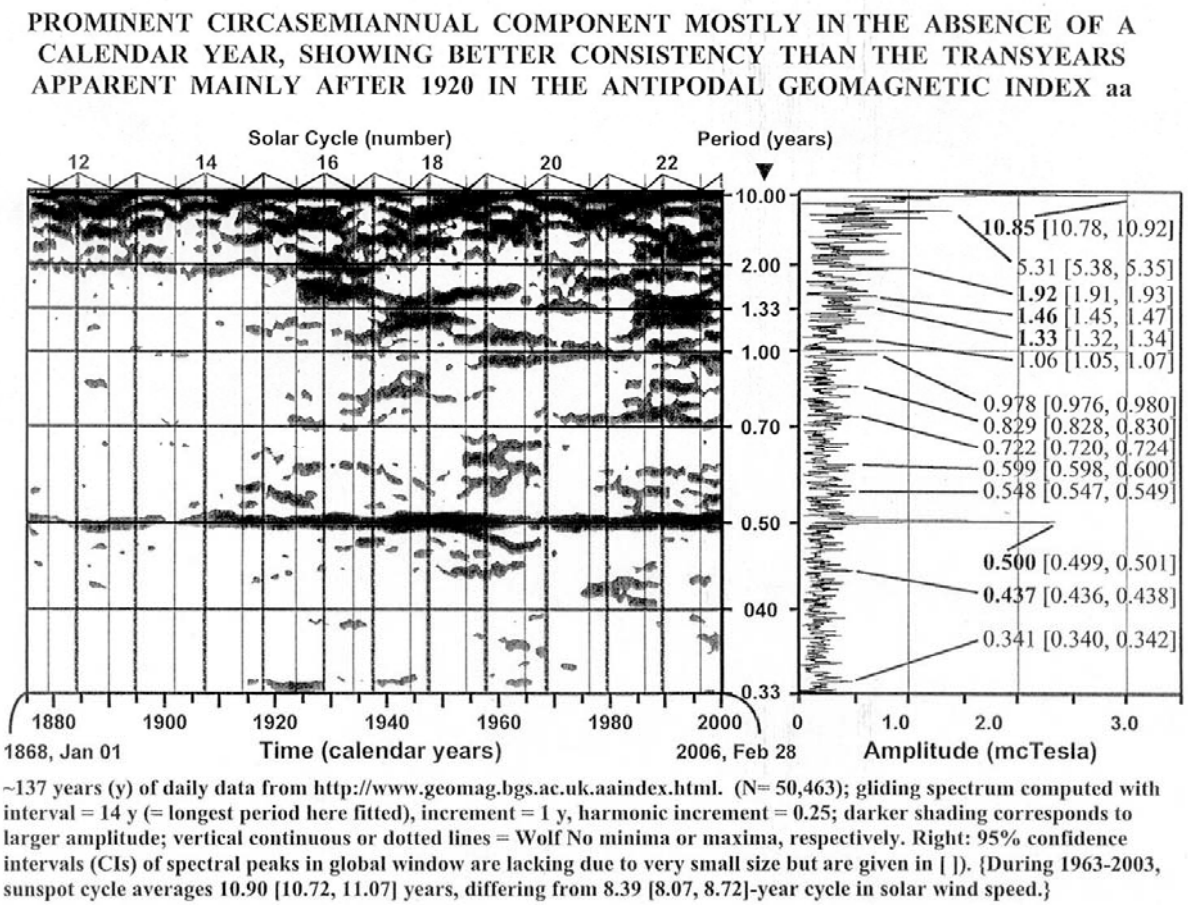


Figure 3. The merits of studying variation in time with the overall data summary, as done in Figure 2, are here implemented by a separate aligned gliding spectral window (left) and a global spectral window of the antipodal geomagnetic disturbance index aa. © Halberg.

Chronomics are thus in keeping with the assumption that a BEL cycle may originate in the interplanetary magnetic field (IMF), notably since it was not detected as a constant component with coronal holes, Figure 1. The solar wind may act directly and/or by displacing galactic cosmic rays and/or via terrestrial magnetism, as suggested by the finding of a BEL cycle in a planetary geomagnetic index, Kp, Table 1. The consequences of BEL may pertain to other aspects of the environment, such as temperature, in which a concomitant 35-year variation was consistently documented (31). While the periodicity of a "Brikner" or Brückner cycle was questioned (32, 33), the results in Table 1 are presented to add evidence concerning its degree of generality, with estimates of the uncertainty involved and a hint at a mechanism underlying the BEL's origins (as noted specifically in the solar wind that may act upon the biosphere directly and/or by the effect of displacing galactic cosmic rays and/or by affecting terrestrial magnetic disturbances).

Discussion. A presentation complementary to that in Table 1 is shown in a wavelet spectrum provided in Figure 2 for the geomagnetic activity index Ap (top), and for Zürich (Wolf) relative sunspot numbers (bottom). This wavelet approach has the advantage of resolving the time course of a spectral component, which more often than not varies by drifting and bifurcating in frequency and in amplitude by waxing and waning to the point of disappearing and reappearing, be it because the signal is lost or because it is too weak to emerge from the noise. In this figure, the power corresponding to each period indicates a strong time-dependence, including intermittency. The

thick contours plotted in this figure enclose regions of greater than 95% confidence for a red noise process. Also important is the cone of the influence region, delineated by a paraboloidal curve, where edge effects arising from truncation of the time series can be important. Hence the region external to this curve is considered with this qualification. In Figure 2 (top), a strong contour corresponding roughly to a 32-year variation is readily apparent, and is continuous, whereas Figure 2 (bottom) showing the wavelet spectrum of Zürich (Wolf's) relative sunspot numbers along a much longer abscissa (1840-2003) than that for Ap (1932-2003), the component corresponding to 32 years is clearly intermittent. This result can be aligned with extended cosinor analyses which did find the BEL cycle in a 40-year series during a relatively recent span, but did not detect an about 33-year variation in the Zürich numbers available to and interpreted by Brückner as not pertinent, or in a much longer series of Zürich numbers.

Thus, an about 33-year variation in sunspots is intermittent by cosinor and by a wavelet spectrum (Figure 2, bottom), but an exception is the span from 1967 to 2007, when it is demonstrable by cosinor with one of the models used, as a descriptor of the waveform and in that case, it had the smallest amplitude, Table 2. By contrast, during the same 40-year span, the circatridecadal component of heart rate of a clinically healthy man (RBS) had the largest amplitude in the infradian spectral region in the domain of years and decades. The related weak counterpart in Zürich (Wolf's) numbers to a relatively more prominent biospheric tridecadal component can perhaps be interpreted as indicating that a BEL cycle is genetically coded. Heliogeophysical cycles (in the solar wind and/or other aspects of the IMF, Table 1, or the length of the sunspot cycle) may have exhibited a transtridecadal cycle for billions of years. This renders it likely that the tridecadal component in human heart rate is coded in genes, and a remove-and-replace approach (8, 34, 35) can help clarify this problem.

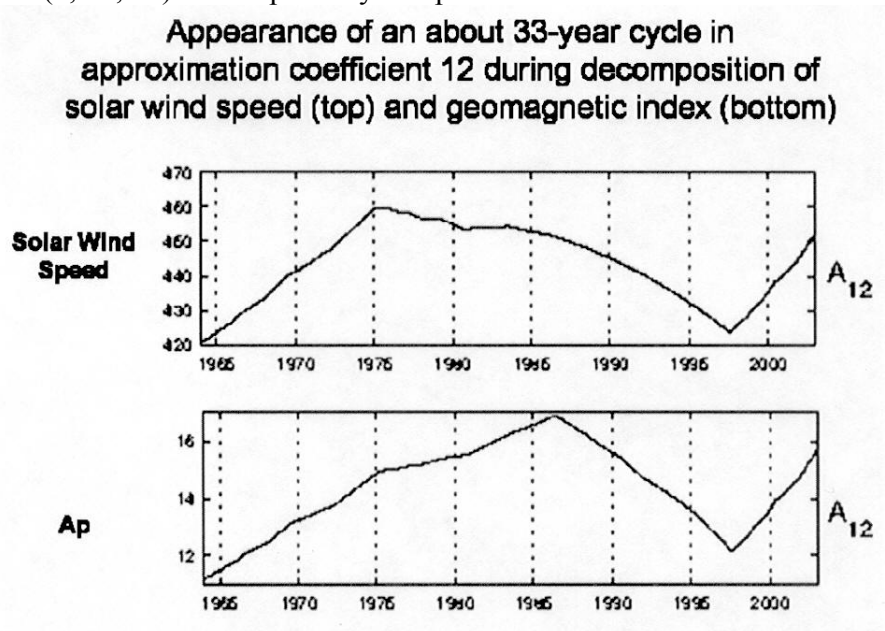


Figure 4. Similar cycle lengths characterize solar wind speed and geomagnetism, yet the lengths of the ascending versus the descending stages differ in the same Schwabe cycle. Partial results from wavelet decomposition using Daubechies wavelets.

Table 2: Periods and their uncertainties in Zürich (Wolf) numbers¶

Variable (units)	MESOR (units)*	Period (y) [CI]	Amplitude [CI]	Acrophase (°) [CI]*	Congruences
ENVIRONMENT					
Schwabe value, S (Wolf numbers [WN], count)	72.74 [69.96, 75.83]	32.82 [23.40, 42.16]**	13.91 [9.45, 18.37]	-218 [-199, -238]	S1
		10.56 [10.34, 10.78]	65.08 [59.28; 70.89]	-217 [-213, -221]	S2
		8.02 [7.52, 8.52]	16.83 [11.34, 22.32]	-83 [-68, -98]	

¶ Components fitted concomitantly: CIs (95% confidence intervals) in [ ].
*MESOR = midline-estimating statistic of rhythm; 1 cycle = 360°.
**This component, validated by two separate programs as descriptor of the waveform in the particular 3-component model used, was not detected with statistical significance when the shorter-than-10-year component was omitted, or when Zürich numbers over spans longer than the one considered herein were similarly analyzed.

Since Figure 2 (top) shows an about 33-year variation in geomagnetic activity, documented in Table 1 only globally, without depicting its time course, it strengthens an inquiry into the origin of the BEL cycle in space weather. Table 1 reveals a congruent period for solar wind speed (SWS) and Kp, suggesting, as wavelet analyses do (27) that the solar wind and/or the broader interplanetary magnetic field and/or galactic cosmic rays, may all be considered as possibly underlying the BEL cycle, which all methods used validate as a transdisciplinary entity. In Brückner's original data, it is an aeolian, nonstationary entity (31).

Figure 4 bears upon another aspect of the extent of agreement between solar wind speed (SWS) and geomagnetics gauged by Ap (27). The daily average values of solar wind speed and the Ap index during the span from 1964-2003 were subjected to wavelet decomposition using Daubechies wavelet ('db3' from the wavelet tool kit of MATLAB for 12 levels of successive approximations and details). The circatranstridecadal periods seem to be the same, but an asymmetry suggests that the effect in SWS persists in Ap while the strength of SWS starts declining. The coefficients obtained on reconstruction, plotted against time to identify various oscillations present (not shown) include a circatranstridecadal cycle demonstrated for SWS and geomagnetics (Ap), Figure 4. The two variables have a common time domain insofar as the cycles' length is very similar. SWS, however, has a faster (shorter) ascending stage and a slower (longer) descending stage while the opposite holds true for Ap, Figure 4.

Figure 3 is of methodological interest, showing for a limited spectral window the merit of complementing a global summary of periods with CIs (right) with a gliding least-squares spectrum, an approach applicable to non-equidistant data, with the qualification that long gaps could create artifacts. Figure 1 shows a spectrogram of (equidistant) data on coronal holes for which a 35.6-year period had been reported but could not be confirmed by cosinor. It is readily apparent that a peak in that spectral region occurs only during the beginning of the last fourth of the graph and is short-lived, and that the main periods in this variable are in the region of trial periods shorter than 30 years and are not likely to account for a BEL cycle. Of historic interest, however, is a 33-year peak reported by Samuel M. Silverman (36) and by Clough (37) who in 1933 wrote about the BEL cycle in the frequency of aurorae, Nile floods, Arizona pine growth and wheat prices.

It will be desirable in the future to fit multiple cosine models to the now longer time series that have accumulated since Egeson's, Brückner's and the Lockyers' time, e.g., on rainfall and temperature and accordingly, to stack data for the cycle lengths found as plexograms for an analysis of variance, and to compare waveforms in this way and/or by Daubechies wavelets (Figure 4). Brückner's terrestrial variables and other biospheric data may or may not reveal an asymmetry of their stages, but if they did so, their resembling the SWS pattern may suggest that the effect of the SWS is direct or vice versa, if the pattern had a slow ascending and a faster descending stage, terrestrial magnetic disturbance may be the proximate cause of other environmental (temperature, rainfall) or biospheric (human heart rate) BEL cycles. Any pattern of geomagnetics should be best gauged by the longer (than Ap) antipodal aa series to explore any direct effect of terrestrial magnetism, tasks for the future. In the interim, it can be noted that by the criterion of congruence, some components in biospheric variables have overlapping or overlying CIs of their periods corresponding to those of geomagnetics; others are congruent with periods of the solar wind, and fewer biospheric periods are congruent with both helio- and geomagnetics. Beyond the criterion of congruence, a remove-and-replace approach (8, 34, 35) to the time courses of possibly interacting variables is highly desirable and awaits implementation, the sun willing, since this entity does the removal and replacement or at least the addition and subtraction, i.e., the waxing and waning of amplitudes.

Brückner preceded Chizhevsky in recognizing the broad impact of cosmos-related climate change. Chizhevsky in turn assembled, among many others, data on "universal human military-political activity" from 1748 until 1922 (38). Our meta-analysis by an extended cosinor of data from Chizhevsky's graph, taken off a curve (at guesstimates of the intervals used), yields mostly an anticipated number of previously reported components in solar variability. The major component in the decadal/multidecadal range is a Schwabe cycle of about 10.1 years accounting for about 13.2% of the total variance. The corresponding percentage rhythm (PR) contributed by a Gleissberg cycle of about 77.3 years is 9.1%. There is also a global cycle contribution with a period of about 17.7 years, with a PR of 8.2% and an unaccounted-for neighboring spectral peak at about 14.4 years with a PR of 7.2%. The Hale cycle component of about 22.5 years accounts for 5.4% of the variance. A further period of about 30.74 (95% CI: 27.53, 33.95) years with a PR of 5.1% provides another hint of the broad (here including military and political) importance of the BEL cycle, among other related consequences of weather in extraterrestrial space in human affairs, in violence (39-42) and in war as well as peace, beyond "any change from wet and cold to dry and warm climates", that according to Brückner determined immigration from Europe to the USA and the westward migration within the USA (43). The topic of secular periods of solar activity and synchronous variation in terrestrial phenomena, reviewed by H.W. Clough in 1933 (37), can also be extended to include the biosphere. It is hardly surprising to find that the BEL cycle is a prominent component, second only to the Schwabe cycle in the spectrum of the aurora (36).

Conclusion. The BEL transtridecadal cycle characterizes the proton temperature and the speed of the solar wind, among other aspects of heliogeomagnetics. The interplanetary magnetic field may contribute one of the aeolian nonstationary origins of terrestrial BEL cycles, to be aligned with the many other nonphotic as well as photic cyclic aspects of the variable sun, in whose atmosphere we reside (44), and its broader cosmos.

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BODY MASS INDEX (BMI), PULSE PRESSURE (PP) AND PREMETABOLIC SYNDROME

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Aim. To complement the detection of pre-hypertension (1, 2) and pre-diabetes (3, 4) with chronobiologically interpreted ambulatory blood pressure (BP) and heart rate (HR) monitoring by focus with the same approach upon obesity.

Background. On 140 clinically healthy adults, Abramson et al. (5) reported a positive association of markers of inflammation and BP variability. In a slightly extended subject population, the MESOR of HR and the pulse pressure (PP) were found to be positively associated with C-reactive protein (CRP) (6). Vascular variability disorders (VVDs) (7), such as CHAT (Circadian Hyper-Amplitude-Tension, a condition characterized by an excessive circadian BP variation), were also detected in this population of clinically healthy subjects (6).

Method. The data from Abramson et al. (5, 6) are reanalyzed herein with another smaller sample of clinically healthy immigrants from Silicon Valley (8) to examine any relation to BMI of PP and markers of inflammation.

Results. Figure 1 shows an association of PP with BMI ($r=0.418$, $P<0.001$) which holds separately for subjects with BMIs below and above 30 kg/m^2, as seen in Figure 2. A similar relation is found for men and for women in the USA, but only for women in 7-day records from the Czech Republic. Figures 3 and 4 show some association with BMI of CRP ($r=0.431$, $P<0.001$) and tumor necrosis factor ($r=0.164$, $P<0.042$). Figure 5 is in keeping with the assumption that inflammation, gauged by CRP, relates to PP ($r=0.296$, $P < 0.001$). We had earlier found in young

healthy individuals that an increased BMI is associated with a lower double amplitude of systolic and diastolic blood pressure (8).

Discussion. All of the correlation coefficients reported herein are below 0.5, and there are discrepancies in that a gender difference seen in less unreliable 7-day records from the Czech Republic is not reproduced in the less reliable 24-hour profiles from the USA. That profiles for 2, 3 and 4 days scan fail when longer series separate severe or early outcomes from health has been reported earlier (4, 9).

The US sample allowed a check on ethnic differences that were not found in the limited available sample. The gender difference found in Europeans in Europe, but not in "white" Americans, remains a puzzle. The data suffice, however, to suggest that prospective studies are warranted to investigate, notably in schools, any associations of VVDs, such as an elevated PP, with other aspects of physiology and pathology, notably obesity (10), so as to institute timely preventive treatment.

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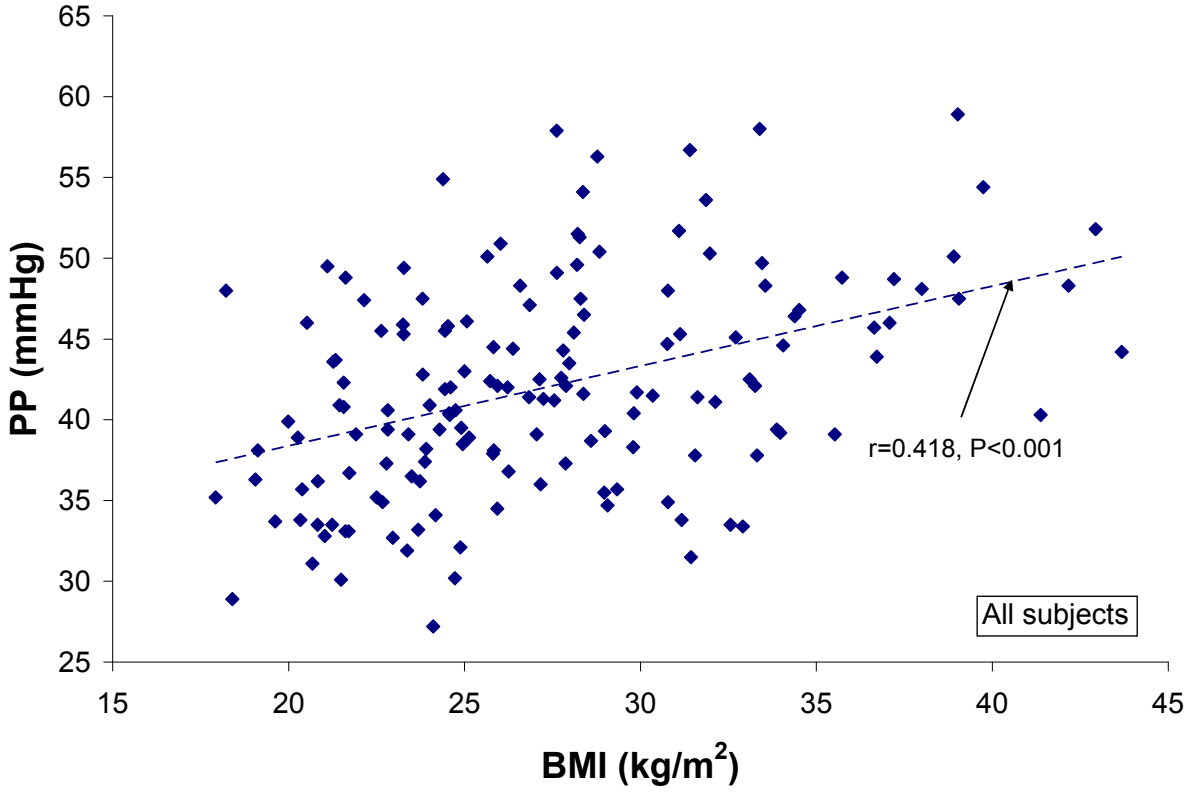
65
60
55
50
45
40
35
30
25
PP (mmHg)
15
20
25
30
35
40
45
BMI (kg/m2)
r=0.418, P<0.001
All subjects

Figure 1

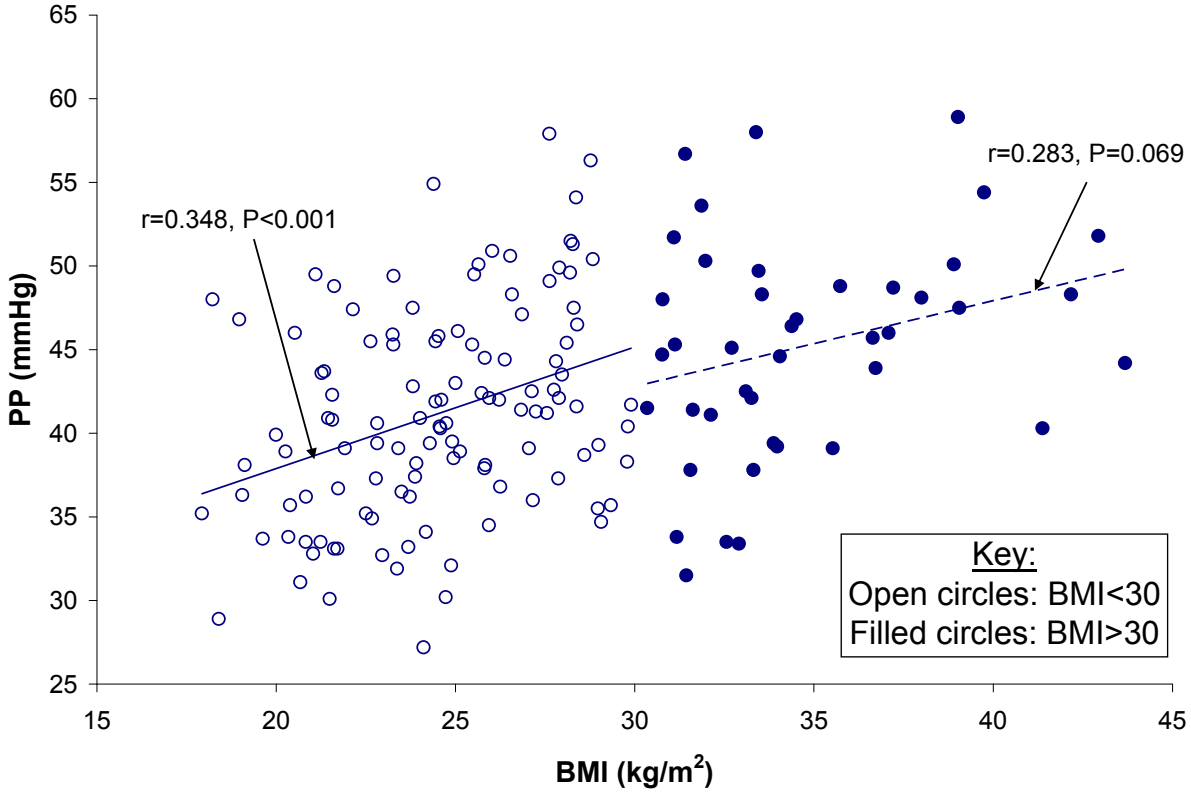
65
60
55
50
45
40
35
30
25
15
20
25
30
35
40
45
PP (mmHg)
BMI (kg/m2)
r=0.348, P<0.001
r=0.283, P=0.069
Key:
Open circles: BMI<30
Filled circles: BMI>30

Figure 2

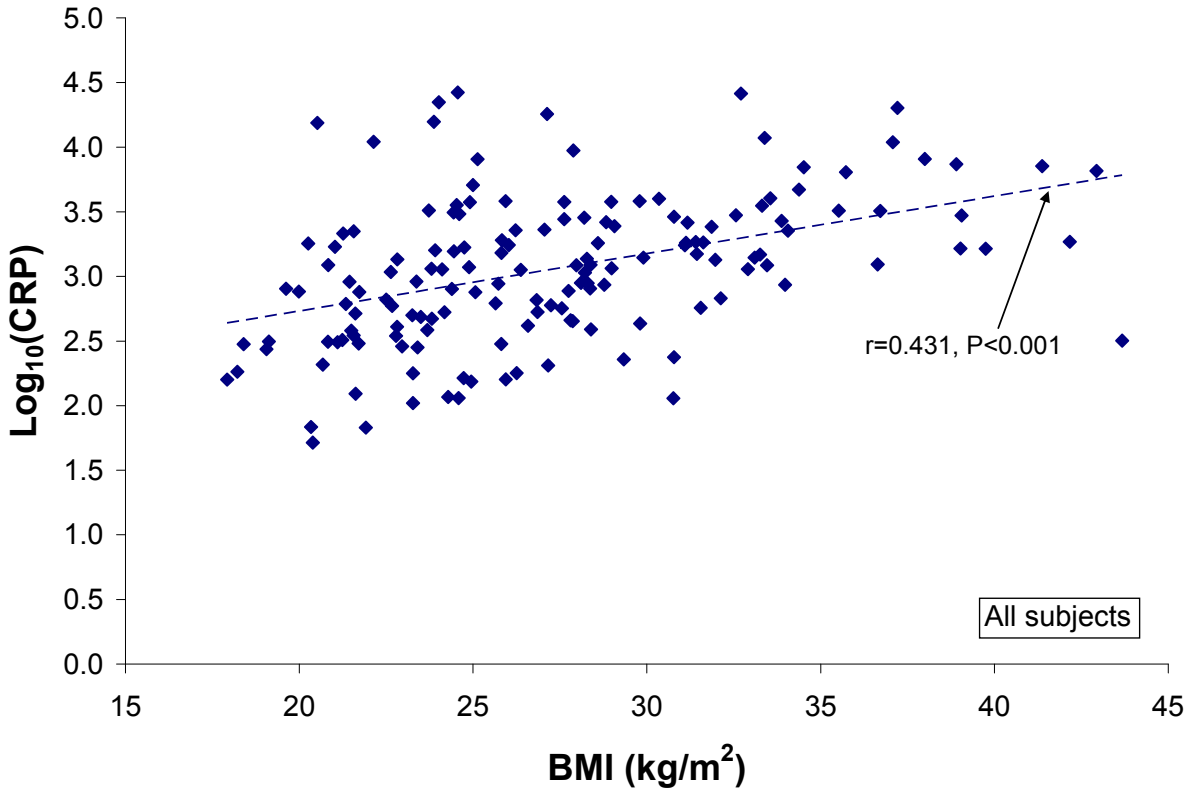
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Log10(CRP)
15
20
25
30
35
40
45
BMI (kg/m2)
r=0.431, P<0.001
All subjects

Figure 3

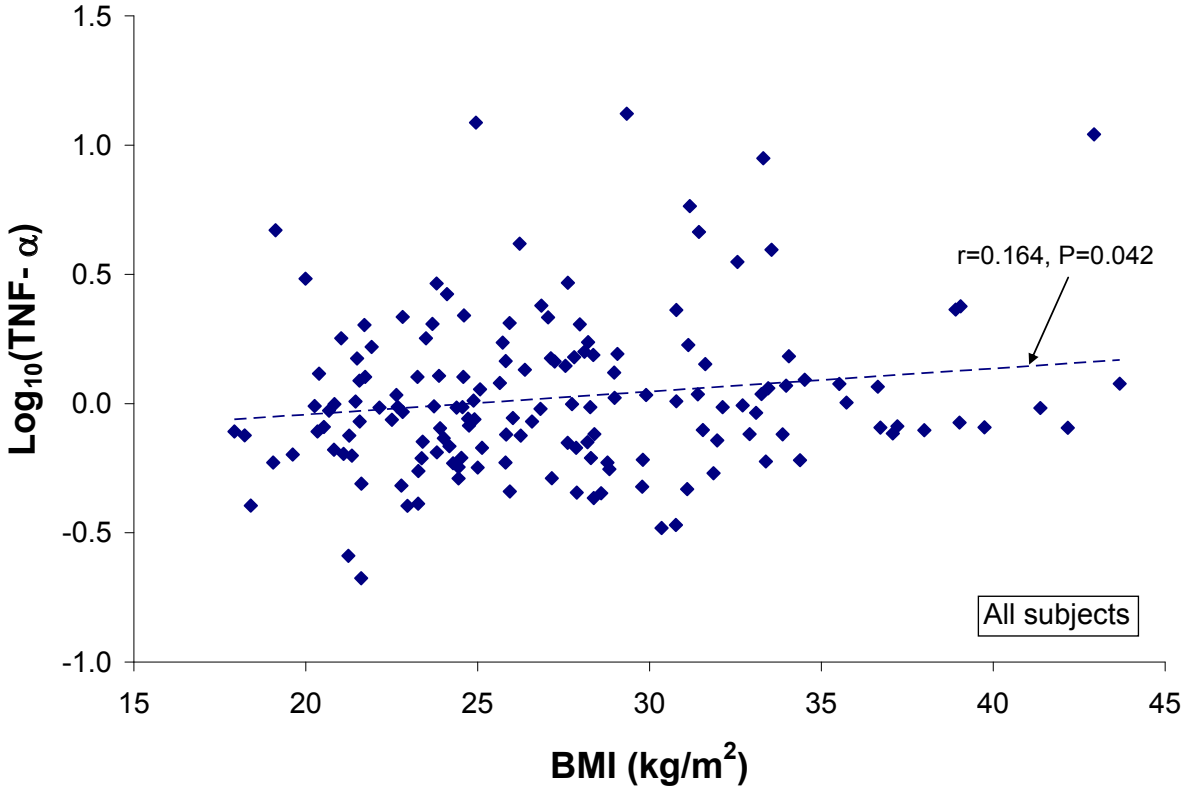
1.5
1.0
0.5
0.0
-0.5
-1.0
15
20
25
30
35
40
45
Log10(TNF- α)
BMI (kg/m2)
r=0.164, P=0.042
All subjects

Figure 4

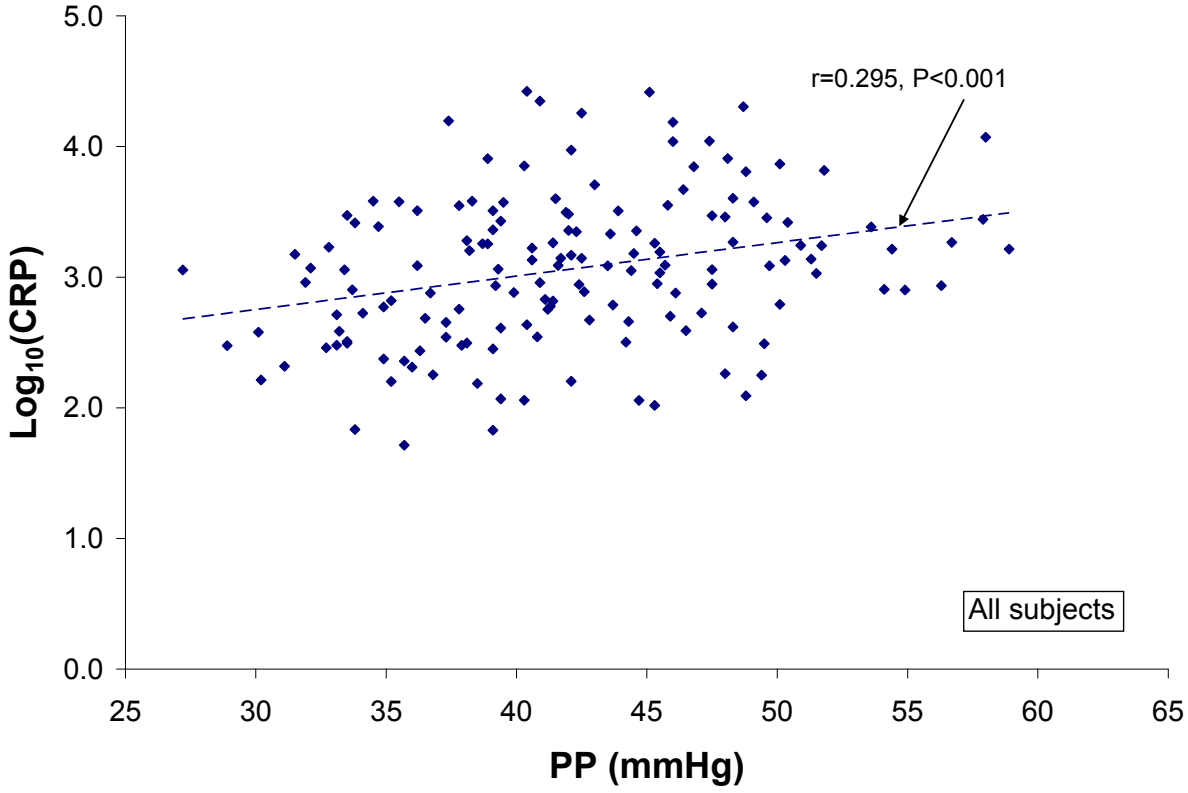
r=0.295, P<0.001
All subjects
Log10(CRP)
PP (mmHg)
5.0
4.0
3.0
2.0
1.0
0.0
25
30
35
40
45
50
55
60
65

Figure 5

Auroral aeolian periodicity during 1545-1724, including the Maunder minimum

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Abstract. Myocardial infarctions increase in frequency in association with a magnetic storm (1-3), as does the aurora. Geomagnetic disturbances are accompanied by a decrease in heart rate variability (4-6). We here assess cyclicity, with its uncertainties when possible, in the incidence of aurorae in the 16th, 17th and earliest 18th centuries (1545-1724) in central Europe, with focus upon the Maunder minimum (from 1645 to 1715). During the second, but not the first half of this span, 95% confidence limits could be and were computed for each parameter separately, albeit not conservatively, for a persisting circadecadal component, using the 1-parameter approach of Marquardt's nonlinear algorithm (7).

Background. The yearly incidence of aurorae during the span 1545-1724 compiled by Wilfried Schröder and Hans-Jürgen Treder (8) was analyzed by linear-nonlinear rhythmometry with the extended cosinor (9-11; cf. 7). A global least-squares spectrum reveals several peaks, among which one corresponding to about 11.4 years is not the most prominent. Of similar or larger prominence are other peaks corresponding to periods of about 139-150, 72, 47, 29, and 23.4 years, the latter close to a peak of about 22 years previously reported by Usoskin, Mursula and Kovaltsov for sunspot activity (12-14), and of about 18.8, 12.7, 8.3, and 7.4 years, as well as to periods shorter than 6 years, beyond our scope herein.

Methods. The question investigated is whether any relative prominence of an about 11-year cycle, as reflected in observations of the northern lights, as an (only approximate) proxy for sunspots, was present during the Maunder minimum (from 1645 to 1715) and, if so, whether any of its characteristics were altered (8, 15, 16). Least squares spectra were computed from 35-year intervals (corresponding roughly to the Brückner-Egeson-Lockyer cycle) pergressively moved by increments of 5 years throughout the time series, the first interval spanning the years 1545-1579 and the last one spanning the years 1690-1724 (30 intervals, among which 8 occurred during the Maunder minimum and 14 did not even partially cover the Maunder minimum). The trial periods varied between 35 and 3.5 years, in harmonic progression with a harmonic increment of 0.2.

For each interval, results at a trial period of 10.5 years (anticipated best fitting period for Zürich numbers (also called Wolf numbers, after Rudolf Wolf; available only after 1700) were considered, namely the percentage rhythm (PR, i.e., the proportion of variance accounted for by the fitted 10.5-year cosine model), the MESOR (M, midline estimating statistic of rhythm), amplitude (A, half the extent of predictable change within one cycle), and relative amplitude (expressed as % of MESOR). The period of the component accounting for the highest variance among the trial periods in the least-squares spectra was determined for each interval, together with its PR.

Using a trial period of 11 years, nonlinear analyses also determined the best-fitting period with a measure of its uncertainty and that of its corresponding A, using Marquardt's algorithm (7). 95% confidence intervals were determined as 1-parameter limits and as conservative limits (estimated jointly for all parameters).

Results. Results from both approaches are summarized in Table 1. The different endpoints from linear rhythmometry were compared by Student t-test between intervals prior to (outside) or during the Maunder minimum. Results need to be qualified by the fact that intervals were overlapping, thereby failing to respect the assumption of independence.

Table 1: Circadecadal point estimates of auroral cycles' incidence before and during the Maunder minimum*, with uncertainties**

Interval Start	End	Period, τ (years)	1-parameter** (95% CI of τ)		Amplitude, A (N/y)	(Conservative** 95% CI of A)		(1-parameter** 95% CI of A)	
1545	1579	9.92	(8.09,	11.75)	1.72	(-0.40,	3.84)	(0.41,	3.03)
1550	1584	9.18	(7.89,	10.46)	2.54	(0.06,	5.01)	(1.00,	4.07)
1555	1589	9.36	(8.23,	10.49)	2.42	(0.19,	4.65)	(1.04,	3.81)
1560	1594	8.28	(7.13,	9.44)	2.14	(0.13,	4.16)	(0.89,	3.40)
1565	1599	9.54	(8.47,	10.61)	2.70	(0.62,	4.79)	(1.41,	4.00)
1570	1604	10.79	(8.23,	13.36)	2.05	(-0.30,	4.39)	(0.59,	3.50)
1575	1609	11.07	(8.76,	13.38)	2.03	(0.06,	4.00)	(0.80,	3.26)
1580	1614	11.57	(9.59,	13.55)	2.23	(0.14,	4.32)	(0.93,	3.53)
1585	1619	14.85	(11.15,	18.56)	1.39	(-0.18,	2.96)	(0.42,	2.36)
1590	1624	10.66	(8.01,	13.31)	1.26	(-0.63,	3.15)	(0.09,	2.43)
1595	1629	11.22	(8.03,	14.41)	1.31	NS			
1600	1634	12.34	(6.79,	17.89)	1.01	NS			
1605	1639	9.06	(5.51,	12.60)	0.83	NS			
1610	1644	11.02	(0.62,	21.42)	0.50	NS			
1615	1649	9.50	(4.81,	14.20)	0.75	NS			
1620	1654	NS							
1625	1659	12.00	(6.16,	17.85)	0.81	NS			
1630	1664	11.02	(5.40,	16.65)	0.67	NS			
1635	1669	12.11	(7.95,	16.27)	0.64	NS			
1640	1674	17.22	(7.85,	26.59)	0.59	NS			
1645	1679	7.40	(5.51,	9.29)	0.51	NS			
1650	1684	9.15	(7.02,	11.27)	0.63	NS			
1655	1689	10.24	(5.95,	14.53)	0.45	NS			
1660	1694	10.66	(6.89,	14.44)	0.57	NS			
1665	1699	9.91	(5.10,	14.72)	0.38	NS			
1670	1704	12.71	(9.18,	16.24)	0.77	(-0.44,	1.99)	(0.02,	1.53)
1675	1709	11.95	(8.42,	15.49)	1.42	(-0.85,	3.69)	(0.00,	2.83)
1680	1714	12.04	(8.51,	15.56)	1.65	(-0.87,	4.17)	(0.08,	3.21)
1685	1719	11.35	(9.11,	13.60)	2.99	(-0.59,	6.57)	(0.77,	5.21)
1690	1724	13.10	(9.30,	16.91)	2.72	NS			

*Trial period: 11 years; Interval: 35 years; Increment: 5 years; NS: not statistically significant. Note that the last three spans during the Maunder minimum allow assessment of the uncertainty of the period estimate by a 95% confidence interval of the amplitude which does not overlap zero (last 3 columns).

**One-parameter and conservative limits were computed according to Marquardt's algorithm (7).

Whether intervals only partially covering the Maunder minimum are included or excluded in the comparison, Student-t tests show that, as expected, the Maunder minimum is associated with a smaller PR at a trial period of 10.5 years, and that both the MESOR and amplitude are smaller, Table 2. Of interest, however, is the observation that there is no statistically significant difference in the relative amplitude (underlined), Table 2. Moreover, among the trial periods in the least-squares spectra, the period of the component contributing most to the overall variance is shorter during the Maunder minimum, Table 2. This is best seen for the frequency (1/period), which follows a uniform distribution, whereas that of the period is long-tailed, Table 2. The difference in PR at the best-fitting period between intervals prior to or during the Maunder minimum is much smaller than that at the fixed 10.5-year period. Whereas the difference remains statistically significant when intervals partially covering the Maunder minimum are excluded, it is not statistically significant when all intervals are included, Table 2. Best-fitting periods corresponding to the longest or shortest trial periods were excluded, as they indicated that a maximum could not be reached within the window investigated.

Table 2: Comparison of results from linear rhythmometry *outside* and *during* the span from 1645-1715, the Maunder minimum*

	Intervals compared							
	All intervals (20 vs. 8)				Interval overlapping 1645-1715 excluded (14 vs. 8)			
	Means		Student t	P	Means		Student t	P
Endpoint	Outside	During			Outside	During		
At trial period of 10.5 years								
PR	11.5	5.3	1.767	0.088	15.1	5.3	2.857	0.010
M	3.37	1.93	6.495	<0.001	3.57	1.93	9.378	<0.001
A	1.17	0.58	2.150	0.040	1.37	0.58	3.284	0.004
A/M(%)	34.3	29.4	0.563	0.578	37.9	29.4	1.250	0.226
At trial period accounting for largest variance in least-squares spectra								
Period (years)	13.6	6.51	2.046	0.051	15.2	6.51	2.571	0.018
Frequency (1/period)	0.112	0.198	-2.958	0.007	0.088	0.198	-4.495	<0.001
PR	27.7	23.6	1.487	0.149	30.6	23.6	2.964	0.008

*PR: Percentage Rhythm (proportion of variance accounted for by fitted model; %); M: MESOR (**m**idline-**e**stimating **s**tatistic **o**f **r**hythm; rhythm-adjusted mean); A: Amplitude: measure of half of extent of predictable change within one cycle; M and A expressed as N of aurorae/year.

Discussion and Conclusion. By the criterion of Marquardt's 1-parameter 95% confidence interval, the persistence of cycles during the second half of the Maunder minimum is documented with the uncertainties involved, whereas only point estimates of the amplitude could be computed during the first half of the Maunder minimum (cf. also 15). The results in Table 1, insofar as they lend themselves as a proxy, must be viewed in the light of observation on sunspot activity reporting that the change in the Maunder minimum was abrupt (12-14). Abruptness is indeed suggested by our failure to compute a 95% confidence interval for the period around the start of the Maunder minimum (1620-1654 interval). The loss of statistical significance for a Schwabe cycle, gauged by the overlap of zero by the 95% confidence interval for the amplitude, however, starts with the 1595-1629 interval, preceding the Maunder minimum. The aurorae, just like geomagnetic fluctuations, may not necessarily be the best proxy for sunspot activity, but may be a sensitive proxy. Other approaches based on sunspots are pertinent (12-14) and their report of an abrupt change in the Maunder minimum is here confirmed, notwithstanding the prior loss of statistical significance here reported before 1645, actually during a span including the Thirty Years

War, which devastated central Europe and thus did not allow for many observations. It would be interesting to scrutinize any records of cardiovascular and other disease during vs. before and after the Maunder minimum as another proxy for solar effects in the biosphere (17, 18).

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On Gaps and Interpolation Methods to Avoid Errors in Period Estimation with Conventional Time Series Analysis

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Abstract

While methods for time series analysis have been developed to deal with missing values in equidistant time series and/or in altogether non-equidistant data, commonly available software usually assumes data to be sampled at equal intervals. In the presence of gaps, data are sometimes compressed to eliminate the gaps without adjusting the time scale. This procedure leads to errors in period estimates and alterations of the actual frequency/time structure in spectrograms. An obvious example consisting of a 7-day record of systolic blood pressure was simulated. Gaps of 6 hours on 6 instances randomly distributed over the 7 days were introduced and the resulting data analyzed in various ways. Several methods of interpolation are considered to fill gaps, so that programs applicable only to equidistant data can be used. Results from a linear prediction by singular value decomposition (LP-SVD) are presented, showing how in the selected case, it can restore the actual time structure in conventional spectrograms. These results are compared with those of least squares spectra and chronobiological serial sections that are readily applicable to non-equidistant data.

Introduction

Spectrograms depict the time-frequency dependence of analyzed signals. Under usual conditions, the locations of peaks correspond to frequencies present in the signal at given instants in time. Unfortunately, input signals often present deficiencies, mostly associated with a transitory absence of measurements (such as interruptions of self-measurements during sleep). These gaps sometimes appear frequently for short time spans, or they can last for longer spans on fewer occasions, for instance in association with instrument failure. When gaps are ignored by compressing the data, the actual frequency/time structure is altered, leading to erroneous period estimates. Some peaks shift in the frequency domain, some may be lost and others may be spuriously generated. This leads to important errors in period estimations.

Accordingly, an analysis of data with gaps is far from straightforward. Least squares spectra can bridge a few missing values, but as the gaps widen, there comes a point when artifacts predominate because of insufficient information. As long as critical information is not lost, interpolation methods may also be used to fill the gaps, thus allowing the data to be analyzed by a large selection of conventionally available methods of time series analysis. In general, discontinuous data produce spectra with parasitic oscillations of the sin(x)/x type, whose amplitudes may be important enough to render any analysis useless. On the other hand, simple interpolation schemes may fail to represent the characteristics of the signal. Instead, we have opted for a variant of a linear prediction approach.

Interpolation methods

A number of methods permit the estimation of missing parts of a signal. Their common characteristic is the analysis of the available signal to extract a set of coefficients, which best describe the mutual interdependence of the measured points (in the least-squared sense). These so-called auto-regressive techniques lead to several common algorithms, depending mostly on the definition of the target error function, which is to be minimized. First, we have tried the auto-correlation method [1]. It has the advantage of producing stable solutions, but makes an assumption that the signal is zero outside the analyzed interval, and may produce important undesirable end-point effects. Another formulation of this approach is the auto-covariance method [2, 3], which works on signals extending beyond the analyzed intervals, but whose solutions are not guaranteed to be stable. Indeed, in some cases our solutions were unacceptable, because of large deviations of the predicted points from the general trends of the analyzed signals. Another approach is the Burg's algorithm [2, 4], which appeared in the context of maximum entropy methods. It is stable and takes into account both forward and backward prediction, but is known for introducing bias in frequency estimation and for splitting peaks into several components, particularly for higher-order estimations. Thus far, the best results have been obtained with the LP-SVD (linear prediction by singular value decomposition) method [5]. This technique is robust and worked well in all cases for which we have conducted tests.

In order to obtain a set of predicted points as close as possible to the signal from which they are derived, we have adopted the following procedure. For each gap in the input data we analyze two sets of points: the one directly preceding it and that which follows the gap. For the first set we apply the LP-SVD method to calculate a forward prediction, covering the gap. Next, we calculate the backward prediction for the second set of points. Ideally, they should produce two identical sets of predictions. In practice, however, this is not the case. It is due to noise inherent in the data, as well as to the finite length of the two data sets from which predictions are obtained. Then, we combine the two predicted sets of points, by computing a weighted average, based on the assumption that the further we stray from the end of valid data (i.e. to the right from the end of the first data set and to the left from the beginning of the second data set), the lower the probability that the prediction is correct. The end result is substituted back to the original time series, and it is this full signal which is further transformed into a spectrogram.

Illustrative example

An example of the application of this approach is given in Figures 1-6. While the selected illustrative example may appear obvious to some, it was purposely chosen to unmistakably show that data compression, occasionally misused by some investigators, is not an option when the time structure of a phenomenon needs to be assessed. Fig. 1 (top left) shows the original data, a synthetic signal with noise, consisting of 168 points, representing a signal with a period of 24 hours, sampled once an hour for seven consecutive days. The simulated signal has a mean value of 120 mmHg, a circadian amplitude of 20 mmHg and an acrophase of -270° (18:00). Noise consists of uniformly distributed random numbers in the range of -5 to +5 mmHg. Data were removed over 6 intervals, each covering 6 hours. Fig. 1 (middle left) shows the series with gaps. Fig. 1 (bottom left) shows the series resulting from considering all available data as being continuous, as if there were no gaps, an approach that is tempting but intuitively unreasonable. Fig. 1 (right) illustrates the corresponding least squares spectra. A spectral peak at 24 hours is readily apparent for the original series (top right). Very similar results are obtained for the series with gaps, the only difference being a slightly higher noise level that in some cases could be misinterpreted as small peaks (middle right). A clear shift in frequency occurs, however, when gaps are ignored and data are considered to be continuous (bottom right), validating the

prediction from intuition. Indeed, instead of having 7 peaks in 168 hours, corresponding to a period of 168/7 = 24 hours, the compressed series consists of 7 peaks in 168 – 6x6 = 132 hours, corresponding to a period of 132/7 = 18.9 hours.

Fig. 2 is obtained by fitting a 24-hour cosine curve by least squares to data in a 24-hour interval displaced throughout the time series by 1 hour. This procedure is known as a chronobiologic (or chronomic) serial section based on the least squares fit of cosine function(s) [6-8]. The data from Fig. 1 are shown again in the top row. In the second row, the lower curve represents the MESOR (midline estimating statistic of rhythm, a rhythm-adjusted mean value), and the distance between the two curves corresponds to the 24-hour amplitude of the signal, plotted at the midpoint of the 24-hour interval considered for analysis. The 24-hour acrophase (phase of the maximum) is plotted in the third row. The P-value from the zero-amplitude (no-rhythm) test is shown in the fourth row and the number of data per interval is plotted in the fifth row. It can be seen that for the original data series (left), the number of data is constant, that the MESOR, 24-hour amplitude and acrophase assume similar values throughout the time series, and that the circadian rhythm is invariably statistically significant. In the presence of gaps (middle), the number of data per interval changes as a function of time, but affects only slightly the estimates of the MESOR and 24-hour amplitude and acrophase, statistical significance being invariably reached as well. But when the data are compressed by ignoring the gaps (right), large variations in the MESOR and 24-hour amplitude are observed as a function of time, and the 24-hour acrophase is steadily drifting to earlier and earlier times, in keeping with the shift to a higher frequency (or shorter period), as seen in the least squares spectrum (Fig. 1, bottom right).

Fig.3 shows the spectrogram of the original data without gaps. Basically, spectrograms are Fourier transforms of a product of original data and a window function, which moves in time. The window length is adjustable and affects the time and frequency resolutions. Herein, the frequency resolution was maximized by setting the window length to the number of data N (N/2 at both ends of the time series). In the LP-SVD algorithm, 1/3 of the number of points used to predict data was used as number of coefficients.

In Fig. 3, the dashed black horizontal line marks the 24-hour “target” period. Fig. 4 shows the same spectrogram, obtained on data with 6 gaps, eliminated by compressing the remaining data points. One can see a large shift in frequency, appearing now at 19.25 hours. An attempt to obtain a spectrogram from a fragment of data, consisting of continuously sampled points, for a short time between gaps, leads to Fig. 5. The significant width of the frequency profile is due to the very small number of available points. Fig. 6 shows the spectrogram of data, where gaps were replaced with points, obtained from predictions, as described above. As can be seen, we have recovered the correct period of 24 hours. Results in Fig. 6 do not relate to the original data but to a series that has been modified to fill the gaps by the LP-SVD algorithm. Hence, it does not reflect the greater uncertainty of the location of the spectral peak by spreading out of the contours at times when original data are missing, a task for future work. The satisfactory result in Fig. 6 does not guarantee that the method will work in all cases. We are working on modifications, aimed at improving this approach by introducing different statistical weights due to differences in lengths of the data segments used in forward/backward predictions.

Discussion

The LP-SVD algorithm is not the only approach available to fill gaps. An alternative approach suggested by Professor Christopher Bingham consists of computing a spectrum from an autoregressive operator computed from an autocorrelation function computed from the non-missing data, yielding a very sharp peak near a frequency of 1/24 hours with an order of the

autoregressive operator of 15. With missing data, however, the autocorrelation function is often not positive definite, in which case there is a somewhat artificial limit on the order of the autoregression. Such a least squares approach may not be far removed in spirit from the LP-SVD algorithm, which attempts to filter out some of the noise in the predictors in the autoregression, so as to come closer to the autoregressive relationship that the underlying mean function is assumed to have.

Self-measurements may be missed during sleep and instrument failure may be responsible for gaps, for instance in physiological data collected by ambulatory monitors or in physical data recorded by satellites. It seems important to include, as blanks, in each analysis of a given time series also analyses of a set of (say 100) noise series generated to simulate the characteristics of the actual data in terms of sampling and noise, which may be colored rather than white. Just as in the development of laboratory techniques, there invariably were blanks and standards, the same precautions should apply in chronobiology and chronomics. Standards could consist of comparing results from several approaches on complete reference time series analyzed as such or after removing data to match the sampling of the actual time series under study, to see whether the time structure is at all altered by the presence of gaps, and, if so, to what extent.

Spectrograms provide a global view of the time-frequency dependencies in analyzed signals. Since our attention herein was focused on periods, the subsequent optimizations concern the frequency resolution, at the expense of the time dimension. Consequently, exact time instants at which frequencies change are blurred. For this reason, it is beneficial to compare the results obtained from spectrograms with those coming from several different approaches, such as chronomic serial sections and gliding or global least square spectra. The combination of results from several sources can only be beneficial for the understanding of the studied phenomena.

It should also be stressed that whatever the method used to fill gaps, the assumption is made that data that would have been collected during gaps carry no new information. If this is not the case, results will be misleading, as will those obtained with methods based on least squares. Extreme caution is thus to be used whenever gaps are not reasonably few and far apart.

Conclusion

The best validation of a periodicity detected in a time series that has a transdisciplinary counterpart record is to compare their time/frequency behavior, e.g., by spectrograms and by chronomic serial sections that provide for a specific spectral component uncertainties for each parameter (MESOR, amplitude, and acrophase). Notably when dealing with wobbly signals with characteristics such as period, amplitude and/or phase that change as a function of time, it is then possible to assess by a remove-and-replace approach [9, 10] whether the changes in the time series of interest coincide with or are congruent with those of the counterpart series, serving as reference.

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Acknowledgements: The kind and critical comments of Professor Christopher Bingham are gratefully incorporated in this note within the confines of the authors' competence.

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Legends to figures

Figure 1. Test series here illustrated for noninvasive cardiology by systolic blood pressure (left): original equidistant data (top), with six 6-hour gaps randomly distributed (middle), and after elimination of gaps by compression (bottom). Corresponding least squares spectra (right) are characterized by a 24-hour spectral peak as long as the original time scale is preserved, in the absence (top) or presence (middle) of gaps, but with a peak spuriously shifted toward a shorter period of about 18.7 hours (bottom). In this obvious illustrative example, the erroneous period estimate can be derived intuitively from the chronogram showing 7 cycles in 168 – 6x6 = 132 hours, corresponding to a period of 132/7 = 18.9 hours, close to the spectral peak when only integer harmonics are assessed.

Figure 2. Chronobiologic-chronomic serial sections of the original data without gaps (left), with gaps (middle), and after compression of the gaps (right). The spuriously shorter period detected in the latter case is evidenced by the downward drift of the 24-hour acrophase to earlier and earlier times. The acrophase (phase of the maximum of the 24-hour cosine fitted by least squares to data in a 24-hour interval displaced by 1 hour throughout the time series) is expressed in (negative) degrees, with 360°≡24 hours, and 0° set to 00:00).

Figure 3. Spectrogram of original data (no gaps). The horizontal dashed black line at 24 hours represents the "target" period of the simulated signal. The outer contours correspond to the bandwidth of the detected component, with narrower and narrower contours associated with the increasing strength of the signal best detected in the middle of the time series, when the short-term Fourier transform is using all data available for analysis. Results closer to the start or the end of the data series only use partial data, a fact also accounting for the larger bandwidth as compared to that at the middle of the time series.

Figure 4. Spectrogram of data with gaps that have been compressed. A shift in frequency is clearly observed, the signal's period estimate being well shorter than the "target" of 24 hours, represented by the horizontal dashed line.

Figure 5. Spectrogram of partial data (second fragment covering the span from the 15^{th} to the 34^{th} hour). Whereas the estimated period is close to the target of 24 hours, the frequency resolution is much poorer, as evidenced by the much broader bandwidth, in keeping with the much shorter length of the series used for analysis (only 20 hours).

Figure 6. Spectrogram of data with gaps filled by means of a linear prediction by singular value decomposition (LP-SVD) algorithm. In the case examined, the signal is sufficiently well restored to allow the detection of a 24-hour signal similar to that found in the original data without gaps (see Fig. 3). Results do not convey the loss of information in relation to missing values that should then be associated with a greater uncertainty of the location of the spectral peak, as reflected by a spreading out of the contours.

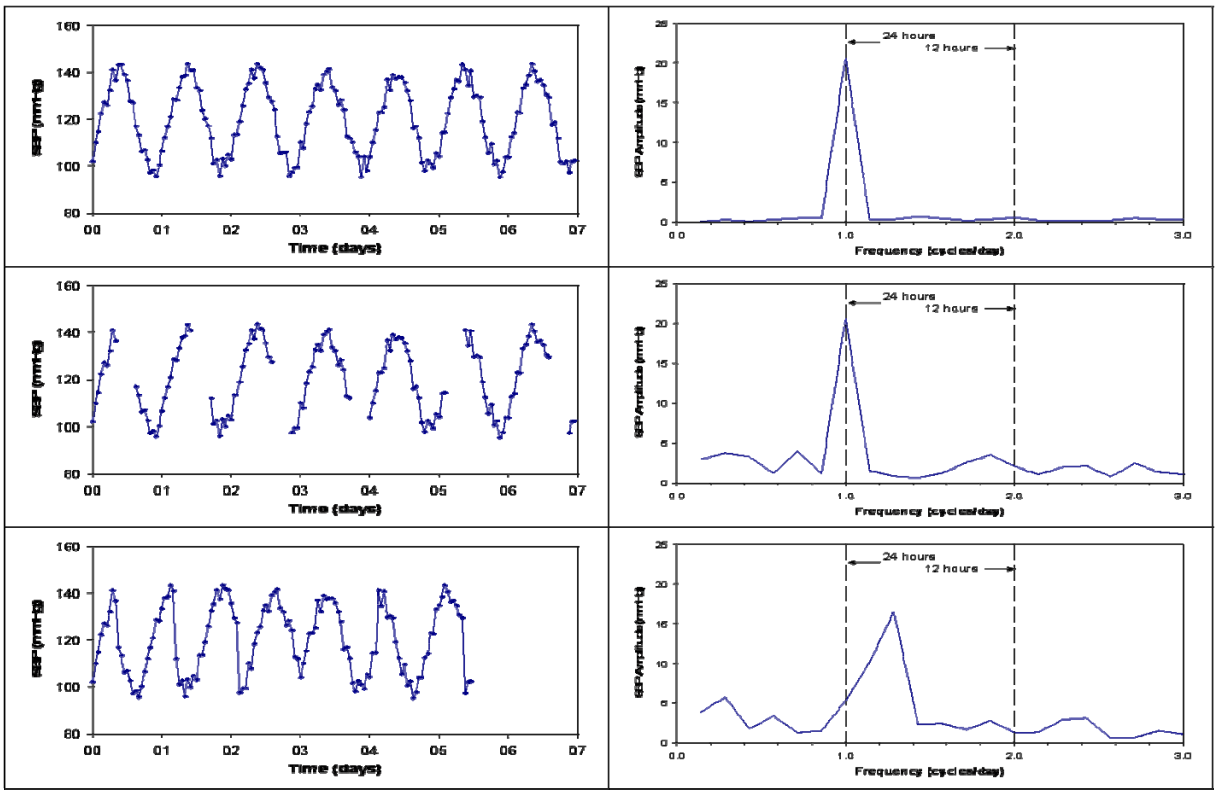

Figure 1

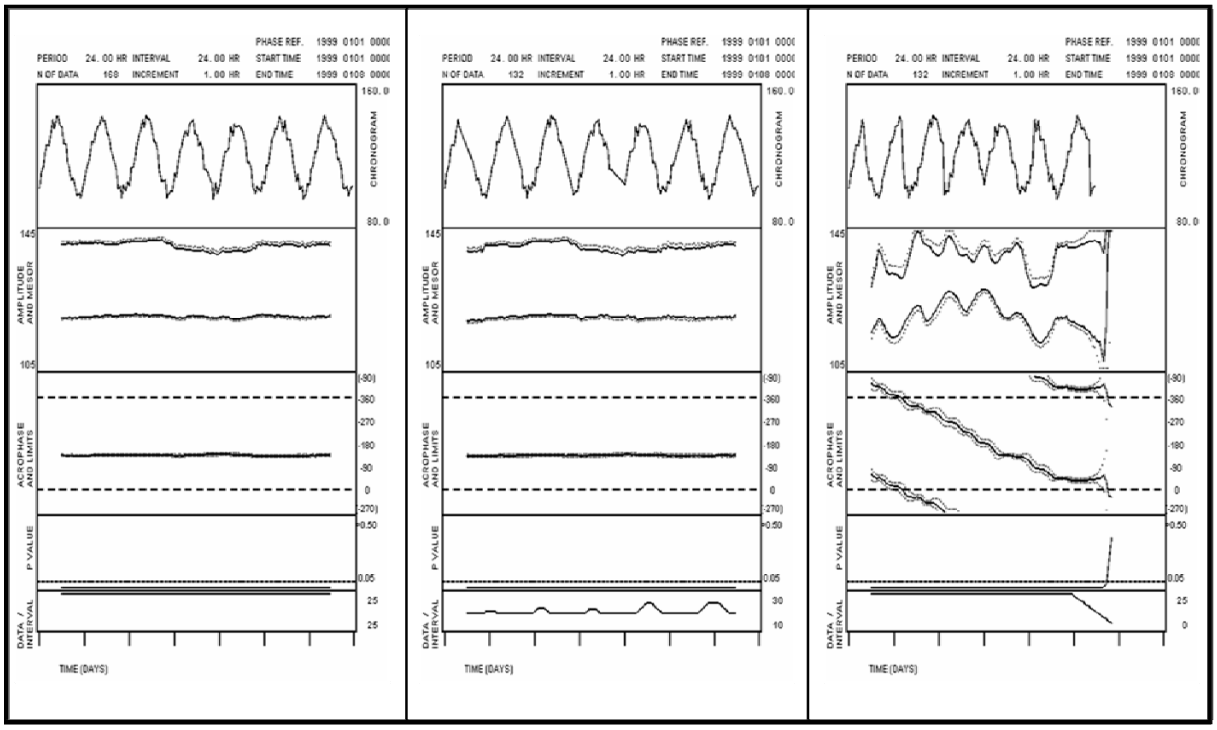

Figure 2

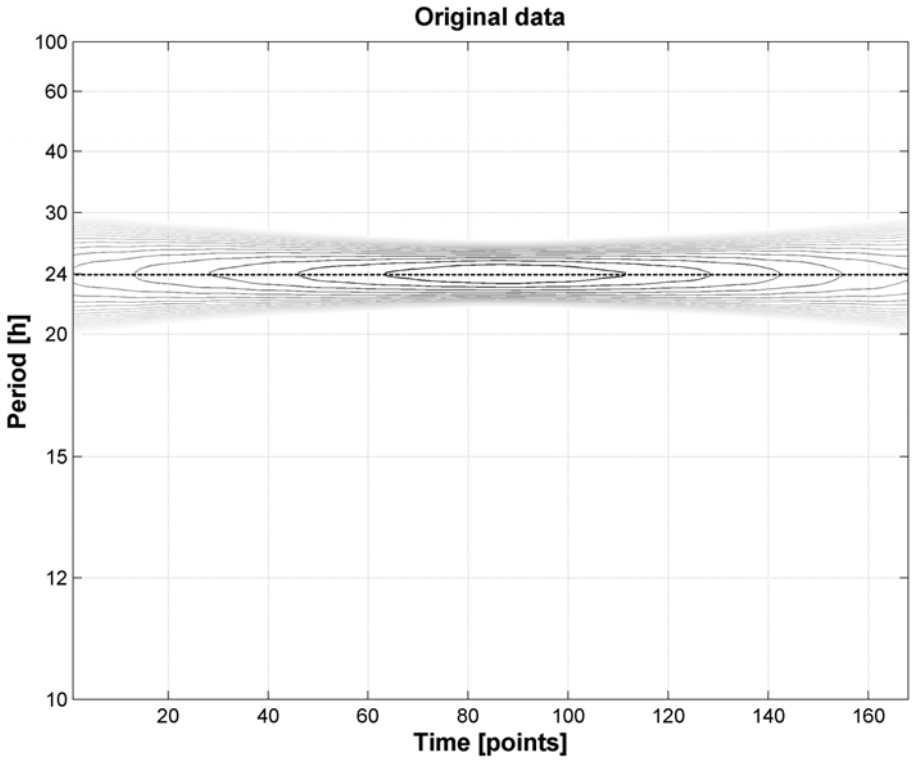

Figure 3

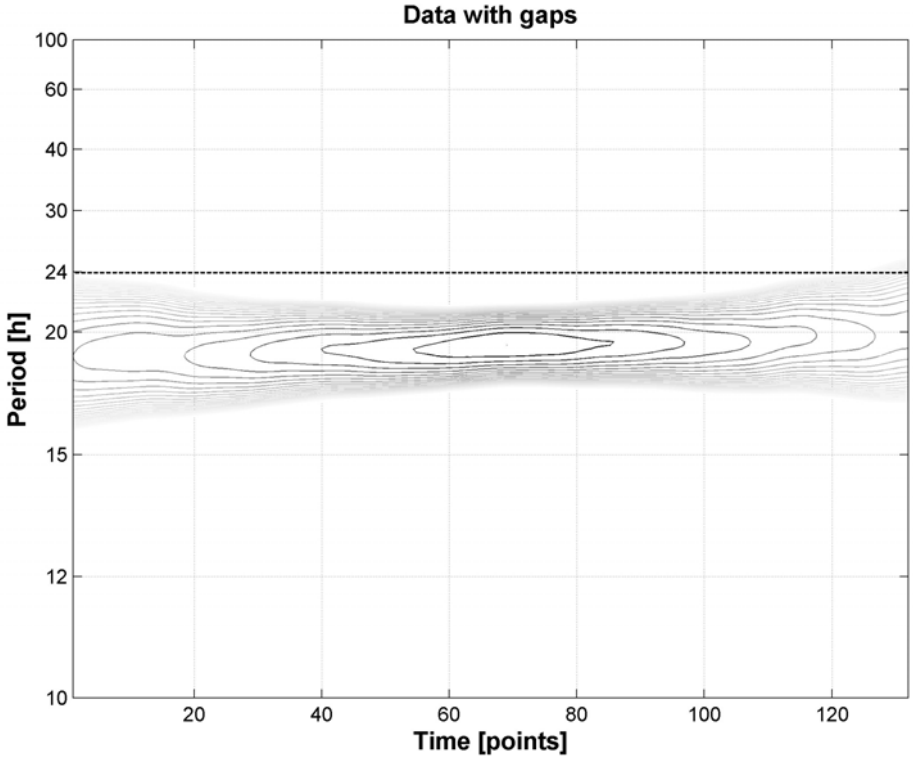

Figure 4

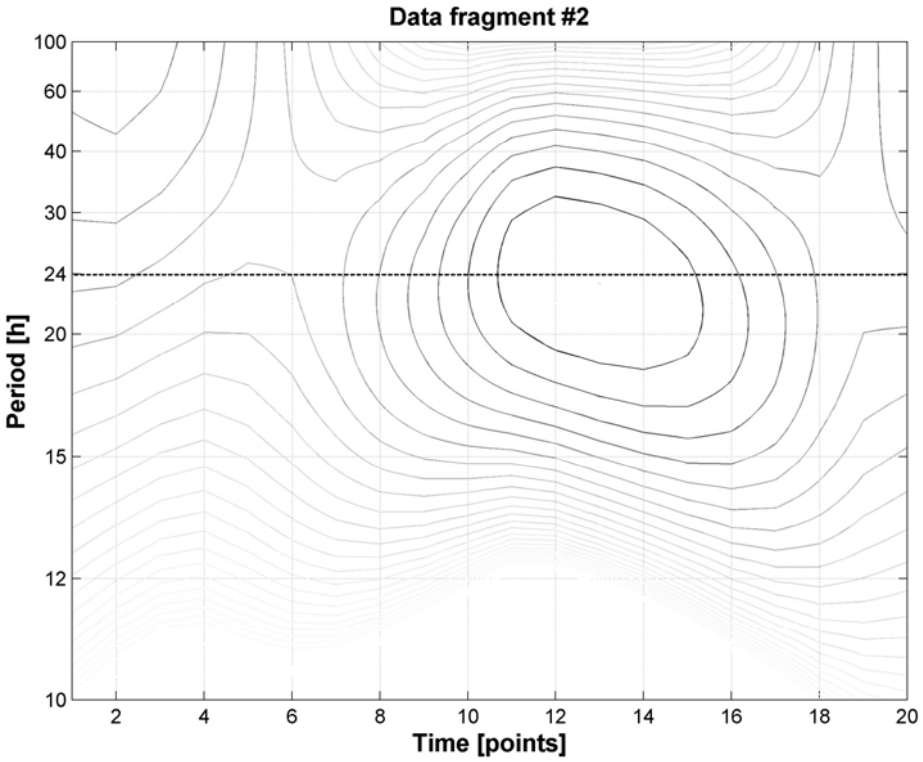

Figure 5

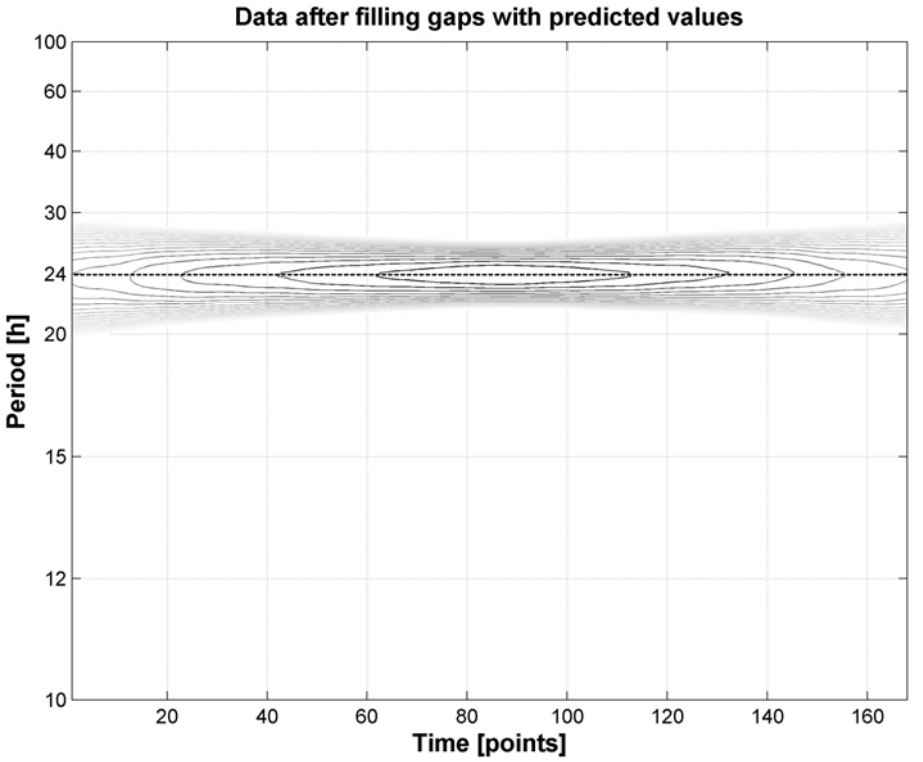

Figure 6

Ambulatory profile in a non-ambulatory subject: a sphygmochron with gaps (when we should measure again, not interpolate)

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Aim. To document that non-ambulatory individuals can obtain a monitoring profile over time for a computer comparison with peer group limits, a sphygmochron, while pursuing a very active life.

Background. Elsewhere in these proceedings, we indicate different methods for interpolation when there are gaps in the data and the dangers arising from compressing the data when they are included for an assessment of their time structure. Here in turn we summarize the data with large unintended gaps occurring for technical reasons and this handicap notwithstanding, briefly indicate the usefulness of the results for a preliminary assessment by sphygmochron.

Subject. HH, a male adult professional 46 years of age, uses a wheelchair for mobility. On August 6th, 1991, due to a strong impact on his spine after a bicycle downhill accident, he was diagnosed as paraplegic with a complete lesion at TH 4-6, accompanied by a haematopneumothorax and several lesions in higher segments of the spine up to C1 without any functional restrictions following these. The diagnosis can be compressed to complete paraplegia at TH4-6 and is up to date until present. Functional restrictions of inner organs are within the typical restrictions for complete paraplegia resulting from injury of higher segments of the thoracic spine. HH carried the TM-2430 ambulatory blood pressure and heart rate monitor manufactured by A&D (Tokyo, Japan) during a visit in Minnesota in July 2008 and resumed monitoring with interruptions upon his return to Innsbruck in August 2008.

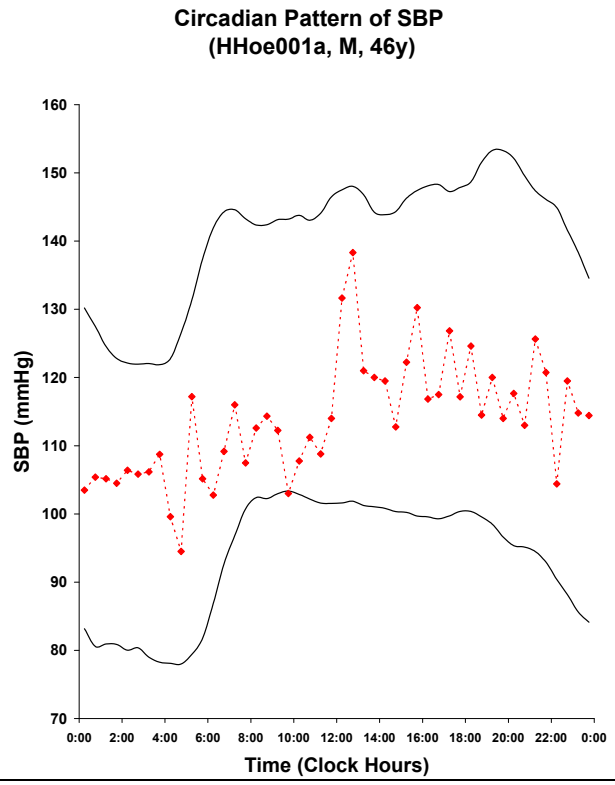

Figure 1. Plexogram (a term used for stacking data over an idealized day, as done here at half-hour intervals for 24 hours, or along any other time scale) shows acceptability of systolic (S) BP values of HH, a male professional with paraplegia using a wheelchair for mobility, while active in his chosen health-related profession revealing changes along the 24-hour scale, here confounded by transmeridian dyschronism, since the subject was monitoring after a flight from Austria to Minnesota and after a return flight. © Halberg.

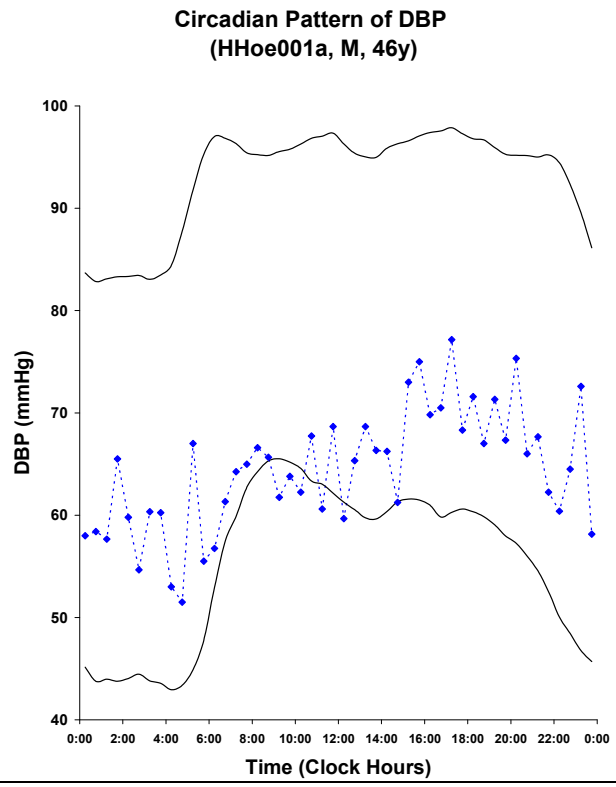

Figure 2. Acceptability of diastolic (D) BP of HH, revealing, as does Figure 1, an up-down pattern that can be tested for circadian rhythmicity. © Halberg.

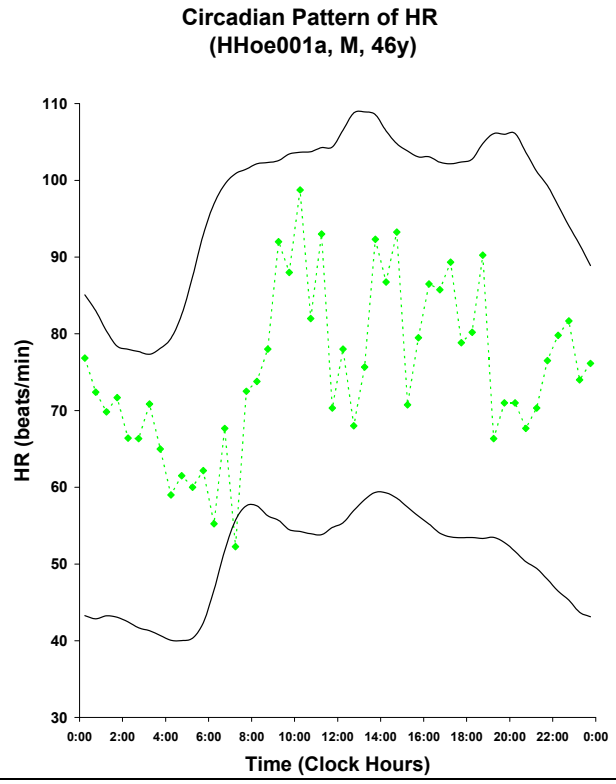

Figure 3. Acceptability of HR of HH showing variability from well below 60 beats/min to nearly 100 beats/min. © Halberg.

SPHYGMOCHRON-TM

Monitoring Profile over Time;
Computer Comparison with Peer Group Limits

Blood Pressure (BP) and Related Cardiovascular Summary.

Name:---------- Patient #: HHoe001a
Age: 46 Sex: M
Monitoring From: 28 07 2008 22:30 To: 09 08 2008 17:01
Comments:

CHRONOBIOLOGIC CHARACTERISTICS

	SYSTOLIC BP (mmHg)		DIASTOLIC BP (mmHg)		HEART RATE (bpm)	
	Patient Value	Peer Group Reference Limits	Patient Value	Peer Group Reference Limits	Patient Value	Peer Group Reference Limits
ADJUSTED 24-h MEAN (MESOR)	113.5	98.4-135.1 Range	64.4	60.3-87.2 Range	76.2	56.4-91.2 Range
PREDICTABLE CHANGE (DOUBLE AMPLITUDE)	16.74	6.4-39.40 Range	11.82	4.84-29.80 Range	19.44	5.26-36.20 Range
TIMING OF OVERALL HIGH VALUES (ACROPHASE) (hr:min)	15:59	11:48-17:40 Range	16:18	11:08-16:48 Range	15:03	11:44-17:20 Range

	STD (MIN; MAX)*	STD (MIN; MAX)*	STD (MIN; MAX)*
PERCENT TIME OF ELEVATION	0.0%	0.0%	0.0%
TIMING OF EXCESS	00:00 (hr:min)	00:00 (hr:min)	00:00 (hr:min)
EXTENT OF EXCESS DURING 24 HOURS HBI*	0 (mmHg x hour)	0 (mmHg x hour)	0 (mmHg x hour)
10-YEAR CUMULATIVE EXCESS	0 (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)

INTERVENTION NEEDED			**MORE MONITORING NEEDED**
No			Annually
Yes	Drug	Non-Drug	As soon as possible
			Other specify_____

Prepared By_____ Date____/____/_____

1) Unusually long standing or lying down during waking: unusual activity, such as exercise, emotional loads, or schedule changes, e.g. shiftwork; etc.; 2) Salt, calories, kind and amount, other, etc.

Figure 4. Sphygmochron consisting of an upper parametric and a lower non-parametric part indicating absence of any chronobiologically detectable abnormality. © Halberg.

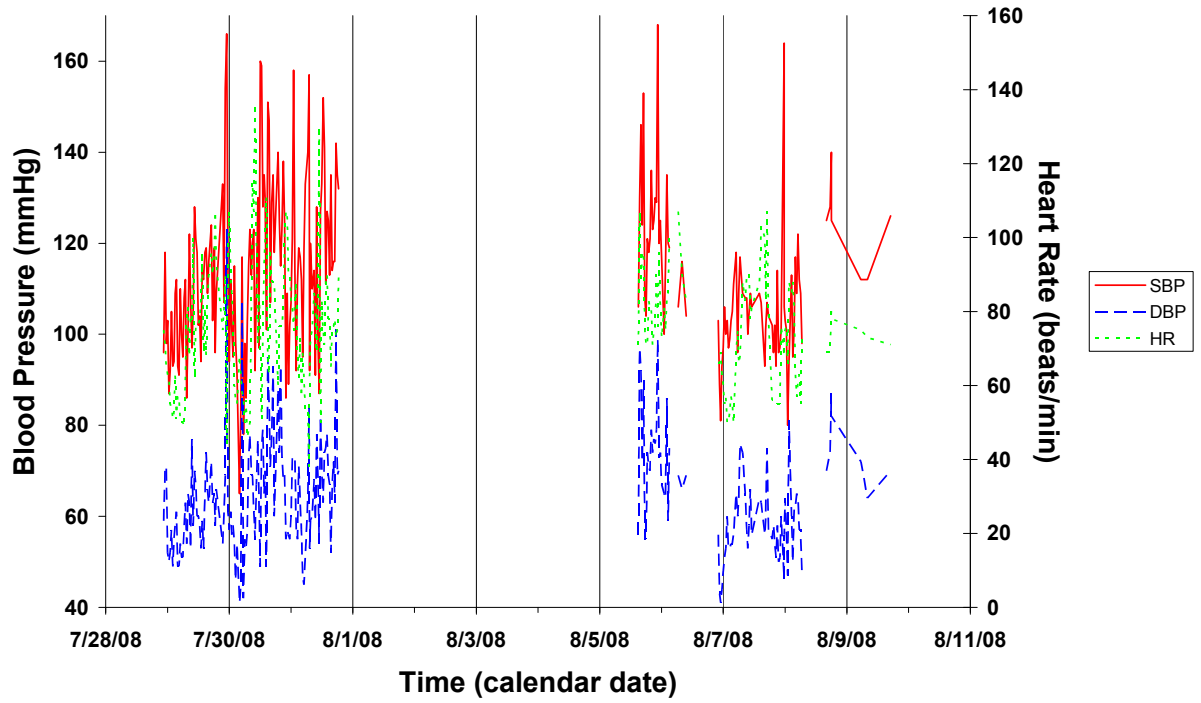

Figure 5. Dense record around July 30 in Minnesota and interrupted record in August in Innsbruck. © Halberg.

Results. When non-parametrically his circadian pattern is demonstrated by stacking data from different days at the same intended 48-hour timepoints, 30 min apart, of an idealized day, we obtain the curve in Figure 1, in which continuous lines show the limits of acceptability for systolic (S) BP, derived from clinically healthy peers matched by gender and age (1-3). We find that with the exception of one measurement, all SBP mean values are within these limits for HH. Figure 2 presents corresponding data on HH's diastolic (D) BP which again, with just 5 exceptions (vs. 43 acceptable values), is within the peer group limits. Figure 3 shows the acceptability of all but one HR mean out of 48. A summary for different days is shown for each of these three variables and from three other derived variables in Table 1, which shows the great variability of mean values from day to day for SBP from 106 to 123 mm Hg.

Figure 4 shows a summary by sphygmochron. All parametric endpoints also show acceptability insofar as for the three variables summarized, the values are all within also-shown acceptable limits. We do not recommend the pattern of measurements that underlies this sphygmochron based on original data displayed in Figure 5. We do wish to emphasize that even a very severely handicapped professional can use the instrumentation and that, gaps notwithstanding, a tentative diagnosis of an acceptable BP can be postulated which in our experience, rather than being filled in by computations, is best complemented by an uninterrupted long record to look for infradian as well as circadian endpoints.

Table 1: Means, their ratios, and standard deviations of 6 vascular variables investigated

Wakeup Time = 7:00 Bed Time = 23:00
Begin Day Time = 10:00 End Day Time = 20:00
Begin Night Time = 0:00 End Night Time = 6:00

Systolic Blood Pressure (SBP)

Day	24-Hour			Day Time			Night Time			DNR%
	N	Mean	StDev	N	Mean	StDev	N	Mean	StDev	
1	43	109.37	15.91	18	111.78	9.55	13	98.77	8.23	11.89
2	45	113.56	21.47	19	126.74	19.95	12	95.67	15.27	27.36
3	55	122.58	17.46	29	124.14	15.66	12	116.50	17.15	6.23
4	49	106.06	12.53	12	103.42	4.96	6	117.83	11.16	-13.59
5	18	109.56	14.78	5	123.60	14.57	12	104.67	11.52	17.28
6	3	116.67	8.08	1	126.00	0.00	1	112.00	0.00	12.00
Overall	213	113.02	17.77	84	119.11	16.50	56	105.45	15.29	12.09

Diastolic Blood Pressure (DBP)

Day	24-Hour			Day Time			Night Time			DNR%
	N	Mean	StDev	N	Mean	StDev	N	Mean	StDev	
1	43	60.88	11.99	18	62.72	5.93	13	52.92	3.84	16.09
2	45	65.69	14.98	19	73.00	14.09	12	56.33	17.27	25.37
3	55	69.24	12.52	29	71.83	12.31	12	60.50	10.26	16.36
4	49	59.06	9.10	12	60.17	6.00	6	69.33	9.69	-15.52
5	18	63.11	11.89	5	72.40	14.67	12	60.50	8.52	18.86
6	3	68.67	4.16	1	70.00	0.00	1	72.00	0.00	-2.91
Overall	213	63.93	12.69	84	68.49	11.97	56	59.00	11.53	14.84

Heart Rate (HR)

Day	24-Hour			Day Time			Night Time			DNR%
	N	Mean	StDev	N	Mean	StDev	N	Mean	StDev	
1	43	72.47	16.80	18	84.44	12.30	13	55.08	4.97	40.53
2	45	79.49	21.27	19	84.00	19.93	12	68.75	17.19	19.19
3	55	77.11	14.43	29	81.14	14.46	12	71.17	11.52	12.93
4	49	72.88	16.32	12	81.33	17.96	6	82.83	9.60	-2.06
5	18	74.17	13.05	5	80.80	15.59	12	71.50	12.12	12.54
6	3	73.00	2.00	1	71.00	0.00	1	75.00	0.00	-5.48
Overall	213	75.39	16.87	84	82.38	15.68	56	68.30	14.07	18.67

Mean Arterial Pressure (MAP)

Day	24-Hour			Day Time			Night Time			DNR%
	N	Mean	StDev	N	Mean	StDev	N	Mean	StDev	
1	43	77.05	12.41	18	79.07	6.57	13	68.21	5.03	14.11
2	45	81.64	15.58	19	90.91	13.39	12	69.44	15.41	26.29
3	55	87.02	12.86	29	89.26	11.99	12	79.17	10.58	11.60
4	49	74.73	8.69	12	74.58	5.09	6	85.50	9.35	-14.61
5	18	78.59	11.87	5	89.47	14.46	12	75.22	7.61	18.12
6	3	84.67	4.37	1	88.67	0.00	1	85.33	0.00	3.94
Overall	213	80.30	13.17	84	85.36	12.19	56	74.48	11.41	13.55

Pulse Pressure (PP)										
Day	24-Hour			Day Time			Night Time			DNR%
	N	Mean	StDev	N	Mean	StDev	N	Mean	StDev	
1	43	48.49	10.87	18	49.06	6.91	13	45.85	5.64	6.62
2	45	47.87	16.49	19	53.74	19.64	12	39.33	13.26	30.09
3	55	53.35	13.52	29	52.31	13.27	12	56.00	15.93	-6.92
4	49	47.00	12.01	12	43.25	5.33	6	48.50	8.64	-11.17
5	18	46.44	10.84	5	51.20	4.82	12	44.17	12.49	15.14
6	3	48.00	8.00	1	56.00	0.00	1	40.00	0.00	33.33
Overall	213	49.09	13.26	84	50.62	13.02	56	46.45	12.81	8.50

Double Product (DP)										
Day	24-Hour			Day Time			Night Time			DNR%
	N	Mean	StDev	N	Mean	StDev	N	Mean	StDev	
1	43	79.50	22.43	18	93.99	13.41	13	54.35	6.37	49.86
2	45	89.90	26.73	19	103.61	15.61	12	65.95	20.24	41.89
3	55	93.99	19.93	29	100.22	19.14	12	82.44	15.99	18.92
4	49	77.67	20.81	12	84.33	19.82	6	97.74	15.64	-17.27
5	18	80.88	15.79	5	98.49	11.71	12	74.31	11.80	29.90
6	3	85.07	3.96	1	89.46	0.00	1	84.00	0.00	6.42
Overall	213	85.21	22.66	84	97.15	17.65	56	72.31	19.32	29.15

Discussion. The data and the analyses reveal that an active paraplegic can wear the cuff with the monitor during daily activities and during sleep at night. While for the first number of days of monitoring he noticed a reduction in the quality of sleep, he did remark that while active yet sitting, without having to move the wheelchair around, the measurement is not much of a burden. Again, one must not generalize from an exceptionally active and strong individual. It can be anticipated, however, that in the foreseeable future there will be a further simplification of the instrumentation needed for automatic ambulatory chronobiologically interpreted BP and HR monitoring. With such affordable instrumentation, medicine will change in keeping with an extended view (4, 5). The current view of health care is based on spotchecks in health care offices. An extended view will prevent us from flying blind by providing a view of variability and of any rules in that variability that reflect life as it may have evolved from the big bang, as a small part of the concomitantly evolving cosmos. In the health care of individuals, the view will be extended by a positive definition of health replacing health defined as the absence of disease. The endpoints from continued monitoring will be dynamic; already today they can detect prediabetes, prehypertension and a premetabolic syndrome (3, 6, 7). By the introduction of a sphygmochron in elementary and secondary education (8), their discussion for medical students will then become superfluous and will be replaced by analyses far beyond the sphygmochron here illustrated.

Conclusion. A severely handicapped professional using chronobiologically interpreted BP monitoring, can manage to use the current available instrumentation (e.g., from A&D) to evaluate greatly changing variables automatically, even though he is restricted to a wheelchair. Such monitoring as a sine qua non extends the view and practice of health care by computer aided self-help, as an aspect of social medicine.

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C-ABPM reveals solar cis-halfyear and transyear signatures in human diastolic blood pressure

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Aim. To seek in human diastolic (D) blood pressure (BP) a theoretically predicted solar beat period (1) which was amply documented in physics (2-11) and in biomedicine (12-20).

Subject, method and background. GSK, a physician-scientist, 72 years of age at the start of automatic, chronobiologically interpreted ambulatory BP monitoring (C-ABPM) with few gaps around the clock for >10 years (from March 31, 1998, to June 29, 2007), used a TM-2421 instrument from A&D (Tokyo, Japan). Analyses were by extended cosinor that had already revealed the cis-half-year in sudden cardiac death in some but not in all geographic regions tested (12-14). Earlier studies had also revealed spectral components with a period, τ, longer than a calendar year, dubbed transyears (12-20).

Results. In the spectral window of data of GSK, now covering a decade, a predicted ~0.422-year component was a peak, as were a far-transyear of 1.202-year length and a near-transyear.

Discussion. Several medical scientists and opinion leaders have self-measured their BP systematically a sufficient number of times a day for chronomic (time structural) analyses, from the time of encountering chronobiology until their death (21, 22); they set an example for others who also may not wish to base treatment on single spotchecks in a health care office. Cosinor-interpreted self-measurements, advocated by many long ago (23), while helpful and currently gaining access into practice, were not readily feasible, however, without a noteworthy interruption of activities during waking and (what matters more) disturbance of sleep (24). New, relatively unobtrusive instrumentation now makes C-ABPM possible and cost-effective and will save lives. Illustrative results and problems encountered in as-one-goes self-surveys, among others (25), by GSK (26) have been published. GSK's thorough record also revealed that both MESOR-hypertension and CHAT (circadian hyper-amplitude-tension) can be intermittent conditions even under treatment, and treatment is best adjusted based on monitoring, rather than "flying blind" (27). Since an ~0.42-year and a transyear had been predicted based on theory about beat periods of solar rotations (1), and had been found not only in solar-terrestrial physics but also in biology, we anticipated such a period, and indeed found it in GSK.

Conclusion. Monitoring blood pressure and heart rate for health care can also serve transdisciplinary science, seeking signatures of the sun's activity in the biosphere.

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Pain and the cardiovascular system revisited in a long-term monitoring

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We report a perhaps individualized threshold in pain-associated systolic (S) and diastolic (D) blood pressure (BP) elevation and the lack of a corresponding increase, instead a decrease in heart rate (HR) in the case of an elderly man (GSK) with MESOR-hypertension (1). He used the TM-2421 ambulatory monitor manufactured by A&D (Tokyo, Japan), recording BP and HR at half-hour intervals around the clock with very few interruptions, by now for over 10 years, so that an unusually thorough objective assessment is possible. The data in Figures 1-3 show first a gradual and an abrupt increase in pain, quantified as-one-goes along a scale of 1-10 and an apparently differing response of BP and HR. A threshold for BP elevation with pain is apparent in GSK for BP and HR. HR may respond with a lowering rather than an increase. The responses to pain are abrupt, but subside in response to physical therapy. A BP decrease with a lowering of pain is seen for SBP and DBP and an increase for HR. Conceivably, BP monitoring during painful procedures may provide an objective measure of response, and may deserve further testing in gauging the extent of physical intervention and the response to physical and other therapy on groups, even when such studies are noted for the given individual, in case the macroscopic changes described herein await further quantification by parameter tests (2) and cumulative sum control charts (3).

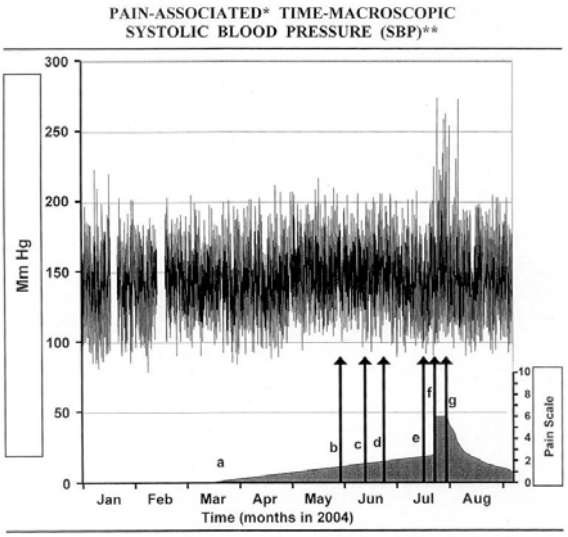
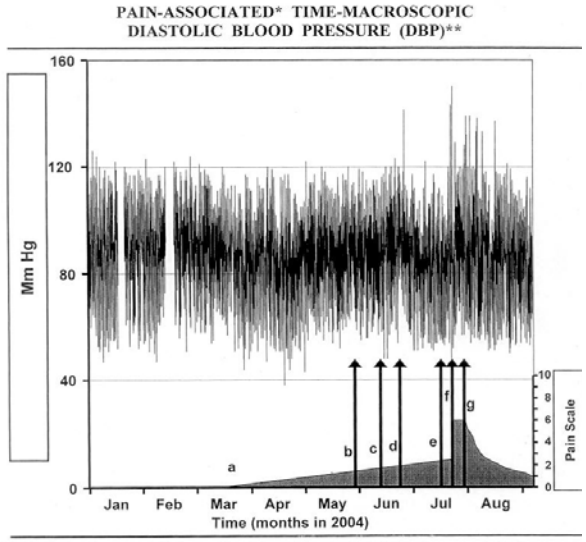
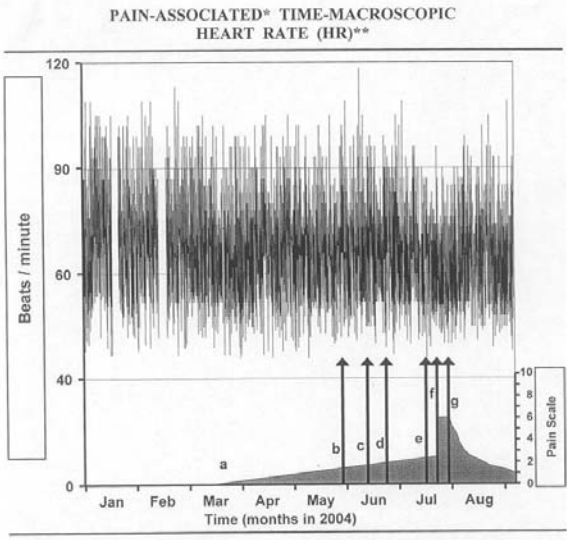


Figure 1. Gradual increase in pain is not associated with an increase in blood pressure (BP) up to an abrupt pain increase associated with an abrupt increase in systolic (S) BP which quickly responds to a lowering of pain by return of SBP to pre-pain values, in response to physical therapy in an elderly man, GSK. © Halberg.



* Shading at bottom: rated along a 10-grade scale (up to 6 in GSK during span studied)..
** Original data from monitoring every 30 minutes with few gaps by a man, 78 years of age (GSK, physician-scientist).
Marks: a = beginning of pain in the right hip and femoral areas; b = X-ray reveals suspicion of a tumor, c = MRI exam; d = MRI finding: intraosseous cyst close to acetabulum; e = additional MRI concluding: severe stenosis in lumbar part of spinal channel; f = very intensive manual orthopedic exam produced increasing pain; g = physical therapy begins, pain gradually decreases.

Figure 2. Diastolic blood pressure (DBP) response to pain and to physical therapy in an elderly man, GSK. © Halberg.



* Shading at bottom: rated along a 10-grade scale (up to 6 in GSK during span studied)..
** Original data from monitoring every 30 minutes with few gaps by a man, 78 years of age (GSK, physician-scientist).
Marks: a = beginning of pain in the right hip and femoral areas; b = X-ray reveals suspicion of a tumor, c = MRI exam; d = MRI finding: intraosseous cyst close to acetabulum; e = additional MRI concluding: severe stenosis in lumbar part of spinal channel; f = very intensive manual orthopedic exam produced increasing pain; g = physical therapy begins, pain gradually decreases.

Figure 3. Changes in heart rate (HR) in response to pain and physical therapy in an elderly man, GSK. © Halberg.

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HARM VS. BENEFIT FROM LOSARTAN WITH HYDROCHLOROTHIAZIDE AT DIFFERENT CIRCADIAN TIMES IN MESOR-HYPERTENSION OR CHAT

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Abstract. Two new male patients, Sa, 65 years of age, with MESOR-hypertension (MH), and Su, 66 years of age, with **c**ircadian **h**yper-**a**mplitude-**t**ension, CHAT, were studied by **c**hronobiologically interpreted automatic **a**mbulatory **b**lood **p**ressure (BP) and heart rate (HR) with 7-day/24-hour monitoring **m**onitoring, C-ABPM 7/24. The last 7 days of a no-hypotensive-treatment (Rx) span were monitored [1)] and compared with C-ABPM 7/24 for effects on BP and HR at the end of several weeks on 50 mg Losartan -- (L) [2)] followed by L with 12.5 mg hydrochlorothiazide (L+H) [3)] -- both 2. and 3. at breakfast and then on a set of 5 differently timed treatment spans on L+H, administered (to approach 5 different circadian stages) upon awakening or 3, 6, 9 or 12 hours after awakening [4)-8)]. At the end of each L+H Rx stage, and earlier at the end of no Rx or L only at breakfast or L+H only at breakfast, BP was also monitored for 7 days (C-ABPM). Circadian characteristics were assessed by cosinor on each day's data and compared among the 5 Rx times by a 1-way analysis of variance. A circadian rhythm characterized the responses of the MESOR (M) and circadian amplitude (A) of systolic (S) and diastolic (D) BP and of pulse pressure (PP) of Su and the response of SBP-M and DBP-M of Sa. In Su, the effect was desired at the two late test times (9 and 12 hours after awakening) but at 3 earlier test times, the circadian overswing was actually increased. The effect of L+H in the morning in Su was harmful; in the evening beneficial. Such undesirable effects are currently not picked up in data that are not collected and/or analyzed chronobiologically. Care providers who collect data that do not lend themselves to a chronobiologic analysis or refrain from using C-ABPM, offered cost-free by BIOCOS, may in very many people unintentionally induce a risk greater than a high BP, and hence may do harm. Ignorance is no excuse, certainly not in the face of a series of prior consensus meetings advocating an indispensable chronobiologic approach in keeping with "first do no harm" (1).

Introduction. **C**hronobiologically interpreted **a**mbulatory **b**lood **p**ressure (BP) **m**onitoring (C-ABPM) underlies an individualized approach for reliably diagnosing vascular variability disorders, VVDs, such as MESOR-hypertension (MH), or CHAT, short for **c**ircadian **h**yper-**a**mplitude-**t**ension (1, 2) or an above-threshold pulse pressure, and once the diagnosis is ascertained, C-ABPM is best continued for finding the appropriate timing for the administration of non-drug or drug treatment. By a C-ABPM one may avoid harm due to timing that escapes notice in current practice, but if detected can be readily corrected, sometimes only by changing the timing of drug administration.

Background. For 240 mg of diltiazem, a change of treatment from 08:30 to 04:30 reduced both the MESOR and the circadian amplitude (3). CHAT, associated with sotalol 80 mg given

twice daily, can be avoided by omitting the evening dose (4). More generally, a long series of studies in the laboratory shows gains from chronotherapy summarized in Table 1.

Subjects and methods. For the patients investigated, the schedule of monitoring with a device (TM-2421 or TM-2430) for ambulatory monitoring from A&D (Tokyo, Japan) and their laboratory determinations are shown in Tables 2 and 3. Methods of analysis are given with their results in Tables 4-6 and in Figures 1-12.

Results. Figure 1 illustrates for SBP that the kinds of time series investigated cannot be readily quantified and compared by the unaided eye, just as most cells are not seen without microscopes. Figures 2 and 3 show results for the SBP M and A, analyzed in Figure 4: both effects (upon M and upon A) are circadian rhythmic. Figures 2 and 3 also show that the SBP MESOR had been lowered at all test times by L+H, but not the circadian amplitude. What is most important, at 3 of the 5 treatment times, CHAT, a risk of stroke greater than a high BP (2), is exacerbated rather than reduced.

Figures 5-7 show results for Su's DBP M and A and a rhythm is again present, indicating that treatment can and should be optimized by timing. Figures 8-10 summarize the statistically significant circadian rhythms in the response of the SBP-M of patient Sa and one of lesser (borderline) statistical significance in Sa's SBP-A. Sa's DBP-M also responds rhythmically to L+H, as seen in Figure 11, as does the pulse pressure of Su but not of Sa in Figure 12.

Discussion. The failure of current health care to diagnose and treat risks greater than that of MH such as a 7-day CHAT (1) -- that may need only a change in the timing of medication to be eliminated (1-6) and that can be exacerbated by unmonitored and/or chronobiologically uninterpreted treatment -- can be compared historically with the resistance to antisepsis and asepsis (7).

We paraphrase Oliver Wendell Holmes, who had recognized the problem of puerperal fever before Semmelweis and Lister (8) did, and hope that chronomic facts (Holmes referred to "medical logic"), will be further checked, considered and taught in modern-day schools (9, 10). A single office BP measurement is no longer regarded as reliable by opinion leaders (11), and even an around-the-clock profile (1) cannot reliably detect a VVD, nor can a day-night ratio do equally so with statistical significance in the light of outcomes (12-16). An international project on The BIOsphere and the COSmos, BIOCOS (17), provides participants with an 80% reduction in the purchase price of automatic monitors of BP and HR for ambulatory use and with chronomic analyses in the light of an accumulating reference data base, qualified by gender and age in exchange for the data. Some readers may use this opportunity for their own health care and/or that of their family, friends and acquaintances. Some may decide to monitor themselves in the long term for basic science as well. Treatments at different times are not equivalent. Just as does the marker rhythm of tumor temperature in the treatment of cancer, Table 1 (18), C-ABPM offers an opportunity for increasing therapeutic benefit and preventing harm. Moreover, C-ABPM allows 1. an optimal diagnosis, 2. optimal timing and 3. an ongoing check of treatment effects and 4. indications for change when needed.

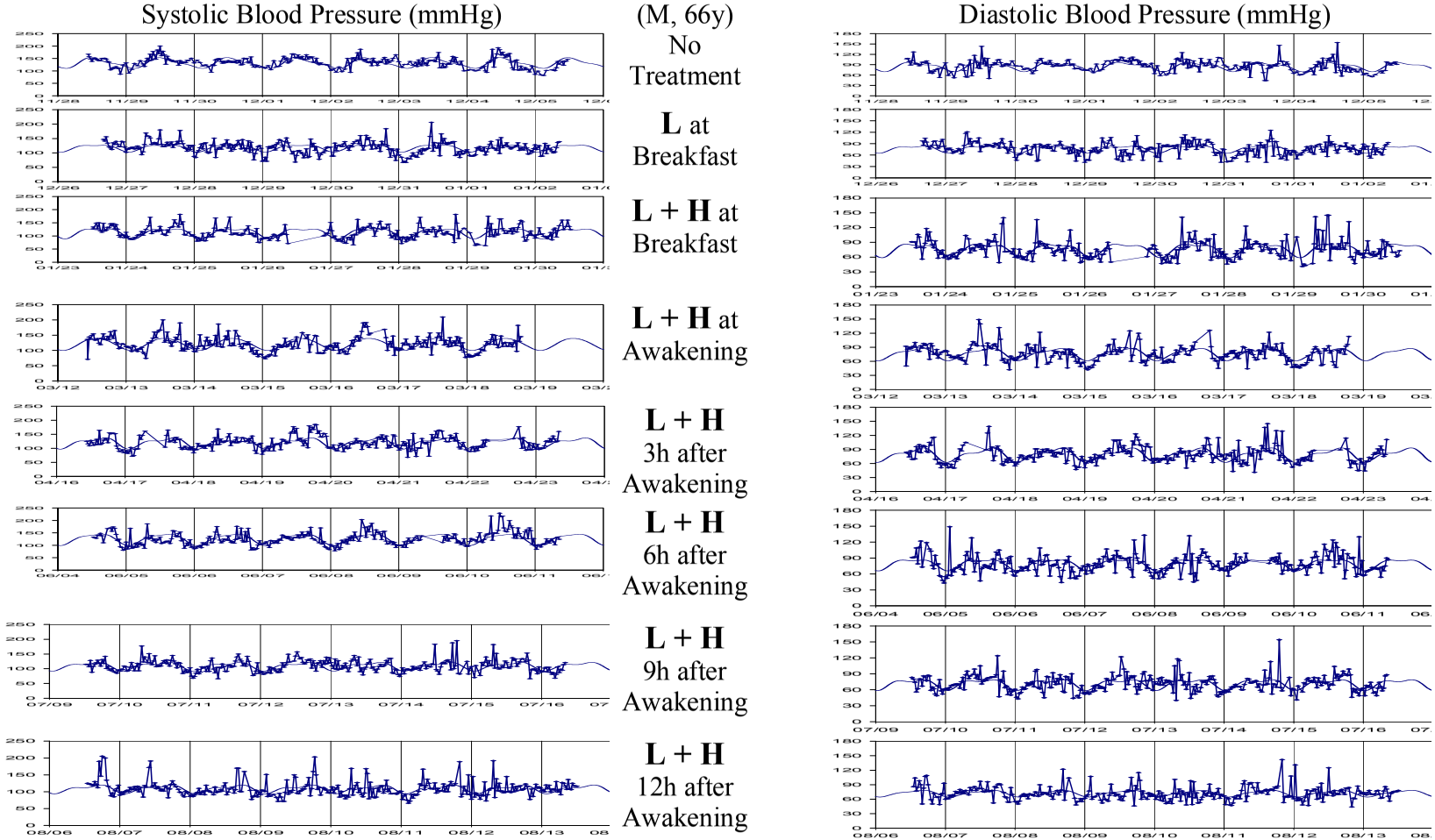


Figure 1. Original data of Su, a male patient 66 years of age, with CHAT (**c**ircadian **h**yper-**a**mplitude-**t**ension) before (on top) and after treatment (Rx) with 50 mg of Losartan (L) alone or L with 12.5 mg of hydrochlorothiazide (L+H), at breakfast in the second and third rows, respectively. The next 5 rows show data with Rx at awakening and at 3, 6, 9 and 12 hours thereafter. Albeit not shown, similar data for other variables of the same patient and for another male patient, Sa, 65 years of age, were also obtained. 7-day cosine curves were fitted to all data from both patients, but a single value for each, the MESOR, M, and amplitude, A, from the fit to the 7-day series as a whole did not allow detection of the circadian or circaseptan rhythm stage-dependence of the response whether evaluated by ANOVA or a single cosinor (not shown). A summary of separate fits of a 24-hour cosine to each 24-hour (rather than a single 168-hour) data section sufficed to get statistically significant results, obtained from tests of the zero A assumption (when each time series in the last week of one of the 5 treatment times yielded 7 separate daily Ms and As). Similar calculations for a circaseptan response would require data over 7 or more circaseptan cycles. © Halberg.

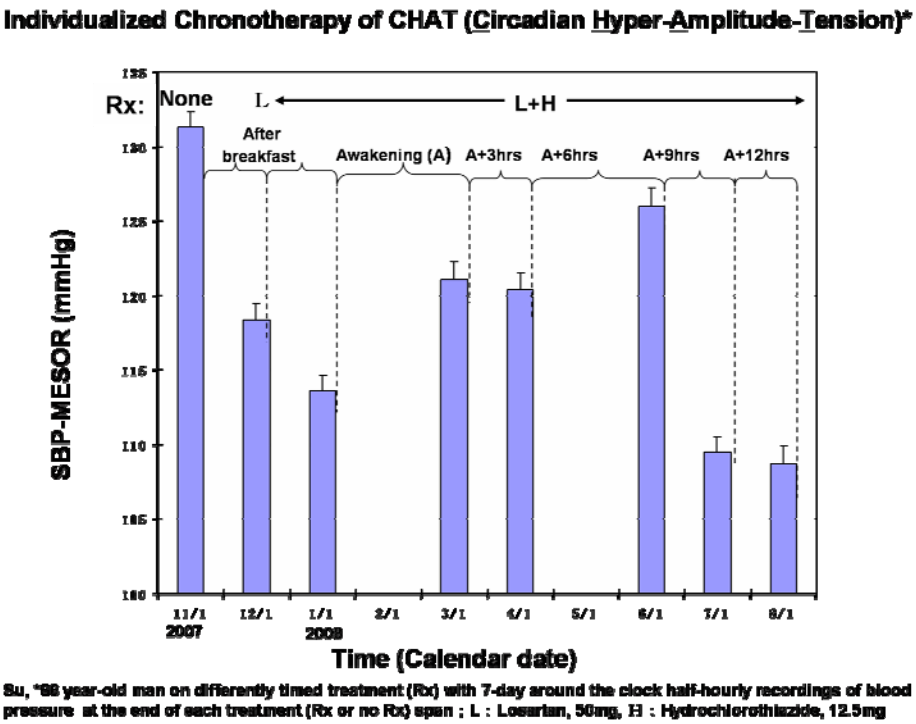


Figure 2. All treatments with Losartan (L) 50 mg and hydrochlorothiazide 12.5 mg lowered circadian systolic blood pressure MESOR at all test times in analyses in Figure 4, but this response was not quantitatively the same, Tables 4 and 5 and Figure 4. © Halberg.

Chronomic (time-structural) surveillance starts with a chronobiologically interpreted 7-day around-the-clock record (C-ABPM) which (until affordable automatic monitors become available for everybody's continuous surveillance) suffices only to rule out, but not to rule in and to treat a VVD. When the 7-day record is repeatedly abnormal and confirms the VVD, it serves to recognize and treat any risk elevation as well as overt disease, but again not blindly. Monitoring is to be continued to ascertain whether and, if so, for how long treatment effects last, be it for lowering an increased risk and/or in surveilling the success or failure of BP M or A lowering or raising, as need be. Once longitudinal records are available, statistical inference can be obtained for the individual patient by means of parameter tests (19) and by sequential testing such as that by the self-starting cumulative control chart (20).

An initial decline in M coincides with the start of treatment (21 and Figure 15 therein). Relying on an N-of-1 chronobiologic pilot design, treatment time in relation to clock-time was then advanced by 4 hours, initially every 17 days, and at shorter intervals thereafter. Rx at 12:00 was associated with a reversal of the up-to-then continuous decrease. For that subject, TT in (21), treatment in the evening was associated with an elevation in the circadian amplitude of BP. It is clear that treatment has to be individualized when in Su treatment in the morning elevated the

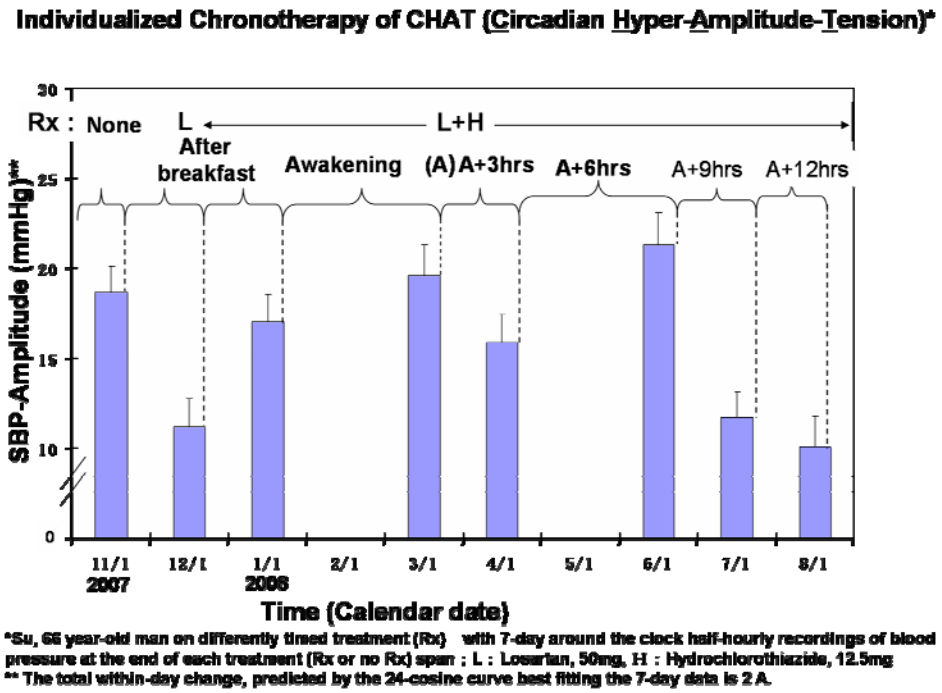


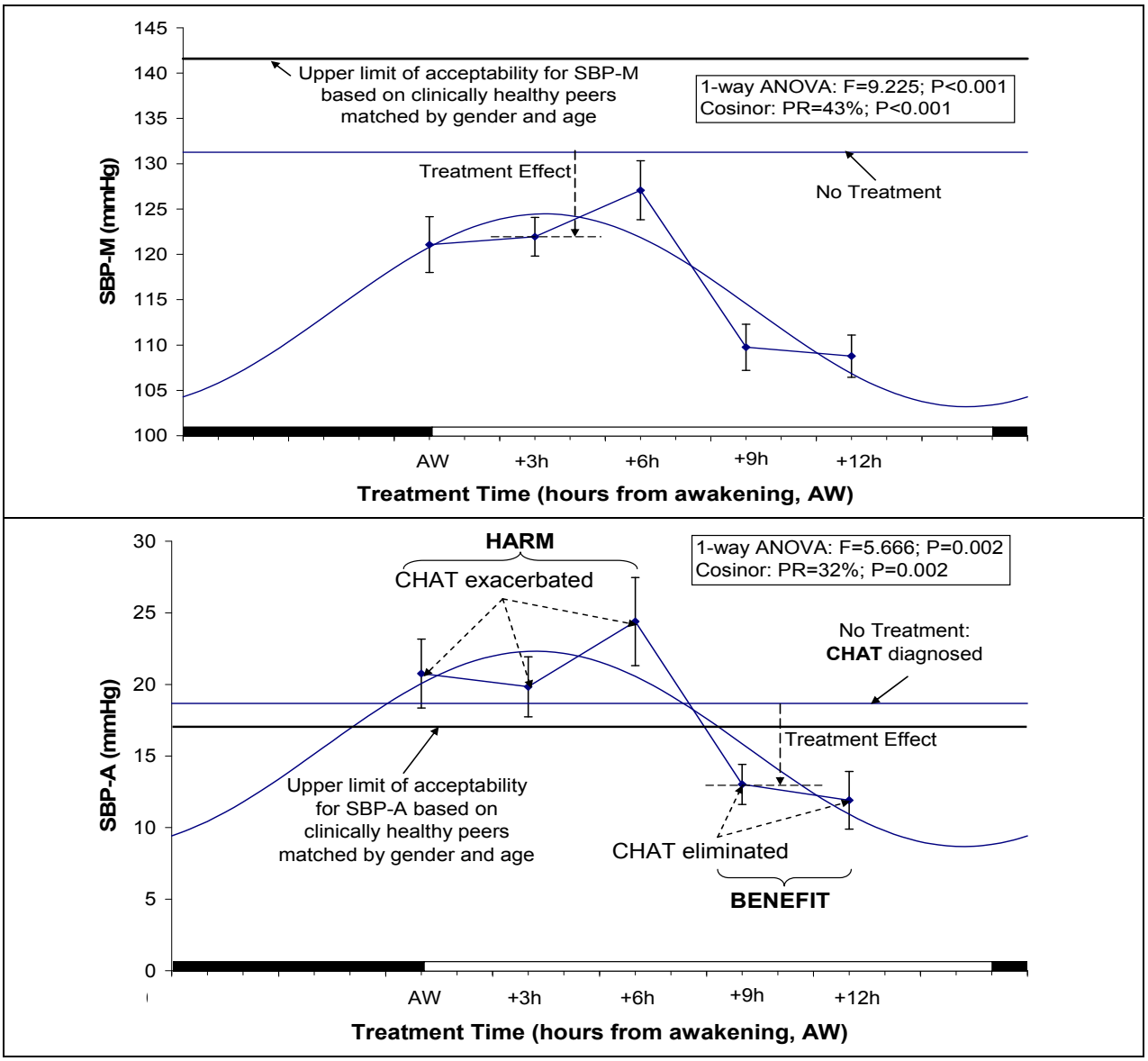
Figure 3. Very different responses to treatments with Losartan (L) 50 mg and hydrochlorothiazide 12.5 mg of the circadian amplitude of patient Su's blood pressure, analyzed in Table 5 and Figure 4. © Halberg.

amplitude, inducing or exacerbating CHAT, while treatment in the evening eliminated CHAT. Such an increase in circadian amplitude of BP may induce iatrogenic CHAT in many other, possibly millions of patients, thereby increasing cardiovascular disease risk unknowingly.

Against this background, it must be re-emphasized that in Su, who had (mild) CHAT to start with, treatment with L+H exacerbated CHAT in the morning, but not when the same dose was given in the evening, Figures 4 and 7 (cf. also 21 for the difference in patient TT). We must not generalize, but individualize by monitoring, so that we do not fly blind (22) to the possibility that by eliminating the lower risk of MH, we acquire the higher risk of CHAT. The large risk of CHAT is illustrated elsewhere (6 and Figure 2 IIA-C therein). It was shown in another study that switching the timing of medication every day was too fast a schedule (23). In the present study, the intervals between spans of treatment at different clock-hours were of several weeks, and only the last week was monitored. During this final monitoring week, there were trends, Table 6. The as-one-goes weekly analysis of the monitoring may be used for deciding on the interval between changes in medication, while also accounting for trends (21). In the case of Su and Sa, a week's monitoring after several weeks on the drug has allowed the detection of response rhythms. Shorter yet uninterrupted monitoring, e.g., with initial changes every 17 days, has also worked (21) and when a first cycle of treatments is repeated to once more reascertain the best time, the interval between changes may be shortened (21).

Conclusion. The monitoring of Su and Sa and much earlier background information should suffice to recommend that any patient on treatment for high BP should be monitored to find out the best treatment, apart from ruling out that other VVDs are not traded for a lower BP average.

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 exarcerbates CHAT, a condition that carries a risk of morbid events greater than an elevated mean value of blood pressure.

Figure 4. Monitoring of patient Su reveals for his systolic blood pressure a good time for both a hypotensive effect and a lowering of an excessive circadian amplitude by treatments with Losartan (L) 50 mg and hydrochlorothiazide 12.5 mg when medication is taken 9 or 12 hours after awakening. Note from the lower graph on amplitude, A, that the same treatment given on awakening or 3 or 5 hours thereafter can actually do harm, further raising an already elevated circadian A. Neither CHAT nor the effect of treatment upon this condition are conventionally detectable in office visits and escape a 24-hour profile as well when it is

not interpreted in the light of chronobiologic reference standards, and even when it is so interpreted, the record is not long enough to rule out a transient abnormality that may be only a physiological response.

Changing the timing of medication during consecutive spans shows differences in the efficacy of treatment. An empirical approach to chronotherapy, here implemented immediately after diagnosis, should ascertain that the treatment is effective and not harmful. Optimization of treatment effects by timing can be achieved for the individual patient by systematically changing, e.g. advancing the clock-hour of treatment on a standardized routine of activity and sleep. Successful treatment of MESOR-hypertension assessed by a self-starting cumulative sum (control) chart was aimed earlier to optimize hypotensive treatment for a then-just-diagnosed 24-year-old individual (TT) who switched his Rx first every 17 days by 4 hours and then mostly at shorter intervals. A statistically significant decrease in MESOR was indicated by the breakout outside the decision interval of a negative (CUSUM) line (21). With continued Rx, the blood pressure MESOR leaves the decision interval, indicating a statistically significant decrease in overall blood pressure. At a certain timepoint, the amplitude is increased, and this can be immediately detected by C-ABPM with CUSUM when monitoring is continuous, as shown elsewhere (17 and Figures 15 and 16 therein). © Halberg.

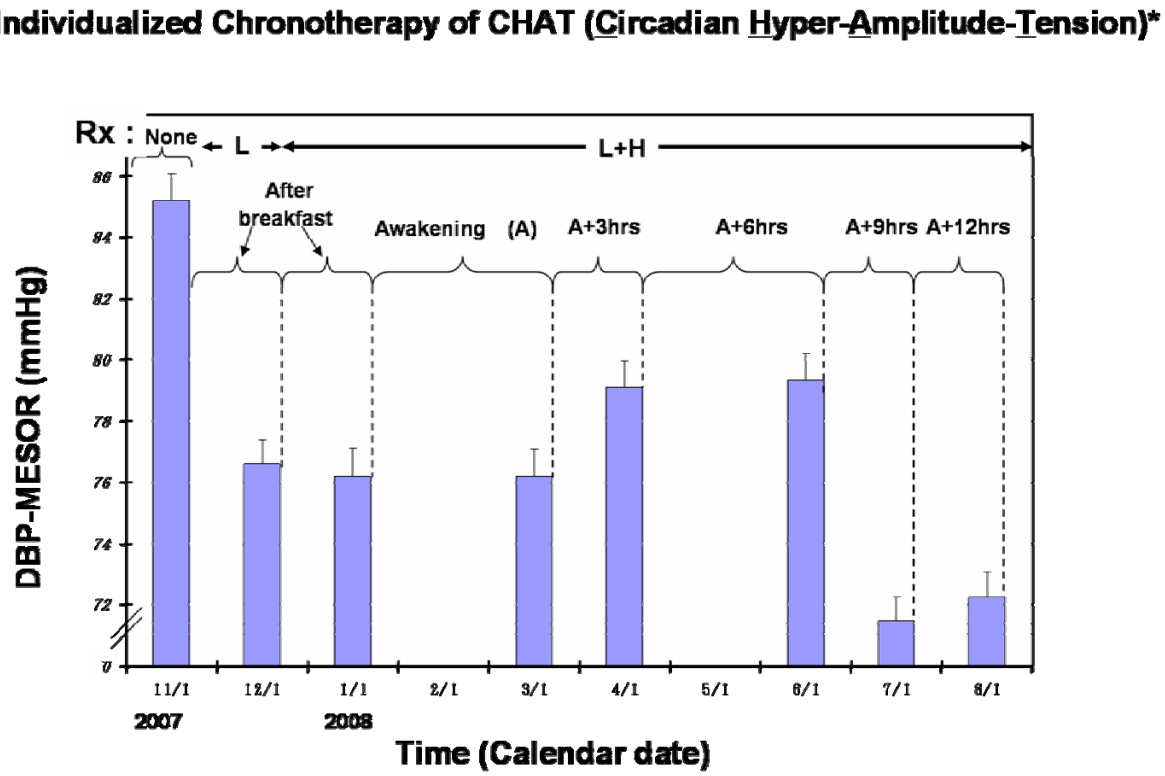


Figure 5. All treatments with Losartan (L) 50 mg and hydrochlorothiazide 12.5 mg lower the MESOR of patient Su's diastolic blood pressure but again not equally, Table 5. In this patient, treatment in the evening lowers the excessive SBP amplitude. © Halberg.

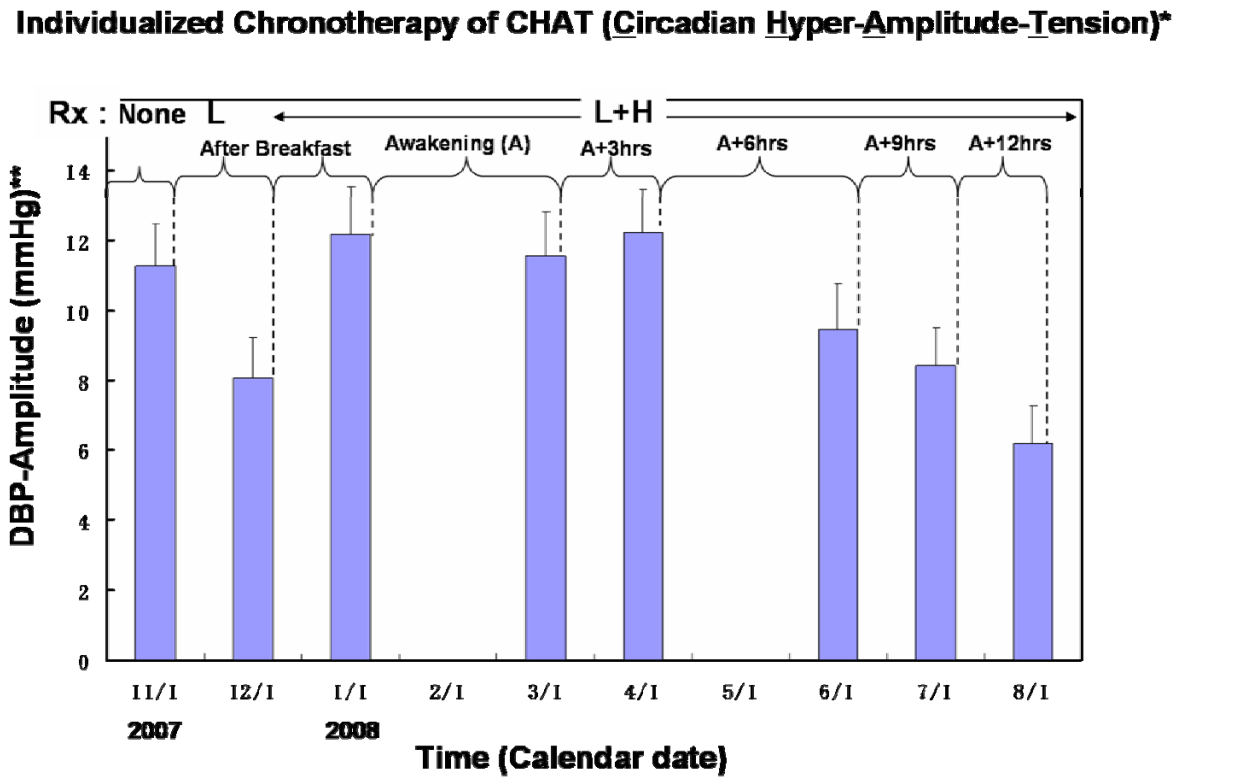


Figure 6. Treatments with Losartan (L) 50 mg and hydrochlorothiazide 12.5 mg affect the circadian amplitude, A, of diastolic blood pressure of patient Su in different ways, raising the high normal amplitude further, at 3 hours after awakening, including CHAT, vs. lowering the A as desired (see Table 5) when the same dose is given in the evening. © Halberg.

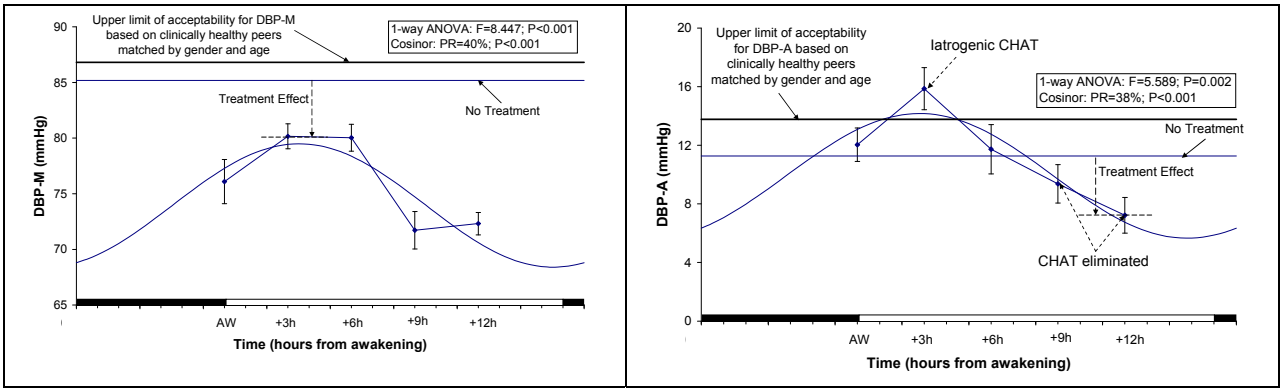


Figure 7. Patient Su: Effects of Losartan (L) 50 mg and hydrochlorothiazide 12.5 mg upon the diastolic blood pressure MESOR and amplitude show a very great circadian time-dependence, whether by analysis of variance or cosinor (P<0.001). A MESOR-hypotensive effect is greater 9 and 12 hours after awakening than at earlier times in the day, and CHAT at these times is eliminated while it was induced with the same treatment taken 3 hours after awakening. © Halberg.

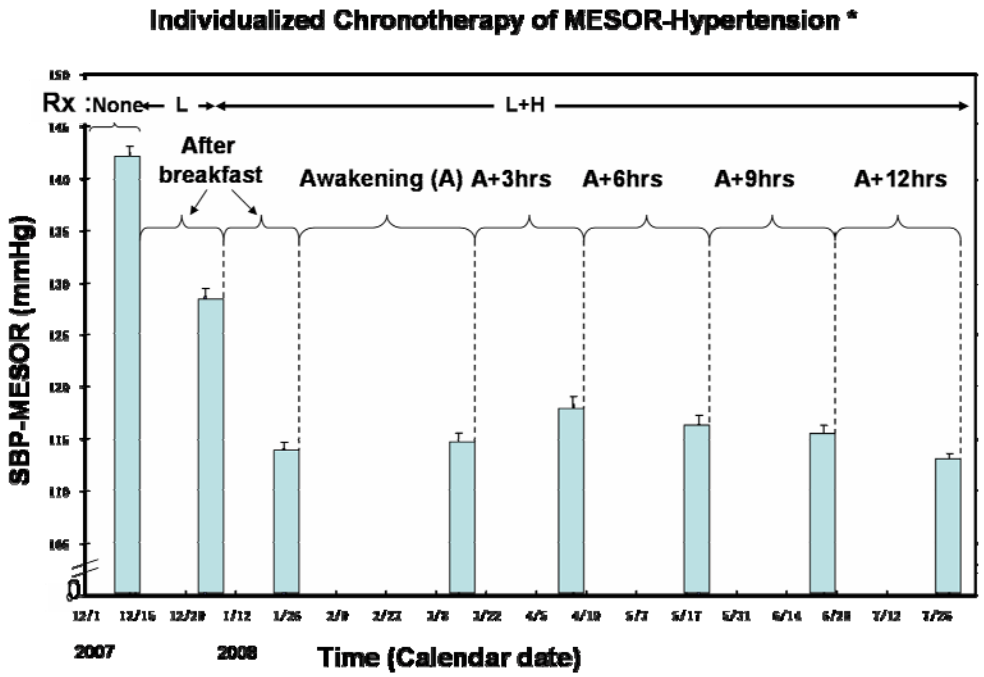


Figure 8. All treatments with Losartan (L) 50 mg and hydrochlorothiazide 12.5 mg lower the systolic blood pressure M of patient Sa (Tables 4 and 5). © Halberg.

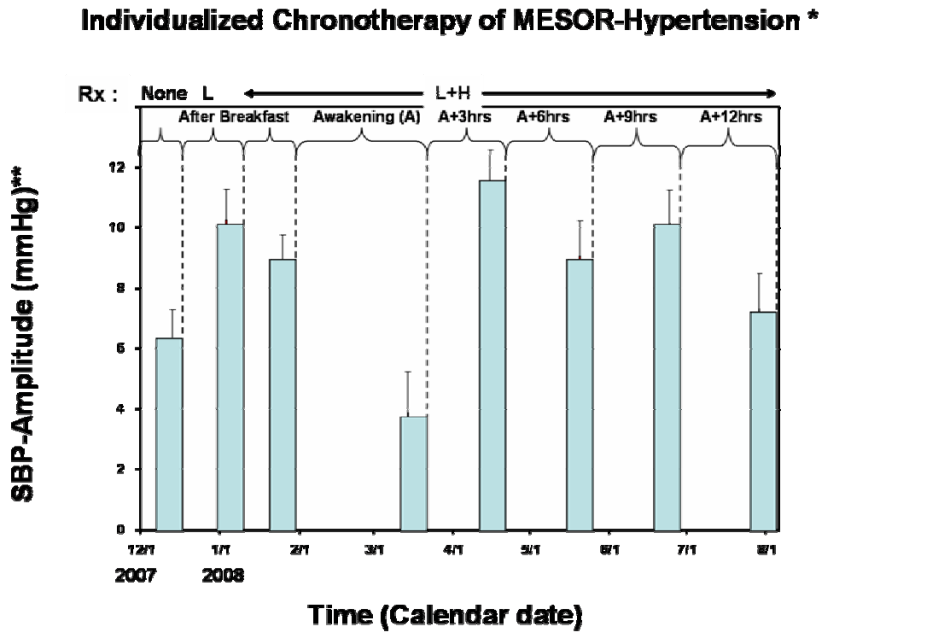


Figure 9. Along the 24-hour time scale, there are differences in the response to Losartan (L) 50 mg and hydrochlorothiazide 12.5 mg of the circadian amplitude of patient Sa's systolic blood pressure. A marked circadian blood pressure response rhythm is of borderline statistical significance (Table 4). © Halberg.

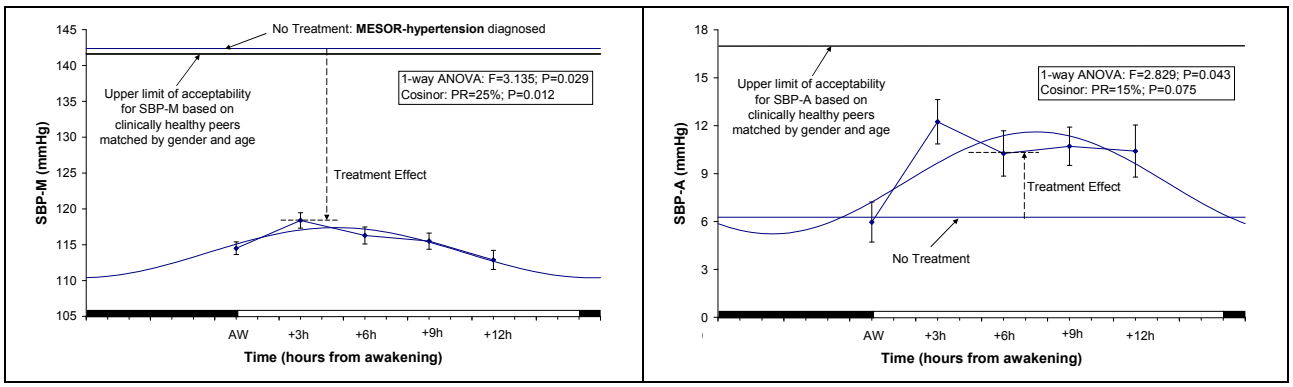


Figure 10. Patient Su: A cosinor and an analysis of variance show a circadian periodic response of the systolic MESOR to Losartan (L) 50 mg and hydrochlorothiazide 12.5 mg. The analysis of variance also shows a difference in response of the circadian amplitude of systolic blood pressure of patient Sa. © Halberg.

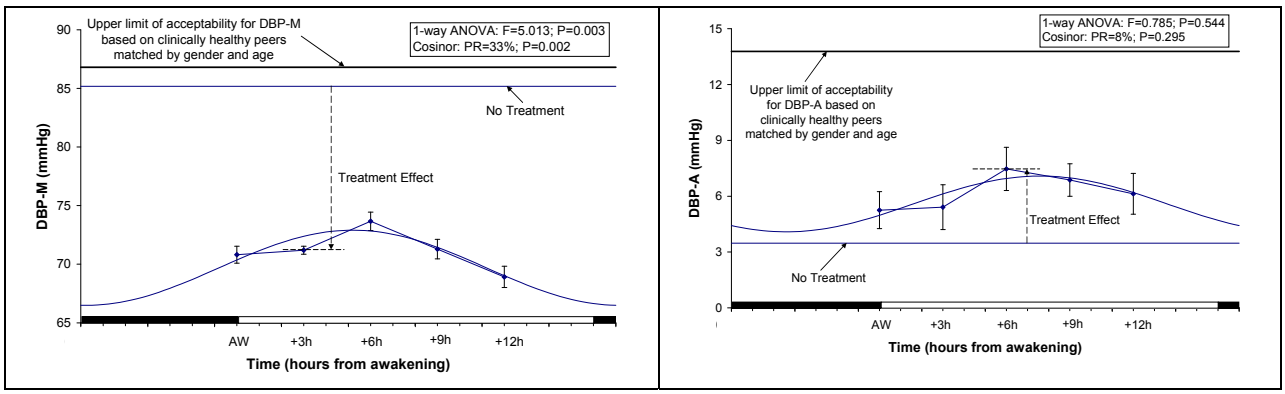


Figure 11. Patient Sa. A cosinor and an analysis of variance show a circadian periodic response of the systolic MESOR to Losartan (L) 50 mg and hydrochlorothiazide 12.5 mg. The analysis of variance also shows a difference in response of the circadian amplitude of systolic blood pressure of patient Sa. © Halberg.

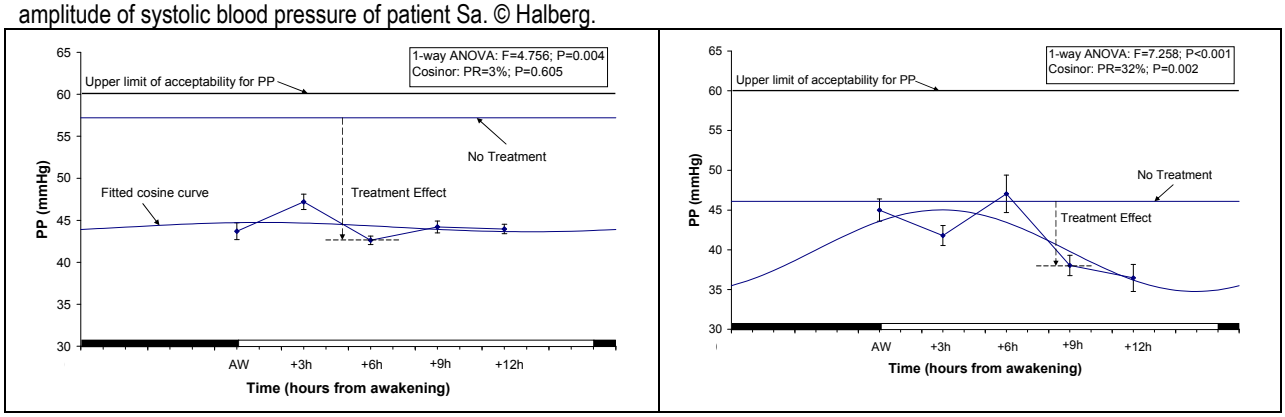


Figure 12. Patient Sa (left) and patient Su (right): Losartan 50 mg combined with hydrochlorothiazide 12.5 mg reduce, with circadian stage dependence, a somewhat elevated pulse pressure which is still within the physiologic range for patient Sa, with a time effect validated by ANOVA (top), but no rhythm is seen by cosinor. There is again a statistically highly significant circadian response rhythm in pulse pressure, validated by cosinor and ANOVA for patient Su, with **c**ircadian **h**yper-**a**mplitude-**t**ension (bottom half). © Halberg.

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Support GM-13981 (FH), University of Minnesota Supercomputing Institute (GC, FH), MSM 0021622402

Table 1: Susceptibility rhythms leading to individualized inferential statistical chronopharmacology and chronotherapy

Year	Description	Author(s)
1952, 1953	2800-fold increase in sensitivity of a corticosteroid assay by accounting for circadian stage (Figure 1 in 2 vs. 1)	Halberg (1, 2)
1955	Circadian susceptibility rhythm to noise	Halberg, Bittner, Gully, Albrecht & Brackney (3)
1955	- - - - - - - - - - " - - - - - - - - - - - - an endotoxin	Halberg, Spink, Albrecht & Gully (4)
1958	Manipulability of a susceptibility rhythm by lighting regimen	Halberg, Jacobson, Wadsworth & Bittner (5)
1958	Detection of (growth) hormone effect on mitoses depends on circadian stage	Litman, Halberg et al. (6)
1959	Effect of ethanol depends on circadian stage	Haus, Hanton & Halberg (7)
1959	Individualized sequential testing	Johnson, Haus, Halberg & Wadsworth (8)
1959	Circadian susceptibility rhythm to a drug (ouabain)	Halberg & Stephens (9)
1960	LD50 to whole-body X-irradiation depends on circadian stage	Halberg (10, discussion)
1961	Circadian susceptibility rhythm to Librium	Marte & Halberg (11)
1963	- - - - - - - - - - " - - - - - - - - - - - - acetylcholine	Jones, Haus & Halberg (12)
1964	- - - - - - - - - - " - - - - - - - - - - - - fluothane	Matthews, Marte & Halberg (13)
1967	Cosinor method	Halberg, Tong & Johnson (14)
1969	Methodological and conceptual context	Halberg (15)
1969	Chronotherapy with penicillin	Reinberg et al. (16)
1970, 1972	Chronotherapy with arabinosyl cytosine (ara-C)	Cardoso et al. (17), Haus et al. (18)
1973	Rhythm in chronotherapeutic indices of hydrochlorothiazide and adriamycin	Halberg et al. (19), Levine et al. (20), Shiotsuka et al. (21)
1974, 1975	Formulation of rules of chronopharmacology and chronotherapy; demonstration of shift of susceptibility rhythm to adriamycin by meal timing	Halberg (22-24)
1977	Doubling of 2-year survival by timing radiotherapy	Halberg (25)
1979	Ara-C chronotherapy brings about cancer cures	Halberg, Nelson, Cornélissen, Haus, Scheving & Good (26)
1979	More antihypertensive chronotherapy	Güllner, Bartter & Halberg (27)
1992	Individualized cancer marker-guided chronochemotherapy	Halberg et al. (28)
1995	More antihypertensive chronotherapy and its optimization by timing	Halberg et al. (29)
1997	Individualized sequential testing of chronotherapy	Cornélissen, Halberg, Hawkins, Otsuka & Henke (30)
2004	"Tree of life"	Halberg et al. (31)
2006	Toxicity marker-guided chronochemotherapy	Halberg et al. (32)

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Table 2: Monitoring spans on patients investigated and timings on treatment (Rx)*

*Su: 66-year-old man, height 167 cm, body weight 70 kg, BMI 25.1, with **c**ircadian **h**yper-**a**mplitude-**t**ension (CHAT)*

Patient	start	end	medication	timing	medication start
1	20071128	20071205	No hypotensive drug		start
	20071226	20080102	Losartan50mg*	after breakfast	20071206
	20080123	20080130	L+H1Tab*	after breakfast	20080110
	20080312	20080318		0 h	20080131
	20080416	20080423		3 h	20080320
	20080604	20080611		6 h	20080423
	20080709	20080716		9 h	20080612
	20080806	20080813		12 h	20080717

Sa: 65-year-old man, height 163 cm, body weight 58 kg, BMI 21.8, with MESOR-hypertension

Patient	start	end	medication	timing	medication start
2	20071213	20071220	No hypotensive drug		start
	20080103	20080110	Losartan50mg*	after breakfast	20071221
	20080125	20080201	L+H1Tab*	after breakfast	20080111
	20080314	20080321		0 h	20080202
	20080415	20080421		3 h	20080322
	20080520	20080527		6 h	20080423
	20080624	20080701		9 h	20080528
	20080729	20080805		12 h	20080702

*L: Losartan 50mg; L+H: Losartan 50mg + hydrochlorothiazide 12.5mg

Table 3: Laboratory data of patients investigated during treatment with Losartan 50 mg and Losartan 50 mg + hydrochlorothiazide 12.5 mg*

*Su: 66-year-old man, height 167 cm, body weight 70 kg, BMI 25.1, with **c**ircadian **h**yper-**a**mplitude-**t**ension (CHAT)*

Pt	start	end	NaCl	Ualb	UV	NorAd	Ad	BNP	PRA	Ald	Cr	UA	Na	K	T-ch	TG	HDL-ch	LDL-ch	BS	HbA1C
1	20071128	20071205	11.24	40.1	2100	525	33	15.4	8.5	106										
	20071226	20080102	12.11		1760															
	20080123	20080130	12.45	7.8	1960	818	24	6.8	120	99.5	0.93	4.4	139	4.2	185	70	65	106	163	6.1
	20080312	20080318	12.73	7.4	1950	451	26	7.4	22	46.7	0.87	4.9			172	137	62	83	204	6.2
	20080416	20080423	10.91		1800	267	24	9.6	23	66.5	0.87	5.5	139	4	176	99	56	96	163	6.2
	20080604	20080611	16.57	17.8	1610	377		14.6	16	71.5	0.81	3.7			180	171	63	95	158	6.3
	20080709	20080716	13.38		940	410		11.4	31	72.6	0.81	4.3	140	4.3	172	107	55	94	141	6.3
	20080806	20080813	11.3	9.2	1150	335	20	8.1			0.81	4.1	140	4.1	176	94	53	104	220	6.4

Sa: 65-year-old man, height 163 cm, body weight 58 kg, BMI 21.8, with MESOR-hypertension

Pt	start	end	NaCl	Ualb	UV	NorAd	Ad	BNP	PRA	Ald	Cr	UA	Na	K	T-ch	TG	HDL-ch	LDL-ch	BS	HbA1C
2	20071213	20071220	14.9	4	2700	555	120	14.0	2	70.2	0.86	2.7	141	4.2	210	138	55	132	112	
	20080103	20080110	15.72		2970															
	20080125	20080201	7.94	5	2700	721	197	8.0	31	98.5	0.87	3.6	142	4.3	208	127	49	128	107	5.3
	20080314	20080321	8.4	4	1930	805	116	6.0	260	109	0.88	3.3	138	4.2	213	214	48	129	112	5.1
	20080415	20080421	10.23		3050	639	69	7.0	58	137	0.89	4.3	139	4.3	229	85	57	156	106	5.3
	20080520	20080527	9.39	3	2280	587	122	9.0	30	117	0.89	3.4	140	4.2	214	94	55	136	106	5.3
	20080624	20080701	10.72	5	2640	572	88	10.0	110	105	0.88	3.5	138	4.1	200	171	44	118	102	5.3
	20080729	20080805	14.5	6	2650	337	87	15.0	87	108	0.91	3.6	139	3.8	214	128	49	140	103	5.3

*L=Losartan 50mg; L+H=Losartan 50mg + hydrochlorothiazide 12.5mg
NaCl=Sodium intake (g/day), Ualb=urinary albumin (mg/day) , UV=urinary volume (ml/day) NorAd=Noradrenaline (pg/ml), Adrenaline (pg/ml)
BNP=brain natriuretic peptide (pg/ml), PRA=plasma renin activity (pg/ml), Ald=aldosterone (pg/ml), UA=uric acid, Na and K serum concentrations, Tch=total cholesterol, TG: triglycerides, HDL: high density lipoprotein, LDL: low density lipoprotein, HbA1C=A1C hemoglobin.

Table 4: Summary of effects investigated by analysis of variance in two men, Su, 66 years of age, and Sa, 65 years of age*

		SBP		DBP		HR		PP		HR/SD	
ANOVA		F	P	F	P	F	P	F	P	F	P
Su	M	9.23	6.18	8.45	<0.01	1.36	0.27	7.26	<0.01	1.47	0.24
	A	5.67	<0.01	5.59	<0.01	0.44	0.78				
Sa	M	3.14	0.03	5.01	<0.01	3.57	0.02	4.76	<0.01	0.32	0.86
	A	2.83	0.04	0.78	0.54	0.32	0.86				

*S: systolic; D: diastolic; BP: blood pressure (mm Hg); HR: heart rate (beats/min); PP: pulse pressure; HR/SD: standard deviation (SD) of HR; M: MESOR (**m**idline-**e**stimating **s**tatistic **o**f **r**hythm), a chronome (time structure)-, in this case circadian rhythm-adjusted mean; A: Amplitude (one-half of the total change accounted for by the fitted cosine curve); F: F-test; P: P-value from test of equality of parameters.

Table 5: Summary of effects investigated by cosinor in two men, Su, 66 years of age, and Sa, 65 years of age*

Variable		PR	P	MESOR ± SE	Amplitude (95% CI)	Acrophase (95% CI)
Su (patient with **c**ircadian **h**yper-**a**mplitude-**t**ension, CHAT)	SBP-M	43	<0.001	113.8 ± 2.10	10.6 (5.2, 16.1)	-154° (-116, -176)
	SBP-A	32	0.002	15.5 ± 1.7	6.6 (2.4, 11.2)	-153° (-101, -181)
	DBP-M	40	<0.001	73.9 ± 1.1	5.5 (2.6, 8.5)	-158° (-120, -180)
	DBP-A	38	<0.001	9.9 ± 1.0	4.3 (1.9, 6.6)	-147° (-99, -174)
	HR-M	3	0.658	71.5 ± 0.7	0.8 ( )	-162° ( )
	HR-A	5	0.454	6.8 ± 0.9	1.5 ( )	-172° ( )
	PP	32	<0.01	39.9 ± 1.3	5.1 (1.8, 8.4)	-149° (-95, -179)
	HR-SD	4	0.515	13.0 ± 0.9	1.0 ( )	-324° ( )
Sa (patient with MESOR-hypertension)	SBP-M	25	0.012	113.8 ± 0.76	3.5 (1.1, 5.9)	-175° (-135, -198)
	SBP-A	15	0.075	8.4 ± 1.0	3.2 ( )	-217° ( )
	DBP-M	33	0.002	69.7 ± 0.5	3.2 (1.5, 4.9)	-183° (-161, -200)
	HR-M	27	0.007	74.6 ± 0.9	4.2 (1.5, 6.9)	-176°(-140, -197)
	HR-A	4	0.539	10.1 ± 1.1	1.7 ( )	-173° ( )
	DBP-A	8	0.295	5.6 ± 0.7	1.5 ( )	-219° ( )
	PP	3	0.605	44.2 ± 0.6	0.6 ( )	-121° ( )
	HR-SD	3	0.641	11.3 ± 0.8	1.2 ( )	-186° ( )

*S: systolic; D: diastolic; BP: blood pressure (mm Hg); HR: heart rate (beats/min); PP: pulse pressure; HR-SD: standard deviation (SD) of HR; M: MESOR (**m**idline-**e**stimating **s**tatistic **o**f **r**hythm), a chronome (time structure)-, in this case circadian rhythm-adjusted mean; A: Amplitude (one-half of the total change accounted for by the fitted cosine curve); PR: percent rhythm; P: P-value.

Table 6. TRENDS AS A FUNCTION OF TIME

	Systolic BP			Diastolic BP		
Study Stage	slope (mmHg/day)	r	P	slope (mmHg/day)	r	P
Patient Sa						
NoRx	-1.558	-0.226	**<0.001**	-0.592	-0.145	**0.008**
Losa	0.136	0.019	0.727	-0.263	-0.061	0.255
PBkft	-0.319	-0.049	0.376	0.052	0.012	0.822
P-00	-0.469	-0.053	0.336	-0.378	-0.075	0.169
P-03	0.957	0.111	0.056	0.211	0.036	0.532
P-06	-0.790	-0.095	0.083	-0.514	-0.088	0.110
P-09	0.032	0.004	0.940	0.364	0.073	0.189
P-12	0.703	0.089	0.110	0.245	0.044	0.432
Patient Su						
NoRx	-1.984	-0.193	**0.001**	-0.876	-0.111	0.064
Losa	-2.148	-0.201	**<0.001**	-1.338	-0.165	**0.003**
PBkft	-0.179	-0.016	0.780	-0.239	-0.027	0.646
P-00	-1.172	-0.091	0.127	-1.408	-0.153	**0.010**
P-03	0.074	0.006	0.914	-0.366	-0.040	0.495
P-06	2.337	0.176	**0.002**	0.182	0.021	0.711
P-09	-0.237	-0.023	0.681	-0.267	-0.035	0.535
P-12	-0.707	-0.063	0.265	-0.174	-0.024	0.665

Time-specified norms reveal full systolic but incomplete diastolic early MESOR-hypertension, MH

Yoshihiko Watanabe[12], Germaine Cornélissen[3], Kuniaki Otsuka[2], Miguel Revilla[4], Jerzy Czaplicki[5], Othild Schwartzkopff[3], Jarmila Siegelova[6], Franz Halberg[3] and the broader BIOCOS project

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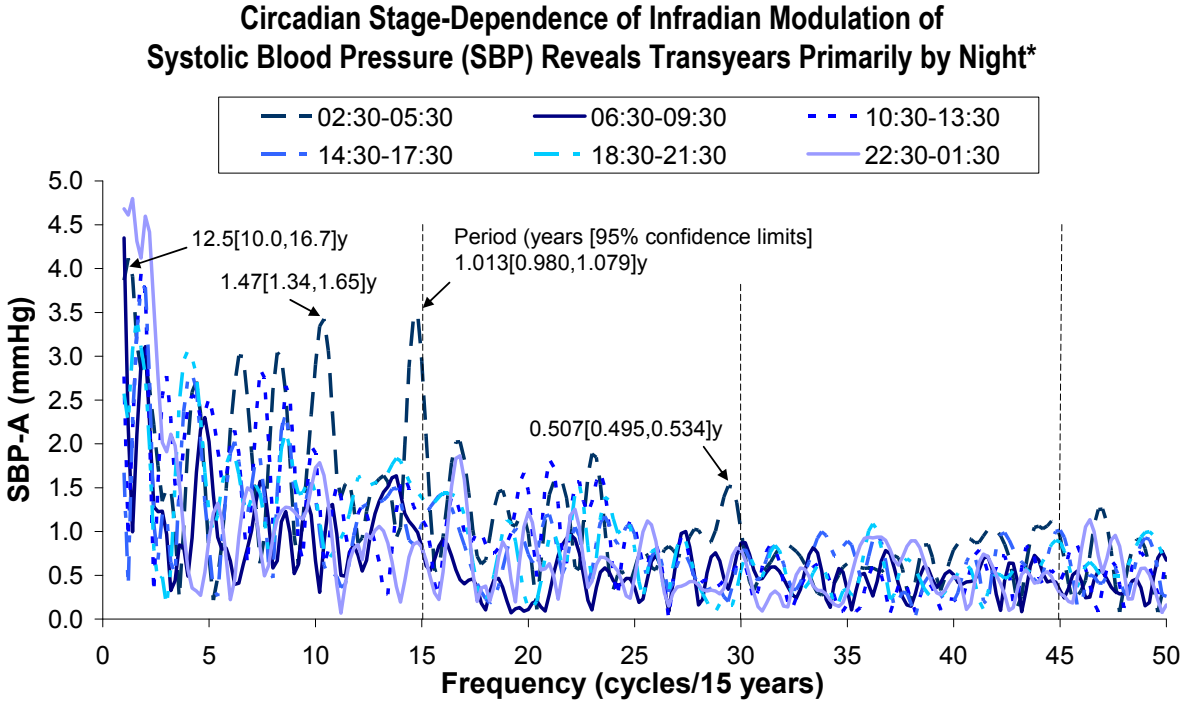
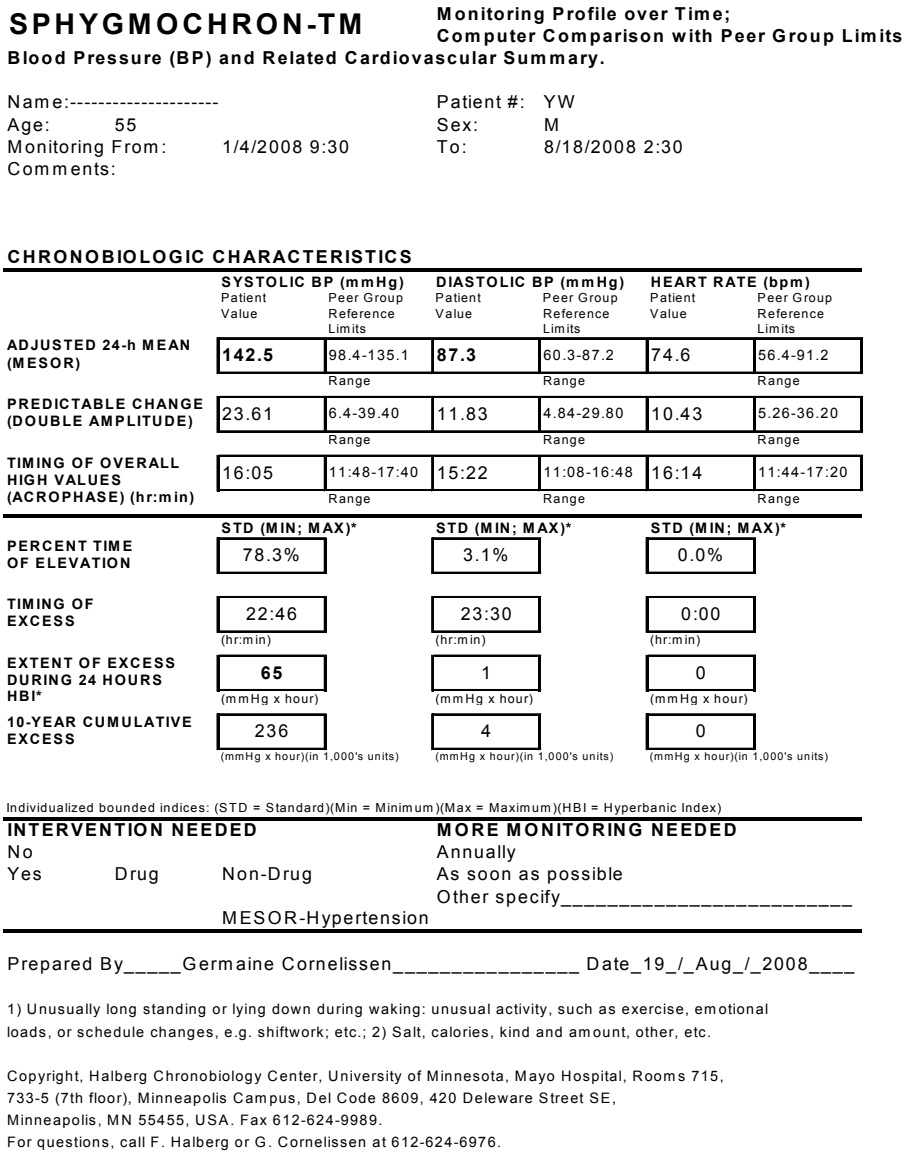
Aim. Relatively unobtrusive, (on a family-and-friends basis easily) affordable instrumentation for relatively dense (e.g., half-hourly) automatic blood pressure (BP) and heart rate (HR) monitoring has become available, serving for ambulatory use (ABPM) in the hands of an international project on The BIOsphere and the COSmos, BIOCOS (corne001@umn.edu), for a chronobiologic (C) parametric (cosines-fit-based) and non-parametric (time-qualified stacking-based) interpretation, i.e., for C-ABPM. With C-ABPM for at least 7 days/24 hours, a reliable



* Results by population-mean cosinor summarizing data collected during 6 different 4-hour intervals (data at separate clock hours analyzed separately); Data from YW (M, born 23 Nov 1952), cardiologist who monitoed himself around the clock mostly at 30-min intervals with only few short interruptions from August 1987 to Jan 2003 (between ages 35 and 50).

Figure 1. Data collected around-the-clock for 15 years by YW at half-hour intervals were averaged hourly. Data from each clock hour (24 separate time series) were analyzed by least squares spectra. Results from 4 consecutive clock hours (assigned at midpoints) were summarized by population-mean cosinor and compared among the six 4-hour circadian stages (shown as six curves in this graph). © 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:

CHRONOBIOLOGIC CHARACTERISTICS

	SYSTOLIC BP (mmHg) Patient Value	SYSTOLIC BP (mmHg) Peer Group Reference Limits	DIASTOLIC BP (mmHg) Patient Value	DIASTOLIC BP (mmHg) Peer Group Reference Limits	HEART RATE (bpm) Patient Value	HEART RATE (bpm) 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)

INTERVENTION NEEDED
No
Yes Drug Non-Drug
MESOR-Hypertension

MORE MONITORING NEEDED
Annually
As soon as possible
Other specify_____

Prepared By_____Germaine Cornelissen_____ Date_19_/_Aug_/_2008____

1) Unusually long standing or lying down during waking: unusual activity, such as exercise, emotional loads, or schedule changes, e.g. shiftwork; etc.; 2) Salt, calories, kind and amount, other, etc.

Figure 2. The top section of the sphygmochron, between the first two heavy horizontal lines, shows that the MESOR of SBP is outside the limit of acceptability for peers, as is the MESOR of DBP. For SBP in Figure 3, most single mean values by clock-hour and -minute are within peer-group limits, albeit very close to the upper continuous line limit in Figure 3. In Figure 4, the stacking of the data can mislead to call "normal" what is already abnormal. The DBP MESOR's deviation from the upper limit is small, 0.1 mmHg. It may seem far-fetched to base decisions on a difference of a small fraction of 1 mmHg for individuals used to judge at best a few 24-hour profiles or single values. In the case of YW in turn, there are sets of values for over half a year, here summarized in Figures 2-5, and further information in the light of 21 years of previous sphygmochrons. We conclude, from the upper parametric part of the sphygmochron in this figure, that we detect earliest abnormality in DBP as well as SBP, at variance with the lower half of the sphygmochron providing results from the inspection of a non-parametric stacking section with an abnormality only of SBP. © Halberg.

diagnosis of MESOR-hypertension (MH) can be more thoroughly approximated than in the now-conventional approaches, but eventually dense monitoring from birth to death is advocated. Non-drug treatment, including relaxation and diet, notably a reduction of sodium intake, if and only if documented as desirable by monitoring, is then pertinent (1, 2). When non-drug intervention fails,

drug treatment can be considered again with continued monitoring and an optimization of any effect by timing, in keeping with an international consensus meeting (3).

Background. A physician-scientist, YW, has been using C-ABPM for over 2 decades (4-10). He started at 35 years of age in August 1987 with half-hourly measurements around-the-clock with the aim (in August 2008) of continuing the monitoring. He has used and plans to further use the accumulating time series for the analysis of aging as it may differ in various circadian and other rhythm stages (11), and, as the case may be, to detect any anomaly seen as a vascular variability disorder (VVD) (12). At the same time, YW has been seeking and finding signatures of heliogeomagnetic and/or of any other non-photic environmental factors (5), including those of the about (~) 10-year Schwabe cycle (13). The half-hour density of the data also allows the study of interactions between circadian stages and different infradian rhythms that are dependent upon or are demonstrable only during certain limited stages of the about-daily cycle (10, 11, 14). Different time series, each limited to a specific fraction of the 24-hour day, used to approximate different circadian stages (10, 11), can lead to inferences different from each other and from those drawn from around-the-clock data, Figure 1.

In addition to cardiologic and transdisciplinary research, we here explore or demonstrate, as the case may be, the practical merits in an improved health care by an individualized computer-aided self-surveillance of one's cardiovascular variability. This aim was clearly stated in Ignaz Zadek's doctoral thesis for his medical degree in Berlin in 1880 (15) and published one year later (16). Zadek wanted to focus on BP variability in a given patient (15, 16). His concept was extended by Theodore C. Janeway of Johns Hopkins University in 1904 (17). It should be noted that Janeway, an opinion leader in his time, before examining a patient insisted on gathering enough data to study periodic variation***s*** (we emphasize his use of the plural "variations", indicating his interest not just in the change from day to night along the 24-hour scale, but also in variability from day to day and along longer time series such as years [18]). There are many rhythmic variations of BP in addition to circadians (18-22). Beyond finding periodicities mimicking the Schwabe cycle on himself noted above, YW has also already demonstrated about-yearly cycles that drift and can be absent for long spans (of years), replaced by transyears, cycles with periods, τ, longer than a year, mimicking the τs found in the solar wind's speed and proton content (20, 21).

Method. While the extended cosinor (23-25) and cross-spectral analyses were used for research, a sphygmochron, as a BP and related cardiovascular summary, Figure 2, was prepared on the continuously accumulating data as discussed elsewhere (18, 26) and as a screen for a VVD that was found, namely systolic and diastolic MESOR-hypertension, based on a computer comparison with peer group limits of YW's last over-7-month long section of his 21-year monitoring profile over time.

Results. Figures 3-5 are plexograms, showing 48 averages of data stacked at intervals of 30 minutes along an idealized 24-hour scale, irrespective of day of sampling. Each point corresponds to the average of many values at roughly the same clock-hour and minute within a bin on different consecutive days from January 4 to August 18, 2008. It is clear from Figure 3 for SBP that the majority of these plexogram values are (as yet) only very slightly, yet clearly outside the normal range, delineated on the basis of data from clinically healthy peers of the same gender and age. For diastolic BP in Figure 4, only three of 48 average values are unacceptable (3.1%), yet they all approach the upper limit of acceptability. All HR values in Figure 5 are well within the range of peers matched by gender and age.

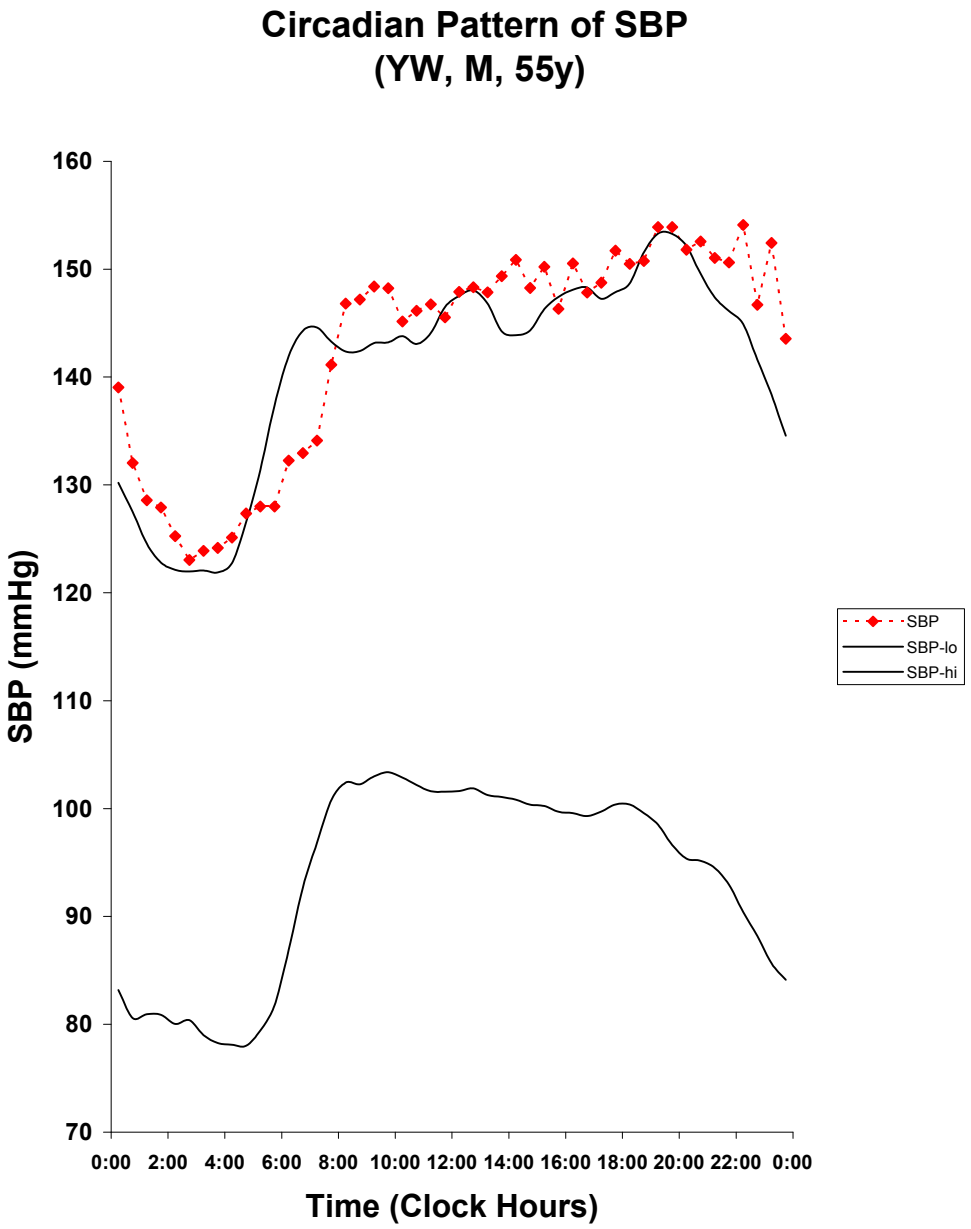


Figure 3. Data covering 7.5 months stacked around the clock at half-hour intervals. Most of the SBP values lie slightly but clearly outside the upper limit of peers of the same gender and age. See discussion in Figure 2 legend. © Halberg.

In the upper parametric portion of Figure 2, the conclusion that SBP was abnormal is derived first from an abnormal MESOR of 142.5 mmHg for SBP. The abnormality of SBP is also seen from stacking, a nonparametric approach (summarized in the section between the second and third heavy horizontal lines): the extent of excess for this variable exceeded the upper limit of acceptability of 50 mmHg x hour for a basic index (limit not shown). Furthermore, the percentage time above the upper limit was found more than three-fourths of the time (78.3%), a further nonparametric result.

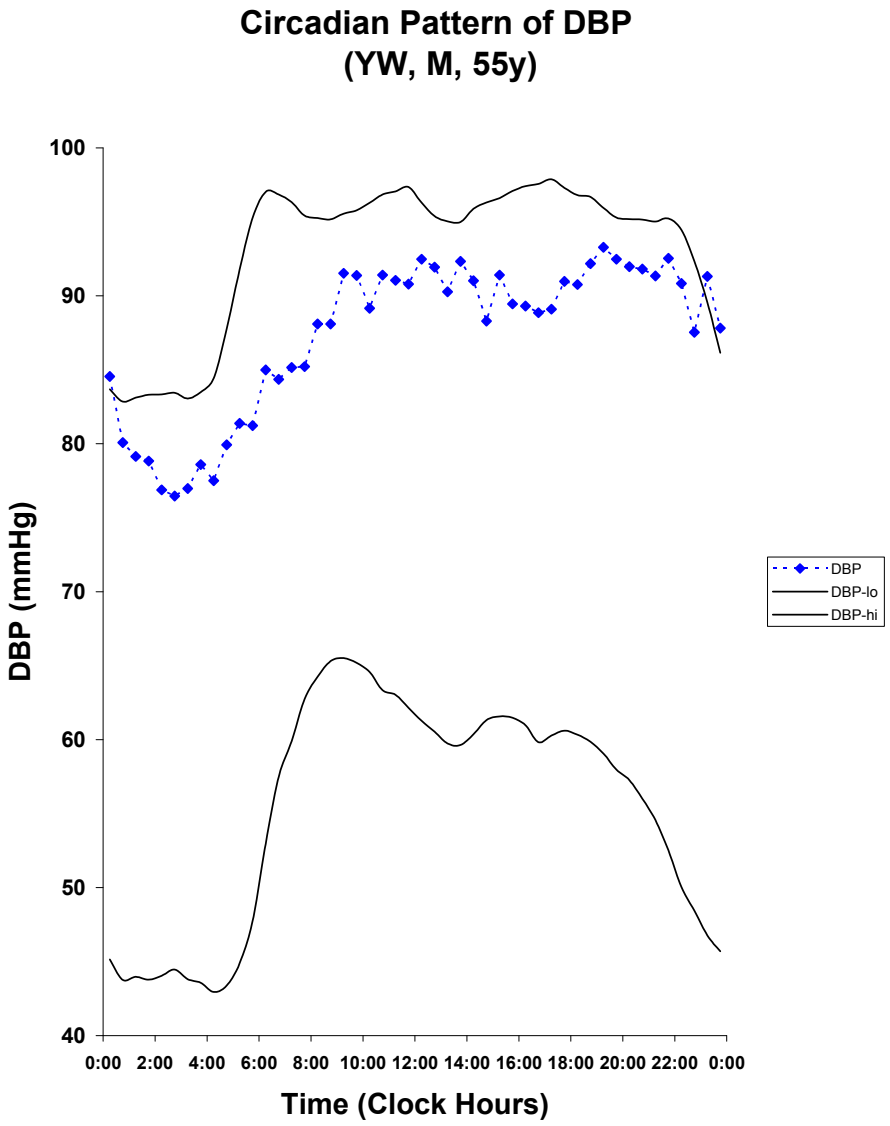


Figure 4. DBP values are high, close to but mostly below the upper limit of acceptability. Nonetheless, as seen in Figure 2, their MESOR is abnormal. The cosinor detects abnormality in the time-qualified normal range. © Halberg.

By contrast, in the lower part of the sphygmochron DBP abnormality is observed only 3.1% of the time and excess is practically zero (1 mmHg x hour rather than over 50 as for SBP). In this case, however, the upper parametric portion is the decisive diagnosis: the DBP MESOR, a rhythm-adjusted average, is above the upper limit by 0.1 mmHg, a difference which will seem trivial for anyone used to looking at **the** "true" (imaginary) single BP measurement or even at the mean of a 24-hour profile. The merit of this diagnosis cannot be suggested based on a single case, but it is in keeping with the assumption that, on a population basis, for each mmHg, an increase in risk does occur when the population size is large enough, and if a population is still larger, the increase of 0.1 mmHg will also count. If a line is to be drawn somewhere, the sphygmochron shows that most systolic values are above and most diastolic values are high yet below the prediction limit of peers.

The point of a sphygmochron in the case of YW at this time is that there is a double systolic and diastolic BP disorder that constitutes a solid warning and is best treated and that can be picked up by cosinor while DBP is still in the range of peers.

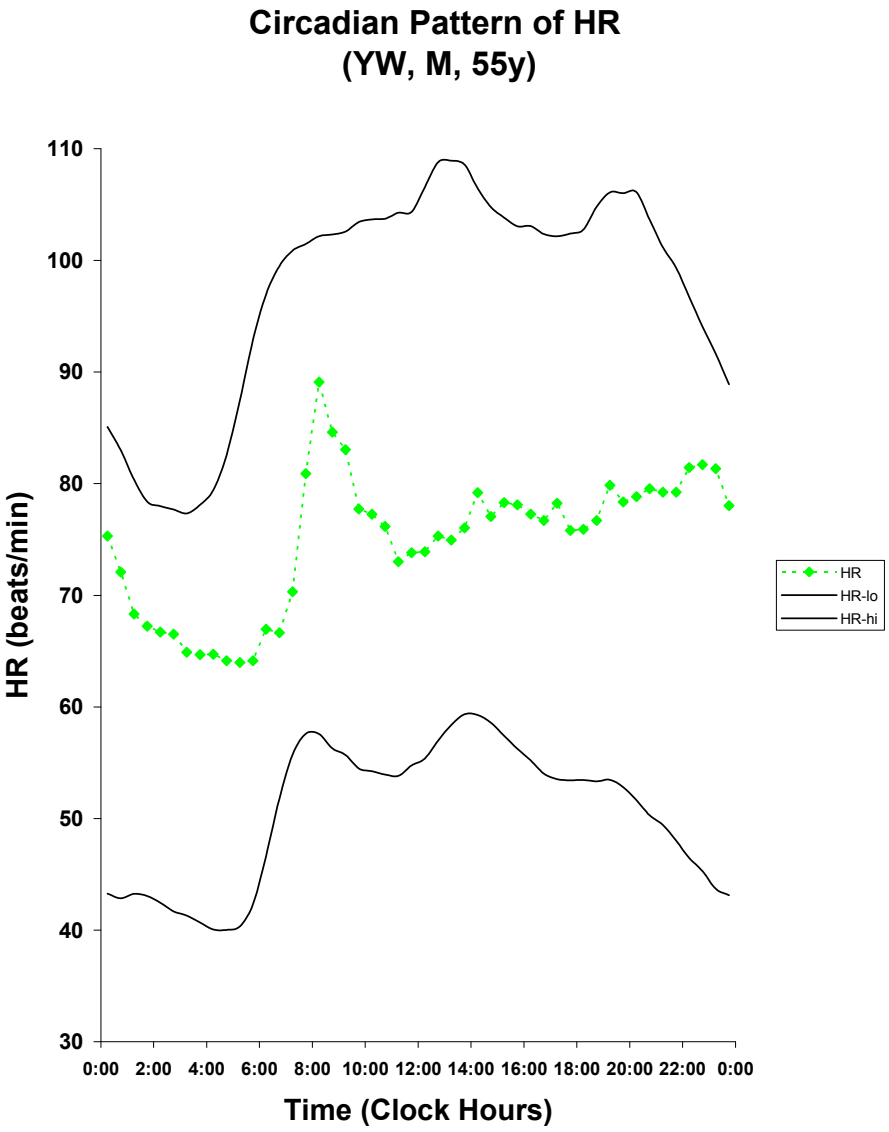


Figure 5. HR values are well within the normal range of peers, distant from both upper and lower limits. © Halberg.

Whether drug or non-drug treatment is indicated must remain the decision of the cardiologist/scientist/subject, who at this time prefers to lower his salt intake, fully aware that the lowering of sodium intake must not be done blindly, without monitoring. This dietary manipulation can raise rather than lower BP-M in a small number of subjects, whereas it is apparently not pertinent on still other subjects (2). Only testing again while monitoring BP and manipulating sodium intake can provide an answer that has to be sought for each given individual.

Discussion. Garages are monitored continuously to prevent crime, including rape. Experimental animals are being monitored to develop new drugs. Those for whom the drugs are

being developed should also be monitored to find out when non-drug treatment should start as well as when drug treatment should begin, once non-drug approaches are documented by C-ABPM to have failed. In the case of YW, the stage has been detected when, on an over half-yearly C-ABPM basis, both SBP and DBP became parametrically abnormal, something that summaries and displays of stacked data could confirm for SBP but not (yet) for DBP. This inspection of stacked data fails to indicate abnormality in DBP, as compared to peers of the same gender and age, but not values close to the upper limit. Do we witness the moment when the MESORs have become abnormal, but not yet the underlying single values? Did an increase in circadian amplitude precede that in MESORs, as in the case of an Okamoto rat (27), and did an increase in LVMI (28) precede the MESOR-increases? All of these questions await further scrutiny in YW's database and in time series of others.

A methodological point to be emphasized for both variables is that, in the case of YW with an assessment of cosinor yielded parameters, abnormality can be detected early before a nonparametric approach detects it in DBP as well as SBP.

Conclusion. C-ABPM, when continued as a tool of preventive cardiology, can detect an earliest individualized VVD and can prompt intervention while the same data serve for transdisciplinary research (29).

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Differing far-transyear/calendar year amplitude ratios in blood pressure vs. heart rate in adolescence

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Abstract. We mapped the time structure during childhood and adolescence of systolic (S) and diastolic (D) blood pressure (BP) and heart rate (HR) to find that a far-transyear dominated over the calendar year in a boy's (FW) spectra of BP and vice versa in the spectrum of HR. Only transyears and no calendar year components were found in the BP and HR of the boy's father (YW) in a record starting at 35 years of age and continuing for over a decade around the clock at 30-minute intervals.

Background, Subject and Method. The extended cosinor (1-3) was used on data from FW, a clinically healthy boy who had been monitored for the first 40 days of life at half-hour intervals, revealing a gradual transition from dominant (non-photic) infradian (about half-weekly and weekly) components to a (photic) circadian rhythm (4). Here, we examine the relative prominence of non-photic infradians in the para-annual spectral region, also mapped in the boy's father (5, 6). Near-transyears (1.00 year < [τ {period} - CI {95% confidence interval}] < [τ + CI] < 1.20 years) and far-transyears (1.2 years ≤ [τ -CI < [τ + CI] < 1.9 years) have been documented elsewhere (7).

Results. Figure 1 describes for FW the well-known trends during childhood and adolescence of BP and HR self-measured daily on awakening. As anticipated, the trend is ascending in systolic (S) BP and diastolic (D) BP (top two rows) and descending in HR (bottom row). The trends in BP appear linear, those in HR curvilinear. Hence the two BP series were linearly detrended, whereas a second-order polynomial was used to detrend the HR data. Results from the extended cosinor on the residuals are shown in Figures 2 and 3 and are partly summarized further in Table 1. The data suffice to assess, with uncertainties, a transyearly component that is more prominent than the yearly (circannual) component for SBP and DBP, while a calendar year dominates the spectrum of HR. All three variables reveal a component longer than a year in the category of a far-transyear (7). A 7-day synchronized circaseptan rhythm and a precise 3.5-day rhythm are seen for the HR of FW (Figure 3), whereas only a circasemiseptan component is societally synchronized in SBP but not in DBP, and a circaseptan peak differs from precisely 7 days in both SBP and DBP.

Discussion. Information from series of single measurements at a fixed clock-hour is not necessarily the same as that based on around-the-clock profiles and can mislead, as shown on himself by YW, the father of FW (5) and by others elsewhere (8, 9). Results on infradians can differ as a function of circadian stage to the extent that a circasemiannual component of probable geomagnetic origin is apparent in BP measurements taken in the evening for 22 years by a father (SBS) starting measurements in his 60s, whereas in the spectrum of his measurements taken in the morning, there is a valley at the 0.5-year trial period (8). SBS's son, RBS, started self-measurements in his early 20s and is still self-measuring in his own 60s (10). An alignment of measurements from two generations provides a perspective over most of a lifetime, yet remains to be qualified in that inferences remain tentative. With this background, it is noteworthy that in data collected at awakening, in the BP of FW, a transyear prevails, whereas an about-yearly change is statistically significant but of lower amplitude, Table 1. The reverse is true overall for HR in FW, Table 1.

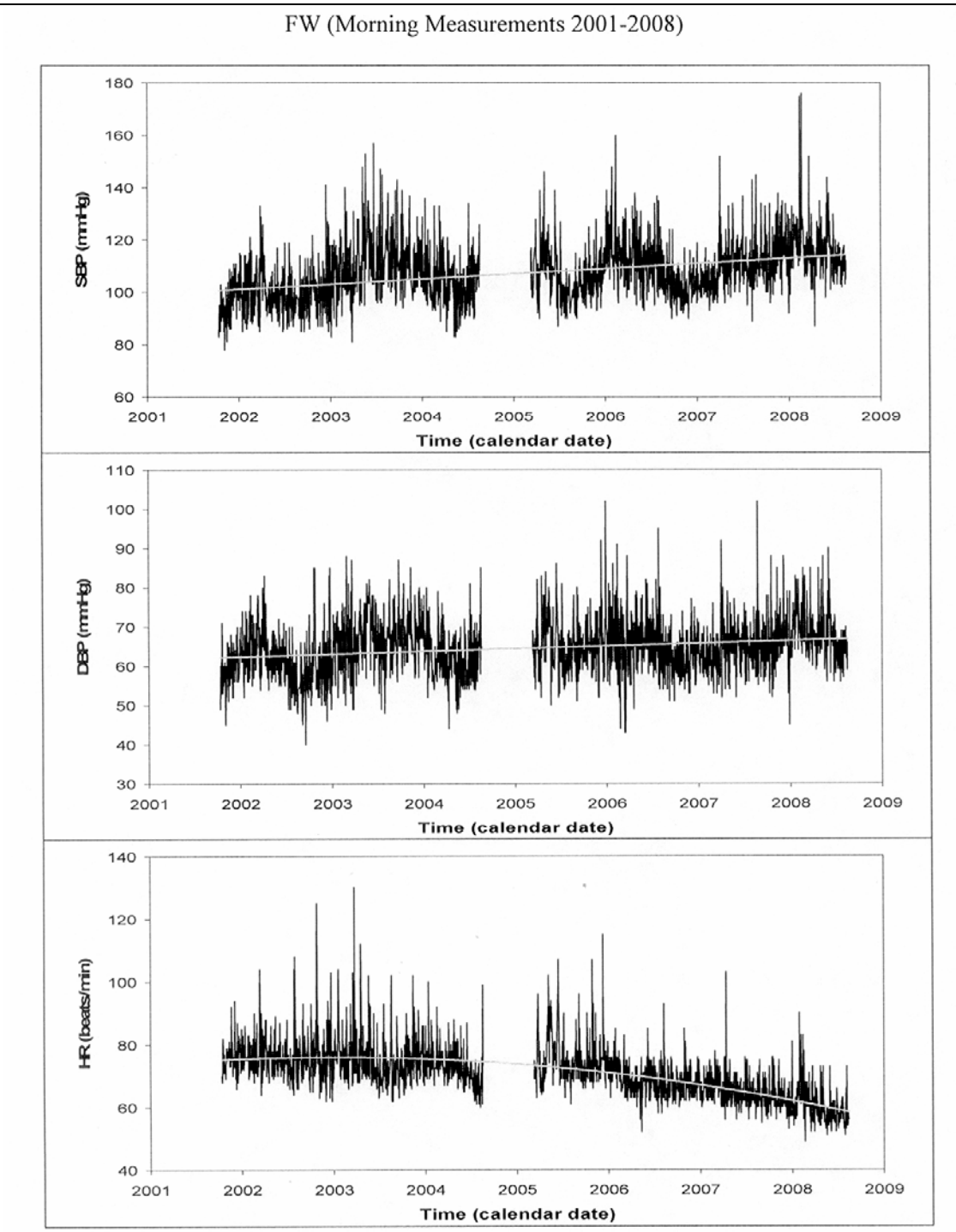

Figure 1. Time course of systolic (S) and diastolic (D) blood pressure and heart rate (HR) measured daily upon awakening by a boy (FW) 8 to 15 years of age, participating in familial autorhythmometry. © Halberg.

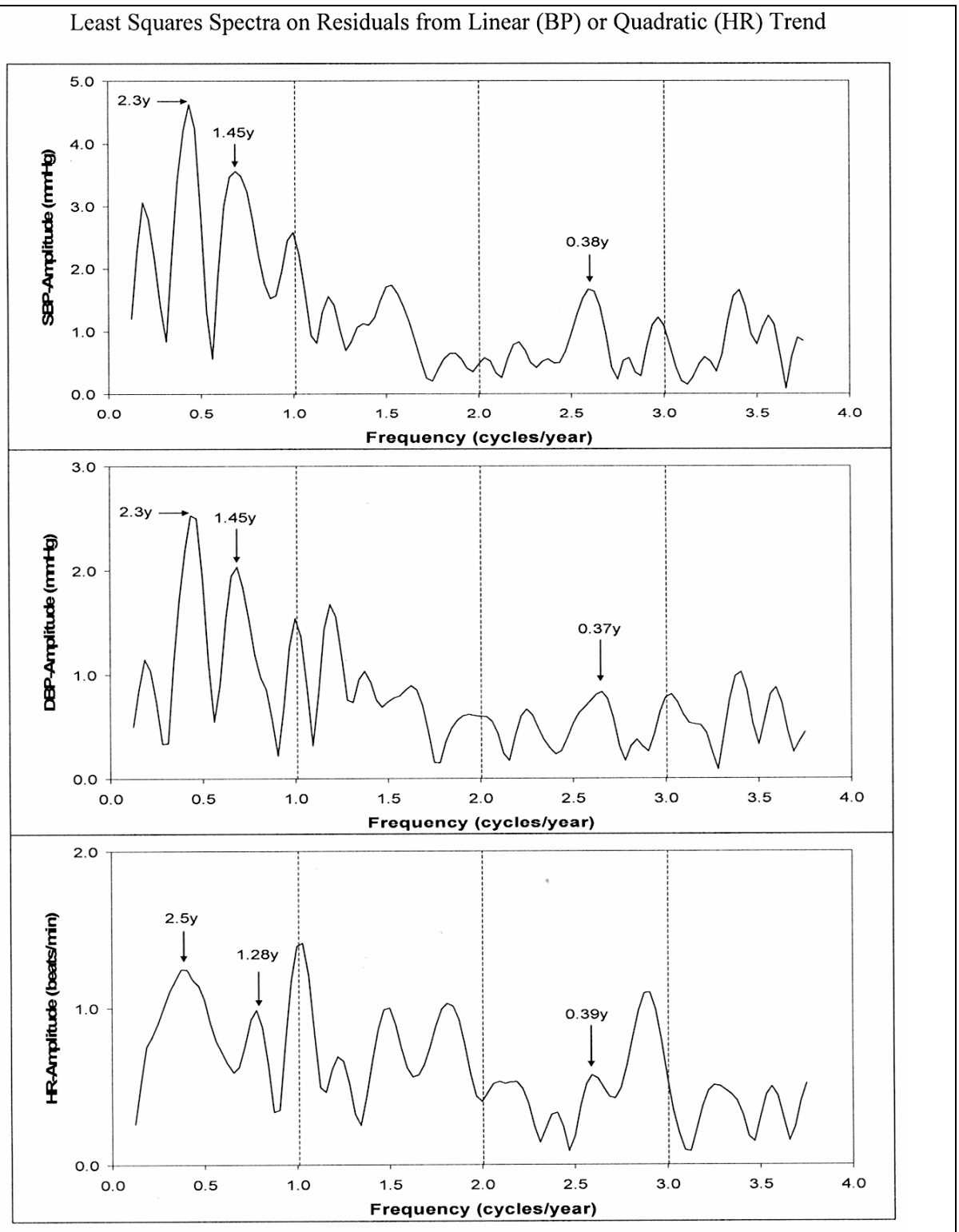

Figure 2. Components in a spectral window of the systolic (S) and diastolic (D) blood pressure (BP) and heart rate (HR) of FW. Note that as compared to the calendar year component's amplitude, A, numerically, the A of the also-present transyears is larger for SBP and DBP and smaller for HR (see also Table 1). © Halberg.

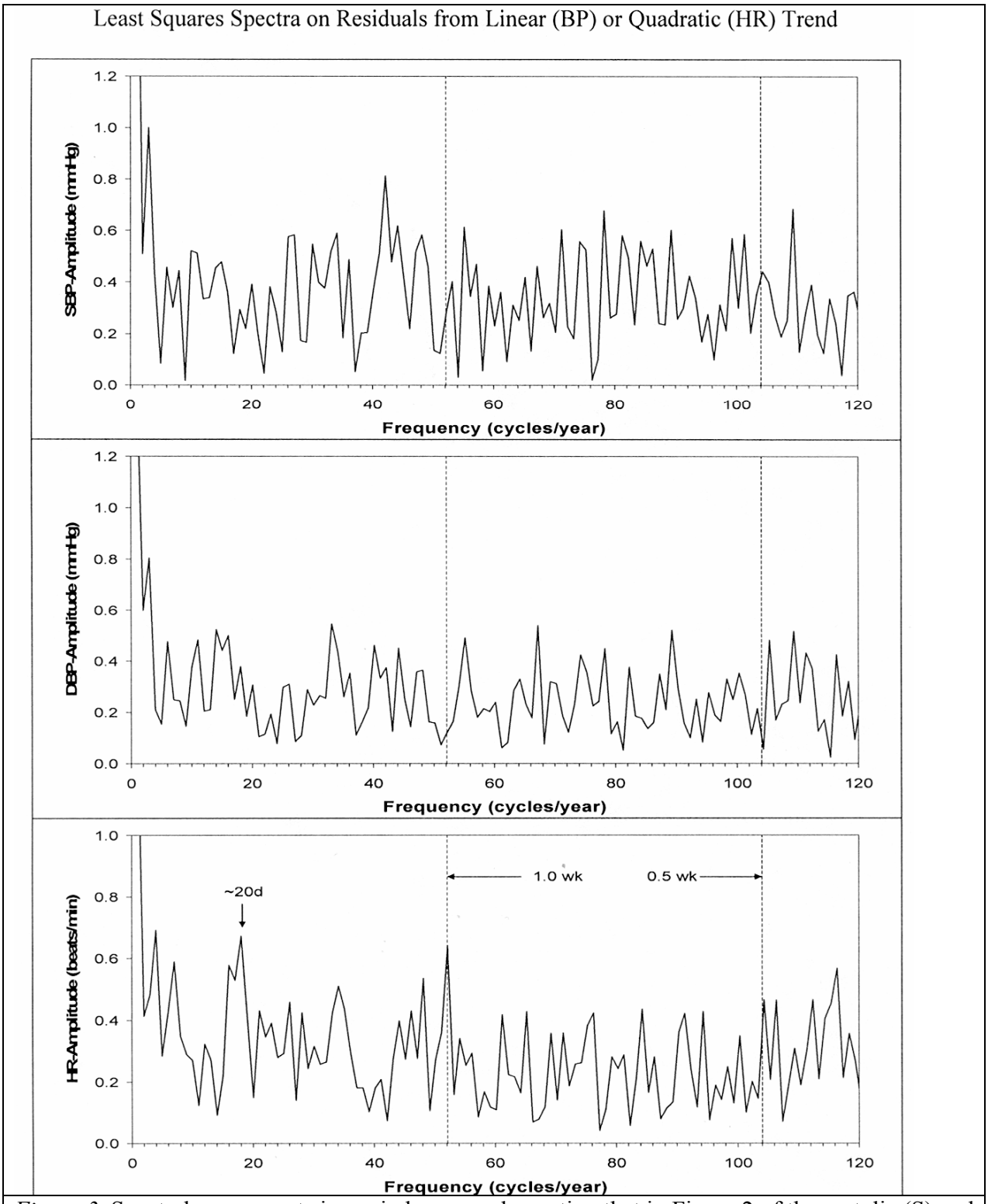

Figure 3. Spectral components in a window complementing that in Figure 2 of the systolic (S) and diastolic (D) blood pressure (BP) and heart rate (HR) of FW. Note the 7-day synchronized circaseptan component with a circasemiseptan in HR but no corresponding prominent societally-synchronized component in BP. © Halberg.

In the case of FW's father, between 35 and 55 years of age, transyears replace any calendar-yearly component in BP and HR. It remains to be clarified whether the spectral structure of measurements taken at other clock-hours differs from that in the morning, as shown for SBS (8) and YW (6, 11). Transyears are also found in the incidence of natality as a population phenomenon in some geographic locations such as the Philippines (12) and Brazil (13), but not in Japan (14) or Italy (15).

In a spectrum, transyears characterize the incidence of sudden cardiac death in some geographic locations, where they can replace the calendar year, but not in other locations (7, 16), where there is only a calendar year, and at still other sites, both a calendar year and a transyear coexist. Transyears are also reported in spectra of the incidence of strokes (17) and epilepsy (18) in Slovakia. The mapping of the infradian aspects in physiology and pathology opens new perspectives in the otherwise neglected range of infradian cycles, as yet ignored by reference only to time-unspecified normal values.

Conclusion. Transyears, signatures of the solar wind's speed, can characterize the human circulation on awakening, during a span bracketing puberty in an 8-15-year-old boy (FW). Without extrapolating the details here recorded to other clock-hours and other individuals, it seems worthwhile to extend the monitoring of the circulation to families in order to recognize early infradian as well as circadian abnormality and to attempt to treat it (cf. 6).

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Table 1: Transyear dominates over calendar-year in blood pressure, and vice versa in heart rate for a boy (FW)*

Variable (units)	Trial period (years)	Period (years) (95% CI)	Amplitude (A) (95% CI)	Amplitude ratios (%) (vs. 1-year A)
SBP (mmHg)	1.30	1.45 (1.41, 1.50)	3.56 (2.58, 4.54)	137
	1.00	1.006 (0.977, 1.035)	2.60 (1.59, 3.61)	
	0.40	0.384 (0.377, 0.390)	1.68 (0.68, 2.67)	65
DBP (mmHg)	1.30	1.47 (1.42, 1.53)	2.05 (1.38, 2.71)	133
	1.00	0.996 (0.953, 1.028)	1.54 (0.86, 2.22)	
	0.40	0.377 (0.368, 0.386)	0.83 (0.17, 1.50)	54
HR (beats/min)	1.30	1.28 (1.20, 1.36)	0.99 (0.33, 1.65)	69
	1.00	0.983 (0.950, 1.016)	1.43 (0.79, 2.07)	
	0.40	0.346 (0.340, 0.351)	1.11 (0.47, 1.75)	78

* Extended cosinor analyses of daily systolic (S) and diastolic (D) blood pressure (BP) and heart rate (HR) self-measurements upon awakening by a boy during about 8 years from 8 to 15 years of age (13 Oct 2001-16 Aug 2008). 95% CI: 95% confidence interval; amplitude: measure of one-half of the extent of change within one cycle predictable by the fitted cosine model. In YW, the father of FW, no yearly component is demonstrable during a decade of data obtained during a span when he was 35 to 46 years of age, preceding by another decade the diagnosis of MESOR-hypertension. Aligning the results from monitoring of both father and son along the scale of age may provide information but will eventually have to be checked by lifetime monitoring of families. Until then, the best that can be done is to monitor more subjects opportunistically.

Transyears, no calendar-year in blood pressure decades before MESOR-hypertension: normal or abnormal?

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Aim. To map, in a clinically healthy cardiologist/scientist (YW) (1-7), any infradian cycles that characterize the blood pressure (BP) and heart rate (HR) for a possible diagnostic use of their alterations during a decade preceding the parametric diagnosis of both systolic (S) and diastolic (D) MESOR-hypertension.

Subject. The first section (August 26, 1987, to August 4, 1998) of a 21-year record of YW, is analyzed herein by the extended cosinor, in retrospect after the diagnosis of MESOR-hypertension (MH) was established on the basis of YW's data from January to August 2008, both parametrically and nonparametrically for SBP and parametrically for DBP by a sphygmochron, a summary over time of BP and related variables, interpreted in the light of reference values from peers matched by gender and age (8).

Methods. Original data from 1987 to 1998 are shown in Figure 1 between two horizontal lines that correspond to the mean ± 3 standard deviations for SBP, mean arterial pressure (MAP) and DBP, all based on oscillometric measurements, and HR. Values outside these lines are compressed to fit within the lines and the rest of the ordinate. The unaided eye sees ups and downs but cannot quantify the time structure (chronome) of these variations. Daily averages, shown in Figure 2 (left), are analyzed by linear least-squares spectra (9-14), with results shown in Figure 2 (right).

Results. Both a near-transyear and a far-transyear are seen in the spectra of SBP, DBP and HR, demonstrated in Figure 2 (right). Their 95% confidence intervals also given in Table 1 do not overlap the precise calendar year, which actually corresponds to a trough rather than a peak for the case of SBP and DBP and is on the descending slope (no peak) for HR.

Discussion. Two other subjects with treated MESOR-hypertension, FH (15) and GSK (16), documented earlier that transyears can replace the calendar yearly component. The latter in turn, in a record of self-measurements of BP by a clinically healthy normotensive subject (RBS), who monitored himself about 5 times a day from 20 to 60 years of age, was prominent and dominated over transyears that were also present (17). An about 1.3-year transyear component was invariably detected in all of several dozen decades-long series examined thus far (18, 19). Whether or not a MESOR-hypertensive subject has an alteration in the para-annual range of the BP and HR spectra, e.g., in one or several infradian amplitude ratios, is currently only a basic question. It will have to be examined in data from many subjects in health and disease. It may gain practical meaning once affordable unobtrusive automatic instrumentation becomes available for lifetime automatic sequentially chronobiologically analyzed monitoring for which the analytical procedures are available (10-15, 20).

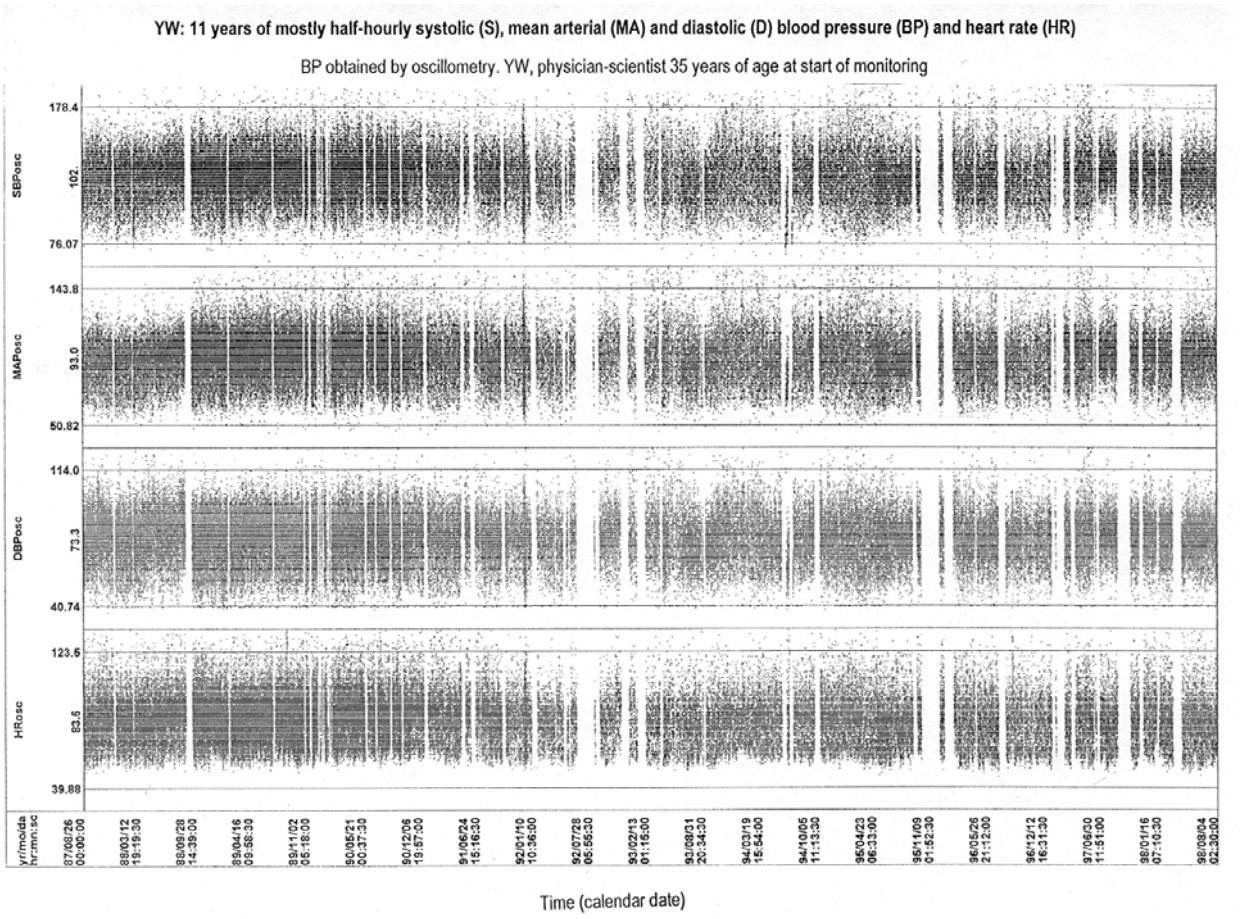

Figure 1. Display of original truncated data. © Halberg.

Conclusion. Whether or not the dominance of transyears over calendar years in the human adult constitutes an infradian aspect of pre-hypertension, found thus far in one subject by longitudinal BP monitoring, remains to be clarified on additional subjects.

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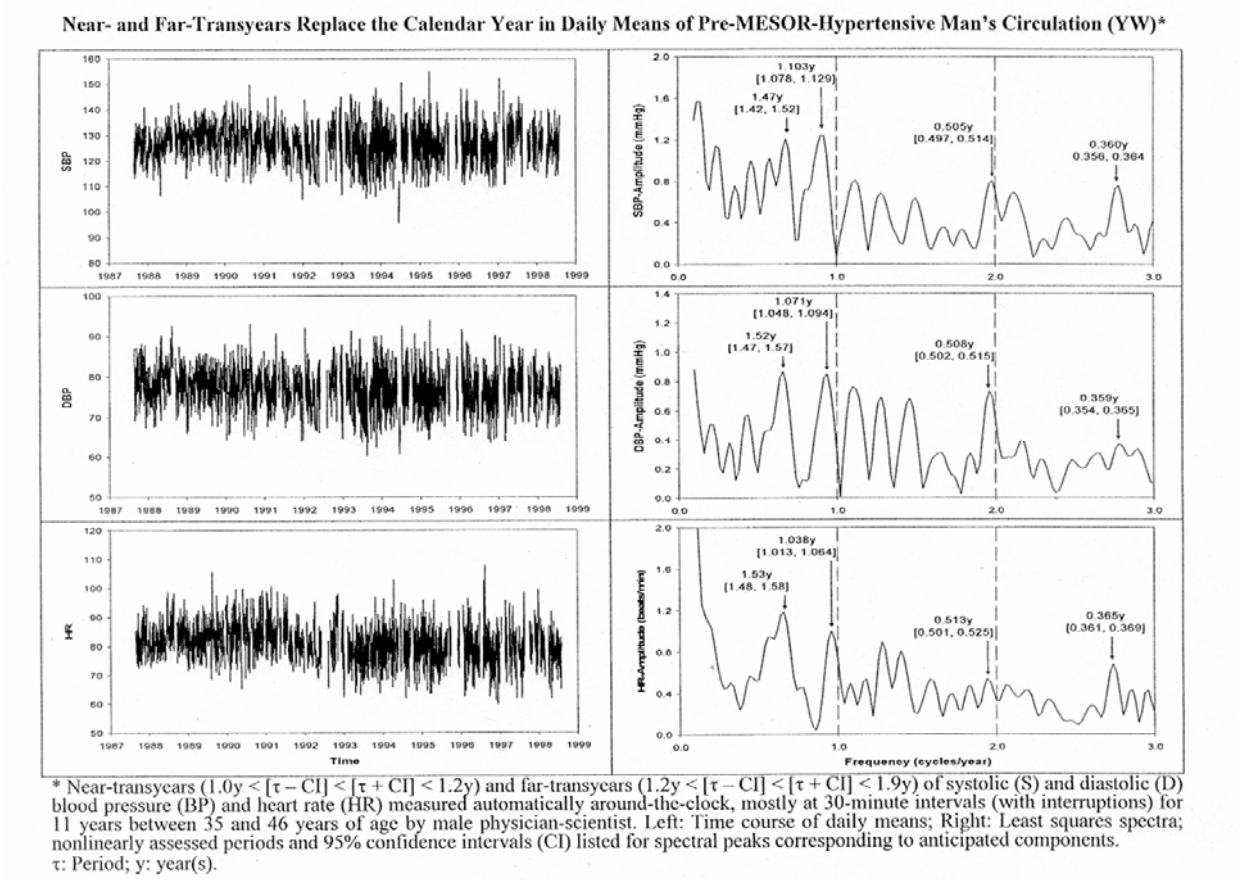

Figure 2. Daily means, computed from data in Figure 1, are shown on the left. Results from least squares spectra show the relative prominence of anticipated spectral components on the right and in Table 1. © Halberg.

Table 1: Para-annual infradians in the pre-MESOR-hypertensive circulation at ages 35-46 y (YW, male physician-scientist)*

Period Variable	Far-transyear (95% CI)			Near-transyear (95% CI)			Half-year (95% CI)			~0.36-year (95% CI)		
Systolic BP	1.47	(1.42,	1.52)	1.103	(1.078,	1.129)	0.505	(0.497,	0.514)	0.360	(0.356,	0.364)
Diastolic BP	1.52	(1.47,	1.57)	1.071	(1.048,	1.094)	0.508	(0.502,	0.515)	0.359	(0.354,	0.365)
Heart rate	1.53	(1.48,	1.58)	1.038	(1.013,	1.064)	0.513	(0.501,	0.525)	0.365	(0.361,	0.369)

*BP: blood pressure; CI: confidence interval of point: near-transyear: 1.00 y < [τ {period} - CI {95% confidence interval}] < [τ + CI] < 1.20 y; far-transyear: 1.2 y ≤ [τ - CI] < [τ + CI] < 1.9 y.

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Chronomics: Anxiety disorder in adolescence and heart rate asynchronized with weekly schedule

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Abstract

Circadian rhythms that are not synchronized by the environment have been associated with emotional disorders. Automatic hourly around-the-clock measurements of blood pressure (BP) and heart rate (HR) of a 14-year-old Japanese boy for 38 days allow a test for asynchronization with the daily and/or weekly routines. Transient, barely synchronized about 7-day (circaseptan) components in BP and the lack of an external circaseptan synchronization of HR were found in this boy. Findings may relate to his history of transient sweating and palpitations that prevented him from attending school at 13 years of age and/or to his family history of vascular disorders.

Introduction

Evidence for a lack of synchronization with the environmental routine of the about 24-hour core temperature rhythm had led to the coining of *circadian* (1) and to a Ross Pediatric Conference (2). Circadian desynchronization of adrenocortical function from the societal routine, specifically with a view of emotional disorders, including mania and depression, was reviewed in 1968 (3) and continues to be actively investigated in the laboratory as in the clinic (4-8). Focus upon circaseptan and other infradian rhythms is not new. Our meta-analyses of BP and HR in a thesis published in 1880 and republished in 1881 allow us to demonstrate about 3.5- and about-7-day rhythmicity in addition to changes along the 24-hour scale. Janeway in 1904 wrote about BP periodicities in plural; he could have been referring to about 24-hour and about 7-day rhythms (1).

Automatic longitudinal vascular monitoring on an adult patient during an episode of depression revealed differential systolic (S) vs. diastolic (D) BP vs. HR behavior in the spectral region of one week, Figure 1 (9). Here, we show partial lack of circaseptan synchronization of HR, if not of BP with the societal 7-day routine, of interest in particular in a 14-year-old Japanese boy who had episodes of anxiety in school. Such a spectral finding has been earlier related to an episode of depression in an adult (9) and the symptoms of transient sweating and palpitations at 13 years of age in this boy came to mind. Adolescents with anxiety disorders are reportedly at an increased risk of subsequent anxiety, depression, illicit drug dependence and educational under-achievement as young adults (10; cf. 11). This boy's data are also of particular interest from the viewpoint of earliest BP rhythm alterations and high BP later in life (12). He has a family history of vascular disease, and from this viewpoint his BP and HR had been monitored every 30 minutes during the first 40 days of his life (12).

Case report

The boy'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 on 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).

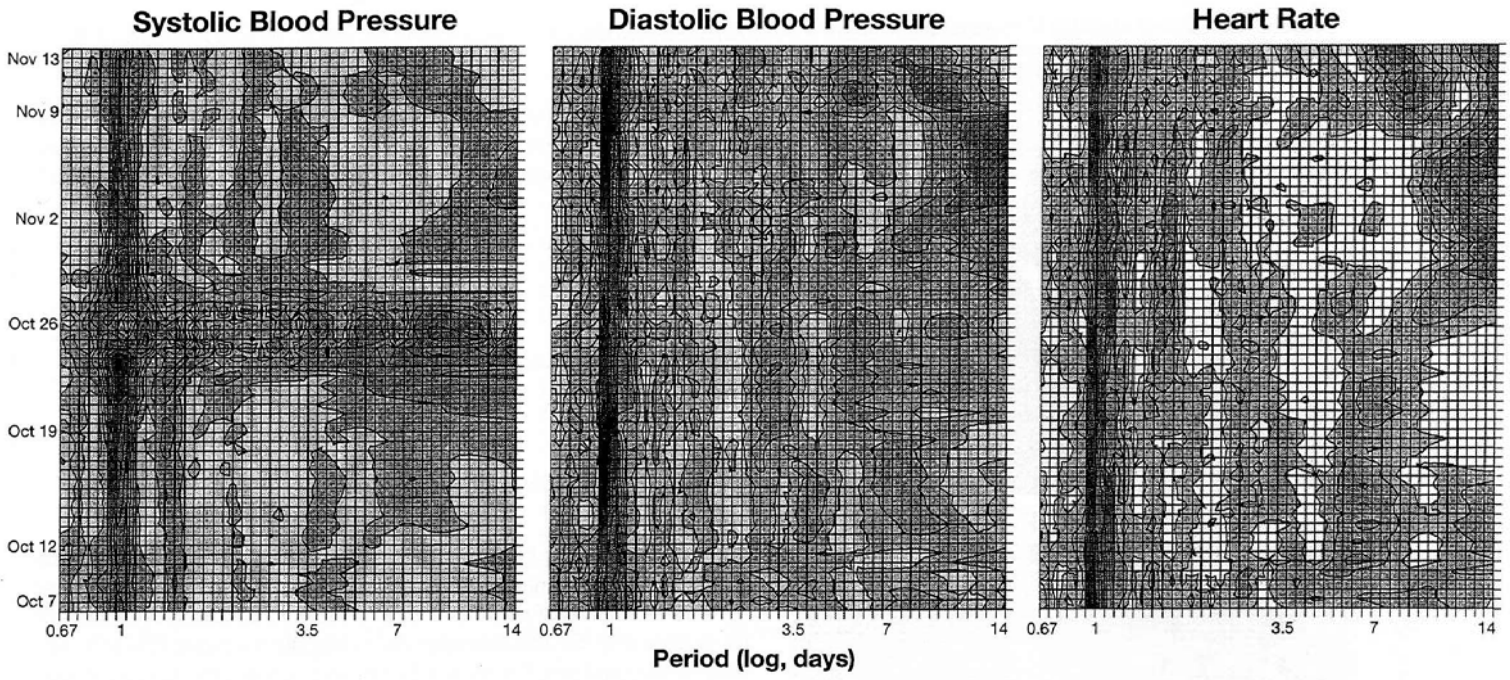
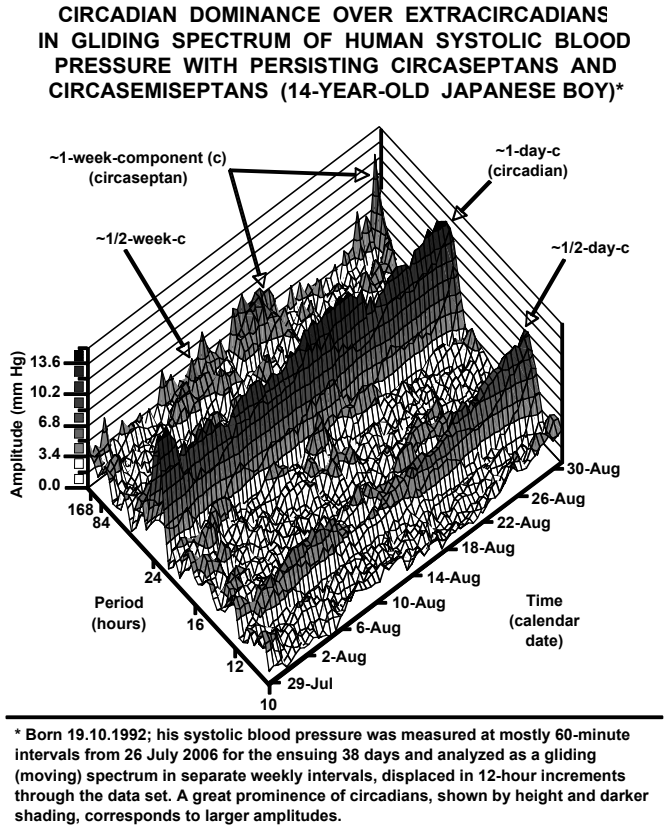


Figure 1. Contour map from a moving periodogram on data of a 42-year-old woman with bipolar emotional illness. The period is plotted on the abscissa and time on the ordinate. A different behavior is evident in the circadian band of systolic blood pressure (SBP), as compared with the behavior of diastolic blood pressure (DBP) and heart rate (HR), during the episode of depression occurring around October 26. During depression, the circadian band of SBP fades greatly (it practically disappears) and the main variance moves to the infradian region (to the right), whereas a comparable change is not apparent for DBP and HR. © Halberg.

Thereafter, once a week, he monitored BP and HR for 24 hours at 60-minute intervals for 8 weeks, until April 4, 1993. At 9 years of age on October 13, 2001, he started to monitor his BP and HR once daily in the morning.

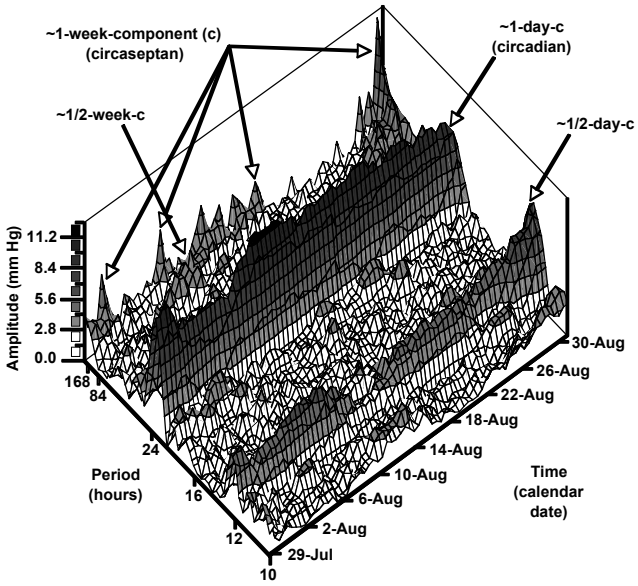
Problems arose at 13 years of age: In February 2005, he passed his junior high school entrance examination. In March, he graduated from elementary school; in April he entered a private junior high school, but during this month he could not attend school because of feelings of anxiety about the school. From April to July he spent most of his time at home. In July, he started to attend a public junior high school, where he made good friends. In 2006, when his best friend moved out of town, he made new friends in his new class, and in April 2006 he started swimming school. At 14 years of age, he was monitored again. His BP and HR were measured automatically with a TM-2430 monitor from A&D (Tokyo, Japan), mostly every hour by day and night from July 26 to September 10, 2006. Figures 2-4 show a circadian rhythm's consistent predominance in a gliding spectral window, while Figures 5-7 show combined gliding (left) and global spectral windows ("global" only in the sense of summarizing the entire series). The 24-hour synchronized circadian rhythm stands out for all three variables in all of the gliding and global displays. The 24-hour synchronization is apparent numerically on the right, in that the 95% confidence interval of the period overlaps 24 hours and that of the 12-hour harmonic overlaps 12 hours, the latter component likely an expression of a nonsinusoidal circadian waveform. In Figure 7, the non-overlap of 168 hours by the 95% confidence interval of the circaseptan period of HR indicates a lack of synchronization of the subject's pulse with a weekly schedule.



*** Born 19.10.1992; his systolic blood pressure was measured at mostly 60-minute intervals from 26 July 2006 for the ensuing 38 days and analyzed as a gliding (moving) spectrum in separate weekly intervals, displaced in 12-hour increments through the data set. A great prominence of circadians, shown by height and darker shading, corresponds to larger amplitudes.**

Figure 2. Time structure of systolic blood pressure showing circadian dominance and infradian intermittency while an about half-day component may reflect variability in the circadian waveform of a 14-year-old Japanese boy. © Halberg.

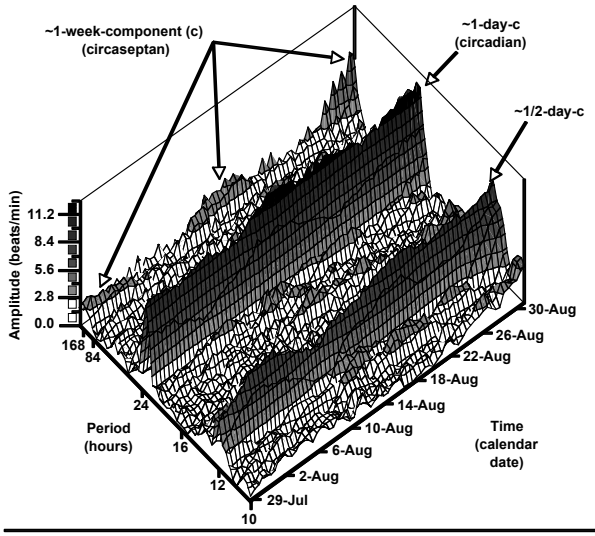
CIRCADIAN DOMINANCE OVER EXTRACIRCADIANS IN GLIDING SPECTRUM OF HUMAN DIASTOLIC BLOOD PRESSURE WITH PERSISTING CIRCASEPTANS AND CIRCASEMISEPTANS (14-YEAR-OLD JAPANESE BOY)*



*** Born 19.10.1992; his diastolic blood pressure was measured at mostly 60-minute intervals from 26 July 2006 for the ensuing 38 days and analyzed as a gliding (moving) spectrum in separate weekly intervals, displaced in 12-hour increments through the data set. A great prominence of circadians, shown by height and darker shading, corresponds to larger amplitudes.**

Figure 3. Time structure of diastolic blood pressure showing circadian dominance and infradian intermittency while an about half-day component may reflect variability in the circadian waveform of a 14-year-old Japanese boy. © Halberg.

CIRCADIAN DOMINANCE OVER EXTRACIRCADIANS IN GLIDING SPECTRUM OF HUMAN HEART RATE WITH INTERMITTENTLY PERSISTING CIRCASEPTANS (14-YEAR-OLD JAPANESE BOY)*



*** Born 19.10.1992; his heart rate was measured at mostly 60-minute intervals from 26 July 2006 for the ensuing 38 days and analyzed as a gliding (moving) spectrum in separate weekly intervals, displaced in 12-hour increments through the data set. A great prominence of circadians, shown by height and darker shading, corresponds to larger amplitudes.**

Figure 4. Time structure of heart rate showing circadian dominance and infradian intermittency while an about half-day component may reflect variability in the circadian waveform of a 14-year-old Japanese boy. © Halberg.

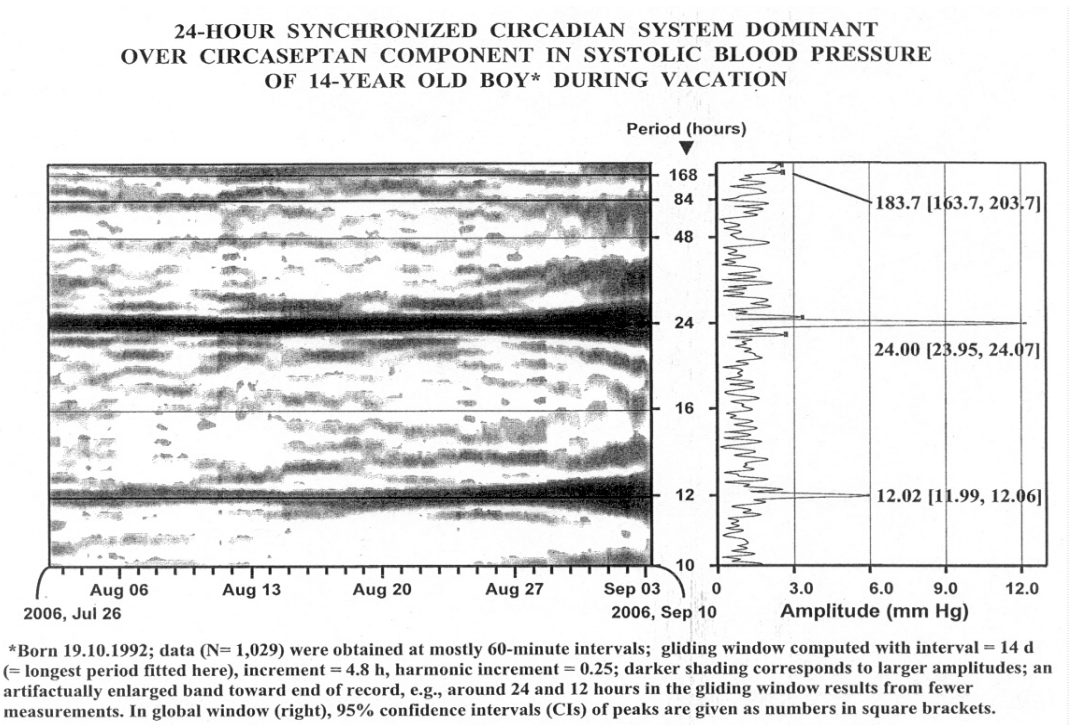


Figure 5. Gliding spectrum (left) aligned with global spectrum (right) of systolic blood pressure of a 14-year-old Japanese boy. Note that the 95% confidence intervals of the period of three components cover the week, day and half-day, respectively. © Halberg.

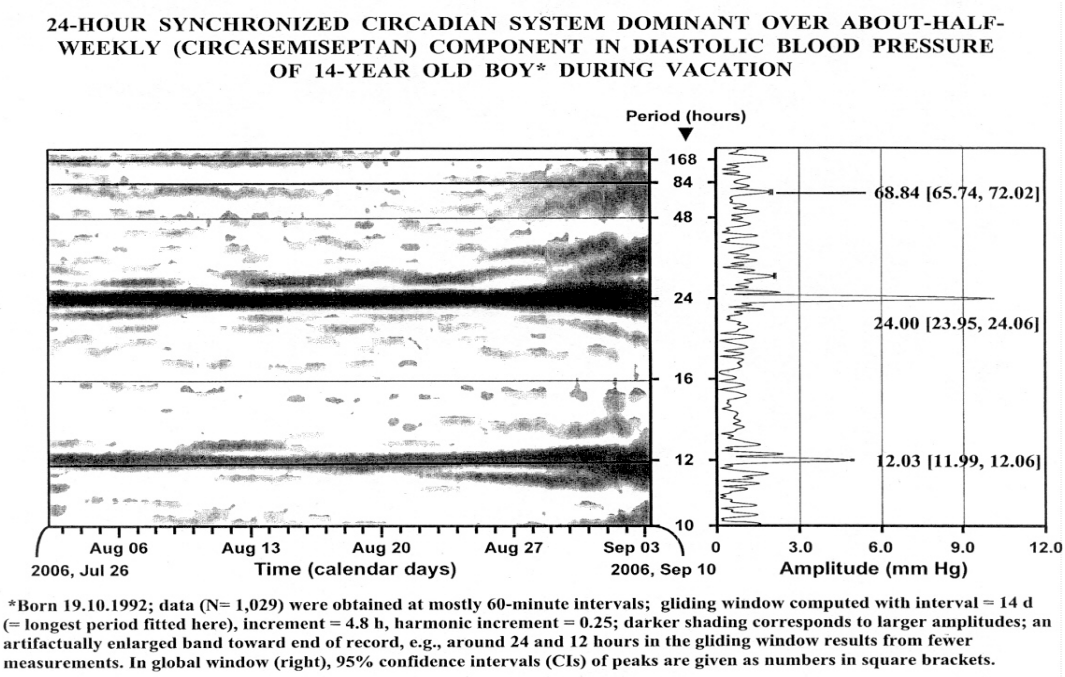


Figure 6. Gliding spectrum (left) aligned with global spectrum (right) of diastolic blood pressure of a 14-year-old Japanese boy. Note that 95% confidence interval of an infradian peak does not cover the precise half-week (= 84 hours). © Halberg.

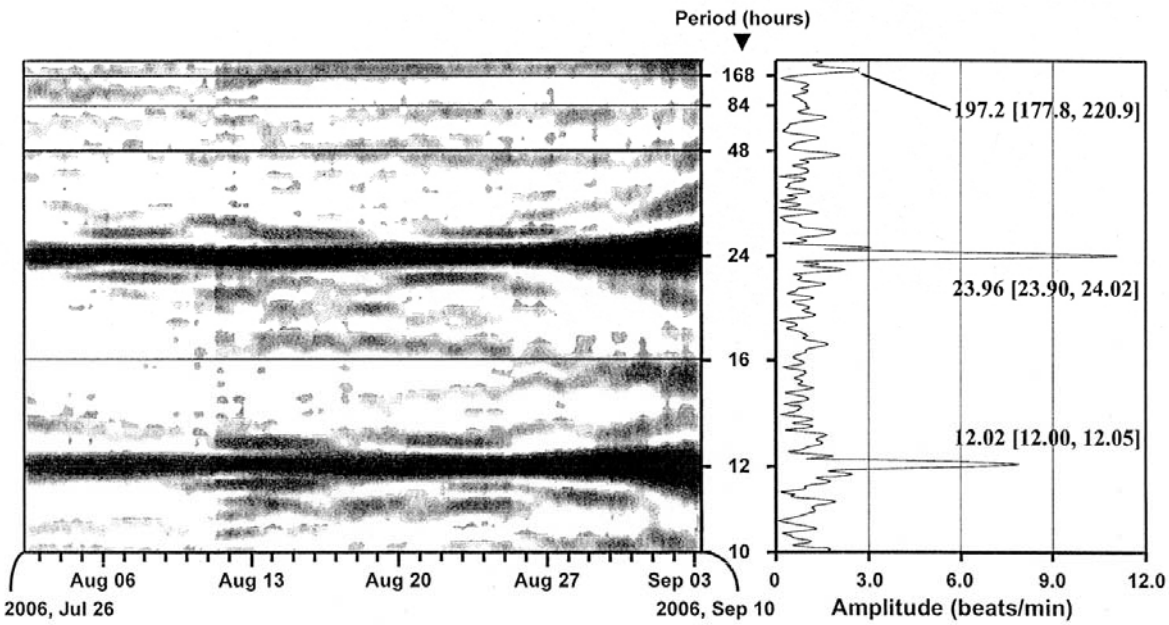


Figure 7. Gliding spectrum (left) aligned with global spectrum (right) of heart rate of a 14-year-old Japanese boy. Note lack of circaseptan synchronization by 95% confidence interval of a circaseptan component not covering a precise week (= 168 hours). © Halberg.

Table 1: Nonlinear estimation of about 7-day and about 21-day periods (τ, in days) in the circulation of a Japanese boy (14 years of age)

	Spectral region	Circaseptan		Circavigintan
Variable	Kind of data	Original	Daytime means	Original
Systolic blood pressure (SBP)		7.64* (6.78-8.50)	Not statistically significant	21.97* (16.7-27.2)
Mean arterial pressure (MAP)[c]		Not assessed	7.41* (6.67-8.15)	
Diastolic blood pressure (DBP)		7.45† (6.53-8.37)	7.37* (6.74-8.00)	
Heart rate (HR)		**8.19* (7.39-8.99)**	**8.05* (7.29-8.81)**	
SBP x HR[c]		Not assessed		

*P<0.05; †borderline statistical significance; [c]calculated
Note (in bold) that for variables involving heart rate, the 95% confidence intervals (given in parentheses) of the circaseptan period do not cover the precise week.

Table 1 shows again that the 95% confidence interval of the circaseptan period of HR does not cover the precise week, as do the corresponding 95% confidence intervals of SBP and DBP, yet the confidence intervals of these variables also barely cover 7 days. The external circaseptan asynchronization of HR is further supported and extended in analyses restricted to the daytime means: in these time series, the circaseptan periods not only of HR but also of the double product both have a 95% confidence interval that does not overlap precisely 7 days. The corresponding confidence intervals of the circaseptan periods of DBP and mean arterial pressure barely cover precisely 168 hours. Longer series would have been required to detect for the boy's BP any probable external circaseptan asynchronization with the societal routine.

Table 2: Larger cardiovascular prominence of circaseptans in neonates and of circadians in adults, gauged by amplitude ratios (AR)*

	Mean AR and 95% confidence interval		Comparison	
Variable	Neonates (40)	Adults (15)	Student *t*	(P)
Systolic BP	2.23 (1.66, 2.99)	0.15 (0.09, 0.24)	9.545	(<0.001)
Diastolic BP	1.57 (1.18, 2.09)	0.13 (0.08, 0.21)	9.024	(<0.001)
HR	2.32 (1.78, 3.01)	0.16 (0.11, 0.25)	11.848	(<0.001)

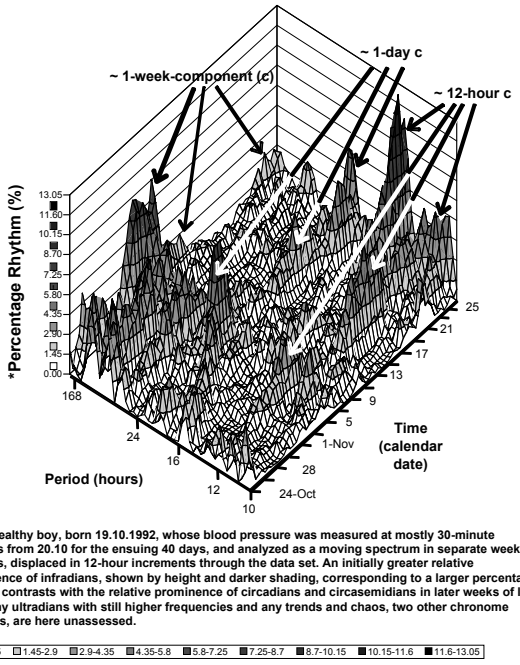
*Data series on BP and HR analyzed by the least-squares (cosinor) fit of 24-hour and 7-day cosine curves to data series each covering at least 7 days around-the-clock.
The prominence of circaseptans early in extrauterine life raises the question whether this chronome component may have evolved by resonance with solar wind-related (geomagnetic) disturbance and/or may (also) currently constitute a response to our cosmos. The endogenicity of BP and HR circaseptans is supported by their free-running under conditions of an isolette for prematures or in social isolation for adults or for SBP in an afebrile boy (with intermittent fever) on a daily routine in the presence of a 24-hour synchronized circadian of locomotor activity.

Discussion

In the BP and HR of a clinically healthy-appearing newborn with a family history of vascular disorders and cancer, about 7-day and other infradian (with a period longer than 28 hours) cycles dominate during the first several weeks of life in terms of a much larger double amplitude (extent of predictable change) as compared to that of the circadian variation (12). This finding is in keeping with Table 2, summarizing earlier studies on 40 newborns by comparison to data on 15 adults. Circadian variations, initially less prominent than infradians, Figures 8-10, become dominant only after the third week of life for the ensuing weeks (and until late in maturity). Again at 14 years of age, we find about 7-day variations persisting in SBP and DBP and HR. In these variables, circaseptans can disappear and reappear. Their behavior is quasi-persistent, revealed as intermittent for all three variables and showing an alternation of circaseptans with circasemiseptans in SBP and DBP during adolescence, Figures 2 and 3, as they did postnatally (12).

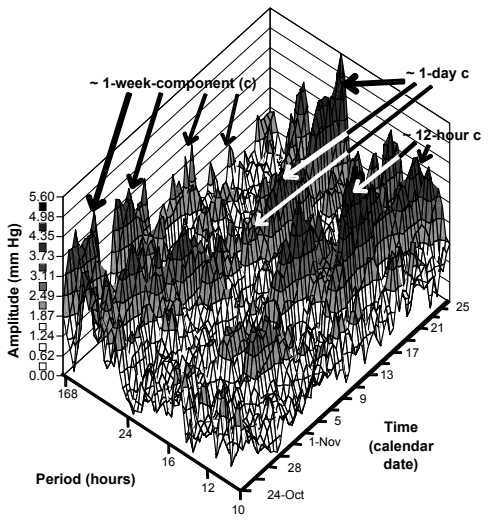
The subject was monitored during vacation. In the presence of a fully 24-hour synchronized circadian rhythm, a circaseptan asynchronization with the societal week of HR (and of the double product) characterizes an adolescent who happened to exhibit a transient anxiety disorder, consisting of sweating and palpitation, at 13 years of age, while attending school. As noted, after graduation from elementary school in March 2005 (at 13 years of age), in April he entered a private junior high school but anxiety prevented him from attending it. From April to July he spent

most of the time in his home. In July, he started to go to a public high school, could soon socialize, made friends there and at the time of this writing seems to be content. Whether his circaseptan asynchronization of HR was a residual from an anxiety disorder comes to mind in view of a prior association between alterations of circaseptan rhythms during an episode of depression in an adult (9), but to our knowledge control data on other adolescents covering weeks are not available. There is evidence, however, for altered HR variability in patients with panic disorder (13).



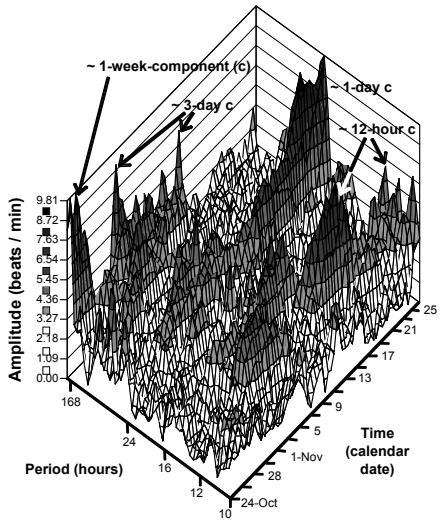
** in a healthy boy, born 19.10.1992, whose blood pressure was measured at mostly 30-minute intervals from 20.10 for the ensuing 40 days, and analyzed as a moving spectrum in separate weekly intervals, displaced in 12-hour increments through the data set. An initially greater relative prominence of infradians, shown by height and darker shading, corresponding to a larger percentage rhythm, contrasts with the relative prominence of circadians and circasemidians in later weeks of life, while any ultradians with still higher frequencies and any trends and chaos, two other chronome elements, are here unassessed.

Figure 8. Changing relative prominence* of some components in a partial spectral element of the postnatal human systolic blood pressure chronome**. Infradian-to-circadian moving systolic blood pressure spectrum of a boy at term: side view of relative prominence. © Halberg.



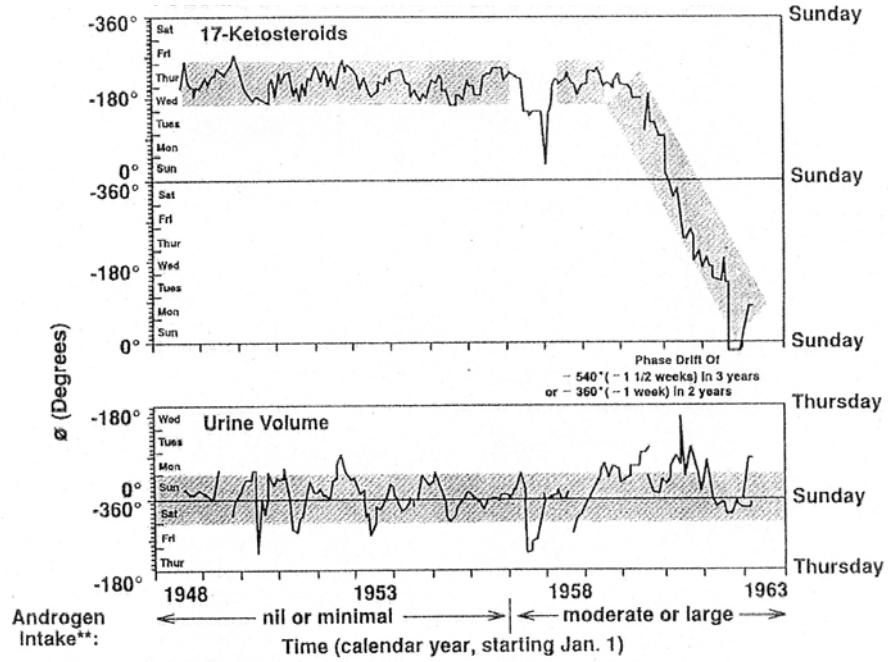
* in a healthy boy, born 19.10.1992, whose blood pressure was measured at mostly 30-minute intervals from 20.10 for the ensuing 40 days, and analyzed as a moving spectrum in separate weekly intervals, displaced in 12-hour increments through the data set. An initially greater prominence of infradians (see ~ 1 week c, left), shown by height and color, corresponding to a larger amplitude, contrasts with the prominence of circadians and circasemidians in later weeks of life, while any ultradians with still higher frequencies and any trends and chaos, two other chronome elements, are here unassessed.

Figure 9. Changing relative prominence* of some components in a partial spectral element of the postnatal human diastolic blood pressure chronome**. Infradian-to-circadian moving diastolic blood pressure spectrum of a boy at term: side view of relative prominence. © Halberg.



*** in a healthy boy, born 19.10.1992, whose heart rate was measured at mostly 30-minute intervals from 20.10 for the ensuing 40 days, and analyzed as a moving spectrum in separate weekly intervals, displaced in 12-hour increments through the data set. An initially greater prominence of infradians (see ~ 1 week c, left), shown by height and color, corresponding to a larger amplitude, contrasts with the prominence of circadians and circasemidians in later weeks of life, while any ultradians with still higher frequencies and any trends and chaos, two other chronome elements, are here unassessed.**

Figure 10. Changing relative prominence* of some components in a partial spectral element of the postnatal human heart rate chronome**. Infradian-to-circadian moving heart rate spectrum of a boy at term: side view of relative prominence. © Halberg.



* Chronobiologic serial section. Period: 7 days; interval: 182 days, increment: 28 days.

** All data obtained on the days of intermittent male sex hormone self-administration and following these treatments for up to several weeks (when 17-KS excretion was elevated) omitted from analysis.

Figure 11. Circaseptan acrophases, ϕ, in the 17-ketosteroids and volume of urine excreted by a healthy man*. Different behavior of the about-weekly variation in urinary excretion of 17-ketosteroids (top) and urine volume (bottom) recorded by a clinically healthy man after self-administration of androgen. The acrophase (phase of maximum) of a 7-day cosine curve is plotted on the ordinate, expressed in (negative) degrees, with 360˚ equated to 7 days, and 0˚ (reference) set to midnight between Saturday and Sunday prior to start of data collection. Analyses performed on data in a 182-day interval progressively displaced in 28-day increments throughout the 15-year record (abscissa). © Halberg.

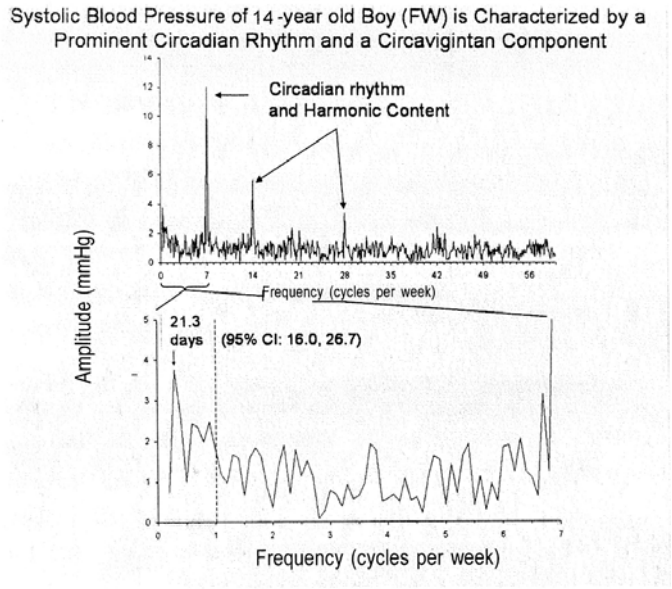


Figure 12. About 21-day component in spectrum of systolic blood pressure of a 14-year-old Japanese boy. © Halberg.

In addition to the social routine's precise 7-day schedule, physical environmental conditions also involve cyclic counterparts to a near-week such as a near 7-day oscillation in geomagnetic activity (1) and in rainfall (14). Components corresponding in period length to those detected for the subject were not found in the geomagnetic index Kp during the 38 days of his monitoring. His HR is asynchronized with the geomagnetic variation as well as from the societal routine. Circaseptan asynchronization, in the presence of a social weekly schedule in urine volume was demonstrated earlier for the urinary excretion of 17-ketosteroids in a healthy man treated with a heavy dose of androgen, Figure 11 (15).

Figure 12 shows that the SBP of this 14-year-old boy also exhibits an about 23-day (circavigintan) spectral component. The nonlinearly estimated period is of 21.3 days with a 95% confidence interval extending from 16.0 to 26.7 days, when accounting for the prominent circadian rhythm, Figure 12. A similar component has been reported in the 17-ketosteroid excretion of a clinically healthy adult man who collected and analyzed his 24-h urinary 17-ketosteroid excretion over 15 years (15). Hence this component has been tentatively interpreted as the gauge of a possible male sex cycle (the subject does not yet shave). Much additional mapping with unobtrusive affordable instrumentation will be necessary to diagnose asynchronization and other variability disorders of BP and HR at birth or during adolescence, an important task since alteration of variability in the range of acceptable values represents risks greater than hypertension in adults and can be detected by a time structural (chronomic) analysis (16, 17). Toward this goal, Figures 2-7 and 12 constitute first maps that include infradian as well as circadian physiologic variability and show changes in their relative prominence differing in adolescence as compared to analyses of data collected neonatally (12).

Figures 1-10 illustrate an approach by a computer-implemented temporal microscopy of physiological variables. In that context, they introduce an inferential statistical methodology for the study of psychiatric time series in the context of transdisciplinary ones with aeolian wobbly spectral components. The long-term aim is the detection of earliest disease risks at birth and in adolescence by broadening the perspective from now-useful circadians (16-19) to other assessable variations already sought in 1904 and found in data published in 1880 and 1881 (1). The Phoenix Project, a group of Minnesota engineers (http://www.phoenix.tc-ieee.org), aims to build unobtrusive, generally applicable non-cuff, electrode-independent inexpensive instrumentation for

monitoring BP and HR automatically and to provide analytical software for a time-structural analysis in the light of reference values from peers matched by gender and age (http://www.sphygmochron.org/). The analytical service is available cost-free from a project on The BIOsphere and the COSmos, BIOCOS, by contacting corne001@umn.edu.

As to about 3.5- and 7-day cycles, they usually complement the almost-ubiquitous circadians, along with other spectral components including about 20- and 30-day and about 5- and ~6-month rhythms, as well as annual and paraannual ones (20). The recognition that a seemingly free-running about-weekly schedule resides in part in living matter came first from the breakdown products of the very adrenocortical and gonadal hormones (17-ketosteroids = 17-KS) that are important for survival and reproduction; the circadian story repeated itself.

First found was an apparently free-running rhythm in 17-KS with a period close to yet different from precisely 7 days. On weekends, the subject (CH) drank an extra cup of tea and a bottle of beer, a schedule that synchronized the volume he excreted and measured, but not the steroid metabolites contained in his urine which he determined for 15 years by the same method, with the same reagents bought at the outset (15). In other words, the precise 7-day period found for CH in the urine volume in which the metabolites had been determined, coexisted with a period of about (but different from precisely) 7 days in the excreted steroidal metabolite and was also different (desynchronized) from another near-7-day period in the planetary geomagnetic index Kp during the urine's collection span (1, 15).

Second, there was the observation that circaseptans appear after the administration of a single stimulus that carries no 7-day information, as in the case of a partial hepatectomy studied by Hübner (21) in rats and by us after kidney or heart transplantation in rodents and humans (22-24). Single stimulus induction of circaseptans, or rather their manifestation after a single stimulus, traced back to antiquity, was also the topic of a classic book on circaseptans by Günther Hildebrandt and Ingrid Bandt-Reges (25; see also 26).

Third, as to ontogeny, a dominant weekly pattern, much more prominent than the also-present circadian component in the same data, was seen in a survey of more than 181 profiles of BP, each profile on a separate baby, each measured every 30 minutes for 48 hours on different 2 consecutive days of the first week of life (27), and in several hundred additional longitudinal monitorings for several weeks during the first months of life (28). By the fourth week of life, the circadian component usually dominated the human spectrum (12). In a crayfish, the circaseptan dominated the activity pattern at the age of 6 months (29). In the case studied herein, aeolian circaseptans persisted into adolescence, albeit they came and went and were only quasi-persistent.

Fourth, again as to ontogeny, the circaseptans regain relative prominence with elderly age, concurrently with a circadian decrease in amplitude (30).

Fifth, as to phylogeny, the giant unicell *Acetabularia acetabulum,* standardized in light and darkness alternating every 12 hours, thereafter released into continuous light, after signal averaging of electrical activity, shows a circaseptan rhythm with a free-running near-one-week period, with a much larger amplitude than that of the also free-running circadian rhythm (20). Assuming that this alga has not changed in the interim, this eukaryote may tell us about the environmental cycles it adapted to when it developed, perhaps 500 million years ago (31) at a time that physical instruments cannot yet readily trace and the length of the day was several hours shorter than today.

Sixth, like *Acetabularia,* tumor cell cultures, as spheroids or as monolayer, also show a major circaseptan peak in β-ATP concentration, with a superposed circadian in amplitude that is barely one-third of the circaseptan (32, 33). While Acetabularia shows free-running circadians and circaseptans, the tumor cells are 1- and 7-day synchronized and when Acetabularia shows a

dispersion of periods after a first cycle or so, the tumor cells remain 1- and 7-day synchronized for six consecutive cycles. Tumor cell kill by radiation was much better at the circadian and circaseptan peak of the β-ATP marker, as compared to radiation administered at the circaseptan and circadian minimum (32, 33), but the synchronizing stimulus is not identified in this case.

Seventh, remove-and-replace approaches, that led over half a century ago to mechanisms of circadian rhythms (1) also served in the case of circaseptans. About 7-day rhythms opened a new chapter in chronomics, the aligned recording of variables in and around us. Again a remove-and-replace approach proved to be helpful, but it was not via an interference with the organism, such as eye removal leading to free-running or bilateral adrenalectomy or suprachiasmatic nuclear lesioning leading to different consequences in the case of different biological variables. This time it was the cosmos, notably the sun, not the surgeon (in blinding) or genetics (in the case of congenitally blind ZRD mice; 1), that did the removal and the cosmos also was responsible for the replacement: when solar activity had 7-day components in its (Walsh) spectra (computed in St. Petersburg by Vernova et al. (34), human HR (in Minnesota and Connecticut) had these components amplified in its spectrum, and vice versa when these components were lacking in the sun's record, the corresponding components in heart rate were damped, but not lost, showing that they were also partly built in (35; cf. also 15). This coding of the circaseptans in our genes is compatible with resonance. Hence it is hardly surprising to find an occasional pull of a biological circaseptan acrophase by a geomagnetic cycle with a proximal frequency, e.g., for one variable but not for another. While in the case of circadian rhythms the assumption that free-running indicated the built-in nature of rhythms led to successes at the molecular level, in that case and more so in the case of infradians, we must remember that organisms are open systems to their environments and there is in any case a complementary system of the cosmos, that influences along infradian as well as circadian scales the difference between survival and sudden cardiac death (36), suicide (37) and being killed by the hand of others (38-40).

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A transtridecadal cycle in human heart rate: Selective infradian, notably multidecadal solar-physiologic BEL congruences

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Abstract

Noninvasive cardiology surveys vascular variability to detect earliest prehypertension, prediabetes and a premetabolic syndrome. The data obtained for such prehabilitation can also be used to monitor space weather. Thereby, we detect, in the human circulation as in a mental function, genetically coded signatures of irregular nonstationary and hence questioned environmental cycles. By inferential statistical methods and by transdisciplinary counterparts, we here validate a cycle originally documented by plots of data for the unaided eye by three scientists -- Eduard **B**rückner, Charles **E**geson and William J.S. **L**ockyer -- hence dubbed the BEL cycle, from their last-name initials. A set of analytical methods resolves solar-terrestrial-biospheric associations, good or bad, in individuals', populations' and ecosystems' health and illness.

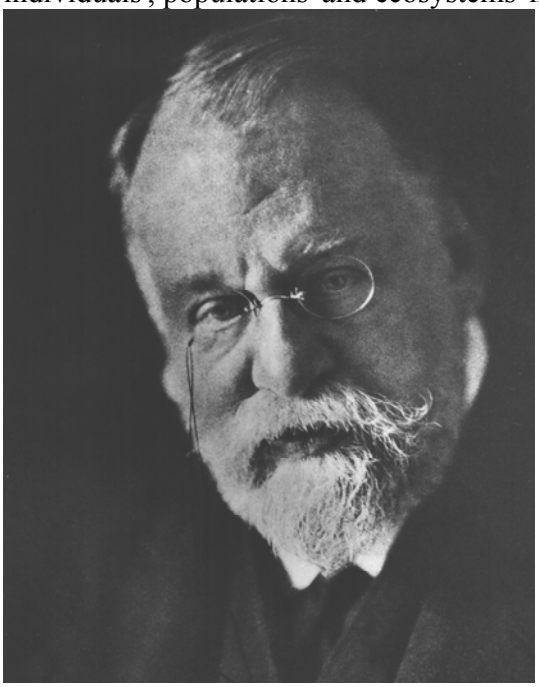


Figure 1. Brückner at an advanced age. Courtesy of Dr. Reinhold Steinacker, O.Univ.-Prof., Head, Vice-Dean; Mag. Walter Lang and Dr. Franz Holawe, Department of Meteorology and Geophysics, Faculty of Geosciences, Geography and Astronomy, University of Vienna, Austria.

Background

In an 1877 book on the history of astronomy, Rudolf Wolf (1) cites observation of meteor showers in the Leonids that have a period of 33 ¼ years, "meaning that a maximum happens only about every 33 years (i.e., 1799, 1833, 1866)". In a 324-page monograph published in 1890, Eduard Brückner (2), Figure 1, very thoroughly compiled extensive data over several centuries in the case of severe winters from 1000 to 1775. He suggested cycles of 34.87 years, which he documented with many tables and figures and an overall chart, aligning variation in environmental temperature, rainfall, ice-free rivers, cold winters and the wine harvest with Zürich relative sunspot (Wolf) numbers. He reported that his cycle was independent of that in sunspots (which he assumed to undergo an about 55-year cycle). Human migrations from Europe to North America and westward within North America were associated by Brückner with his wet-dry cycle (3, 4). Alternations of wet and dry climate and their possible signatures were highly variable from one cycle to the next,

yet when Brückner averaged them for consecutive spans of about 2 centuries each, he arrived at the 34.8-year length; we here refer to an over- (beyond = trans) tridecadal, i.e., transtridecadal or circaquinseptennian cycle.

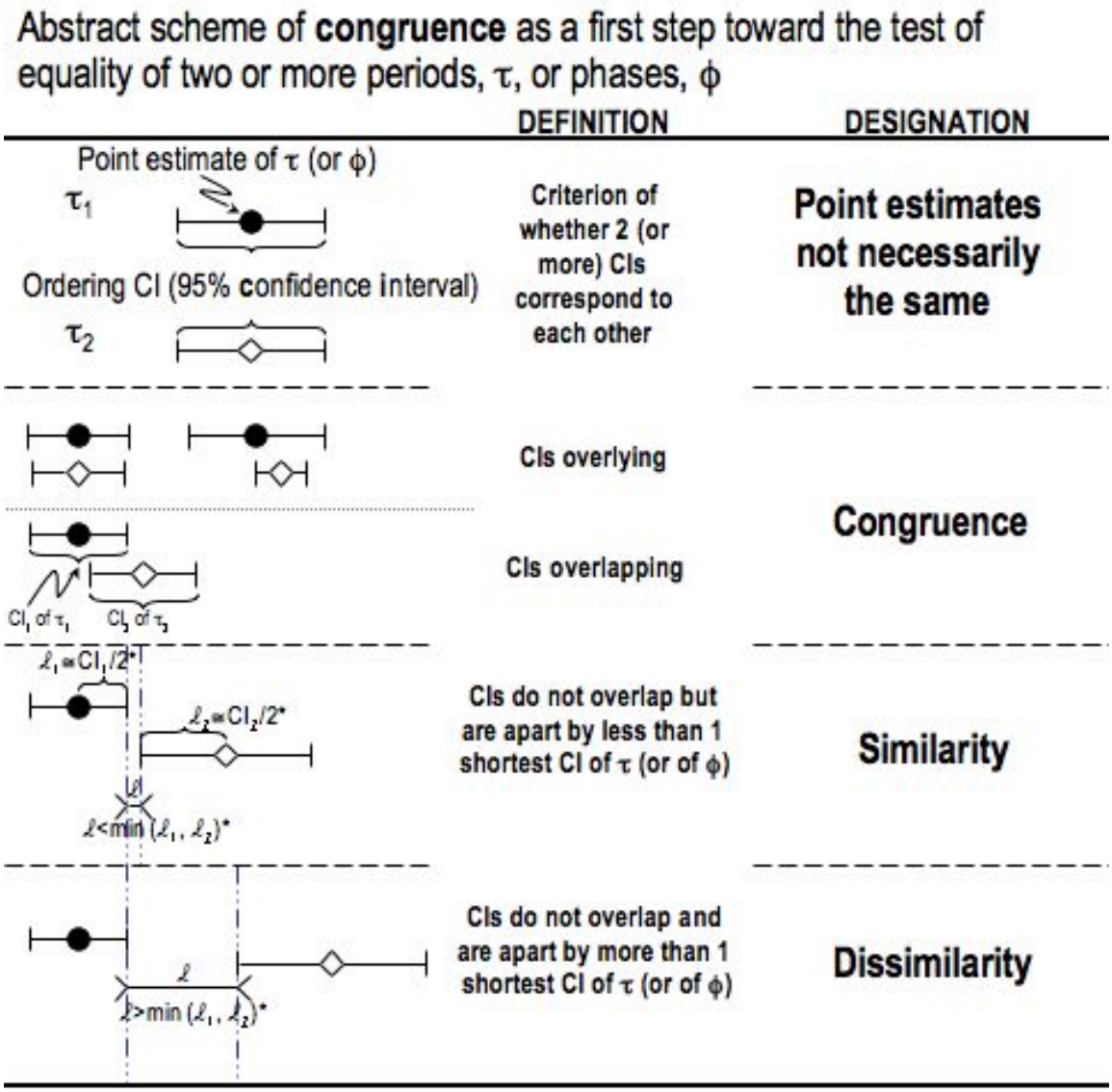
A few months before Brückner (in 1889), Charles Egeson (5) published his research on solar meteorology, reporting a trans-tridecadal weather cycle in rainfall, thunderstorms and westerly winds in the month of April for Sydney, Australia, with the length of the period varying from 33 to 34 years. William J.S. Lockyer (6) deserves credit for finding an ~35-year period in the length of the sunspot cycle and for aligning this cycle with terrestrial weather. In 1901, William Lockyer (6) concluded that the time between consecutive minima in sunspots underwent an about 35-year variation, as did the total spotted area between any two consecutive minima, all in keeping, per Lockyer (6), with Brückner (2): "The climate variations indicated by Professor Brückner are generally in accordance with the 35-year period" (6). W.J.S. Lockyer added that the frequency of aurorae and magnetic storms also shows indications of a 35-year period (6).

Based largely on the details in (1), the story of solar-terrestrial meteorology since antiquity was given 2 years later in the journal Science by William Lockyer's father, Sir Norman Lockyer (discoverer of helium in the sun's atmosphere and founder of the journal Nature) (7). Sir Norman began with a statement in 1903 that remains timely in 2008: "There are very many cases recorded in the history of science in which we find that the most valuable and important applications have arisen from the study of the ideally useless. Long period weather forecasting, which at last seems to be coming into the region of practical politics as a result of the observation of solar changes, is another example of this sequence" (7). Sir Norman Lockyer then traced the history of solar-terrestrial variables to ancient China, which was aware of sunspots and of "a magnetic force which acts upon a needle" (7).

The BEL reports were documented by no more than curves for visual inspection by the unaided eye, a circumstance prompting Arthur Schuster in 1914, at his time the leading numerical investigator of hidden periods in his field, to examine Brückner's data and to question the justification of calling the Brückner cycle a periodicity: he explicitly indicated, however, that he did not wish to detract from the phenomenon's importance (8). Subsequently, S.I. Kostin questioned any "Brückner or 'Brikner'" cycle explicitly (in 1965; 9), while Felix Sigel in 1979 referred to the "Brikner" cycle as a multiple of Schwabe's circadecadal periodicity in Zürich relative sunspot (Wolf) numbers (10). In 2003, in an article on fire cycling, there is again a misspelled reference to "Brikner's climatic cycle", described as "minor" yet properly identified in the range from 36-41 years (11). Since 2000, the GKSS-Forschungszentrum (Geesthacht, Germany) has awarded the Eduard Brückner Prize every three years for outstanding interdisciplinary work in climate research (12); yet several investigators in solar-terrestrial atmospheric physics and/or geophysics in the USA, when asked by one of us in 2008, said they had never heard of the "Brikner" or Brückner cycle. Thus, in 2008 the original discoverers of trans-tridecadals are, at least in the USA, mostly forgotten.

Without citation to Egeson, Brückner or the Lockyers, and without reference to a transtridecadal cycle, the close relation of changes in the length of the solar cycle to climate (11) was documented in 1991 (13); other pertinent papers had been reviewed in a historical context by 1995 (14). A possible 35.6-year variation was reported early in the 21st century in coronal holes (15), yet in a spectrogram, it was a transient. It was not a peak in a (global) analysis of the entire series by the extended cosinor analysis method. 33-year variations were found "... in all the solar-terrestrial parameters ..." in 2006 by Nayar, who applied wavelet decomposition analysis to sunspot numbers and solar wind velocity, among other variables (16).

For cases of both accepted and questioned cycles in or around us, we had proposed that, as three highly desirable steps, a test of the zero-amplitude (no cycle) assumption combined with point-and-interval estimation should be carried out first. Second, we advocated the search for a



Wobbly nature of some natural physical environmental and biospherical spectral components require an inferential statistical approach, e.g., according to Marquardt (J SIAM 1963; 11: 431-441; cf. Halberg F. Acta med rom 1980; 18: 399-440, Refinetti R et al. Biological Rhythm Research 2007; 38 (4): 275-325.). The congruence of anticipated components can be meaningfully assessed to approximate a yet-to-be-developed test of H_0: τ_1 (e.g., environmental τ) = τ_2 (e.g., biological τ) [= ... = τ_k (e.g., sociological τ)], or the already available test at a fixed τ of H_0: $\phi_1 = \phi_2$ [= ... = ϕ_k] (Bingham et al., Chronobiologia 1982; 9: 397-439).

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

Figure 2. Congruence or similarity in characteristics such as the period or phase of a spectral component in two or more concomitantly sampled time series of the same variables or of different variables within intracellular entities, cells, tissues, organs, organ systems, individuals, populations, disciplines and, most interestingly, when they are transdisciplinary, as are transyears or trans- and cis-half-years. © Halberg.

transdisciplinary counterpart, i.e, a component with a corresponding cycle length, defined as congruent by overlapping or overlying CIs (95% confidence intervals) of the periods, τs, involved, Figure 2 (17; cf. 18-20). Third, we advocate, when possible, a remove-and-replace approach (17). These criteria apply when the period of one data series is mimicked transdisciplinarily in another; it then provides strong support in transdisciplinary terms for the reality of aeolians (see below), notably when the intermittent nature of the phenomena in a given discipline prompt "lingering doubts", to cite verbatim a physicist (C. Wolff) questioning his own report of an 0.42-year period. The cycle of about 5 months length was predicted by Charles Wolff (21-24) and found to characterize hard solar flares by Rieger (25) and others (26-34) in other aspects of solar activity; it was biospherically validated in sudden cardiac death (ICD10, code I46.1) in Minnesota, the Czech Republic, Hungary, Austria and Tokyo (35-37), and in suicide (38-40), in circulating melatonin (20), in the 17-ketosteroid excretion of a clinically healthy man during 15 years and in the diastolic blood pressure of a treated MESOR-hypertensive man, GSK, with an intermittent circadian overswing, CHAT (41). The intermittent and otherwise nonstationary waxing and waning in amplitude to the point of disappearing and reappearing, bifurcating and rejoining, and drifting in frequency, found in the solar wind's speed, was dubbed "aeolian".

Results

In a clinically healthy man, RBS, a transtridecadal cycle characterizes his heart rate measured for 40 years about 2-7 times daily (on the average about 5 times daily). A cycle of about 32.9 years stands out clearly in a spectrum (Figure 3 right) and is visualized in a model fitted to the display of original data as a function of time (Figure 3 left). It is congruent with a cycle in Zürich (Wolf) numbers during the same span, which is visualized in Figure 4. The CIs in Figures 3 and 4 give quantitative details (in parentheses) of uncertainties in heart rate and Zürich numbers. The circadecadal congruence differs among the 3 vascular variables in Figure 5. Selective infradian congruence is also seen for circaseptan components in Figure 6.

There is further selective mental-environmental congruence in the transyear window of bioresonance. In a relatively small spectral window of a 36-year series of the around-the-clock estimation of 1 minute (TE), we find four cases of congruent spectral components in this mental function matching those in both solar wind speed (S) and a geomagnetic index, aa (E). There were another four cases of congruence between TE and S only (not E) and two added cases of congruence between aa (E) only (not S) and TE. This may be interpreted as in keeping with both direct effects of S or E and/or of S acting via E.

Selective congruence may be limited to certain circadian stages. This is the case of a human mental function (TE) which is modulated by BEL in a 36-year-long time series, as discussed elsewhere in these proceedings. Congruence may vary in time, i.e., may be transient or intermittent, as in the case of a cis-half-year in 17-ketosteroid excretion vs. that in the planetary magnetic disturbance index Kp, suggesting that the biological counterpart is partly built-in since it persists when the environmental counterpart is not detected.

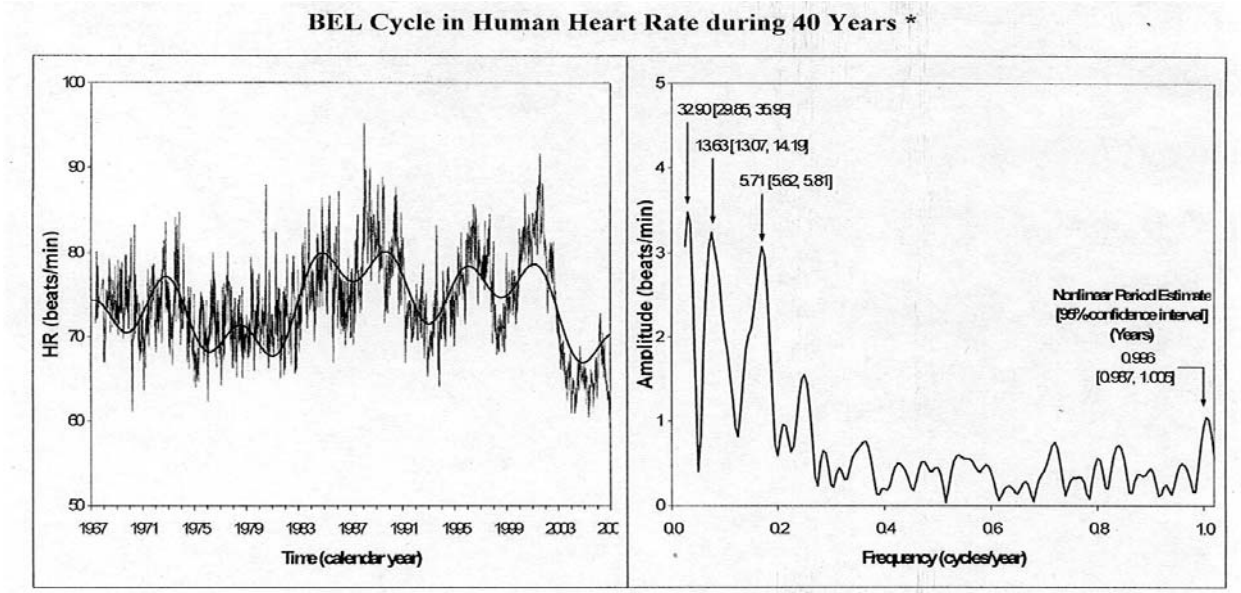


Figure 3. *Weekly averages of data from RBS, clinically healthy man, 21 years of age at start of self-measurements 5-7 times per day during 1967-2006 (N=1978). Transtridecadal Brückner-Egeson-Lockyer cycle (BEL) of 32.9 years in human heart rate of RBS given with its 95% confidence interval in the spectral 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. © 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)*

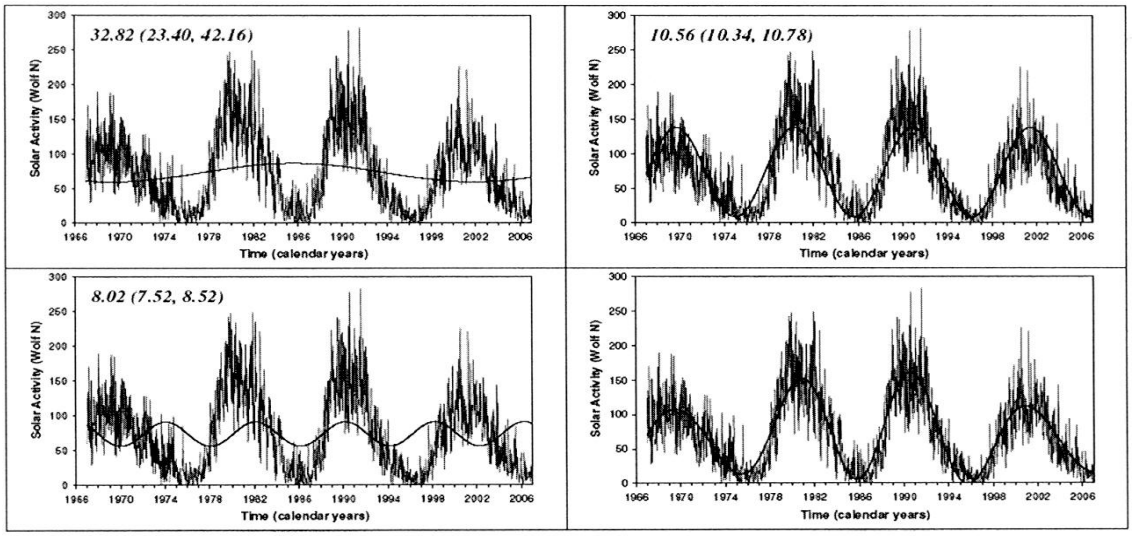
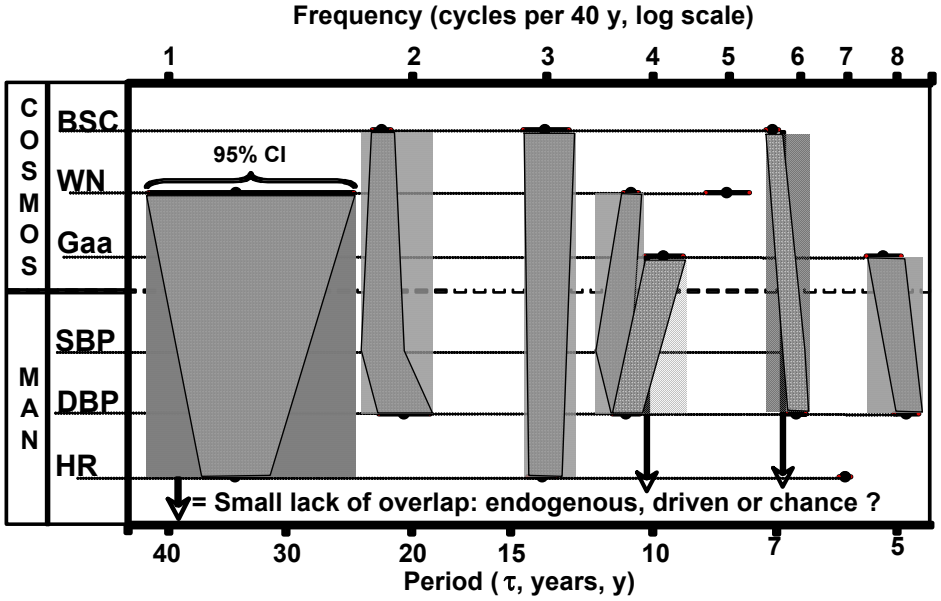


Figure 4. Composite 3-cmponent model fitted to data (bottom right), with contribution by each separate component also shown (top and bottom left) with nonlinearly resolved period (in years) and 95% confidence interval in person. Minor transtridecadal BEL aspect of Zürich sunspot numbers, top left, as 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.

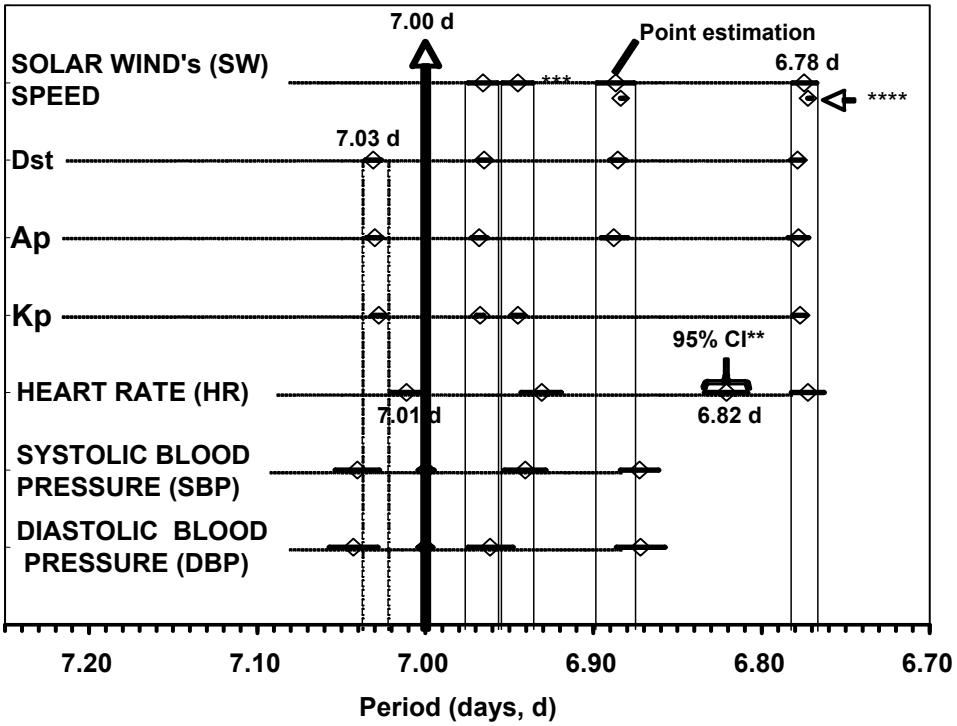
TRANSDISCIPLINARY MAPPING: ENVIRONMENTAL RECIPROCALS TO PHYSIOLOGICAL CYCLES; SOLAR SIGNATURES IN THE HUMAN CIRCULATION: MULTIDECADAL - MULTIANNUAL CONGRUENCE *



*** BSC = Hale's Bipolarity Sunspot Cycle (odd cycles coded negative); WN = Schwabe's relative sunspot numbers (Wolf Numbers); Gaa = Geomagnetic aa-Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HR = Heart Rate. Cardiovascular data collected during 38 y by RBS, a MESOR-normotensive man, 20.5 y old at start of ongoing ~5 daily self-measurements. Width of horizontal bars = 95% confidence intervals (CIs) for all τs. All series in same span (May 11 1967 to Nov 07 2005). Thin connecting lines and shading indicate overlapping CIs. Conclusion (tentative; based on limited data): CIs of τs of some cardiovascular spectral components overlap (when driven ?) or do not overlap (but are near) environmental reciprocal τs (when they are endogenous ?); alternatives, including chance, not ruled out.**

Figure 5. Differential congruence of environmental and physiological peaks in RBS, a clinically healthy man who self-measured blood pressure and heart rate about 5 times a day from the age of ~20 to about 60 years. On top, Hale's **b**ipolarity **s**unspot **c**ycle (BSC) is congruent by the criterion of overlapping, if not overlying 95% confidence intervals of periods with systolic (S) and diastolic (D) blood pressure at some frequencies and with heart rate at a different frequency. Differential congruences are also seen between Zürich relative sunspot numbers or geomagnetics and the physiological variables and further among environmental or physiological variables themselves. Congruences are a first step for the study of biospheric variables by the consequences of subtraction vs. replacement of an environmental frequency. This figure, summarizing 40 years of physiological data, should point first to the need for replicating congruence studies on populations of self-monitoring subjects, since a replication on the same individual is lengthy and involves interactions with age. By the same token, congruence studies are desirable at shorter infradian periods, as in Figure 6. © Halberg.

CIRCASEPTAN CONGRUENCE IN CERTAIN ENVIRONMENTAL SPECTRAL COMPONENTS AND IN SOME CARDIOVASCULAR COUNTERPARTS



* All peaks are statistically significant (P<0.001) by linear-nonlinear least squares cosinor spectra (not corrected for multiple testing). HR, SBP and DBP (N=124,263 each): half-hourly records of GSK, a 72-year old man at start of around-the-clock monitoring; SW (N=69,845) hourly values from http://omniweb.gsfc.nasa.gov/ ; Dst, Ap and Kp 3-hourly data (N=23,376 each) from http://spidr.ngdc.noaa.gov/ .
** CI: confidence interval. *** Two separate spectral peaks without CI-overlapping.
**** All available daily SW data during 1963-2005.

Figure 6. Human heart rate monitored around the clock for over 8 years is characterized by an about 6.78-day circaseptan component with a 95% confidence interval congruent with a matching component found in solar wind speed for the corresponding span as well as for a much longer span of over 40 years of all data available at the time of analysis. A similar component is also found to characterize several indices of geomagnetic activity (Dst, Ap, Kp). A similar component is not found, however, for blood pressure measured concomitantly, characterized by a 7-day synchronized and several other non-7-day circaseptans, two of which are congruent with the periods of indices of helio- and at least 2 indices of geomagnetic activity, of which only one also has a congruence with a period of heart rate. Another period of blood pressure and heart rate, is congruent with geo- but not with heliomagnetic activity. The closeness of the spectral bumps if not hills, however, does not yield the same opportunity for emphasizing selectivity as compared to similar congruences among spectrally well-separated peaks such as those in the decadal and transyearly ranges, Figures 4 & 5. Precisely because of the much better demonstrability of heliogeobiocongruence in the case of distant peaks, those in a crowded very narrow spectral range must not be dismissed by questioning the validity of very many circaseptan components, some of which demonstrably (by chronomic serial section) occur at different times during the observation span. Rules based on lessons learned from congruence among different distant peaks may or may not be found to apply to peaks, e.g., in the circaseptan spectral region. One such rule is that blood pressure and heart rate can be congruent, each with a different spectral component of the same environmental variable in a subject studied over nearly 4 decades, Figure 5. This rule is confirmed and extended by data only over 8 years in the circaseptan range, where the 8 years cover 416 cycles, many more than the 40 years can cover in a circadecadal range (a minimum of 4 decadal cycles and hardly more than a tridecadal cycle). Moreover, any global summary such as those in Figures 5 and 6 is best extended by a chronobiologic-chronomic

serial section that reveals the time courses of the spectral components. Global congruences await analysis of variations in congruence with time. © Halberg.

Conclusion

In all cases of congruence, time courses of corresponding serial data covering preferably the longest available documented spans of the variables involved have to be aligned and examined for any consistent reproducible consequences associated with a remove-and-replace or at least subtraction-and-addition approach (35-40, 42). This requirement does not detract from the basic fact that each of the cycles in and around us, notably those that are found in many disciplines constitute the indispensable control for any endeavor involving a mapped variable along a corresponding time scale. Non-invasive cardiology can use the data collected for prehabilitation as invaluable reference values instead of fictitious, albeit popular baselines (43, 44).

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EFFECTS of Phase II CARDIAC REHABILITATION on INSULIN RESISTANCE and MYOCARDIAL REMODELLING in PATIENTS with ACUTE MYOCARDIAL INFARCTION

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Abstract

Objective. We have designed a new 2-week hospitalized phase II Cardiac Rehabilitation (CR) program in Japan. The purpose of the present study is to determine long-term effects on physical parameters; especially insulin resistance and myocardial remodeling in patients with acute myocardial infarction. **Methodology** Twenty-five patients (20 men, 5 women, mean age: 52±11years, peak CK 2378±1881 IU/l, mean EF 60±18%) with AMI were enrolled in this program. Plasma propeptide of type I procollagen (PICP), HOMA-R and proinsulin were evaluated. The physical status was assessed by the exercise tolerance (AT and peak VO_2), exercise frequency, serum lipid profiles and BMI. All the parameters were evaluated before, 1, 6 and 12 months after the participation in the program. **Results** Serum lipid profiles (HDL cholesterol, triglyceride), BMI, peak VO_2 and AT were improved significantly, PICP was stable at the 1, 6 and 12 months follow-up. Eighty percent of patients had regular exercise activity (REA). There was no significant difference in PICP between REA and the sedentary subjects. Pro-insulin and HOMA-R were stable at the 1, 6 and 12 months follow-up. The change in HOMA-R was not related to exercise tolerance; it strongly correlated with the change in BMI

(r=0.61). **Conclusion** These results suggest that Phase II CR program do not accelerate myocardial remodeling and our 2-week hospitalized Phase II CR program contributes to not only maintain insulin sensitivity but also improve in the management of other cardiac risk factors.

Key words

diabetes – rehabilitation – cardiovascular risk – myocardial infarction – exercise

Introduction

While the mortality from acute myocardial infarction (AMI) has fallen, it remains a leading cause of mortality and morbidity in the Western world. Approximately 50% of deaths from AMI occur in the first hour prior to admission to hospital which emphasizes the importance of primary and secondary prevention. In the past decade several studies suggested that there are some ways to go in this regard, especially the lifestyle changes and risk factor modification in the post-AMI patients. Cardiovascular diseases are the leading cause of death in people with type 2 diabetes (non-insulin dependent – NIDDM). Compared to people without diabetes, people with diabetes have strongly increased risk of coronary heart disease (**1, 2**). People with type 2 diabetes without prior myocardial infarction have as high a risk of death from coronary heart disease as non-diabetic patients with a previous history of myocardial infarction (**3, 4**). Effective management of patients after AMI through lifestyle modification can delay the onset of complications, including cardiovascular and metabolic disorders. However, there are several problems which are not completely solved. First of all, the period of hospitalization during Phase I cardiovascular rehabilitation (CR) becoming shorter as a result of recent advances in medical interventions (stent, PTCA) and also for economic reasons. The lifestyle modification, particularly in terms of daily exercise, cessation of smoking and a balanced food intake, should be acquired during Phase II CR (or so-called recovery stage, since discharge from hospital until return to work) and maintained thereafter. But according to numerous recent reports the participation in the Phase II CR remains still very low - only 9-15% in U.S.A., 14-23% in U.K. and 5-12% in Japan of all the patients after AIM participate in Phase II CR. The main reasons why the participation ratio in Phase II CR is low, are the lack of the primary physician's

recommendation for participation, long commute time (frequent visit rate and long distance to visit local hospitals, so that the patients have a hard time to modify their life-style), patient "denial" of severity of illness and history of depression (**5**). A new 2-week hospitalized phase II cardiac rehabilitation program (2-WCR) has been designed and administered by a multidisciplinary team. The objective of this pilot study was to evaluate the effectiveness of 2-WCRP on insulin resistance and cardiac remodeling in non-insulin dependent (NIDDM) patiens and to clarify whether the physical and psychological status of these patients improved after participation in the program.

Patiens and methods

Twenty-five patients with AMI and NIDDM (age 52.2 ± 11 years, 20 men, 5 women, mean EF 60 ± 18%, peak creatinkinase 2378 ± 1881 IU/l) referred from primary care were enrolled in the 2 weeks lasting rehabilitation program. This program consisted of exercise training, education and counseling, and another 34 patients with AMI who did not participate in the program served as the control group. The physical status was assessed by symptom-limited spiroergometry and determination of exercise tolerance (AT and peak VO_2). Spiroergometry was performed by all patients according to a standardized protocol by Wasserman et al. (1999) (**6**). The test was done at progressively increasing working rate (10 W/min) to the maximal tolerance level on an electromagnetically braked bicycle ergometer. Heart rate was monitored continuously using 12-lead electrocardiograph and blood pressure was measured non-invasively every 2min. The peak workload was recorded; oxygen uptake and carbon dioxide production were calculated breath by breath (CPX/D system, Medical Graphics Corporation, St. Paul, Minneapolis), interpolated, and averaged over 10-s periods. Peak oxygen uptake ($\dot{V}O_{2peak}$) and oxygen uptake at anaerobic threshold ($\dot{V}O_{2AT}$) were determined according to the method by Wasserman et al. (1999). Individual Body Mass Index was calculated according to the formula BMI = weight (kg)/ height^2 (m^2).

Rehabilitation protocol

Two-week non-pharmacological rehabilitation program in hospital was performed as a group based exercise and group (individual) education training. Exercise training consisted of bicycle ergometry (for 2 x 30 min/day at the 80-100% of heart rate at the level of individually

determined anaerobic threshold), walking (1-2 km/day) and stretching performed every day in group classes supervised by a physiotherapist. Education program was done in group classes taught by nurse, physiotherapist and dietitian, and consisted of group lecture (30 - 60 min/day), individual nutrition counseling (60 min/day) and individual discharge instruction (60 min/day).

Biochemical parameters

HOMA-R. The HOmeostasis Model Assessment (HOMA) Ratio is a mathematical model which can estimate an individual's degree of insulin sensitivity and level of beta cell function from simultaneous measurements of fasting plasma glucose and fasting plasma insulin concentrations. HOMA-R models the physiologic glucose-insulin feedback system and estimates an individual's insulin sensitivity based on the assumption that any one combination of glucose and insulin is associated with a given insulin sensitivity, or, conversely, their insulin resistance. HOMA-R has become a much used method for estimating insulin sensitivity and beta cell function in people with non-insulin treated type 2 diabetes.

PICP (carboxyterminal propeptide of type I procollagen). Collagen type I and III are the major fibrillar collagen in the myocardium. PICP is cleaved from the pro-collagen molecule during collagen synthesis and released into the bloodstream. Some studies demonstrated that plasma PICP level in 2-3 weeks after AIM were significantly higher in the group with dilation of myocardium than in the group with no dilation (**8**).

Proinsulin. Proinsulin is a predictor of insulin that is enzymatically cleaved from insulin. Several studies have suggested that proinsulin concentrations are strongly related to cardiovascular risk factors and carotid wall thickness than are insulin concentrations. Increased proinsulin concentrations predict death and morbidity caused by CHD over a period of 27 years, independent of other major cardiovascular risk factors (**9**).

The changes in exercise performance, BMI and selected biochemical parameters were evaluated after 1, 6 and 12 months after discharge home. The physical activity lasting over 20 min and realized more than 2 times per week was considered as home-based regular physical activity.

Ethics

Before inclusion in the study all the subjects provided informed consent. The study was approved by the local Ethics Committee, and conformed with the principles outlined in the Declaration of Helsinki and to the GCP guidelines of the European Community.

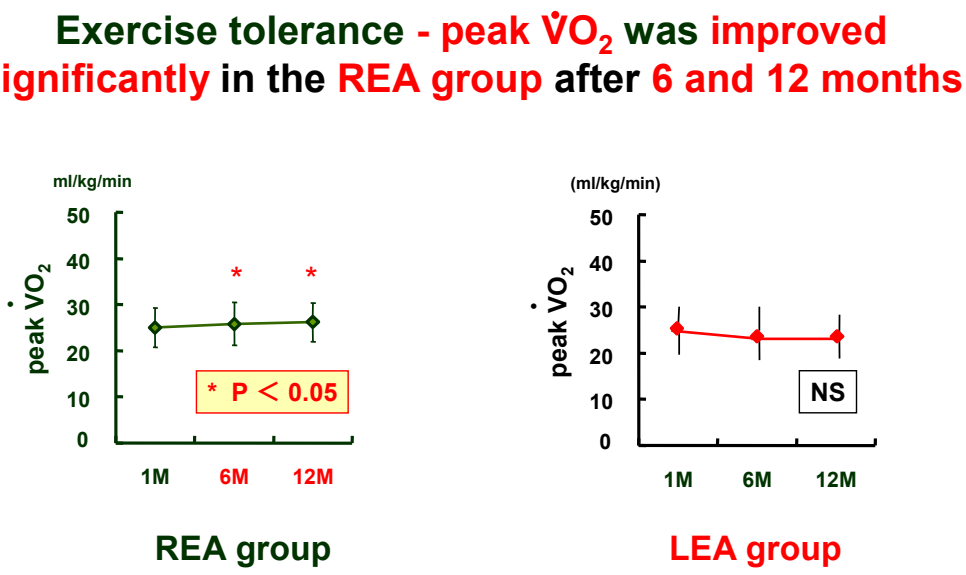
Statistics

All data are presented as mean ± SD. Statistical analysis was performed using the McNemar test of symmetry and Wilcoxon paired test. The P value < 0.05 was considered as significant.

Results

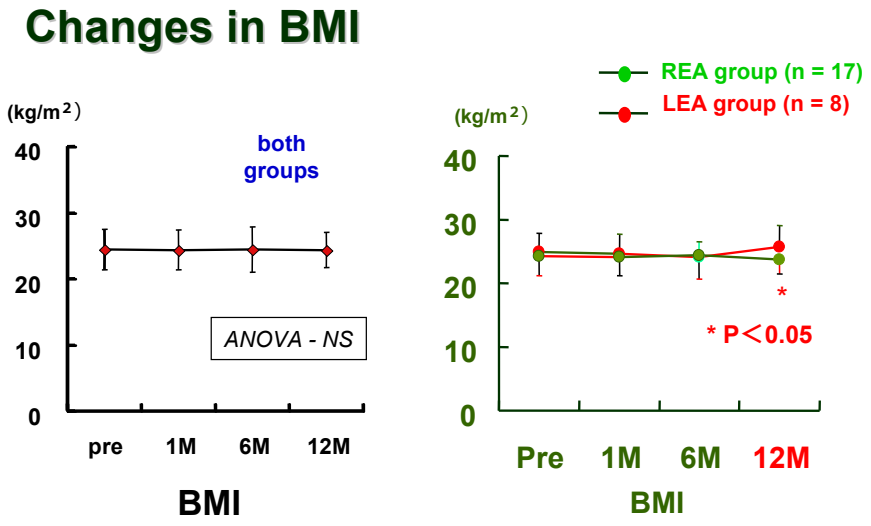
The evaluation of exercise habits revealed, that 17 patients (70%) maintained regular exercise activity (REA group) during long-term follow-up (> 2 times per week), while 8 patients (30%) had lower level of exercise activity (LEA group; < 2 time per week). After participation in the 2-WCRP, the exercise tolerance ($\dot{V}O_{2peak}$) increased significantly (Fig.1)

Fig.1



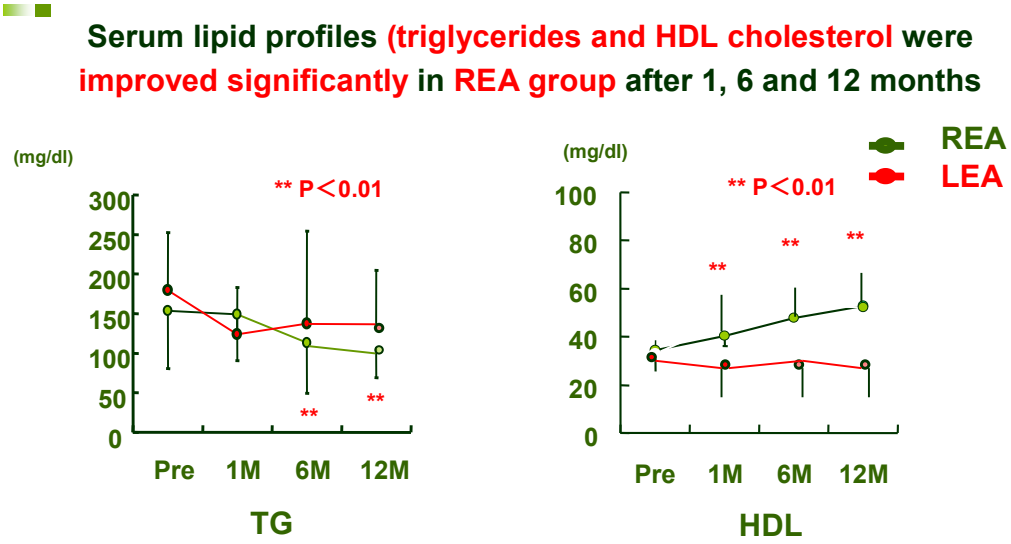
Also the BMI and serum lipid profiles of the patients in REA group were significantly improved (Fig.2 and 3).

Fig.2



total BMI improved significantly in the REA group after 12 months of follow-up

Fig.3



At the 6-month follow-up these parameters remained improved and regular physical activity was maintained. Even at the 12-month follow-up, lipid profiles remained improved and also the

intensity and frequency of regular physical activity was kept. PICP and proinsulin remained stable at 1, 6 and 12 months follow-up and these changes were without statistical significance (Fig.4 and 5). The parameter HOMA-R improved significantly at the long-term follow-up (Fig.4).

Fig.4

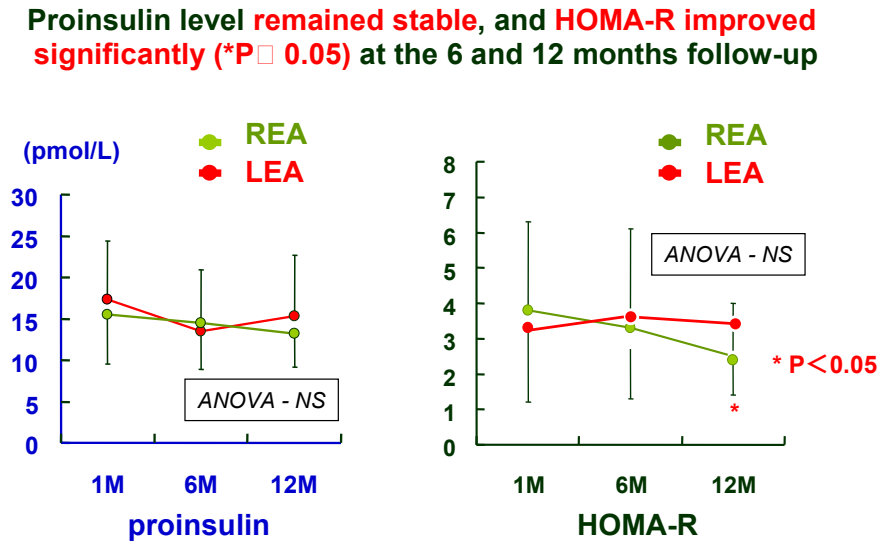
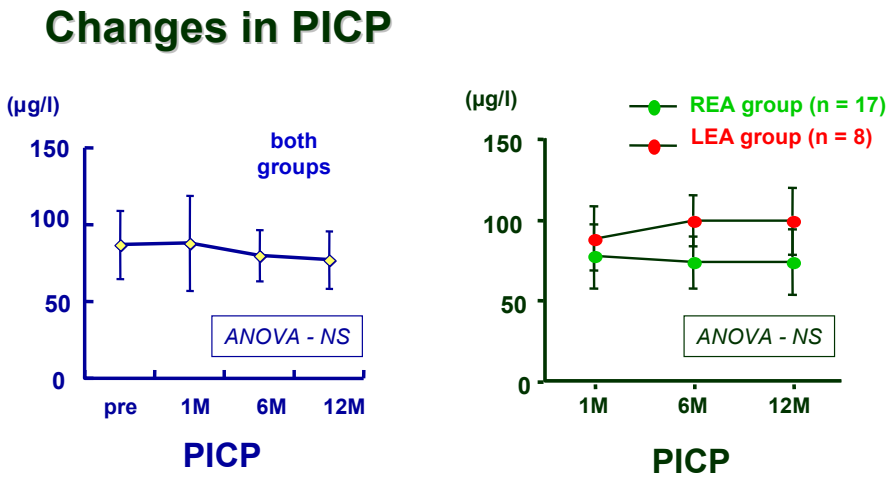
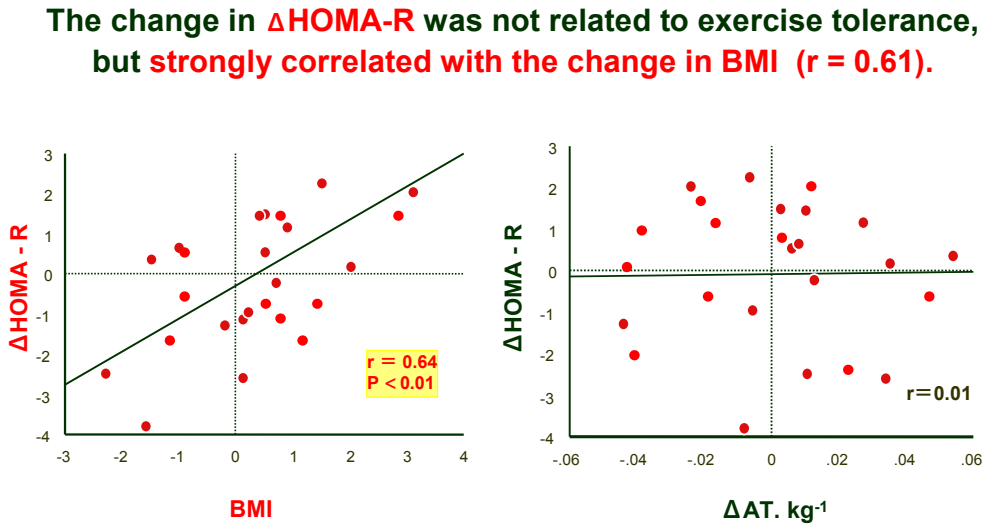


Fig.5



The changes in HOMA-R were not related to exercise tolerance but strongly correlated with the change in BMI (Fig.6).

Fig.6



Discussion

One of the primary aims of cardiovascular rehabilitation is the secondary prevention of risk factors. Modified diets and routine exercise programs effectively lower levels of LDL-C and elevate levels of HDL-C. Exercise substantially reduces systolic and diastolic blood pressures during and after the exercise period. Exercise also contributes to weight loss and improves regulation of capillary blood glucose concentrations in patients with DM. Exercise training programs result in physiologic changes, such as improved peripheral utilization of oxygen and glycolytic-oxidative metabolic capacity, which improve functional capacity to decrease cardiac effort. Blood flow increases during and after active exercise. Physical training elevates muscular metabolic demand, and increased collateral circulation is the presumed mechanism of symptomatic improvement. Coexisting cardiac limitations should be considered when an exercise program is planned. Gradual improvement should be seen within 3-6 months of exercise is a noninvasive and inexpensive activity with minimal complications and is an invaluable first-line treatment for patients with AIM. Most patients with AIM, including those with concomitant

diabetes, can undertake exercise with a high level of safety. However, exercise is not without risk, and the recommendation that people with diabetes participate in physical activity is made on the basis that the benefits outweigh the risks. The American Diabetes Association developed a position statement on exercise in the management of type 1 and type 2 diabetes (**9**). These guidelines aim to minimize the possible risks of exercise for people with diabetes and recommend that particular attention be paid to appropriate screening, program design, monitoring and patient education when developing an exercise program. Nevertheless, people with AIM complicated with diabetes have a poorer short- and long-term prognosis than people without diabetes (**10**). Diabetic patients after AIM have 2x higher mortality than non-diabetics and cardiovascular death accounts for 80% of the mortality in diabetics (**11**). If no contraindications to exercise exist, the type of exercise that a person with diabetes performs is generally a matter of personal preference. Most research documenting the benefits of physical activity for people with diabetes incorporate aerobic activity such as walking, cycling, rowing, or swimming and circuit type resistance exercise (**12, 13, 14, 15**). An area of ongoing concern is the possible adverse effect of physical activity on existing complications of diabetes. It has been suggested that people with complications of diabetes are often told to refrain from exercise for fear of deterioration of the condition and development of further complications (**16**). This leads to further compromise of physical and cardiovascular conditioning. It is important to develop exercise prescriptions for individuals with diabetes complications that will result in improved participation in normal activities and psychosocial well being while minimizing risk of further deterioration. In addition to giving consideration to the varied physical characteristics related to exercise prescription for people with AIM and diabetes, attention should also be paid to the different psychological characteristics associated with exercise adherence. People with NIDDM report a higher frequency of relapse from physical activity programs than the general population (**17**). They often have a low self-efficacy for changing physical activity behavior and have little belief in the beneficial effects of physical activity (**18**). Furthermore, the most frequently cited barriers to physical activity generally relate to AIM and include physical discomfort from exercise, being too overweight to exercise and having little or no support (**19, 20**). These factors, that may reduce exercise adherence, need to be given due consideration when integrating such patients into cardiac rehabilitation. The 2-WCR program is a new multidisciplinary program involving doctors, nurses, cardiac technicians, dietitians, pharmacists and psychologists. As well as a structured

exercise program with cardiac monitoring aimed at optimizing exercise capability, this approach enables the patient's concerns to be dealt with and educated by the appropriate people in the early post-infarction period.

Conclusion

The management of post-AMI patients presents many challenges and also many opportunities to improve prognosis. The benefits of cardiovascular rehabilitation involve the physical, emotional, and psychosocial aspects of a patient's life. With persistence, patients achieve improvements in exercise tolerance and functional capacity. A reduction in cardiac symptoms, as well as perceived stress and anxiety, occurs and lead to improved productivity and psychological well-being. Patients learn to adapt and become self-reliant as they realize that they can influence their hypertension, DM, weight, and smoking activity by means of behavioral and lifestyle modifications. With comprehensive rehabilitation, the patient's QOL improves, they return to work faster than they otherwise might, and their rates of hospital readmission are reduced. It is vital to assess risk factors such as NIDDM and to deal with them appropriately. The 2-week hospitalized phase II cardiac rehabilitation program represents a new approach in standard rehabilitation programs and patients can derive physical and psychological benefit from it. This study suggests that 2-WCR program do not accelerate myocardial remodeling, could provide beneficial effects on the patient's physical recovery phase and may also contribute to the prevention of the onset of other cardiac risk factors.

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ARTERIAL STIFFNESS DETERMINED BY PRESSURE WAVE VELOCITY, AORTIC COMPLIANCE AND CARDIO-ANKLE VASCULAR INDEX

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INTRODUCTION

Stiffness of large arteries has been related to cardiovascular mortality (1). Methods are used to estimate this stiffness include cardiac ultrasound and pulse wave velocity (PWV)(2). The arterial stiffness can be expressed by various indexes. Except PWV it is the aortic compliance and the cardio-ankle vascular index (CAVI) (3). The relationship between these indexes is determined by mathematical equations.

The aim of the present paper was to calculate PWV and CAVI in a group of normotensive and hypertensive subjects where the aortic compliance was non-invasively measured and compare the results with published data obtained from isolated aortas of human cadavers.

METHODS

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

$BETA = \ln(Ps/Pd)*D/dD$ .....(1)

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

$BETA = \ln(Ps/Pd)*2*V/dV$ .....(2)

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

$PWV^2 = (V*dP/dV)/\rho$ .....(3)

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

$V/dV= \rho *PWV^2/dP$.....(4)

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

$BETA = CAVI = \ln(Ps/Pd)*2*(\rho/dP)*PWV^2$..... .....(5)

and volume measurement by ultrasound is superfluous. The last equation express the relationship between CAVI and PWV. On the other hand direct comparison of these parameters with compliance (dV/dP) is not possible because the value V (aortic volume) is missing. The estimates of V from cadaver studies we used in our comparison.
The cadaver study includes 27 aortas from subjects 20 to 83 years old. The results after (4) are published in Kenner Wetterer monograph (5).
The compliance data were obtained by noninvasive measurement from 8 healthy man 27+9 years old (from 21 to 49 years) with 24-hours blood pressure 121+10 / 75+8 mmHg, from 10 not-treated hypertensive man 48+8 years old (from 38 to 58 years) with 24 hours blood pressure values 147+12 / 88+9 mmHg and from 6 hypertensive patients treated with verapamil (slow release formula) 240 mg/24 h for 3 months. The mean age was 43+9 years (from 32 to 53). Twenty four-hours blood pressure values were 143+7 / 88+4 mmHg before treatment and 131+4 / 80+4 mmHg at the time of compliance investigation. The method and the results of compliance measurement are described elsewhere (5).

RESULTS

The results of the cadaver study are seen in Fig.1. From the Fig. it 1 is clear that the slopes of the curves (which corresponds to the compliance dV/dP are pressure dependent. The parameters of the best fitted polynomal curves are seen in Table 1. together with compliance values at 80 mmHg (value of diastolic pressure), the parameters of linear relationship between compliance and pressure and calculated PWV at 90 mmHg (value of mean arterial pressure) and CAVI (which is not pressure-dependent). PWV was calculated after equation (3). Because PWV is aortic pulse wave velocity which is different from cardio-ankle pulse wave velocity, we calculated at first aortic beta after equation (5) and then we calculated CAVI using the regression equation CAVI = 7.5 + 0.15*aortic BETA (3). For CAVI we assume Ps/Pd = 120/80 mmHg.

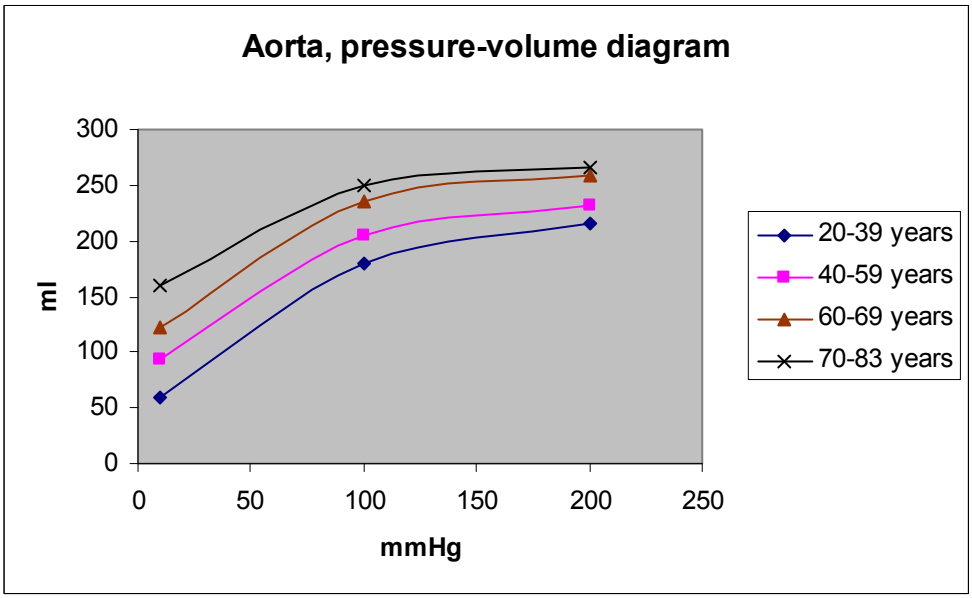

Fig. 1 Pressure-volume diagram of cadavers´ aortas

The results of the analysis of our compliance data are seen in Table 2. The compliance values were non-invasively measured as well as coefficients A and B, which we used for calculation of compliance at 80 mmHg. The volume V was not measured in our study and thus we used the values of V from cadavers' aortas studies for the calculation of PWV estimate again for mean pressure of 90 mmHg. Calculation of CAVI we performed identically as in cadavers' aortas analysis.

Tab. 1 Cadavers´ aortas study

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

Legend: parameters a, b, c correspond to equation; volume = a + b* pressure +c* pressure^2; parameters A, B: compliance = A + B* pressure; dV/dP (80mmHg): compliance at pressure 80 mmHg; PWV: pulse wave velocity; BETA: aortic stiffness; CAVI cardio-ankle vascular index.

Tab. 2 Human noninvasive study

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

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

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

DISCUSSION

Several studies determined the aortic compliance invasively and the values correspond to our non-invasive methods. Also the regression coefficient between diastolic pressure and compliance B (0.0157 ml*mmHg^{-2}) is similar in our study and in study of Lie at al. (x). They found a value B = 0.0131 ml*mmHg^{-2}. In all compliance studies a big variation of compliance among various subjects was observed.

From this point of view it is surprising the accord between cadavers' aortas data and data of living subjects.

Comparison of PWV calculated from our data and PWV measured in healthy subjects revealed that our data corresponds to the high 2.5 centile of PWV variation in cadavers' aortas and in our healthy subjects in all age categories. On the other hand our data from hypertensive and treated hypertensive patients. It is interesting that the stiffness is higher in treated hypertensive patients than in non-treated. This finding can explain the fact, that blood pressure in treated patients was initially higher and the treatment normalize blood pressure relatively quickly but remodeling of arterial wall needs much more time.

Our analysis indicates that all parameters, aortic compliance, PWV and CAVI can be used for estimation of arterial stiffness. It seems to be that stiffness data are more reliable for determination of patient prognosis without treatment than blood pressure measurement. For screening the method must be simple to perform. Here is the CAVI measurement advantage. CAVI is only age dependent. PWV is pressure and age dependent. However CAVI and aortic compliance measurement are not equal. CAVI take into account the atherosclerosis of arteries of lower extremities. Thus aortic compliance and CAVI measurement are complementary.

Aortic compliance is pressure and age dependent but can be relatively simply normalized for distinct value of diastolic pressure. The complicated methodical approach causes a limitation of aortic compliance method for screening purposes.

Support MSM0021622402

SUMMARY

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

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AMBULATORY ARTERIAL STIFFNESS INDEX IN PATIENTS MONITORED FOR 6 CONSECUTIVE DAYS

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INTRODUCTION

Stiffening of large arteries predicts adverse cardiovascular outcomes (1-3). Measurements of arterial stiffness require ultrasound equipment to measure peripheral arteries in the subject in the supine or sitting position (4). The ambulatory arterial stiffness index (AASI) is defined as one minus the regression slope of diastolic on systolic pressure during 24 h ambulatory blood pressure monitoring and might be a measure of arterial stiffness (5, 6). The stiffer arterial tree the closer the regression slope and AASI are ranging from 0 to 1, respectively (7, 8).

In the present paper we attempted to estimate the reliability of AASI determination in individual patients. Studying the infradian rhythms in chronobiology of blood pressure we perform ambulatory blood pressure monitoring for 7 consecutive days (9, 10, 11). This enables us to obtain 6 values of AASI in 6 full consecutive days. The preliminary results from our laboratory were published (12).

METHODS

The set being monitored consisted of fourteen patients after myocardial infarction in the past history more than 6 months before, of mean age 63 ± 6.5 and mean ejection fraction of the left ventricle 43 ± 12.3 %.

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

In the course of rehabilitation they went through 7-day ambulatory monitoring of blood pressure. During blood pressure recording they did not interrupt their pharmacotherapy.

The seven-day blood pressure monitoring was made by using the instrument TM – 2421 of the Japanese firm AD on the principle of oscillometric methods of blood pressure measurement. The regime of measurement of blood pressure was done for 7 days repeatedly every 30 minutes from 5 to 22 h during the day time and once in an hour from 22 to 5 h at night (Siegelová et al. 2004).

The measured blood pressure values for every patient from the monitored set were statistically processed in the form of arithmetic means for systolic and diastolic blood pressure value during each hour for every measured day. The average SBP and DBP and their standard deviations (SD) in the given days were determined by the calculation of arithmetic mean of these values.

These data were used for every consecutive day of seven day monitoring to calculate the slope of diastolic on systolic pressure and to calculate the ambulatory arterial stiffness index (AASI) as one minus regression slope of diastolic on systolic blood pressure.

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

RESULTS

Results of AASI values together with 24-hour mean values of systolic (SBP) and diastolic blood pressure (DBP) of 14 patients are seen in Table 1.

Tab. 1 Variability of 24-hour blood pressure values and AASI in 14 patients calculated for 6 consecutive days

	AGE (Y)	SBP (mmHg)				DBP (mmHg)				AASI				R	
		6 d	±SD	MIN	MAX	6 d	±SD	MIN	MAX	6 d	±SD	MIN	MAX	MIN	MAX
1	74	113	3	110	117	57	2	55	62	0,72	0,13	0,56	0,83	0,14	0,49
2	68	134	3	131	139	86	2	84	89	0,56	0,15	0,32	0,77	0,36	0,77
3	66	128	4	124	134	75	3	73	81	0,70	0,17	0,50	0,99	0,02	0,72
4	56	106	4	102	113	67	4	62	73	0,61	0,22	0,20	0,86	0,19	0,89
5	60	118	3	115	123	63	2	60	66	0,84	0,16	0,59	1,10	-0,20	0,68
6	58	124	7	115	134	66	3	60	70	0,68	0,12	0,51	0,87	0,22	0,71
7	58	126	7	114	137	72	4	64	78	0,61	0,10	0,50	0,79	0,40	0,73
8	60	107	4	103	113	65	4	60	69	0,69	0,12	0,50	0,90	0,13	0,90
9	72	128	4	123	132	63	1	62	65	0,74	0,12	0,54	0,89	0,38	0,69
10	61	113	5	108	119	71	2	68	73	0,69	0,11	0,48	0,83	0,45	0,72
11	54	117	2	112	120	76	1	73	77	0,39	0,09	0,20	0,49	0,59	0,82
12	66	133	6	126	144	87	4	82	91	0,23	0,17	0,02	0,58	0,61	0,94
13	53	141	6	129	147	90	5	80	93	0,22	0,16	0,00	0,44	0,68	0,9
14	70	119	3	115	123	67	5	60	75	0,51	0,2	0,28	0,76	0,34	0,64

SBP, mean systolic blood pressure; DBP, mean diastolic blood pressure; AASI, ambulatory arterial stiffness index; r, correlation coefficient between DBP and SBP; 6d, mean of 6 days values; SD, standard deviation; min, max, minimum and maximum 24-hours values.

The mean systolic and diastolic blood pressure variations are seen in Tab 1 as well as the inter-individual variations of AASI and there are large.

DISCUSSION

The simplest explanation for the variation in AASI is that it reflects spontaneous variability in arterial stiffness from one session to another. However, it should be considered that AASI is under the influence of other sources of variability, which are necessarily related to arterial functional properties (13).

Due to mathematical reasons AASI obtained form standard regression analysis depends on day-night blood pressure change (14), and hence variation in the latter may be expected to induce variation in the former. The reproducibility of day-night blood pressure changes and of the dipper-nondipper classification is far from being optimal. In a recent study (15) in which 150 hypertensive patients underwent 24-hour blood pressure monitoring twice, between session agreement for the dipping-nondipping classification was found to vary from fair-to-

moderate and the coefficient of repeatability of day-night blood pressure change was as high as 42-49 %. Such a large variation can be expected to influence variability of AASI as well. The strong relation between AASI and day-night blood pressure changes is further confirmed by the paradoxical finding that daytime and night-time AASI are both much higher (0.48 ±0.26 and 0.40 ± 0.21) than the corresponding 24-h values (0.31 ± 0.17), emphasizing its limited ability to specifically reflect arterial wall properties (16).

A further source of variation in AASI values is represented by the night/day ratio of blood pressure measurements number. In our study we calculated the AASI from the blood pressure values, given in regiment one per hour. In the literature it was demonstrated that the dependency of AASI of the number of daytime and nocturnal readings is a phenomenon related to the above relationship between day-night blood pressure reduction and AASI (17). The is a need for more substantial data on AASI repeatability in larger cohorts of hypertensive patients and in the normal individuals in any case, due attention should be paid to the influence of day-night blood pressure changes and to that of daytime and night-time between-reading time intervals on AASI and its variability (18).

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

Support MSM0021622402

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PHYSICAL ACTIVITY AND 24-HOUR PROFILE OF BLOOD PRESSURE

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INTRODUCTION

Sedentary life and excessive body mass contribute to the risk of hypertension development (1-8). It has been demonstrated that physical exercises decrease the risk of hypertension development. In our clinic we carry out 7-day ambulatory monitoring of blood pressure (9-12). It enables us to monitor blood pressure changes induced by exercises in the course of the following 24 hours if we compare them with the values in subsequent next 24 hours. This approach takes fully into consideration circadian fluctuation of blood pressure.

The aim of the study was to compare 24-hour course of blood pressure immediately after the exercises with the values from the following day when the patient did no exercises.

METHODOLOGY

The set being monitored consisted of 10 patients after myocardial infarction of the age (63 ± 6,3) 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 they underwent 7-day ambulatory monitoring of blood pressure. During TK recording they did not interrupt pharmacotherapy.

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

The results were processed by using Halberg cosinor analysis. The data were smoothed by a sinusoidal curve. The mean value of the sinusoid, designated MESOR, and amplitude of circadian fluctuation were determined. The measured TK values of each patient from the monitored set were statistically processed in the form of arithmetic means for every hour after the completion of exercises for the time of 48 hours. This enabled us to compare the means in individual hours after the exercises with the hour means obtained 24 hours later, i.e. in the day when the patient did no exercises. We calculated therefore for every patient differences in individual hours between the day immediately after the exercises and the subsequent day without exercises. Statistical significance was tested by Wilcoxon test.

The study was accepted by ethical commission and the patients signed their informed approval.

RESULTS

The result was comparison of two 24-hour profiles of blood pressure, the first one beginning immediately after the exercises, the second one shifted by 24 hours. In the second case the patient did no exercises. Halberg cosinor analysis demonstrated that there are no differences in 24-hour MESOR and circadian amplitude between both profiles both in systolic and in diastolic blood pressure (Fig. 1, 2).

Comparison of hour differences indicated that only in the first hour after the exercises systolic pressure is lower than in the check course ($p<0,01$). Also in the second hour after the exercises the value is lower, the difference, however, is not statistically significant any more. In the other hours both profiles were not different (Fig. 3, 4). We have found no differences in diastolic pressure. The analysis of differences is in accordance with the finding of the same MESOR quantities and amplitudes.

The analysis shows that the exercises do not change profiles of 24-hour blood pressure immediately after the exercises. Positive effect of the exercises must be explained by other mechanisms than by means of blood pressure changes in the day following after the exercises.

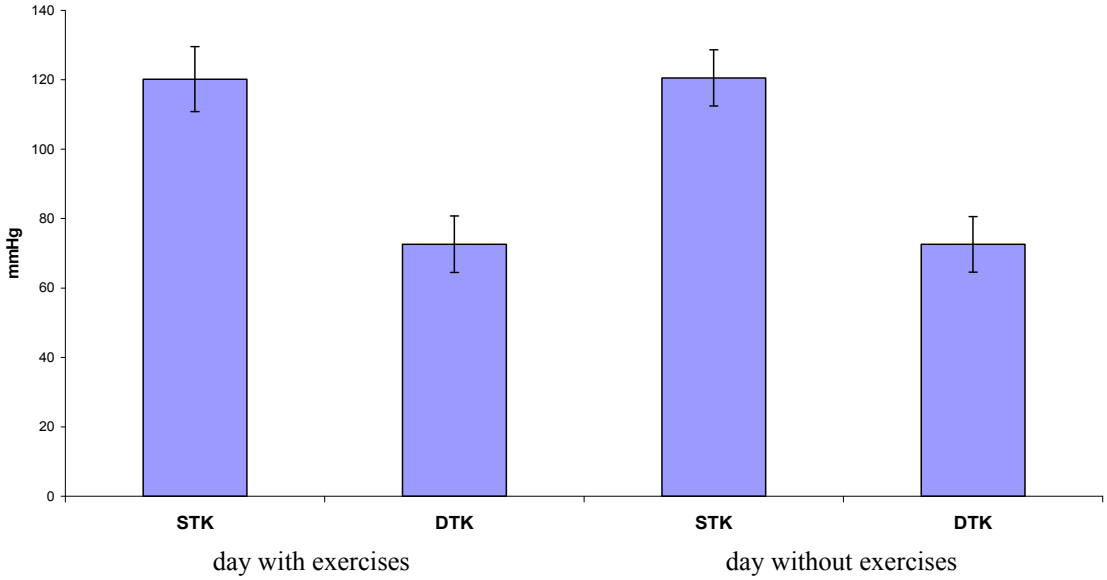

Fig. 1 MESOR of circadian fluctuation of systolic blood pressure and diastolic blood pressure in the day with exercises and in the day without exercises

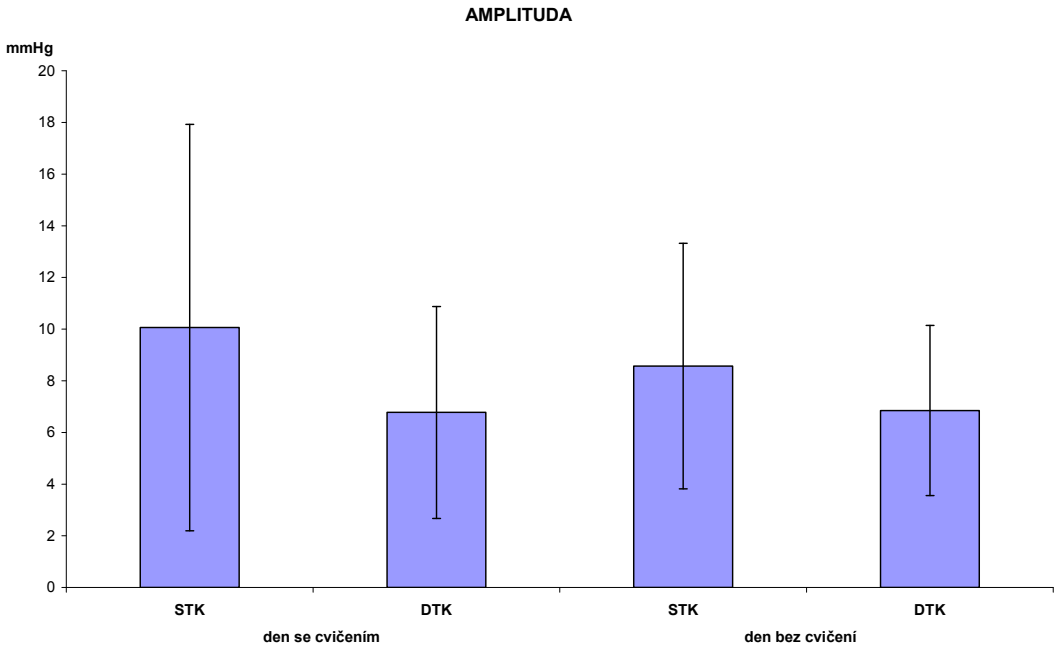

Fig. 2 Amplitude of circadian fluctuation of systolic blood pressure and diastolic blood pressure in the day with exercises and in the day without exercises

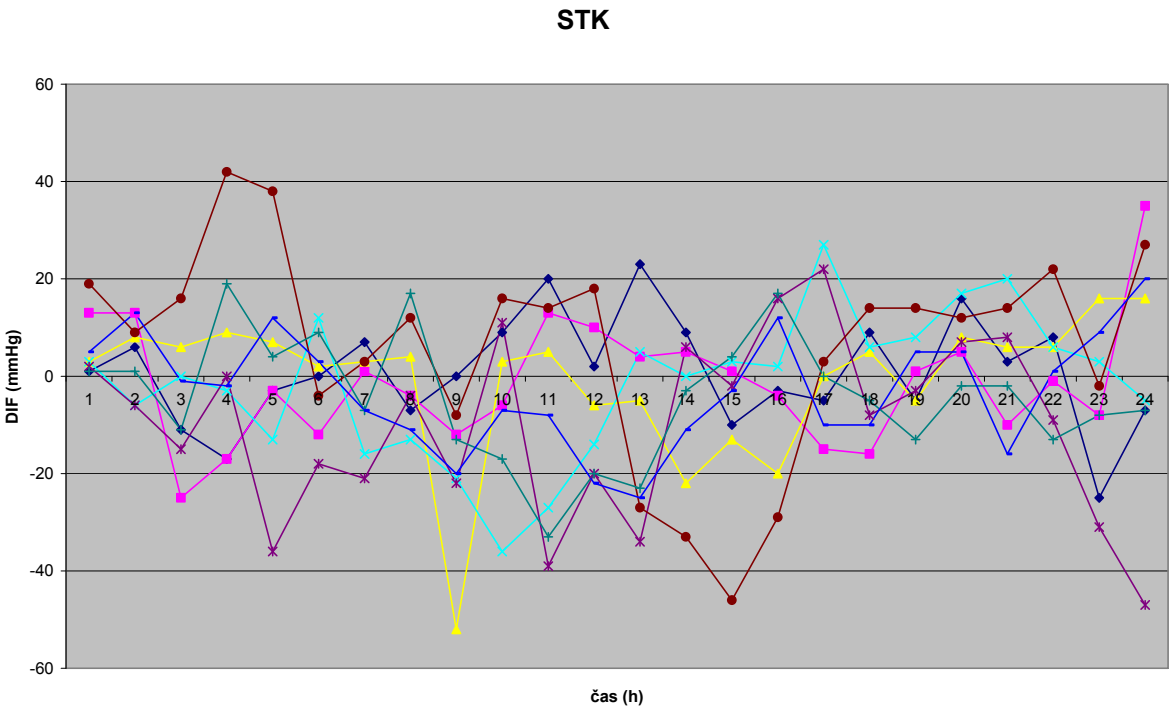

Fig. 3 Difference of systolic blood pressure between the day with exercises and the day without exercises in individual hours of the day

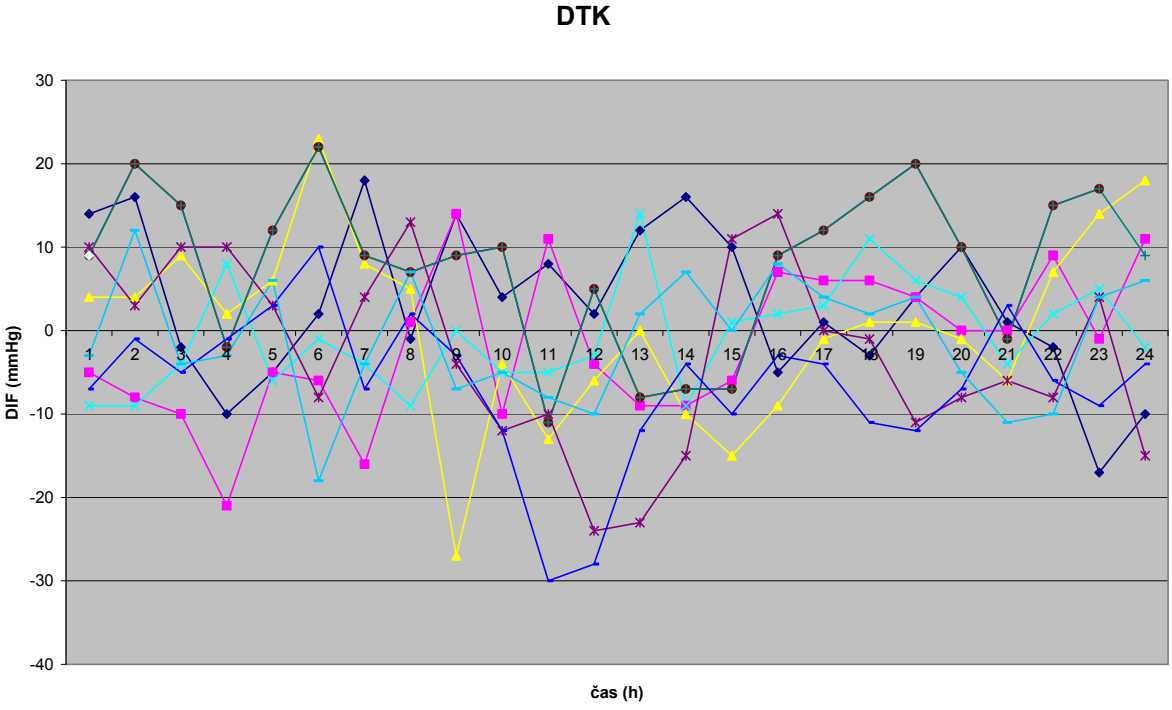

Fig. 4 Difference of diastolic blood pressure between the day with exercises and the day without exercises in individual hours of the day

DISCUSSION

Meta-analysis of controlled studies demonstrated convincingly that aerobic exercises decrease systolic and diastolic blood pressure (13). We have shown that the exercises themselves do not decrease blood pressure in the subsequent hours. Other mechanisms must be therefore taken in consideration. The information found in literature indicate that one of possible explanations can be related to the decrease of body mass. A number of published data and a logical explanation exist. Adipose tissue produces leptin that increases sympathetic activity and thus blood pressure.

It seems, however, that physical activity is positive also when body mass is not decreased. One of possible explanations can be in affecting of psychological stress. Psychological stress increases blood pressure even in young people (14). Physical activity and feeling of a better fitness in patients with cardiovascular diseases reduces their fear of further progression of the disease and stress connected with it, and exercising can therefore be beneficial even due to this mechanism.

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SUMMARY

The aim of the study was to compare 24-hour course of blood pressure immediately after the exercises with the values from the following day when the patient did no exercises. The set being monitored consisted of 10 patients after myocardial infarction of the age (63 ± 6,3) years and ejection fraction (43 ± 12,3) %. In the course of rehabilitation the patients were subjected to 7-day ambulatory blood pressure monitoring. During the blood pressure recording their pharmacotherapy was not interrupted.

The analysis shows that the exercises do not change 24-hour blood pressure profiles immediately after the exercises. Positive effect of the exercises must be explained by other mechanisms than by means of blood pressure changes in the day following after the exercises.

KEY WORDS: circadian fluctuation of blood pressure, physical activity, 7-day ambulatory blood pressure monitoring

INTERVAL AND CONTINUOUS TRAINING IN CARDIOVASCULAR REHABILITATION IN MEN AFTER ACUTE MYOCARDIAL INFARCTION: INFLUENCE ON AEROBIC CAPACITY AND PERFORMANCE ON THE LEVEL OF ANAEROBIC THRESHOLD

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INTRODUCTION

Cardiovascular rehabilitation is a universally accepted part of 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

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

36 men patients after AIM were included into the study. According to ejection fraction of left ventricle (EF) they were divided into two groups. The group with a higher EF (54 ±7,7 %, group K, n=18) went in aerobic phase through the training with continuous work load, the

second group with a lower EF (47 ±12,7 %, group I, n=18) went in aerobic phase through 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, their characteristic is given in Table 1.

Table 1 Characteristic of the set

	Group K	**Group I**
Number (n)	18	18
Age (years)	57 ± 12	60 ± 7
Ejection fraction (%)	54 ± 7.7	47 ± 12.7
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 (1st to 2nd week 40 min; 3rd to 12th week 25 min), toning phase (3rd to 12th 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 motoric system to further load, prevention of muscular-skeletal lesion. It consisted of 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 increase 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±190,6	1225±291.5	0.001	995±209,9	1194±242,6	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

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	0.05	0.6±0.17	0.8 ± 0.26	0.001

WANP = performance on the level of anaerobic threshold

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, but they differed in ejection fraction. Ejection fraction in the group with interval training was considerably lower than in the group with continuous training (low ejection fraction is one of indications for interval training). The benefit of interval training lies in the possibility of obtaining improvement even in risk patients (11). In our study we verified the method in patients with decreased ejection fraction of left ventricle and in patients with residual ischemia and generally low tolerance of work load. In these patients preference should be given to interval training before continuous one, also for safety reasons (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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SUMMARY

The purpose of the study was to examine the effect of two modifications of aerobic training (interval and continuous) during 12 weeks of controlled out-patient cardiovascular rehabilitation program on aerobic capacity and performance on the level of ventilatory anaerobic threshold. 36 males were included in our study. They were divided into two subgroups. Group K (EF 54±7.7 %, n=18) passed aerobic phase of the program with continuous work load, in group I (EF 47±12.7 %, n=18) interval training was prescribed.

Intensity of the training was on the level of ventilatory anaerobic threshold in both groups. The groups did not differ in age. Symptom-limited spiroergometry was provided before and after rehabilitation program. The rehabilitation program was carried out three times a week for 60 min. Oxygen intake was increased in both studied groups (VO_2ANP was increased in „K“ by 13 %, VO_2ANP/kg by about 11 %. VO_2ANP was increased in „I“ by 20 %, VO_2ANP/kg by 20 %). The work load on the level of anaerobic threshold improved significantly (WANP was increased by 15 % in „K“ and WANP/kg by about 17 % in „K“. WANP was increased by about 35 % and WANP/kg by about 37 % in “I”). Statistically significant improvement in aerobic capacity and performance on the level of anaerobic threshold was observed in both groups. Both modifications of aerobic training were well tolerated.

KEY WORDS

Cardiovascular rehabilitation, continuous training, interval training, infarctus myocardium.

BAROREFLEX SENSITIVITY IN MULTIPLE SCLEROSIS

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INTRODUCTION

Disseminated multiple sclerosis (SM) is a chronic system autoimmunity disease causing, on the basis of dissemination of demyelinisation focuses in CNS region, functional neurological deficit. The course is typically episodical, with acute attacks of demyelinisation occurring in irregular intervals and bringing about often increasing motor deficit and loss of sensoric functions (1).

Dysfunctions of autonomic nervous system (ANS) are quite a frequent phenomenon in SM. They are characterized particularly by dysfunctions of urinary bladder, disorder SM of sexual and sudomotoric functions (2-4). Autonomic dysfunctions affecting the cardiovascular system regulation, however, are also documented more and more frequently (5-11). Incidence of these dysfunctions varies as to frequency, importance of abnormities and autonomic reflex tests being used (5,6,10,12,13). Alterations of cardiovascular system parameters SM were demonstrated in SM patients both at rest and during physical load when ANS is responsible for compensation of hemodynamic cardiovascular response to physical stress. Autonomic dysfunctions can lead therefore to limitation of physical load capacity and can contribute to the fatigue of SM patients that has not yet been explained (14-19).

Cardiovascular autonomic functions in SM are most frequently followed-up by means of conventional reflex tests (5,6,20,21). These methods are limited mainly by difficult interpretation and differentiation of the sympathetic or parasympathetic component of cardiovascular regulation by autonomic nervous system.

A contemporary trend in testing of autonomic nervous system is based on examination of heart rate variability (HRV) the results of which we have published already (22,23). Monitoring of baroreflex sensitivity (BRS) is another possibility of evaluation of cardiovascular regulation.

AIM

Our study is aimed at finding out whether disturbed regulation of blood circulation is connected with the degree of clinical disability in the set of patients with disseminated cerebrospinal sclerosis. We evaluated the regulation of blood circulation by means of determination of baroreflex sensitivity (BRS), clinical disability of patients with SM was evaluated according to Kurtzke's Expanded Disability Status Scale, EDSS.

METHODOLOGY

The examined set of patients consisted of patients with diagnoses from neurological outpatients' department for SM of 1st neurological clinic of Faculty of Medicine, Masaryk University, St. Anna Teaching Hospital, and from the team of Unie ROSKA Brno-město. The patients with internal, metabolic and other diseases which could influence validity of the results of autonomic testing, were excluded from the study. The patients were tested in clinically stabilized state of the disease. They confirmed their participation in the study by signing „Informed approval of the patient"; the study was accepted by the relevant ethical commission of St. Anna Teaching Hospital in Brno. Clinical evaluation of disability by EDSS scale was performed before the examination of autonomic nervous system.

EDSS (Kurtzke's Expanded Disability Status Scale) (26) is a standard scale for evaluation of disability of SM patients. It is a neurological examination with evaluation by 0.5 point, in the interval from 0 (no functional disorder or impairment) to 10 (death because of SM), impact of SM disease on 8 basic functional systems.

BRS (baroreflex heart rate sensitivity) characterizes the function of baroreceptors participating in maintaining blood pressure and heart rate and expresses the level of activity of autonomic nervous system. Extension of heartbeat interval R - R (CI) in milliseconds at increasing of SBP by 1 mm Hg is an indicator of BRS. BRS value (ms. $mmHg^{-1}$) is the function expressing the relation between spontaneous fluctuation of SBP and R - R intervals.

The examination was carried out by means of non-invasive continuous recording of heart rate and blood pressure made by TASK FORCE MONITOR (CNS System, Graz, Austria) (25), by beat-by-beat measurement method. 5-minute record was made in

supine position with controlled breathing rate according to the metronome 0.33 Hz, for comparison of the results between the patients. By software processing of continuous recording of heart rate and blood pressure (BP) by sequential analysis there are found events of at least three or more consecutive monotonous changes of SBP with a minimal deviation 1 mmHg/1 heartbeat and, at the same time, at least three consecutive monotonous changes of RR intervals with a minimal change 4 ms/1 heart beat. The events of SBP changes can thus have BP up-events or BP down-events. Then regression terms for all up-events and all down-events and mean values for both types of events are calculated. The results are given separately for up- and down-events and further as the total BRS for all events in ms/mmHg. The values are given as mean ± SD. Impossibility of a reliable measurement of BRS because of low number of events (less than 8) we considered to be a disturbed cardiovascular regulation.

Heart rate variability (HRV) was also examined by the instrument TASK FORCE MONITOR (CNS System, Graz, Austria) (25). We evaluated, by means of spectral analysis, very low-frequency component of HRV (0.02 - 0.05Hz, VLF-RRI), low-frequency component of HRV (0.05 - 0.15Hz, LF-RRI), high-frequency component of HRV (0.15 - 0.50Hz, HF-RRI), total spectral power (HRV TP), index of sympatho-vagal balance (LF/HF), length of cardiac interval (RRI), heart rate SF.

Statistical analysis of the data (program STATISTICA for Windows – version 7.7) was made by means of t-test for independent specimens and Wilcoxon test.

RESULTS

27 patients with verified SM disease, in the remission stage (mean age 43.4 years, duration of SM disease 6.4 let, EDSS 3.25) were examined.

On the basis of evaluation of BRS examination we divided the set into two groups according to the number of down- or up-events of blood pressure. The group A with disturbed cardiovascular regulation consists of patients with BP up-events or BP-down events ≤ 8. The group B consists of patients with the number of events ≥ 8.

Characteristic of anthropometric data and characteristic of SM disease in both groups are in Table 1.

Table 1 Basic anthropometric data and data characterizing SM disease in examined groups (the values are expressed as mean ± SD)

Totally 27 SM patients	Group A (BRS ≤ 8 events)	Group B (BRS ≥ 8 events)
	n= 13	N=14
Gender	2M/11F	3M/11F
Age	46.3 ± 8.7	40.5 ± 6.2
Height [m]	1.7 ± 0.1	1.7 ± 0.1
Mass [Kg]	67.7 ± 12.6	69.0 ± 12.6
BMI	23.8 ± 4.3	23.8 ± 4.1
Body surface area [m^2]	1.80 ± 0.13	1.81 ± 0.14
EDSS	4.2 ± 1.2	2.1 ± 0.5 *
Duration of SM	6.3 ± 7.6	6.5 ± 5.7
RR form	8	9
SP form	4	3
PP form	1	2

RR form- relabs-remittent form of SM disease, SP - form secondary progression, PP - form primary progression, BMI - body mass index, * $p < 0.05$

Examined indicators of baroreflex sensitivity are in Table 2.

Table 2 Results of baroreflex sensitivity (BRS) in monitored groups

Controlled breathing 0.33Hz	Group A	Group B
R-R Interval [ms]	826.3 ± 102.0	837.0 ± 115.9
HR [heartbeat/min]	74.0 ± 9.0	73.4 ± 10.3
SBP [mmHg]	115.0 ± 13.7	114.2 ± 5.4
DBP [mmHg]	78.2 ± 9.8	74.9 ± 4.3
n (number of up-events)	Not evaluated *	12.9 ± 5.3
BRS up-events [ms/mmHg]	Not evaluated *	13.7 ± 6.4
N (number of down-events)	Not evaluated *	15.4 ± 8.8
BRS down-events [ms/mmHg]	Not evaluated *	12.5 ± 4.6
n (number of all events)	Not evaluated *	28.3 ± 13.3
BRS all events [ms/mmHg]	Not evaluated *	13.2 ± 5.4

HR – heart rate, SBP, DBP - systolic, diastolic BP, BRS up-events - absolute value of baroreflex sensitivity for up-events, BRS down-events - absolute value of BRS for down-events, BRS all events - absolute value BRS all events, n – number of recorded events, * not evaluated by sequential analysis of BRS because of insufficient number of recorded events

Additional examined values of heart rate variability (HRV) are given in Table 3 with statistical significance of comparison between the groups.

Table 3 Results of heart rate variability (HRV)

HRV controlled breathing 0,33Hz		Group A	Group B	P
VLF-RRI	[ms²]	357.8 ± 878.5	112.3 ± 93.1	NS
LF-RRI	[ms²]	178.7 ± 312.2	475.4 ± 1070.5	NS
HF-RRI	[ms²]	298.6 ± 551.3	551.1 ± 1356.8	NS
TP-RRI	[ms²]	835.0 ± 1205.3	1138.8 ± 2440.5	NS
LF/HF	[1]	1.4 ± 1.5	1.6 ± 1.3	NS
R-R Interval	[ms]	826.3 ± 102.0	837.0 ± 115.9	NS
SF	[bpm]	74.0 ± 9.0	73.4 ± 10.3	NS

VLF-RRI - very low-frequency component of HRV (0.02 - 0.05Hz), LF-RRI - low-frequency component of HRV (0.05 - 0.15Hz), HF-RRI - high-frequency component of HRV (0.15 - 0.50Hz), TP – total power of HRV, LF/HF - index of sympatho-vagal balance, RRI - interval of RR, SF- heart rate, NS - low statistical significance

DISCUSSION

Disorder of regulation of cardiovascular functions in SM is clinically less frequent, but potentially dangerous (35). These abnormalities were studied in the past on the basis of a number of examination of cardiovascular reflexes with a different measure of informative value. That is why the results and interpretation of disorders of cardiovascular functions often diverge in the published papers. Abnormalities of cardiovascular reflexes were proved controversially in both branches of sympathetic and parasympathetic nervous supply (3,5,6,9-11,29). Saari et al. (2004) (27) documented that the measure of disability in SM correlates with reduction of cardiovascular response and also with the volume of lesions of central nervous system, verified by means of magnetic resonance examination. According to the authors it can be supposed that particularly lesions of midbrain, ale also, even if with a lesser impact, lesions of hemispheres are responsible for most of cardiovascular abnormalities. This hypothesis was indicated already by the results of Acevedo et al. (5) who established connection of cardiovascular dysfunctions in SM with affection of reflex paths in the brain-stem. A partial response to the question whether autonomic cardiovascular regulation in SM is affected by direct mechanism, was given by the study of authors Sanya et al. (28) that investigated carotid baroreflexes in patients with SM separately for parasympathetic and sympathetic cardiovascular regulation. Baroreflex function was not reduced only in

cardiac regulation of baroreflex, also sympathetic regulation of tonus of arterial bed was affected. The authors think that indirect impairment of sympathetic vasomotor regulation can be responsible for postural disorders and vertigo that are described in as many as 49 % of SM patients (29). The finding of sympathetic vasomotor disorder of the function and its correlation with general fatigue in SM was established also in the study of authors Flachenecker et al. (31).

The results of our study indicate that mechanisms of baroreflex control in the group B with EDSS 2.9 with a clearly expressed BRS in the values corresponding to the average age of healthy population seem to be in the range of reference standard values (36, 37,38). In this group there were measured values of BRS of BP up-events 13.7 ± 6.4 ms/mmHg, BP down-events 12.5 ± 4.6 ms/mmHg and mean BRS for BP total-events 13.2 ± 5.4 ms/mmHg.

On the other hand, in the second group of SM patients (group A) for BRS determination by sequential method in 13 patients was not found a sufficient number of BP up-events or BP down-events. This difference between the groups A and B can be hypothetically explained by dissimilarity of autonomic regulation of BRS and increase of sympathetic tonus in the group A can be supposed. The group A does not differ statistically significantly from the group B either in anthropometric values or in duration of the disease (6.3 ± 7.6 vs. 6.5 ± 5.7 let). The groups do not differ either in proportional representation of the forms of SM disease. It can be explained by the significant difference of the extent of clinical disability of autonomic nervous system. In the group A there is a larger measure of disability according to EDSS (3,6 ± 1,4) than in the group B (2.9 ± 1.4). We have not found, however, correlation between the indicators of BRS and EDSS. HRV indicators show a generally lower total power (TP) in the group A (835.0 ± 1205.3 ms^2) than in the group B (1138.8 ± 2440.5 ms^2) and decrease of LF and HF of HRV component as against the group B (178.7 ± 312.2 vs. 475.4 ± 1070.5ms^2; 298.6 ± 551.3 vs. 551.1 ± 1356.8 ms^2); it was not statistically significant, however.

On the basis of our results we can conclude that a lower degree of clinical disability need not be connected with cardiovascular regulation impairment and a higher degree can mean its impairment at the level of baroreceptors. Question arises whether reduced baroreflex sensitivity of heart rate will increase the risk of occurrence of cardiovascular diseases in SM patients. Fleming et al. (34) found out that elderly SM

patients have a lower probability of falling ill with such diseases as acute IM, heart failure, hypertension, angina pectoris and cerebrovascular diseases than their contemporaries of the same age. Slawta et al. (33) documented on the group of 123 women with SM that the risk of heart diseases is approximately the same as in normal population. Even if we meet serious cardiovascular diseases in connection with SM relatively rarely in our clinic, there exists a possibility of lesion of cardiovascular functions in SM patients. Verification of our results requires, however, further examination of SM patients.

CONCLUSION

Sequential analysis of baroreflex sensitivity of heart rate established in 14 patients (group B – mean age 40.5 ± 6.2, duration of the disease 6.5 ± 5.7, EDSS 2.9 ± 1.4) baroreflex regulation to be in compliance with the reference values. This method could not be evaluated in 13 patients (group A - mean age 46.3 ± 8.7, duration of the disease 6.3 ± 7.6, EDSS 3.6 ± 1.4) because of a low number of recorded up- or down-events. We regard the difference between the groups A and B as dissimilarity of autonomic regulation of BRS. The results indicate that a lower degree of clinical disability need not be connected with cardiovascular regulation impairment and a higher degree can mean its impairment at the level of baroreceptors.

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SUMMARY

Our study is aimed at finding out whether disturbed regulation of blood circulation is connected with the degree of clinical disability in the set of patients with disseminated cerebrospinal sclerosis. We evaluated the regulation of blood circulation by means of determination of baroreflex sensitivity (BSM), clinical disability of patients with SM was evaluated according to Kurtzke's Expanded Disability Status Scale, EDSS.

Patients and methodology: We examined 27 patients with clinically defined disseminated sclerosis in the remission stage (mean age 43,4 yeaSM, duration of SM 6,4 yeaSM, EDSS 3,25). The examination was carried out by means of non-invasive continuous recording of heart rate and blood pressure made by TASK FORCE MONITOR (CNS System, Graz, Austria), by beat-by-beat measurement method. 5-minute record was made in supine position with controlled breathing rate according to the metronome 0,33 Hz. By software processing of continuous recording of heart rate and blood pressure by means of sequential BSM analysis there were evaluated up-events, down-events and total BSM for all events. On the basis of evaluation of BSM examination we divided the set into two groups. The group A (13 patients, mean age 46,3 ± 8,7, duration of the disease 6,3 ± 7,6, EDSS 4,2 ± 1,2) consisted of patients with the number of up- or down-events ≤ 8. The group B (14 patients, mean age 40,5 ± 6,2, duration of the disease 6,5 ± 5,7, EDSS 2,1 ± 0,5) consisted of patients with the number of events ≥ 8.

Results: Sequential analysis of BSM in the group B: up-events 13,7 ± 6,4 ms/mmHg, down-events 12,5 ± 4,6 ms/mmHg, all events 13,2 ± 5,4 ms/mmHg. In the group A BSM could not be evaluated by sequential analysis because of a low number of recorded up- or down-events, which we regard as disturbed cardiovascular regulation.

Conclusion: Sequential analysis of baroreflex sensitivity of heart rate established in 14 patients (group B – mean age 40,5 ± 6,2 yeaSM, duration of the disease 6,5 ± 5,7 yeaSM, EDSS 2,1 ± 0,5) baroreflex regulation to be in compliance with the reference values. This method could not be evaluated in 13 SM patients (group A – mean age 46,3 ± 8,7 yeaSM, duration of the disease 6,3 ± 7,6 yeaSM, EDSS 4,2 ± 1,2) because of a

low number of recorded up- or down-events indicating disturbed cardiovascular regulation of blood circulation.

EFFECTIVITY OF PHYSIOTHERAPY IN STROKE IN ACUTE PHASE

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INTRODUCTION

Optimal rehabilitation of stroke (CMP) is based on analysis of factors influencing the rehabilitation potential of the patient. These factors include: measure of disablement, other diseases, level of cognitive functions, limitation of daily life activities, barriers in the neighbourhood and social integration. Several tests are used for quantification of the monitored parameters (1, 2, 3, 4, 5).

Testing of condition of the patients before and after the treatment is a necessary part of determination of medical treatment and evaluation of effect of physiotherapy. It enables to compare successfulness of various medical treatments and quality of clinical workplaces by means of an objective evaluation. Testing by means of special scales and tests made or suitable for the given group of patients gives evidence of the measure of functional disablement and enables to determine:

- functional potential of the patient
- functional prognosis
- treatment efficacy

It objectifies condition of the patient and enables statistical evaluation and comparison of effect of therapy and shows the actual range of disablement in comparison with the stated diagnose.

CMP is a serious disease. Quality of life in stroke is given not only by local neurological symptoms, such as motor and sensory deficits of neurological functions and aphasia, but also by the presence of negativity, depression, fatigue, vascular dementia and frequent falls with injuries and bone fractures (2). Testing of condition of the patients after stroke in acute rehabilitation is necessary for evaluation of the process of the whole disease and for verification of both medication therapy and complete rehabilitation.

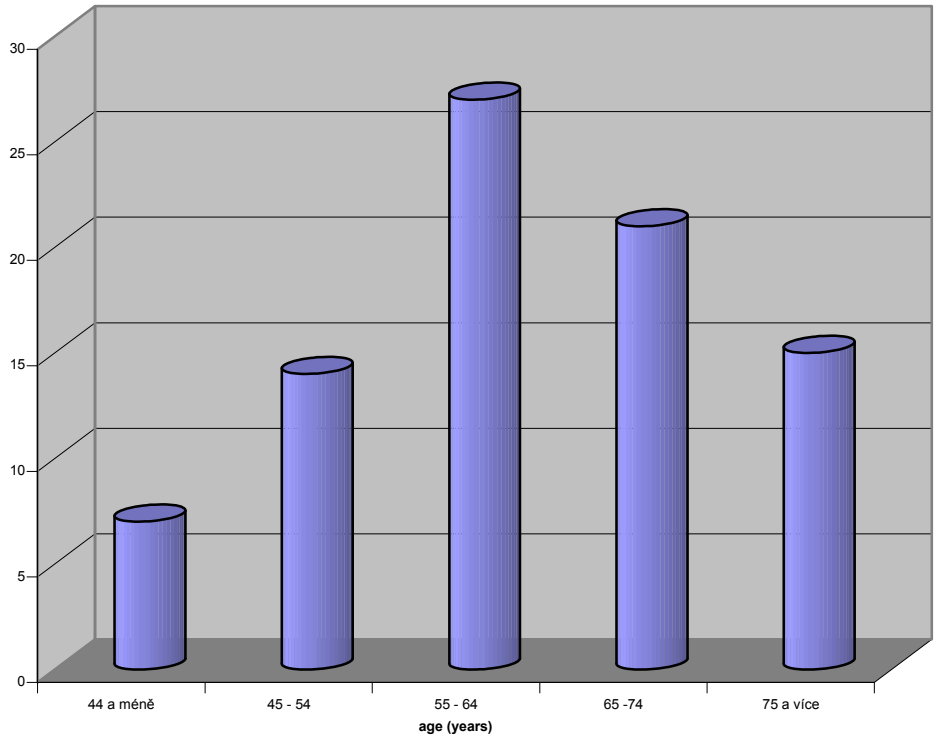
AIM

The aim of the study was analysis of affecting functional state of the patients after stroke (CMP) with moderate and light disablement with intensive rehabilitation treatment.

METHODOLOGY

The group consisted of 96 patients of average age 62,1 ± 12,0 years (range 30 -91 years) with the diagnose I 60 – I 69 (generally impairment of CNS with motor disorder) with moderate and light affection of motor and cognitive functions, evaluated according to the measure of functional disablement (Functional Independence Measure, FIM, 6, 7, 8), who were hospitalized after acute attack of CMP in Ist neurological clinic of St. Anna Teaching Hospital in Brno. In the group there were 36 women of average age 61.6 ± 13.4 years (range 30-83 years) a 60 men of average age 62,5 ± 11,3 years (range 34-91 years). Age distribution of the monitored group is in Table 1.

Table 1. Age distribution of patients with stroke



The average duration of hospitalization was 14,2 ± 7,5 days (minimum 3 days and maximum 42 days) and 78 patients were discharged from hospital for home care, 18 patients to a long-term care hospital. Arteria carotis interna sinistra was the most often affected arterial territory in this group. Lateralization of the disease is in Table 2.

Table 2. Lateralization of the disease

Lateralization of the disease	
Symptoms	number
right-hand side hemiparesis	39
left-hand side hemiparesis	35
VB territory (CVS, cerebelum sy)	22

VB territory – vertebrobasilar territory, CVS – central vestibular syndrome

The following test scales were used for evaluation of the disablement measure and possibilities of monitoring (9, 10, 11, 12):

For evaluation of activity (disability):

Functional independence measure (FIM)

Barthel test (BI) – assessing independence

For measurement of impairment:

Mini-mental state examination according to Folstein (MMSE) – evaluation of cognitive functions and mental conditions.

Evaluation of the general condition and walking according to Chedok McMaster rehabilitation centre, Canada (CH)

For evaluation of quality of life:

Index of quality of life - short version of SF 36- Index of quality of life Short Form (SF 36)

The tests ware carried out on the first day of rehabilitation (entry) and then at discharging from neurological clinic (exit).

Methods of rehabilitation

Rehabilitation treatment in our clinic was made on the basis of the prescription and the contents of exercise unit, choice of exercises and methodologies was based on kinesiologic analysis, functional examination of independence and current condition of the patient. Intensity was, as necessary, 1-2x daily of individual exercises at least 5 days in a week with application of facilitation elements and methods, the patients were provided also with logopaedic and psychological care.

The study was accepted by local ethical commission and the patients signed their informed approval. The results are presented as average ± standard deviation. For statistical evaluation Wilcoxon test for paired values was used.

RESULTS

We give the results of functional state of CMP patients at neurophysiotherapeutic treatments acquired by means of test scales. Examinations were made at the beginning of rehabilitation and at discharging from neurological clinic. The results are presented in the form of tables.

Evaluation of activity (disability):

Table 3 Evaluation of functional state by means of FIM in patients with stroke in acute phase

characteristic of the group	FIM entry x ± SD	FIM exit x ± SD	difference exit-entry	statistical significance
whole group (n = 96)	98.2 ± 15.7	110.9 ± 13.5	12.7	p< 0.01
group of women (n = 36)	99.8 ± 16.8	112.8 ± 11.8	13	p< 0.01
group of men (n=60)	98.0 ± 15.0	109.8 ± 11.7	11.8	p< 0.01

n – number of patients, SD – standard deviation, x – average, p< 0,001-level of statistical significance; FIM - functional independence measure

Table 4 Evaluation of functional state by means of BI in patients with stroke in acute phase

characteristic of the group	BI entry x ± SD	BI exit x ± SD	difference exit-entry	statistical significance
whole group (n = 96)	78.2 ± 16.7	94.5 ± 8.6	16.3	p< 0.001
group of women (n = 36)	76.9 ± 17.5	93.5 ± 9.5	16.6	p< 0.001
group of men (n=60)	78.9 ± 16.4	95.0 ± 7.9	16.1	p< 0.001

n – number of patients, SD – standard deviation, x – average, p< 0,001- level of statistical significance; BI-Barthel index

Evaluation of impairment:

Table 5 Evaluation of functional state by means of MMSE in patients with stroke in acute phase

characteristic of the group	MMSE entry x ± SD	MMSE exit x ± SD	difference exit-entry	statistical significance
whole group (n = 96)	25.2 ± 4.7	28.0 ± 2.6	2.8	p< 0.001
group of women (n = 36)	25.3 ± 4.8	28.2 ± 2.5	2.9	p< 0.001
group of men (n=60)	25.1 ± 4.7	27.8 ± 3.0	2.7	p< 0.001

n – number of patients, SD – standard deviation, x – average, p< 0,001- level of statistical significance; MMSE- Mini mental State Examination

Table 6 Evaluation of functional state by means of CH in patients with stroke in acute phase

characteristic of the group	CH entry x ± SD	CH exit x ± SD	difference exit-entry	statistical significance
whole group (n = 96)	79.8 ± 16.2	92.0 ± 11.6	12.2	p< 0.001
group of women (n = 36)	79.1 ± 17.5	91.5 ± 12.4	12.4	p< 0.001
group of men (n=60)	80.2 ± 15.5	92.4 ± 11.1	12.2	p< 0.001

n – number of patients, SD – standard deviation, x – average, p< 0,001- level of statistical significance; CH - test: Chedock Mc Master Rehabilitation center

Evaluation of quality of life:

Numerical formulation of dimensions of life quality – individual dimensions influencing quality of life are based on the questionnaire SF-36 and are calculated as mean values of specific questions from the questionnaire structured in a particular way. These dimensions attain the values from 0 to 100. A lower value means generally worse value of the given dimension and decreases total quality of life, a higher value means generally better value of the given dimension and increases total quality of life.

The patients in all monitored groups evaluated Physical role, i.e. limitation of physical activity because of health state, as the worst part of quality of life. Mental health was evaluated as the best one.

Elderly patients (70 years of age and older) assessed their general physical health to be the worst. The biggest differences are apparent in perceiving Emotional role in the group of men and women, namely 21,8, with better subjective perception of women. Then quite a big difference was recorded in the categories Physical role, evaluated better by women with the difference 11,2, and Pain, tolerated better by men with the difference 9,3.

Table 7 Dependence of final functional state according to FIM on index of quality of life – general mental and physical health SF 36 in patients with stroke in acute phase

	FIM x PCS	FIM x MCS	PCS x MCS
	correlation coefficient	correlation coefficient	correlation coefficient
whole group	0.175 NS	0.053 NS	0.485**
group of women	0.123 NS	0.096 NS	0.557*
group of men	0.237 NS	-0.015 NS	0.469*
group under 70 years of age	0.197 NS	0.067 NS	0.685**
group of 70 years of age and older	0.074 NS	-0.355 NS	0.112 NS

n – – number of patients, SD – standard deviation, x – average, p< 0,001- level of statistical significance; FIM - functional independence measure, MCS – total motoric score, PCS – mental total score

DISCUSSION

Rehabilitation in patients after CMP is aimed at achieving maximal functional independence. Rehabilitation treatments were based on the recommended medical treatments of CMP (13, 14, 15, 16, 17). In these patients so called 24-hour therapy program proved to be suitable requiring cooperation of doctors, attending staff, physiotherapists, occupational therapists, speech therapists, psychologists and family members. Successful therapy lies not only in isolated muscle exercising, however, it is important to practice meaningful, goal-directed activities with the patient, e.g. movements on the bed, shifting from supine to sitting position and then to standing position, training of self-attendance, etc. The patient learns to feel better

his body and to control it in space, to involve the affected parts of his body in routine daily activities, and he is more motivated as well.

Motor disablement of a half of the body is the most typical affection of patients after ictus, for most of them, however, the consequences are much more complex. Moving abilities and cooperation of the patient can be complicated, in addition to the loss of locomotion, from the following reasons:

- disorders of muscle tonus, presented either as hypertonia (spasticity) or hypotonia
- disorders of sensitivity and sensorial functions (neglect, pusher syndrome, hemianopsia)
- psychic troubles, affection of autonomic functions
- disorder of proprioception, disorder of body perception, loss of balance and equilibrium reactions
- disorder of stereognosis, dyspraxie, gnostic troubles
- phatic, communication troubles

The given perception problems result in disturbing the image of one´s own body in space, so called *body image*. The goal-directed stimulation of senso-motor functions has, in this case, a considerable therapeutic effect. It must be emphasized that in one-sided affection of brain, including also ictus, significant troubles at both sides of body occur.

From acute phase of the disease therapeutic rehabilitation is important for further life of the patient. Several facilitation methods are used for affection of voluntary locomotion disorder, muscular unbalance and pathological reflection changes. A number of individual methods were developed, being often named after the authors (*NDT = neuro-developmental treatment-Bobath concept, proprioceptive neuromuscular facilitation-PNF, Brunnström, Rood, Perfetti, Johnstone, Brunkowov, Vojta, Forced use, Method of sensomotoric stimulation, Biofeedback, Templ Fay, Miřatský, Affolter,* 17). Their common feature is a reflection action leading to facilitation of voluntary locomotion, at the same time, however, to inhibition of pathological reflection activity (spasticity). In the states after CMP they can be used in acute phase already, when they influence recurring voluntary locomotion and simultaneously carrying out of purposeful movements in walking and self-attendance activities.

Even if evaluation of the measure of disablement is fundamentally important for assessment of seriousness of stroke, it cannot encompass all main factors influencing quality of life. They include not only health state, but also social and economic conditions, mental state, fulfillment of aims in life, culture and value system in various geographical conditions.

Quality of life is a subjectively perceived level of living by means of which people evaluate their physical, emotional and social abilities (1, 2).

Evaluation of quality of life becomes an integral part of studies in which health state of patients in different branches of medicine is followed for a long time and the conception of quality of life covers a wide scale of perceiving life (2).

Our results show that patients after stroke achieve a lower number of points in subjective evaluation of quality of life, and in all aspects, as it had been expected in generic disorders causing disability (7, 8).

As the questionnaire SF-36 is a simple and cheap means for determination of quality of life, the information provided by this questionnaire could be used both before and after specific therapies for determination of changes in quality of life by means of the changes in points of patients, concurrently with clinical measurements of seriousness of the disease (12).

We asked a question whether there is a dependence of functional state of patients with CMP (tested by FIM) in the time of their discharging from the clinic and quality of life evaluated according to SF 36. According to our results there is no statistically significant correlation of both states.

CONCLUSION

The results proved that a complex therapy along with intensive rehabilitation led in patients after CPM in acute phase to improvement of their functional state and reduction of the measure of impairment of motor and cognitive functions; the differences were statistically significant.

The results show that the patients after CMP assessed their physical health to be worse than mental health.

We have found no relation between FIM and SF 36 in the group of patients after CMP by means of correlation analysis. There is correlation between the index General physical health and the index Mental Health and it is apparent that in younger patients physical health influences significantly mental health. We have not found this significant correlation in the patients older than 70 years of age.

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SUMMARY

The aim of the study was analysis of functional state of patients by means of test scales in the set of patients after acute stroke (CPM) with moderate and light disablement in the course of hospitalization in I neurological clinic LF MU with intensive rehabilitation treatment.

96 patients were examined before and after complete rehabilitation and the measure of functional disablement, functional disorder and quality of life were tested. The results proved that a complex therapy along with intensive rehabilitation led in patients after CPM in acute phase to improvement of their functional state and reduction of the measure of impairment of motor and cognitive functions; the differences were statistically significant.

Key words: stroke, impairment of function, rehabilitation

MUSCLE STRENGTH EXAMINATION OF HAND AND MOTOR SKILLS OF HAND IN PATIENTS WITH CEREBRAL PALSY

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INTRODUCTION

International Classification of Functioning is the document of WHO directing our attention in assessment of patients mainly to functional abilities and possibilities of participation in society (1).

Gross Motor Function Classification System (GMFCS) is an important instrument for evaluation of gross motor skills in children with cerebral palsy (DMO) within the framework of their common functions. Recently, The Manual Ability Classification System (MACS) has been developed as a relevant method of classification for evaluation of fine motor skills of hand in DMO (2,3). The test evaluates fine motor skills by the technique used in GMFCS already. In another aspect, both classification systems are also important for Evidence Based Practice because easy scoring and quick realization enable the common language to be established both for professionals and for parents of children included in a very heterogeneous group of DMO (4). Childhood cerebral palsy involves a diversified group of patients with long-time demands on rehabilitation. Characteristics of DMO are different in individual papers. The group for the research of DMO in Europe Surveillance of Cerebral Palsy in Europe recommends the DMO syndrome to be characterized as follows: It is the category of permanent, but not unchangeable disorders of motion and/or posture and motor functions, evolving on the basis of non-progressive disturbance, lesion or abnormality of the developing immature brain (5).

AIM

The aim of this study is evaluation of the results of The Manual Ability Classification System (MACS), Gross Motor Function Classification System (GMFCS), and muscle strength examination measured by dynamometer in children with cerebral palsy.

METHODS

Set of patients

We examined 51 patients with DMO in the age ranging from 8 years to 26 years 8 months (average age 17,3 ± 4,2). 8 patients were at the age of 8 - 12 years, 20 patients were at the age of 12 - 18 years, 23 patients were older than 18 years. The set consisted of 28 girls and 23 boys. The subtypes of DMO were determined according to the classification of Mr. and Mrs. Bobath.

The patients with DMO suffered from spastic form in 47 cases, in 10 patients it was hemiplegia, in 18 patients diplegia, in 3 patients triplegia, in 16 patients quadruplegia, in 1 patient ataxic form, in 3 patients dyskinetic form. All patients are in charge of Home for handicapped children and youth Kociánka in Brno.

Tests GMFCS and MACS

Functional test for evaluation of fine motor skills in DMO: The patients were included, according to functional skills of hand, on the basis of observation of a physiotherapist in one of 5 levels of MACS (5^{th} level means the most serious disablement). This classification is focused on skills performed by the patient in usual daily situations, it should not serve for evaluation of the maximum potential. It evaluates the common work of both hands.

In the scale of the test of gross motor functions GMFCS the examined patients were included in one of five levels characterizing in the best way their gross motor skills in usual environment on the basis of observation of a physiotherapist (5 means the most serious disablement). This system evaluates gross motor functions on the basis of initiation of motion stressing the sitting position, movements and mobility. The differences between the groups are given by limitations, by necessity of using aids or wheelchair and by reduced quality of motion (2).

The maximum handgrip was measured by hand dynamometer, first on the upper extremity with a lesser motor disablement, and then on the second upper extremity. The examined patients were sitting on a chair or a wheelchair during the measurement. The upper extremity was not supported, the arm was in adduction close to the body, flexion in elbow 90^{o}, central

position of forearm and wrist. The position of some patients was modified because of contractures.

RESULTS

Tests GMFCS and MACS

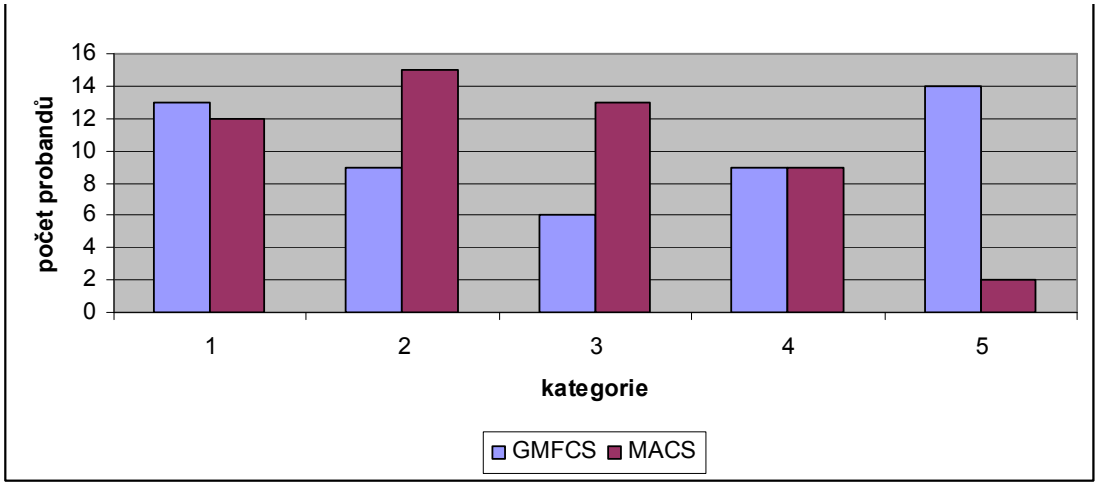
All 51 patients with DMO were included in functional levels 1- 5 according to the test of gross motor functions GMFCS. We assessed the score of the functional test for evaluation of fine motor skills of hand MACS and muscle strength of dominant and non-dominant upper extremities in patients with DMO.

Tab. 1 Correlations distribution of the fine motor skills test (MACS) and of the gross motor skills test (GMFCS) in patients with DMO

	MACS levels					
GMFCS levels	I	II	III	IV	V	TOTAL
I	8	5	-	-	-	13
II	2	2	2	-	-	6
III	2	4	2	-	-	8
IV	-	1	2	-	-	3
V	-	-	11	8	2	21
TOTAL	12	12	17	8	2	51

Distribution of the group into individual categories of gross motor skills (according to GMFCS) and fine motor skills (according to MACS) is in Table 1 and graph 1.

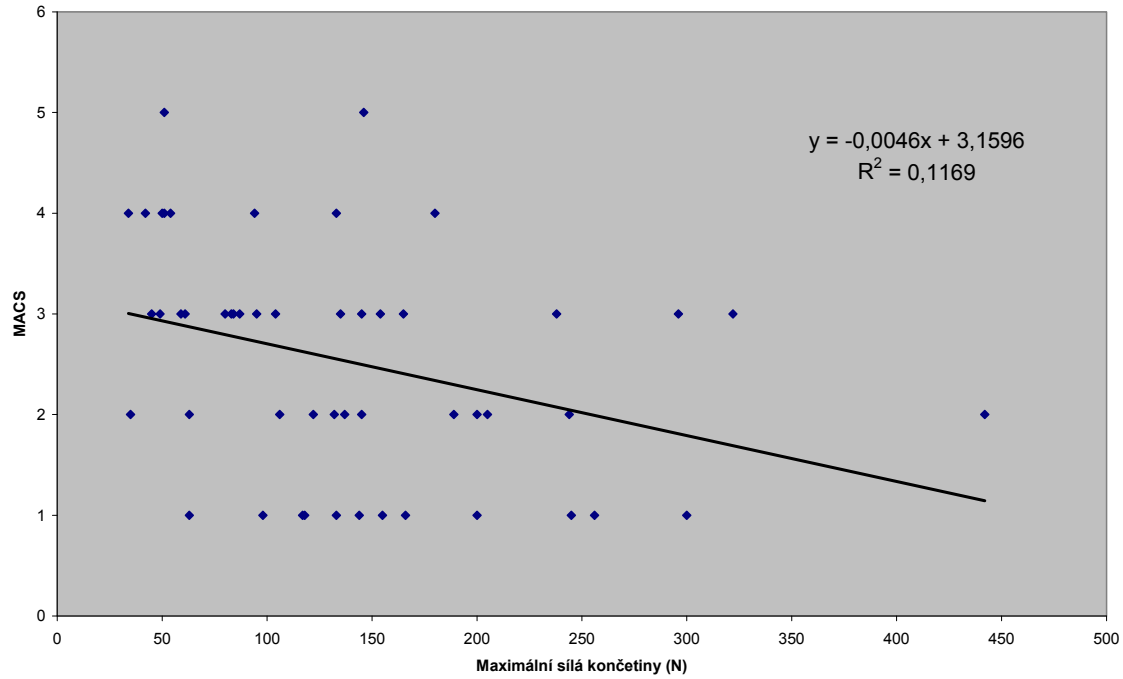
14 patients with DMO (27%) had better results in MACS, conformity in both tests was in 30 patients (59%), 7 patients (14%) had better results in GMFCS. It means that GMFCS does not correlate with MACS in 73% of patients.



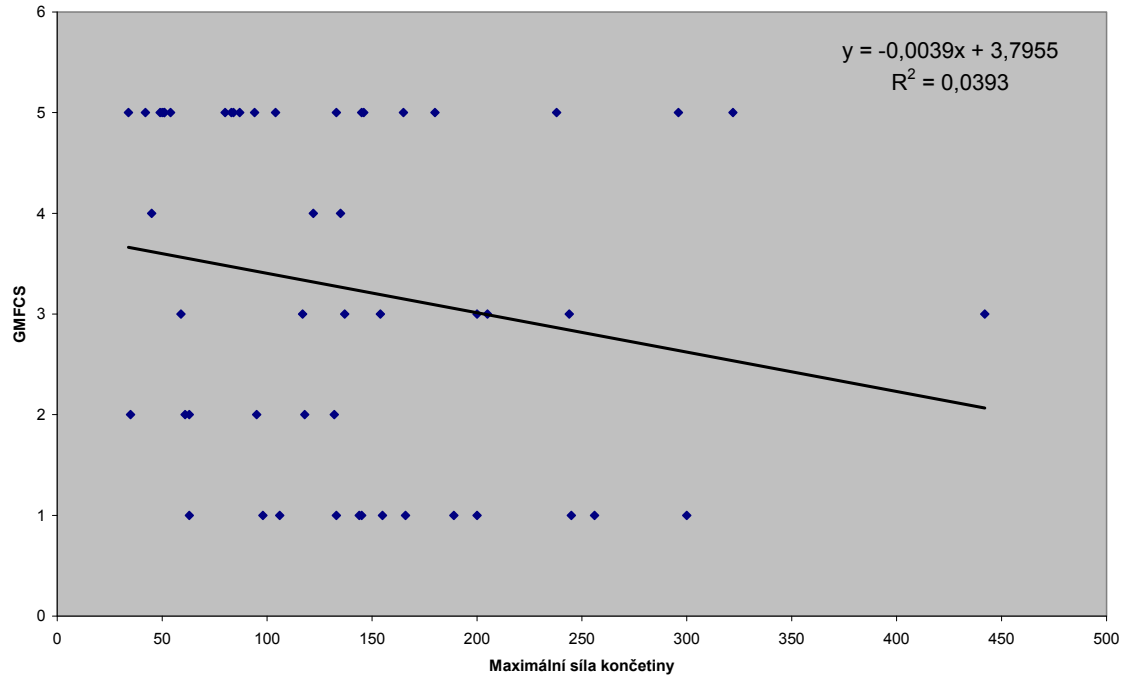
Graph 1 – Results of the test of gross motor skills (GMFCS) and of the test of fine motor skills (MACS) in patients with DMO

Muscle strength in patients with DMO

Muscle strength of the hand with a lesser disablement in the whole set was in the range from 34 to 442 N (average 235.8± 85.9), muscle strength of the second hand was in the range from 5 to 376 N (average 66.7± 66.2). Relationship between muscle strength of the hand with a lesser disablement and functional ability of the hand according to MACS can be seen on graph 3 and relationship between muscle strength and GMFCS is represented on graph 4. Correlation between muscle strength of the hand and MACS is low, but statistically significant ($R= 0.342$; $p < 0.05$); between muscle strength and GMFCS there is no correlation.



Graph 3 - Relationship between muscle strength of the hand with a lesser disablement and functional ability of the hand according to MACS



Graph 4 - Relationship between muscle strength of the hand with a lesser disablement and functional ability of the hand according to GMFCS

DISCUSSION

The test MACS serving for elimination of influence of gross motor skill disorders places emphasis on handling things in personal space of the examined patient. Eliasson et al. gives intrinsic coefficient of correlation in the group of observers physiotherapists 0.97, in the group parents - physiotherapists 0.96 (3).

We expected that correlation between handgrip and motor tests would be low. We confirmed thus the assumption that measurement of strength cannot serve even for a rough estimate of the level of disablement.

Beckung and Hagberg in their study also dealt with the function of hand in DMO, they used, however, for evaluation the test Bimanual Fine Motor Function (BFMF), that cannot be compared either with the score of functional test for evaluation of fine motor skills of hand MACS in patients with DMO or with examination of muscle strength measured by dynamometer, and its reliability has not yet been tested. BFMF is directed more at the disorder, while MACS more at the activity (6).

In evaluation of GMFM and MACS in individual patients with DMO we arrived at similar results as Carnahan et al. in the study of relation of GMFCS and MACS. These authors found conformity between MACS and GMFCS in 53% of patients, better MACS than GMFCS in 20% of patients and better GMFCS than MACS in 27% of patients (7). This leads to the same conclusions as our study.

The score of functional test for evaluation of fine motor skills of hand in DMO MACS describes very well the functional state of the child with DMO. This evaluation can be used for improving the quality of communication between professionals and parents of these children. It is also evident, however, that the function arises from the organ, but the mere description of the state of the organ, e.g. muscle strength measured by dynamometer, does not give a clear picture of the patient in such a varied group as DMO.

Supported by grant MSM 0021622402.

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SUMMARY
The aim of this study is evaluation of the results of The Manual Ability Classification System (MACS), Gross Motor Function Classification System (GMFCS), and muscle strength examination measured by dynamometer in children with cerebral palsy. We examined 51 patients with cerebral palsy in the age ranging from 8 years to 26 years (average age 17.3± 4.2) living in the Home for handicapped children and youth Kociánka Brno. The group consisted of 28 girls and 23 boys.
Maximum handgrip was measured by hand dynamometer in both upper extremities. After the examination by a physiotherapist the patients were categorized according to their gross motor skills using Gross Motor Function Classification System (GMFCS) and fine motor skills using The Manual Ability Classification System (MACS). Muscle strength in the better hand in the whole group ranged from 34 to 442 N (average 235.8± 85.9), in the second hand from 5 to 376 N (average 66.7± 66.2). The results show a weak correlation between muscle strength of handgrip and MACS, but it is statistically significant ($R= 0.342$; $p < 0.05$), correlation between muscle strength of handgrip and GMFCS does not exist.

Key words: cerebral palsy, dynamometry, Gross Motor Function Classification System, The Manual Ability Classification System

QUALITY OF LIFE AFTER CARDIOVASCULAR REHABILITATION IN CHRONIC ISCHEMIC HEART DISEASE

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INTRODUCTION

Rehabilitation of cardiac patients plays a significant clinical and psychological role. It helps the patients in the process of decondition and physiological changes appearing after acute myocardial infarction. Cardiovascular rehabilitation induces the feeling of security and helps the patient to return to normal life activities. Cardiovascular rehabilitation turns out to be important for a better physical performance and a feeling of health (1, 2). It leads to the increase of performance and capacity of the transport system for oxygen. Subjective perceiving of quality of life is also related to it.

Quality of life (QOL) reflects how a person takes his position in the world in the context of culture and value systems in which he lives, and in relation to his aims, expectations, life style and interests (3).

Even if correlation between increased performance and improved quality of life can be expected, this relation is not obvious.

The function of cardiovascular system in patients with heart arrhytmias being at risk of a sudden cardiac death improves in the case of pacemaker implantation. In some cases, however, nervous patients can experience psychological disorders after pacemaker implantation that can be accompanied by anxiety and depressions.

In clinical practice we meet very often with a discrepancy between the opinion of the doctor and the patient.

AIMS OF THE STUDY

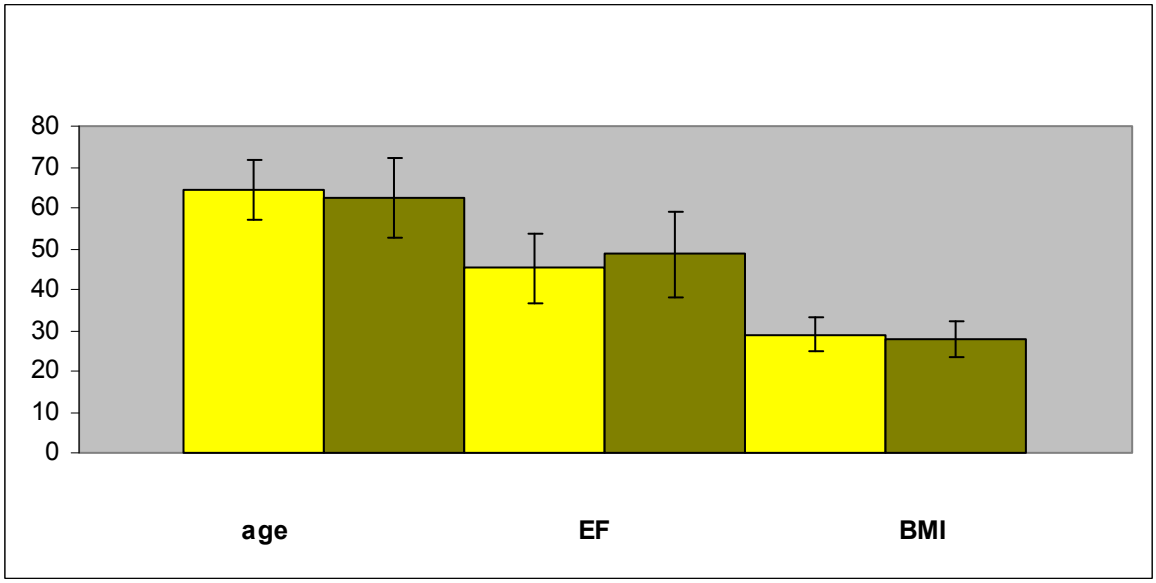
The aim of the study was to compare influence of 12-week combined training on subjectively perceived quality of life and on objectively measured indicators of performance (expressed as maximal achieved performance and performance converted

to 1 kg of the body mass) and on capacity of the transport system (expressed as maximal oxygen intake and maximal oxygen intake converted to 1 kg of the body mass) in patients with ischemic heart disease determined by coronarography with regard to their gender.

METHODOLOGY

The group of examined patients included 84 men (62±9 years) with coronarography determined ischemic heart disease (with means ejection fraction EF 48±10 %) and 19 women (64±7 years, mean EF 46±8 %) who participated in 12-week rehabilitation program.

Graph 1
Basic characteristic of the group of patients



Legend: age (years), EF (%), BMI (body mass index), women – yellow, men – dark

The patients included in cardiac rehabilitation had to comply with the following criteria: they did not suffer acute myocardial infarction or attack of unstable angina pectoris in the period of three months before the beginning of exercises, no patient had valvular defect or insufficiently compensated hypertension.

The patients with serious rhythm disorders, with symptoms of haemodynamic instability, with substantial marks of ischemia at rest or at load were excluded. Also the patients with uncontrolled hypertension and other conditions and diseases making rehabilitation exercises impossible were not included into the group.

Before starting rehabilitation all patients were subjected to basic clinical examination and Doppler echocardiography by the instrument SONOS 5500 (Hewlett Packard).

Before the starting and after the finishing of the rehabilitation program a spiroergometric exercise test on a bicycle ergometer was made. 12-lead electrocardiogram was recorded by the instrument Cardiovit CS 100 – Schiller. Ventilatory-respiratory values were determined by means of the analyzer of gases Pulmonary Function System 1 070 – MedGraphics CPX/D, USA, fitted with software for their analysis and evaluation.

The examination was made in morning hours and the patients were advised beforehand to take the morning dose of their usual medication. The reason of the examination and its expected results were explained to all patients. 12-lead electrocardiogram at rest was monitored from the beginning of the exercise test. Within the adaptation phase lasting 2 – 5 minutes in the sitting position on ergometer for stabilization of parameters the resting values of heart rate (HR) and blood pressure (BP) were read.

The protocol with graded load without interruptions up to the symptom-limited maximum was determined for the examination. The patient kept the speed rate in the range of 50 – 55/min. In the course of examination SF was read from ECG record each two minutes, the examined patient assessed the rating of perceived exertion (RPE) and his BP was measured by auscultation method with a mercury manometer. Respiratory parameters in breath were determined by means of an analyzer of breath gases in real time breath-by-breath. In addition to achieving the symptom-limited maximum generally valid criteria were used for finishing the test, so called end points (4, 5).

Seattle Angina Questionnaire. To find out subjective perception of health state and affecting quality of life, the patients were given Seattle Angina Questionnaire (SAQ) to be filled out in the beginning of the rehabilitation program and after its termination. Questionnaire is divided into five parts (hereafter and in the results SAQ 1-5) and it contains nineteen items altogether.

Part 1 (SAQ 1) The patient indicates how chest pain or anginous pain restricted him during the last four weeks in performing the given activities. The activities are arranged according to physical severity.

Part 2 (SAQ 2) It deals with comparison of the current health state with the period four weeks ago as to the frequency of occurrence of anginous difficulties in performing usual daily activities.

Part 3 (SAQ 3) The patient indicates how many times a day or a week in the past month, in comparison with the same period four weeks ago, he had anginous difficulties and how many times he had to take nitroglycerin because of them.

Part 4 (SAQ 4) The patient indicates subjective feeling of the therapy and his satisfaction with it.

Part 5 (SAQ 5) The last part should describe how the patients feel quality of their life with the present illness and its potential fatal termination.

Rehabilitation program

The ambulatory controlled exercise training program lasted 12 weeks with the frequency three times a week. The training unit lasted 60 min and consisted of four phases (6, 7).

The warm-up phase was aimed at preparing the cardiovascular and locomotive system for additional load, prevention of musculoskeletal lesion. The exercise training was composed of dynamic endurance exercises (simple floor exercises, exercises with gymnastic apparatus) and stretching of muscle groups tending to be shortened.

The aerobic phase took place on a bicycle ergometer (Ergoline REHA E900) controlled by the program ErgoSoft+ for Windows. Intensity of aerobic training was set at the aerobic threshold level.

The strength training was performed on multifunctional toning machines TK-HC COMPACT. Four exercises were done (benchpress, pull down, leg extension on the apparatus and sitting-lying positions**)**. Intensity of strength training was set by the method 1-RM and training loads were determined in per cents of maximum: 30-60 % 1-RM (every week increasing by 10 %). The number of series was 3 - 5 with ten repetitions. Before starting the strength training the patients were thoroughly informed about proper breathing and performing of exercises.

Relaxation phase: modified Schultz autogenic training was used.

Heart rate, blood pressure and RPE degree were monitored in the course of the whole training, during the aerobic phase and in 1-RM test also ECG.

The examination protocol of the study was accepted by local ethical commission and the patients signed their informed approval.

The results are given as average ± standard deviations, for statistical evaluation Wilcoxon test for paired values was used.

RESULTS

After going through the rehabilitation program the body mass and BMI neither in men nor in women were changed and also the initial systolic and diastolic pressure, maximal achieved diastolic pressure, maximal heart rate and both resting and maximal product heart rate-pressure (product of systolic blood pressure and heart rate /100) have not been statistically significantly changed in both cases.

Our results indicated in the group of men (before versus after) a significant change of systolic blood pressure at maximum load (196.9±28.2 mmHg v. 203.4±27.1 mmHg; $p<0.05$), heart rate (HR) initial (64.7±10.9 cpm v. 61.9±10.4 cpm; $p<0.05$). The increase of performance occurred, it is statistically significant only in men, however (graph 2, 3).

Maximal muscle strength increased in the group of men: W_{maxSL} 113.35±33.14 W v. 123.0±35.6 W; $p<0.01$; $W_{maxSL}.kg^{-1}$ 1.3±0.4 W v. 1.45±0.45 W; $p<0.01$.

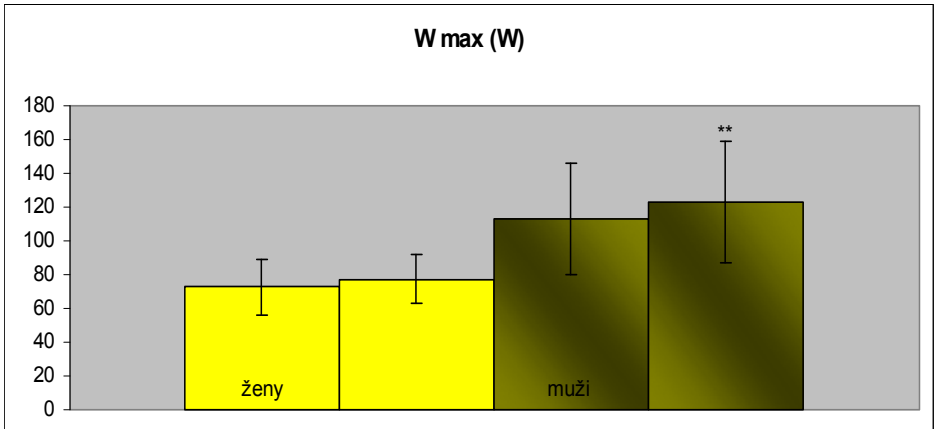
The transport system for oxygen at achieving the symptom-limited maximum (VO_{2SL}) was improved: 1691.±411.8 ml/min v. 1833.8±45.2 ml/min, $p<0.01$; $VO_{2SL}.kg^{-1}$ 19.9±4.8 ml/min/kg v. 21.6±5.7 ml/min/kg, $p<0.01$; MET 5.7±1.4 v. 6.2±1.7, $p<0.01$.

Quality of life measured by means of the questionnaire in the group of men improved after rehabilitation considerably in all aspects: SAQ1 80.7±18.8 v. 84.9±15.8, $p<0.01$; SAQ2 79.6±21.6 v. 86.4±16.1, $p<0.01$; SAQ3 83.5±16.1 v. 88.5±14.4, $p<0.01$; SAQ4 88,4±16,1 v. 93.0±10.4, $p<0.01$; SAQ5 66.6±17.5 v. 73.6±17.6, $p<0.01$.

In the group of women we recorded a significant increase of the transport system capacity: VO_{2SL} 1134.8±155.4 ml/min v. 1215.0±184.6 ml/min, $p<0.05$; $VO_{2SL}.kg^{-1}$ 15.1±2.4 ml/min/kg v. 16.3±2.4 ml/min/kg, $p<0.05$; MET 4.4±0.7 v. 4.70±0.67, $p<0.05$. The questionnaire for quality of life in women indicated increased quality of life in all aspects: SAQ1 69.0±20.5 v. 75.7±16.2, $p<0.01$; SAQ2 78.0±18.2 v. 88.0±16.4, $p<0.05$;

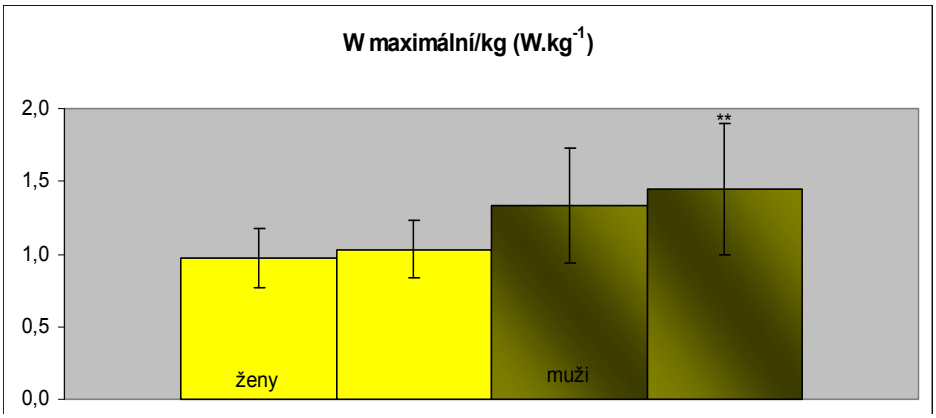
SAQ3 77,5±20,8 v. 84,2±17,1, p<0,01; SAQ4 89,9±12,7 v. 93,9±9,0, p<0,05; SAQ5 62,82±20,6 v. 72,15±17,27, p<0,01.

Graph 2 Increase of maximal performance after cardiovascular rehabilitation in men



Legend: Wmax (W), before and after, women – yellow, men – dark;

Graph 3 Increase of maximal performance (to 1 kg of the body mass) after cardiovascular rehabilitation in men



Legend: Wmax per kg, before and after, women – yellow, men – dark

DISCUSSION

The relation between quality of life and results of functional examination by load was studied in a number of the papers (8, 9, 10). The definition of quality of life given in the introduction to our study. The quality of life is influenced by the particular culture in the given population. That is why it is useful to study the relations separately in all cultural backgrounds. We have proved in our study a positive influence of cardiovascular rehabilitation on quality of life in patients with chronic ischemic heart disease in men and women in the Czech Republic.

CONCLUSION

12-week combined training in men with ischemic heart disease resulted in increase of their performance and capacity of the transport system. They attained a lower heart rate at rest and at the same time increased values of maximal systolic pressure at the achieved higher performance.

As a result of 12-week combined training male patients had fewer anginous difficulties in performing normal daily activities and they did not have to take nitroglycerin because of these difficulties. The men included into the training were also evidently more satisfied with the course and quality of therapy after the training. The most important improvement, however, was achieved, as assumed, in subjective perception of quality of life.

In women with ischemic heart disease 12-week combined training led to increased capacity of the transport system, neither performance nor the other monitored parameters changed significantly, but occurrence of anginous difficulties in performing normal daily activities and necessity of taking nitroglycerin decreased.

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SUMMARY

The aim of the study was to compare influence of 12-week combined training on subjectively perceived quality of life and on objectively measured indicators of performance (expressed as maximal achieved performance and performance converted to 1 kg of the body mass) and on capacity of the transport system (expressed as maximal oxygen intake and maximal oxygen intake converted to 1 kg of the body mass) in patients with ischemic heart disease determined coronographically with regard to their gender.

12-week combined training in men with ischemic heart disease resulted in increase of their performance and capacity of the transport system. They attained a lower heart rate at rest and at the same time increased values of maximal systolic pressure at the achieved higher performance.

As a result of 12-week combined training male patients had fewer anginous difficulties in performing normal daily activities and they did not have to take nitroglycerin because of these difficulties as frequently as before the training. The men included into the training were also evidently more satisfied with the course and quality of therapy after the training. The most important improvement, however, was achieved, as assumed, in subjective perception of quality of life.

In women with ischemic heart disease 12-week combined training led to increased capacity of the transport system, neither performance nor the other monitored parameters changed significantly, but occurrence of anginous difficulties in performing normal daily activities and necessity of taking nitroglycerin decreased.

Key words: Quality of life, combined training, chronic ischemic heart disease, gender difference

AUTONOMIC NERVOUS SYSTEM IN PARKINSON'S DISEASE

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INTRODUCTION:

Autonomic nervous system dysfunction is an integral part of symptomatology of idiopathic Parkinson's disease (PD) from its early outset (3, 19, 21, 24, 29, 36, 37).

Clinical studies examine the function of autonomic nervous system by means of standard autonomic tests – orthostatic test (32), Valsalva´s maneuver (5, 40), isometric exercise test (40), ratio of heart rate increase to 15th heartbeat after standing up from supine position to its decrease to 30th heartbeat (30:15 ratio; 4), ratio of the longest RR interval in expiration to the shortest RR interval in inspiration (E:I ratio; 4), evaluation of reaction of heart rhythm and blood pressure to deep breathing test (5, 40) and tilt table test (4, 25), sympathetic skin response (4, 43) etc.

A number of studies document, according to the applied method of examination, that the progression of autonomic dysfunction is proportional to the course of development of other PD symptoms (5, 23, 25, 28, 32, 40).

Measurement of heart rate variability (HRV) and its analysis is a non-invasive examination revealing autonomic dysfunction in mild stage of PD already (6). Decrease of spectral power in mild stage of PD disablement was documented in short-term HRV examination by Rodriguez (35), Haapaniemi (11) gives consistent results in 24-hour HRV analysis.

Even if spectral power of HRV decreases naturally with increasing age, influence of age as a unique factor inducing this decrease was not confirmed in PD patients. Dysfunction of autonomic nervous system in PD patients demonstrates a marked dependence mainly on the disease progression evaluated according to motor scale UPDRS III or H&Y score (H&Y) UPDRS V (40).

Influence of anti-parkinsonian medication as the only factor influencing the development of symptomatology of autonomic dysfunction was disproved as well. Presence of autonomic dysregulation was described and well documented also in the

studies evaluating spectral power of HRV in patients with idiopatic PD even before starting this medication (9, 20, 26).

Evaluation of the measure of dysfunctions of autonomic nervous system is a permanent subject of the research (1, 4, 5, 7, 23, 30, 41). Most of preceding studies, however, have not yet been dealing adequately with important factors of day time of short-term HRV examination, differences in the extent of disablement by PD, type of dopaminergic or other pharmacotherapy, changes of breathing rate during examination etc. (5).

AIM OF THE STUDY:

Evaluation of disorder of autonomic cardiovascular regulation in PD patients in mild and advanced stage according to H&Y score by means of spectral analysis of short-term HRV examination.

DESIGN AND METHODS:

25 PD patients whose diagnosis was established at the Ist Neurological Clinic of St. Anna Faculty Hospital in Brno were included into the study (8). Absence of other diseases and anti-parkinsonian or other pharmacological therapy influencing results of HRV examination was the condition of inclusion into the study (2, 3, 12, 14, 16, 22, 27, 33, 40). The patients included into the study also met criteria of stable medication without any changeat least in the last 4 weeks before the examination, compliance of usual daily schedule including medication, in the day before the examination without excessive physical activity, in the night before the examination at least 6 hours of good sleep, in the morning before the examination only light breakfast without coffee, tea, alcohol, with regard to the age of patients, at least 2 hours before the examination.

The patients were divided into two groups according to the measure of clinical disablement. H&Y score in the range of 1-1.5 was a criterion for inclusion into the group “SI”; H&Y score in the range of 2-3 was a criterion for inclusion into the group „SII“.

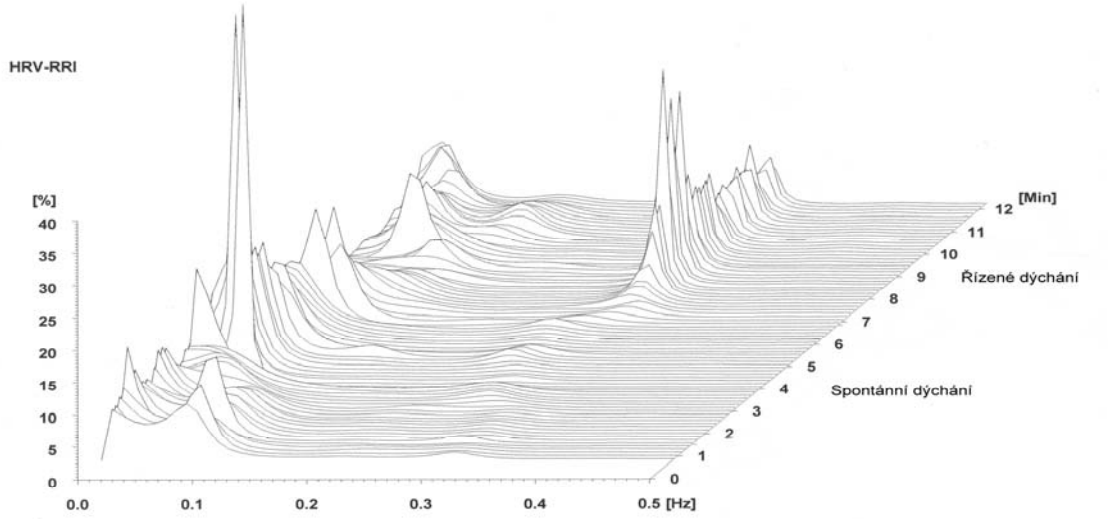
Basic anthropometric characteristics of the groups are given below in Table l as mean ± SD:

Table 1: Basic anthropometric characteristic of evaluated groups of PD patients

	H&Y	AGE (years)	BMI	PD DURATION (years)
Group SI	1.3±0.3	65.7±11.0	24.7±2.5	7.6±3.9
Group SII	2.3±0.4	68.2±7.1	26.7±2.1	5.7±3.0

Examined patients underwent short-term measurement and spectral analysis of heart rate variability in supine position (15, 20). The methodology of metronome-paced breathing rate f = 0.33 Hz (18, 34, 38, 39, 42) was used for reducing the effect of different rate of spontaneous breathing on spectral power in the groups of patients subjected to examination (5, 13, 28, 31, 40). Graphic representation of the effect of controlled breathing on spectral power is given below in Graph 1.

Graph 1: Example of graphic representation of the results of spectral analysis of heart rate variability by the system Task Force Monitor, CNSystems Medizintechnic GmbH.



All HRV tests were accomplished always in morning hours between 9 and 11 a.m.

The measure of autonomic dysfunction evaluated by means of spectral analysis of HRV was compared between the groups of patients with a different degree of clinical disablement according to H&Y.

The differences of values of selected parameters of spectral analysis of HRV between the groups SI and SII were statistically evaluated by Kolmogorov-Smirnov test (test of distribution) and T test (Statistica, StatSoft Inc., version 7, 2004).

The study was accepted by ethical commission of Masaryk University in Brno and all participants of the study signed their informed consent.

RESULTS:

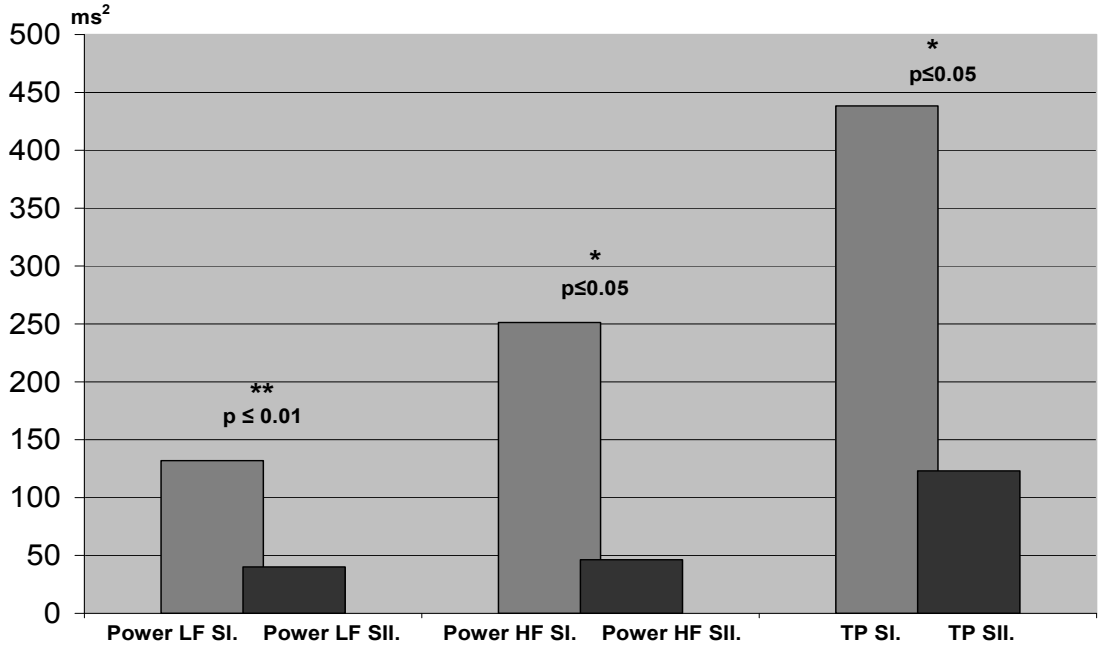
The results of selected parameters of spectral analysis of short-term examination of HRV are given below in Table 2 (mean ± SD): total power (TP, ms^2), power in low-frequency band (0.04-0.14 Hz; Power LF; ms^2), power in high-frequency band (0.15-0.4 Hz; Power HF; ms^2) and ratio Power LF / Power HF (LF/HF).

Table 2: Results of HRV spectral analysis, metronome-paced breathing (f = 0,33 Hz)

	TP (ms^2)	Power LF (ms^2)	Power HF (ms^2)	LF/HF
Group SI	438 ± 411	132 ± 95	251 ± 315	1.0 ± 0.6
Group SII	123 ± 108	40 ± 37	47 ± 62	1.9 ± 2.3
P	*0.018	**0.005	*0.038	N.S.

Graphic representation of the difference of selected parameters of spectral analysis of short-term HRV examination during metronome-paced breathing (f = 0.33 Hz) is given below (Graph 2).

Graph 2: Comparison of selected parameters of spectral analysis of HRV



In statistical comparison of selected parameters of spectral analysis of HRV, a significant difference was found between the group SI with a milder degree of disablement and the group SII with a more advanced degree of disablement according to H&Y. In the group SII a statistically significant decrease of total power (TP) and of power in low-frequency (Power LF) and high-frequency (Power HF) spectral band

occurred. The change of ratio of low-frequency power and high-frequency power (LF/HF) was not statistically significant.

DISCUSSION:

Autonomic dysfunctions in PD patients progress in accordance with progression of the disease (25, 32, 40). Their exact examination and scoring in the present clinical practice are still more important.

Examination of short-term heart rate variability meets demanding criteria of a non-invasive and objective, reproducible, reliable and valid test of autonomic regulation (10, 15, 35). Kallio (20) recommends, because of a higher sensitivity, application of spectral analysis (frequency domain) of HRV before time analysis (time domain). It was proved that the measure of disorder of autonomic control of heart function is identical with the nigrostriatal dopaminerg system disorder (1, 4).

We have demonstrated statistically at two examined groups, SI with a mild degree of disablement (H&Y = 1.3) and SII with a more advanced degree of disablement (H&Y = 2.3), with the difference in the measure of clinical disablement of 1 degree, a significant difference of the total power and the power in low-frequency and high-frequency spectral component in the short-term examination of HRV. We consider the short-term examination and its spectral analysis also to be sufficiently sensitive for evaluation of autonomic dysfunctions progression in PD.

Our results are in accordance with the testing of other authors using similar methods of HRV examination. Linden (25) made a comparative study with two groups of average age 67.6 years with a higher H&Y (2.1 vs. 3.3) and found out also significant decrease of low-frequency and high-frequency spectral power in the group with a higher H&Y in comparison with the group with a lower H&Y.

Rodriguez (35) presents decrease of power in all spectral bands in the group of examined patients with PD of average age 30.8 years in comparison with the group of examined patients with PD of average age 61.9 years and a higher H&Y.

The same results found out by means of spectral analysis of HRV, ie. autonomic dysfunction progression in connection with the disease development, are given also by Deiseroth (5) in his study made on 30 patients in the age of 39-84 years.

Van Dijk (40) determined dependence of a reduced autonomic response in the short-term examination of HRV on age, duration of anti-parkinsonian medication and higher H&Y and, on the contrary, excluded a direct relation with duration of the disease.

Devos (6), unlike the preceding authors, takes in the methodology of examination into consideration also the day time of examination, pharmacotherapy, breathing rate and previous physical load. He compares the results of the short-term examination of HRV of three groups of examined PD patients with a different degree of motor dysfunction according to the motor scale UPDRS III. (7.0 vs. 8.9 vs. 19.0) and of the control group, average age being always 61 years. In all groups of examined PD patients he finds significant differences in all spectral bands of HRV.

The results of Hisayoshi study (17) prove in the mild stage of PD in comparison with the corresponding control group of healthy subjects only decrease of spectral power in the low-frequency band.

The difference in spectral power in the short-term examination of HRV between the group of healthy population and age corresponding to examined PD patients in the mild stage is denied only by Krygowska-Wajs (23). Her methodology of examination does not take into consideration, however, all factors influencing the results of the short-term examination of HRV and does not use methodology of controlled breathing. In another study (24), where she evaluates the changes of heart rate in mild stage of PD by means of the tilt table test (30:15 ratio), a statistically significant difference between the examined patients in mild stage of PD and the check group of healthy population of the corresponding age and sex is already confirmed.

Piha (32) attained the same conclusions on the basis of testing orthostatic hypotension.

Statistically significant changes of spectral power in mild grade PD patients (H&Y = 1.5) in comparison with the control group of healthy subjects are given also by Haapaniemi in his study (11) based on the results of 24-hour HRV examination.

CONCLUSION:

We established a greater disorder of autonomic regulation of heart rate in the group of patients in advanced stage of PD (H&Y = 2.3) in comparison with the group in mild stage of PD (H&Y = 1.3). On the basis of our results demonstrating statistically significant difference between the groups with average H&Y score differing by one

degree (1.3 vs. 2.3) in the spectral power values (TP 438 vs. 123 ms^2, Power LF 132 vs. 40 ms^2, Power HF 251 vs. 47 ms^2) we consider spectral analysis of short-term examination of HRV to be a suitable method of evaluation of autonomic dysfunction in PD patients.

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SUMMARY:

Exact quantitative evaluation method of autonomic dysfunction in Parkinson's disease (PD) for everyday clinical use has not been developed yet.

The aim of this study was to evaluate autonomic cardiovascular regulation in mild and advanced stages of PD with the use of heart rate variability (HRV) examination.

25 patients entered the study and passed short-term HRV examination in supine position with metronome-controlled breathing f = 0.33 Hz.

Following parameters of power spectral analysis were evaluated: Total Power (TP; ms^2), Low Frequency Power (0.04-0.14 Hz; Power LF; ms^2), High Frequency Power (0.15-0.4 Hz; Power HF; ms^2) and Ratio Power LF / Power HF (LF/HF).

The results show statistically significant decrease of TP (438 vs. 123 ms^2), Power LF (132 vs. 40 ms^2) and Power HF (251 vs. 47 ms^2) in the group of patients with a higher mean H&Y (1.3 vs. 2.3; T test). The change of LF/HF was not statistically significant.

The short-term examination of heart rate variability fulfils the criteria for test objectivity, reproducibility, reliability and validity. We proved a higher impairment of autonomic cardiovascular regulation in the group of PD patients with advanced PD (H&Y = 2.3) than in mild PD (H&Y = 1.3). Short-term HRV examination is also sensitive enough to be used for comparison of the difference of autonomic dysfunction corresponding to the change of impairment by 1 grade in H&Y score.

KEYWORDS: Parkinson's disease; autonomic dysfunction; heart rate variability; UPDRS; Hoehn & Yahr score; metronome-controlled breathing; rehabilitation

PATIENTS WITH STROKE: RESULTS OF PHYSIOTHERAPY AND OCCUPATIONAL THERAPY

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INTRODUCTION

Stroke is the third most frequent cause of death. Improved quality of medical care in acute phase of stroke reduced mortality and extended life of disabled persons, many surviving patients, however, are afflicted with serious residual functional deficit in the field of motor and cognitive functions. These patients require then considerable economic cost for further treatment and subsequent long-term care.

After CMP a differential movement ability of hand can be lost and overlooked and uncorrected disorders can be then the cause of the resulting ineptitude of the patient in usual handling activities. A lot of people after stroke live with a substantial sensomotor disability of the upper limb worsening considerably the level of their functional independence. This disability can be frustrating for them, it can increase the risks of their impairment and can bring about worse social contacts.

That is why the early starting of comprehensive rehabilitation that should be able to prevent the origin or at least reduce the measure of various types of disabilities is very important. Occupational therapy (ET) that is dominant in helping to restore personal independence in daily life activities is an integral part of comprehensive rehabilitation. The results of various studies show that the patients who went through ET have a higher degree of independence in daily life activities than the patients without ET (1, 7, 8, 14).

AIM OF THE STUDY

The aim of our study was to evaluate the results of subsequent rehabilitation in 148 patients with diagnosis I60 – I69, general affection of central nervous system on the basis of vascular disease with motor activity and cognitive functions disorder, divided into the group attending only physiotherapy, and into the group going through the combination of physiotherapy and occupational therapy, and evaluation of

independence measure in basic daily activities by means of the test of functional examination (Functional Independence Measure, FIM test) and Barthel test (BT).

GROUP OF EXAMINED PATIENTS

In 2007 174 patients with diagnosis I 60 – 69, CNS affection on the basis of vascular disease with motor activity disorder, were hospitalized in After-treatment and rehabilitation ward in our hospital.

89 of them were discharged to home care ……. 51 %

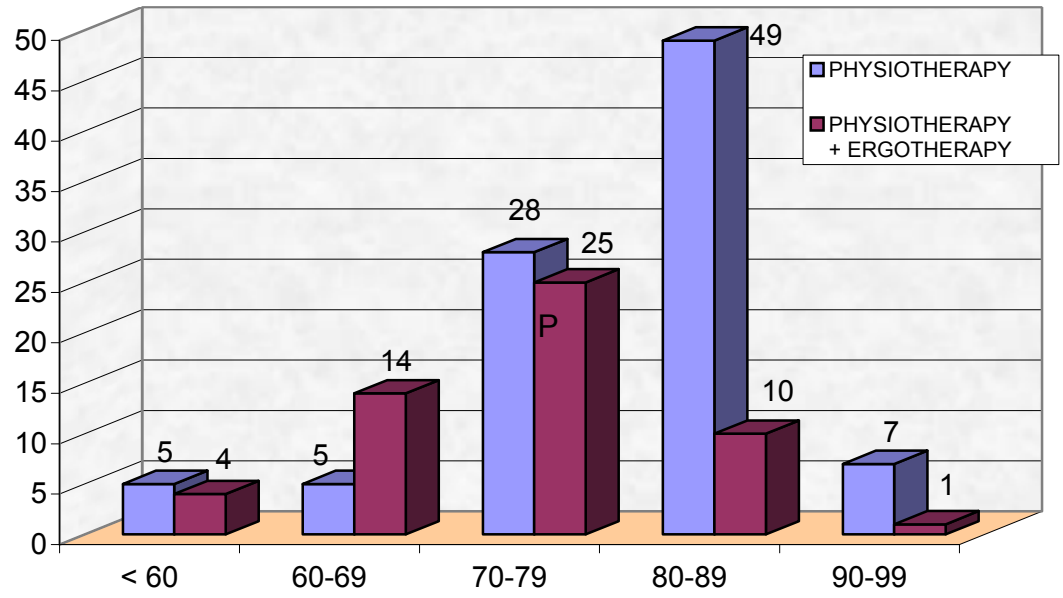
59 of them were discharged to social service institutions …….. 34 %

12 of them were moved back to emergency ward …… 7 %

14 of them died …… 8 %

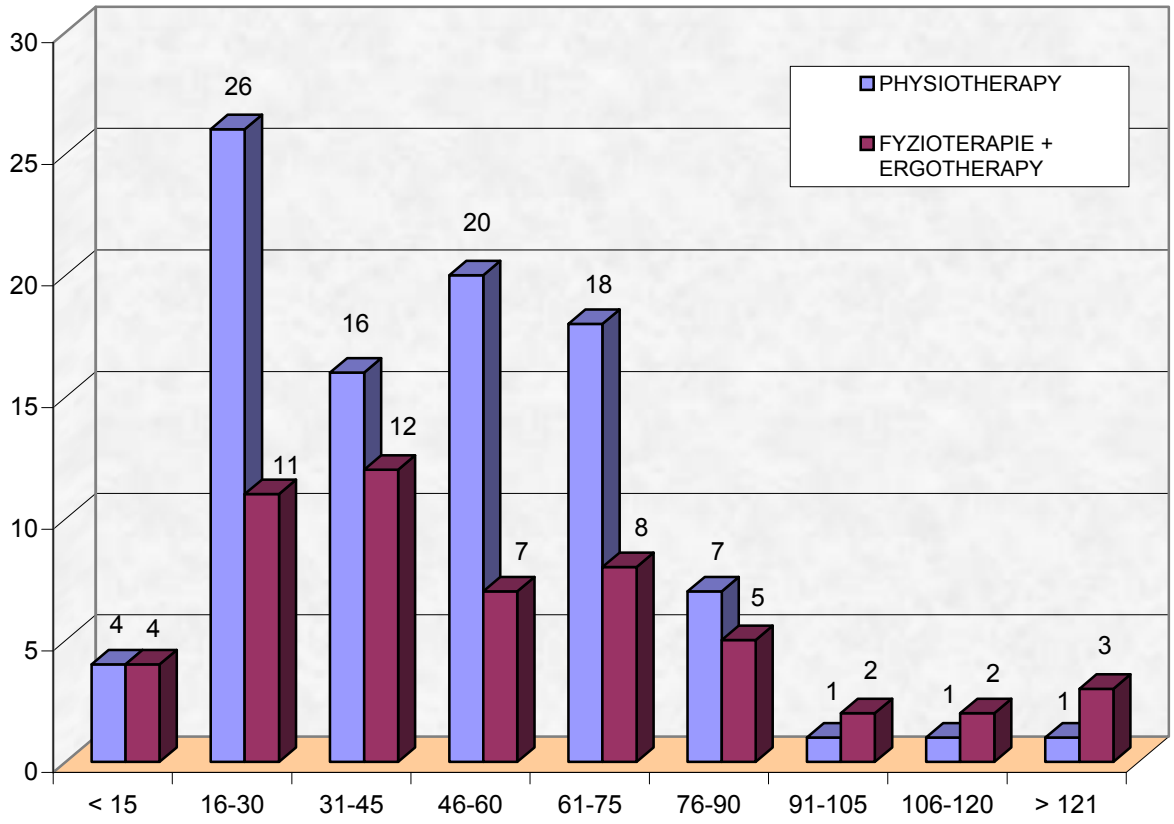
FIM test and BT were evaluated in the group of 148 patients from the total number of 174, who completed the rehabilitation and occupational therapy program and were discharged to home care or to institutions for social services, separately in the group of 94 patients for whom only physiotherapy was prescribed, and in 54 patients who went through both physiotherapy and occupational therapy.

The average age of the patients for whom only physiotherapy was prescribed was 79 years and the average age of the patients, who went also through occupational therapy was 72 years. The age distribution of the patients in both groups can be seen in graph 1.



Graph 1 Age distribution of all 148 patients with CMP

Duration of rehabilitation in our ward on average was 49 days; in the group of patients for whom only physiotherapy was prescribed it was on average 47 days and in the patients for whom also occupational therapy was prescribed it was on average 54 days. Intensity of rehabilitation was 1 hour of individual physiotherapy and half an hour of occupational therapy 5 days in a week.



Graph 2 Duration of hospitalization in patients with stroke

METHODOLOGY

For evaluation of functional fitness of the patients we used the test of Functional Independence Measure (FIM test) and Barthel test, evaluating independence in basic everyday activities and thus suitable for monitoring progress of the treatment.

FIM test – or measurement of functional independence, evaluates 18 activities in 6 categories: 1. Self attendance, 2. Control of sphincters, 3. Displacements, 4. Mobility, 5. Communication, 6. Social abilities. Each item has a scale consisting of seven points,

when 1 means full assistance and 7 full independence. The total score can be 18 – 126 points (2, 5, 6, 9, 11, 14).

Barthel test – test of basic everyday activities evaluates 10 activities: 1. Eating, drinking, 2. Dressing, 3. Taking a bath, 4. Personal hygiene, 5. Continence of defecation, 6. Continence of urination, 7. Using WC, 8. Displacement from the bed to the chair, 9. Walking on even ground, 10. Climbing stair. Individual items are evaluated mainly in three degrees of dependence – does not accomplish (0), accomplishes with assistance (5) and accomplishes independently without assistance (10). The total score can be therefore 0 – 100 points (2, 3, 4, 6, 13, 15).

As Barthel test does not contain evaluation of cognitive components, we used only the corresponding items of evaluation of motor score of FIM test to compare the results with FIM test.

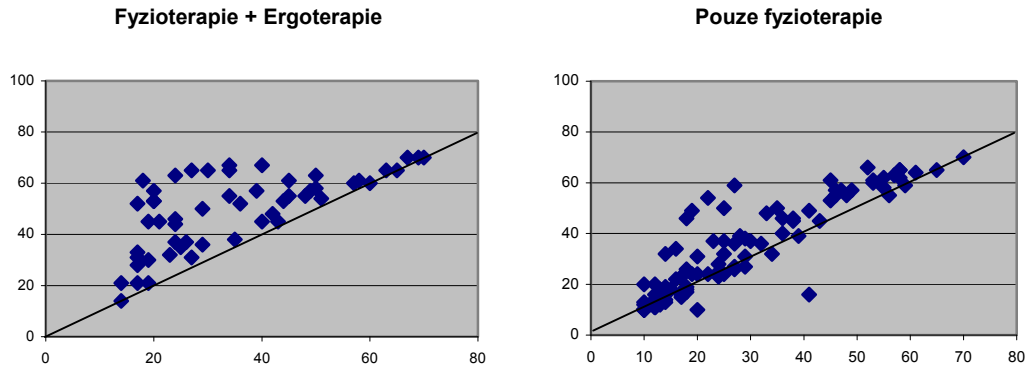
RESULTS

We compared the results of motor score of FIM test and the results of Barthel test at the beginning of rehabilitation and at discharge in the group of 94 patients for whom only physiotherapy was prescribed, and in the group of 54 patients who went through both physiotherapy and occupational therapy (ET).

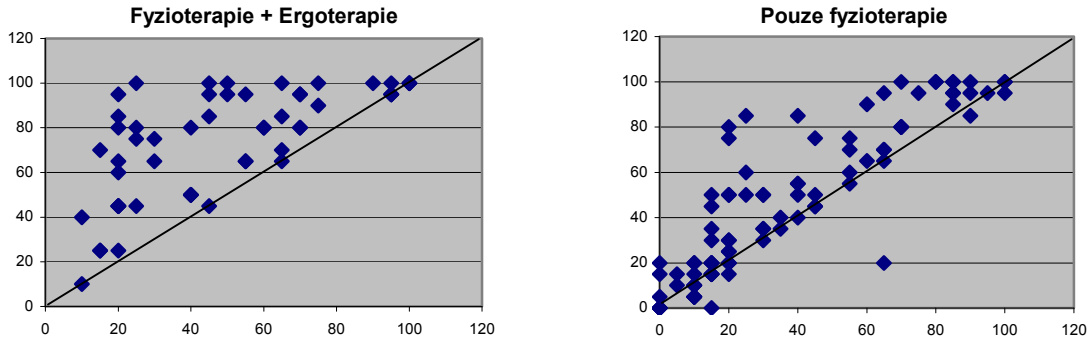
Groups	FIM input	FIM output	Barthel input	Barthel output
Patients with physiotherapy	28±16	34±19**	37±30	47±33**
Patients with physiotherapy and ET	35±16	49±15**	49±27	74±24**

** $p < 0,0001$

For evaluation of functional state of input and output parameters of both tests we used Wilcoxon paired test and the results showed statistically significant improvement of the function at the level $p < 0.001$ in both functional tests in all groups.



Graph 3. Results of functional independent measure (FIM test) before and after 3-month rehabilitation in both groups of patients with CMP



Graph 4 Results of functional Barthel test (BT) before and after 3-month rehabilitation in both groups of patients with stroke

DISCUSSION

Functional disorders accompanying stroke are often a serious complication for senior patients. Conclusions of our tests, however, confirm the assumption that age is not a factor excluding in advance senior patients from the rehabilitation program and that also elderly people are able to improve their physical functions, which leads to improvement of their quality of life and reduces social and economic impacts on the society.

The measured results show that a long-term rehabilitation of patients with stroke connected with occupational therapy brings about a substantial improvement of their independence in basic daily activities. With regard to increasing number of elderly people in the population, connected with a high number of disabilities and polymorbidities, the utmost necessity of prevention and rehabilitation programs directed at this very segment of our population is more and more noticeable (7, 10, 12, 15).

On the basis of functional tests (BT and FIM test) we have proved effectiveness of rehabilitation in the patients after stroke. Rehabilitation and occupational therapy are indicated in all patients, regardless their age and a measure of functional impairment.

CONCLUSION

The results of the test of functional examination after the subsequent rehabilitation of 148 patients with the diagnosis of general affection of central nervous system on the basis of vascular disease with motor activity and cognitive functions disorder, divided into the group attending only physiotherapy and into the group going through the combination of physiotherapy and occupational therapy, showed improvement of both groups of patients in basic daily activities.

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SUMMARY

The aim of this study was to evaluate the questionnaire Functional Independence Measure (FIM) and Barthel test (BT) in 148 patients with stroke with impairment of motor and cognitive functions before and after three months of physiotherapy and combination of physiotherapy and occupational therapy.

Methods: We examined 148 patients with stroke by means of FIM questionnaire and Barthel test.

Results and conclusion: We have found an improvement of functional state in our patients after physiotherapy and combination of physiotherapy and occupational therapy.

Key words: stroke, physiotherapy, occupational therapy, functional independence measure