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CONTENTS

1. **Kenner** Thomas, **Moser** Max
STABILITY AND OSCILLATIONS – AND THE UNIVERSITY AS A COMPLEX LIVING SYSTEM 5

2. **Halberg** Franz., **Cornélissen** Germaine**, Cegielski** Ning, **Hillman** Dewayne, **Halberg** Francine, **Schwartzkopff** Othild, **McCraty** Rollin, **Finley** Judy, **Thomas** Faithe, **Kino** Tomoshige, **Chrousos** George , **Sonkowsky** Robert P., **El-Khoury** Maroun, **Ilyia** Elias
CIRADIAN DYSFREQUENTIA OF CORTISOL, MELANTOIN, DHEA, TESTOSTERONE AND ESTRADIOL 9

3. **Halberg** Franz., **Conrnélissen** Germaine, **Sothern** B. Robert, **Barnwell** Franklin, **Cegielski** Ning, **Ilyia** Elias, **Siegelova** Jarmila
THE MOON‘ S AND THE GENES‘ TIDES AND DOUBLE TIDES PULLING THE BIOSPHERE 23

4. **Cornélissen** Germaine, **Babayev** Elchin, **Halberg** Franz
GENDER DIFFERENCES IN THE CHRONOME OF SUDDEN CARDIAC DEATH INCIDENCE IN THE ABSHERON PENINSULA, AZERBAIJAN 46

5. **Cornélissen** Germaine, **Halberg** Franz, Guillaume Francis, **Schwartzkopff** Othild, **Finley** Judy, **Cegielski** Ning, **Rosch** Paul, **Siegelova** Jarmila, **Ilyia** Elias
GROUNDING OR EARTHING: GLIMPSES AT PHYSIOLOGY AND PATHOLOGY..... 51

6. Cornélissen Germaine, Palermo Judy, Halberg Franz
AEOLIAN CHANGES AND GENDER IN THE INCIDENCE OF CARDIAC ARRESTS IN MINNESOTA..... 57

7. **Huynh** William, **Cornélissen** Germaine, **Huynh** Richie, **Huynh** Ryan, **Halberg** Franz
FEASIBLE AMBULATORY BLOOD PRESSURE AND HEART RATE MONITORING IN AMERICAN SECONDARY SCHOOLS TO ASSESS CHRONOMES IN CLINICALLY HEALTHY ADOLESCENTS 64

8. **Cornélissen** Germaine, **Halberg** Franz, **Siegelova** Jarmila, **Galvagno** Andrea
THE MOON´S IMAGE IN PROLONGED HUMAN ISOLATION 69

9. **Cornélissen** Germaine, **Halberg** Franz, **Finley** Judy, Thomas Faithe, , **Siegelova** Jarmila, **Dusek** Jiri, **Fiser** Bohumil
URINARY OUTPUT AND GEOMAGNETISM REVISITED..... 75

10. **Schwartzkopff** Othild, **Hillman** Dewayne, **Halberg** Franz., **Cornélisse**n Germaine, **Engebretson** Mark, **Katinas** Georgie S., **Chibisov** Sergei M., **Siegelova** Jarmila, **Agarwal** Rajesh, **McCraty** Rollin
CIRCASEMIDIAN AND CIRCASEMISEPTAN GAUGES OF VASCULAR ADJUSTMENT AFTER TRANSMERIDIAN CROSSING OF THREE TIME ZONES 80

11. **Watanabe** Fumihiko, **Cornélissen** Germaine, **Watanabe** Yoshihiko, **Halberg** Franz
A FAR-TRANSYEAR IN THE BLOOD PRESSURE OF A 17-YEAR-OLD MALE 86

12. **Watanabe** Yoshihiko, **Cornélissen** Germaine, **Halberg** Franz, **Siegelová** Jarmila
CHRONOBIOLOGICALLY INTERPRED ABPM (C-ABPM) IN DELAYED SLEEP PHASE SYNDROME 90

13. **Watanabe** Yoshihiko, **Cornélissen** Germaine, **Halberg** Franz, **Hillman** Dewayne, **Fišer** Bohumil, **Dusek** Jiri, **Homolka** Pavel, **Siegelova** Jarmila
INFRADIAN MODULATION OF THE DEVELOPMENT OF HUMAN TRUE WHITE-COAT MESOR-HYPERTENSION 104

14. **Sothern** Robert B., **Halberg** Franz, **Cornélissen** Germaine, **Hillman** Dewayne, **Katinas** Georgie, **Siegelova** Jarmila
COMPLEMENTARY YET DIFFERING RHYTHMIC ASPECTS OF A MAN´S MOOD AND VIGOR IN VARIOUS SPECTRAL REGIONS 120

15. **Fišer** Bohumil, **Siegelová** Jarmila, **Dušek** Jiri, **Pohanka** Michal, **Cornélissen** Germaine, **Halberg** Franz
NIGHT-TO-DAY BLOOD PRESSURE RATIO DURING SEVEN-DAY AMBULATORY BLOOD PRESSURE MONITORING 128

16. **Siegelová** Jarmila, **Havelková** Alena, **Fišer** Bohumil, **Dušek** Jiri, **Pohanka** Michal, Mašek Michal, **Dunklerová** Leona, **Cornélissen** Germaine**, Halberg** Franz
DAY AND NIGHT BLOOD PRESSURE VARIABILITY DURING SEVEN-DAY AMBULATORY BLOOD PRESURE MONITORING 133

17. **Dobšák** Petr, **Sosíková** Michaela, **Al-Mahmodi** Nabil Abdullah Ibrahim, **Frantisová** Michaela, **Tomandl** Josef, **Špinarová** Lenka, **Jančík** Jiří**, Pohanka** Michal, **Fišer** Bohumil, **Siegelová** Jarmila
HOME BASED REHABILITATION PROGRAM USING TRANSCUTANEOUS ELECTRICAL MUSCLE STIMULATION IN PATIENTS WITH CHRONIC HEART FAILURE 139

18. **Konečný** Lumír, **Pochmonová** Jaroslava, **Havelková** Alena, **Siegelová** Jarmila, **Dobšák** Petr
HEART RATE VARIABILITY IN MULTIPLE CEREBROSPINAL SCLEROSIS 146

19. **Havelková** Alena, **Pochmonová** Jaroslava, **Konečný** Lumír, **Fišer** Bohumil, **Pohanka** Michal, **Siegelová** Jarmila
SECOND PHASE OF CARDIOVASCULAR REHABILITATION IN PATIENTS WITH ISCHEMIC HEART DISEASE 158

STABILITY AND OSCILLATIONS - AND THE UNIVERSITY AS A COMPLEX LIVING SYSTEM

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

Abstract

The main interest of chronobiology usually is focused on phenomena, which are controlled by internal clocks. Influence from outside is considered as important if it has influence as Zeitgeber or trigger of internal synchronization or disturbance.
We intend to discuss processes, which influence the stability of some internal or external system and therefore, lead to oscillations. We refer to phenomena, which are connected with the names Schumpeter and Kondratjew and can be observed as oscillations of large living systems. As one example for such considerations we discuss the chronobiology of our University.

Introduction

Oscillations can be found everywhere in nature, in non-living entities of all magnitudes - from subatomic particles to galaxies and even to our whole universe. Well analyzed are glacial periods and correlated oscillations of the temperature of the earth atmosphere. Periods and oscillations in living systems from molecules to cells and from organs to bodies and populations belong to the field of chronobiology (1, 2).

Oscillations within a living body may be induced from an external source, like the sound waves acting on the components of the ear: the tympanic membrane, the ossicles and the oval window. The analysis and discrimination of the incoming oscillations is initiated in the cochlea from where the information is sent to the brain centers.

The transmission of sound-generated waves along the basilar membrane is similar to the transmission of pulse waves in the arteries. The similarity of the arterial pulse waves and the „travelling waves“ in the basilar membrane is remarkable – as was early interpreted by O.F. Ranke (3) who was familiar with arterial pulse waves. It seems remarkable that the “grand-master of biomechanics”, Y.C. Fung together with his coworkers (4) suggested that messages, which are carried from different organs in the arterial pulses may be detected by analyzing the radial pulse. The transmission and reflection of arterial pressure waves may explain the processes, which permit to extract information by feeling and interpreting the radial pulse according to TCM. In the paper the authors (4) state: “although the discrimination is not very strong, the phenomenon is novel, and warrants further investigation.“

Externally induced oscillations are related to auto-oscillations and resonance. E.g.: When a person drives in a car on a bumpy street, internal organs as well as tissues from skin to bone oscillate in resonance. In general, such oscillations markedly influence the "ride quality" within a carriage – a bike, a car or a ship. The appearance of sea-sickness, thus is a chrono-patho-biological phenomenon.

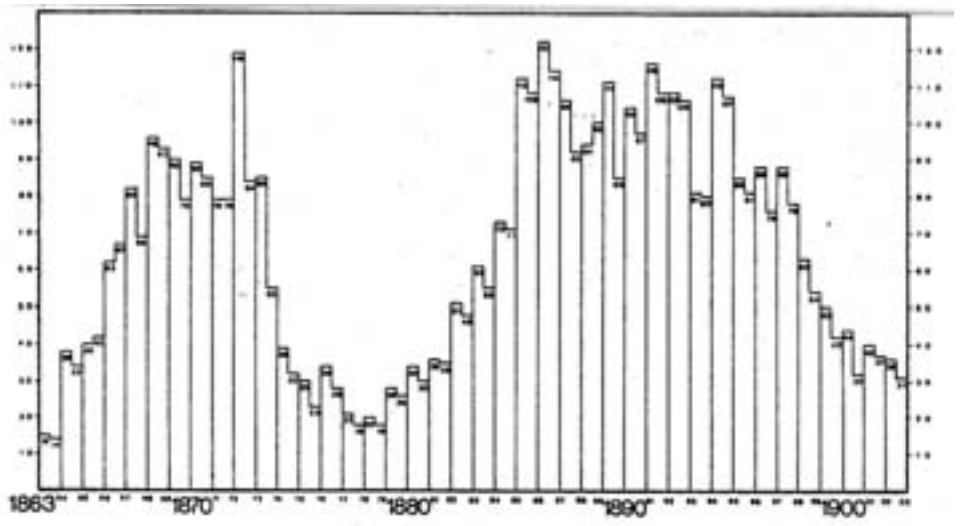
Everybody understands what stability means. Stability of standing straight is improved by very slight swinging oscillations of the body. In terms of control theory one can explain these oscillations, which continuously adjust the position to the correct set point. Similarly a driver adjusts his car to the correct path by slightly moving the steering wheel. Instability of a car is indicated by increasing oscillatory movements and skidding.

One special possibility to produce instability of a system is, to insert a delay between the controlled variable and the controller. One example: if for some reason or because an experimenter has intervened, the baroreceptors recognize a sudden decrease of blood pressure only after several seconds, then the central blood pressure control system reacts too late. The consequence is: the blood pressure starts to oscillate (5).

It is interesting to note that the cellular internal clocks of our body are functioning according to the described method of delay of information. The following is a simplified explanation: The clock-gene generates a protein, which then, after a certain time blocks the function of the gene. After a further time the gene is again activated and the process is repeated with a constant period.

Chronobiology of a University

A group of interacting persons or a society can be described as a living system. The reports about the current and previous crises indicate the appearance of oscillations. It is, therefore, worthwhile to mention the names of Nikolai Dmitrijewitsch Kondratjew (1892 – to 1938) and Josef Alois Schumpeter (1883 – 1850). The latter was Professor of Economy at the University of Graz from 1911 to 1921. Both names are associated with the socalled "Kondratjew-cycles" or "Schumpeter –waves". These cycles or waves, which last about 30 to 60 years are correlated with achievement and development of inventions like weaving, use of steam engines, automobile-engines, aviation, computers etc. Independent of the answer to the question whether this kind of oscillations is a phenomenon of chronobiology, what happens certainly is not possible without life.



Besuch der physiologischen Vorlesungen in Graz von 1863 – 1903 unter Alexander Rollett.

Among old documents in the Department of Physiology in Graz we found the diagram shown in the figure. It demonstrates oscillations of the attendance of students to Phsiology-lectures between 1863 – the year of the foundation of the Medical Faculty – until 1903. There are similar more recent oscillations of the number of medical students in Austria. A recent new law, which since 2005 permits only a limited number of medical students per university and year. It is not clear if this interruption of oscillations has specific consequences.

As a physiologist in the position of Rector of the Karl-Franzens-University in Graz (1989-91) and in the position of Dean of the Medical Faculty (1992-97) I was able to observe my Alma Mater as a complex living organism (6). From the viewpoint of historical development Alois Kernbauer (7) has vividly described the life-cycles of affluence of our University since the foundation in 1585.
One special peculiarity of complex systems like Universities is their nonlinearity. The basic living components like teachers, students and supporting personal have different time-cycles of presence and aging within the system. The system is not closed, but is open to exchange with the environment and, in particular, to influences from outside sources. This includes reforms, which in Austria are ordered by federal laws.

In order to understand the function of a system like a University the aspects of time and timing has to be examined. Quantity and quality of the input-output relations are important and at the same time the different flows of information as well as the relation between information and knowledge including the storage of information and knowledge.
A reform is always something like an experiment, which in any case generates a disturbance. Marked changes in structure and function are the consequence. There exist characteristic time intervals, time periods and time constants, which permit to estimate the time course of normalization after a disturbance. The reaction, at least in part, may be called remodeling indicating the adaptive reaction of the system. An overruling of this reactive process may lead to a condition of shock (8). As an example, the remodeling after the reform of 1975, which changed the university from a rather patriarchic form into a democratic structure continued for at least 10 years, in some peculiar aspects even up to 20 years. From the viewpoint of a physiologist therefore, any reform has to consider quality, quantity and time of necessary adjustments.

The recent reform, which changed the former Medical Faculty to a Medical University had an effect like a cell division. The consequence besides the oppression of student oscillations is a tremendous increase of bureaucracy, and construction activity to create space for personal. One hesitates to discuss the question, if the reform had an influence on the output which justifies the effort of all the modifications.

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CIRCADIAN DYSFREQUENTIA OF CORTISOL, MELATONIN, DHEA, TESTOSTERONE AND ESTRADIOL

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Abstract

We report a circadian endocrine frequency desynchronization from the societal routine of human salivary cortisol, dehydroepiandrosterone, melatonin, estradiol and testosterone, during the latter part of an adynamic episode in the winter of 2009-2010 in JF, a 62-year-old woman. A condition of extreme fatigue and depression that lasted for several months, had recurred half-yearly for the past 20 years. With the methodology of chronobiologic serial sections, we quantitatively assess temporal changes in rhythm characteristics with their uncertainties and explore the sampling requirements for these hormones' circadian variation in both the desynchronized and the 24-hour synchronized state and for salivary aldosterone in the synchronized state. We dub an altered period (i.e., an altered frequency) as *ecfrequentia* if transient or as *dysfrequentia* if associated with illness. *Ecfrequentia* and *dysfrequentia* have the advantages of being hybrids (hybrid vigor), of brevity, having fewer syllables than *frequency desynchronization,* of complementing another rhythm alteration, ecphasia, and thus as a pair they may be more likely to be recognized (ringing bells). The prefix *ec-* from the Greek preposition *ek* (εκ), as in the word *eccentric* (off-center), added to the Latin *frequentia* (frequency), makes *ecfrequentia* mean "off or outlying from the usual pattern of frequency", i.e., outside a given reference standard of peers preferably of the same gender and age. *Dysfrequentia* includes the Greek prefix *dys-,* which like Latin *mal-* meaning "bad" is the opposite of the Greek *eu-* (Latin *bene-*). Ecfrequentia may be used as a general term, but notably in cases when the condition is asymptomatic and/or limited to a 7-day record; the term includes dysfrequentia when the condition is accompanied by symptoms of unwellness.

Case report

A selenosensitive 62-year-old woman's (JF) circulation and all of her endocrine variables investigated desynchronize from the societal 24-hour routine during a (half-yearly recurring) episode of extreme adynamia ("downtime") of an extent that prevents her from getting out of bed (1, 2). We here present chronobiologic serial sections of salivary cortisol, dehydroepiandrosterone (DHEA), melatonin, testosterone and estradiol that were determined both during a downtime and thereafter, and of aldosterone, determined only during a stage of synchronization with society. In all other variables, except for aldosterone, the data start in a downtime, during which an oblique delaying time course of acrophases (peaks in the fitted 24-hour cosine function) are in keeping with a period longer than the 24-hour cosine curve fitted to the data. During resynchronization, the time course of the

circadian acrophases becomes horizontal. 5159 ELISAs are in keeping with endocrine circadian desynchronization of the hormones investigated during the downtime, with a lengthening of their period perhaps as a result of a pull by the moon exerted upon a built-in circadian period. The data also illustrate sampling requirements insofar as the noisier the variable, the longer was the span to demonstrate to the eye the time courses of the acrophases of the variables investigated.

Data. The numbers of assays for each hormone are given on top of each figure. Some changes in the patterns of values, possibly related to changes in the kits used for assay, can be questioned with the naked eye, e.g., in aldosterone. By contrast, other changes may be related to a depression of body activity, such as a lower **m**idline-**e**stimating **s**tatistic **o**f **r**hythm, MESOR, M, and lesser circadian extent of change, the double amplitude, 2A, of cortisol and the opposite for DHEA during the episode extending from the start of determinations to cycle 1 as a whole and as compared to the M and 2A after cycle 2.

Results. Figure 1 shows, in the top row, the original data, in this case of salivary cortisol, as do other figures for other variables. In the second row, the lower curve is the MESOR (M), with the standard error, SE, of M leading from the M to a dot below. The distance between the two curves in row 2 is the circadian amplitude, A, computed by the least-squares fit of a 24-hour (h) cosine curve, and the distance between the upper curve and the dot above it is the SE of A. The circadian acrophase, ϕ, is seen in row 3, where cycles 3 to 6 show a horizontal time course corresponding to 24-h synchronization, with the peak occurring around midday for cortisol (around -180˚). The dots bracketing ϕs are their CIs (95% confidence intervals). The dashed horizontal lines in this row correspond to midnight; when the ϕs approach midnight (0˚ or 360˚), they are doubly plotted. The oblique time course of ϕs shows circadian desynchronization at the start and in cycles 1 and 2, and resynchronization in cycle 3 and up to and including the first part of cycle 6. The fourth row of P-values from tests of the zero-amplitude (no circadian rhythm) assumption shows a dashed horizontal line corresponding to the 5% level of statistical significance. When a 24-h cosine curve is fitted to consecutive 72-h data sections (intervals) displaced in 12-h increments, many of the P-values in Figure 1 are below 5%.

The data on other salivary hormones also show the initial desynchronization and subsequent resynchronization to 24 h, as seen by a more or less oblique time course of ϕs in row 3 up to cycle 3 and 24-h synchronization in this cycle and thereafter. By contrast with cortisol, DHEA and melatonin in Figures 1-3, where $P<0.05$ in many 72-h intervals, data in these intervals on estradiol, testosterone and aldosterone are more noisy, Figures 4-6. No determinations of aldosterone were made during the episode of adynamia, Figure 6. In Figures 4-6, the interval used for analysis should be lengthened, but the 72-h interval used suffices to suggest that estradiol and perhaps testosterone were desynchronized, since the somewhat erratic ϕs cover the 24 h at the start but do not do so thereafter.

Discussion. Chronobiologic serial sections as a local analysis of data in 72-h intervals and global analyses of longer sections of the time series and/or of the series as a whole (2) render these results part of a glocal (glo<u>bal</u> + lo<u>cal</u>) analysis and await follow-up. It is noteworthy that in the summer episode of 2010, following these hormone determinations, the desynchronized circadian period of systolic blood pressure as well as heart rate was of 24.8 h, corresponding to the double tidal period (3). The endocrine determinations allow only the documentation of the earlier circadian desynchronization in the winter of 2009-2010, followed by resynchronization in 2010.

A lengthening of the interval used for analyses to 168 hours (1 week) yields mostly statistical significance, notably during the 24-hour synchronized cycles 3-6 for estradiol, for testosterone, and to a lesser extent for aldosterone, as it does for cortisol. In the case of aldosterone, a phase jump of unknown origin is seen. The desirability of added hormone determinations in JF is apparent from data on systolic blood pressure in cycles 6 and 7 from the recurrence of desynchronization in the second half of cycle 6 and in cycle 7 (not here shown). Further ELISAs could examine whether all variables change concurrently or in a sequence. In the latter case, a hint of the critical mechanism may emerge.

JF is presumably the first patient with an adynamia associated with ecfrequentia or rather dysfrequentia showing a double tidal period in her blood circulation during the last episode investigated (summer 2010) as well as in self-ratings of mood during the prior episodes (preceding winter and summer). The moon's image is also found in one out of three >7-day records in the diastolic blood pressure of her grandchild. It is the more interesting that certainly three major hormones -- cortisol, DHEA and melatonin -- and probably also the noisier estradiol and testosterone in saliva are desynchronized from the societal 24-h routine in this 62-year-old selenosensitive woman in the winter 2009-2010 episode of adynamia investigated; their periods are longer than 24 hours, but shorter than 24.8 hours (2). In the first months of the first two episodes investigated, in self-ratings and of systolic blood pressure and heart rate of the third episode, the period found was 24.8 hours, in keeping with a pull by the moon that can lengthen the period to the point of actual lunar synchronization.

Conclusion. Ecfrequentia, long extrapolated from spotchecks limited at most to daily profiles, is here documented in the phase domain by a scan of more than the entire 24-hour span by acrophases with a delaying oblique time course for over a (lunar) month with resynchronization documented by a horizontal time course of acrophases for the following month(s). The extent to which circadian desynchronization, here clearly established, contributes to concurrent unwellness, and how unwellness can perhaps be prevented by maintaining synchronization, remains to be established.

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Figure 1: JF: cortisol

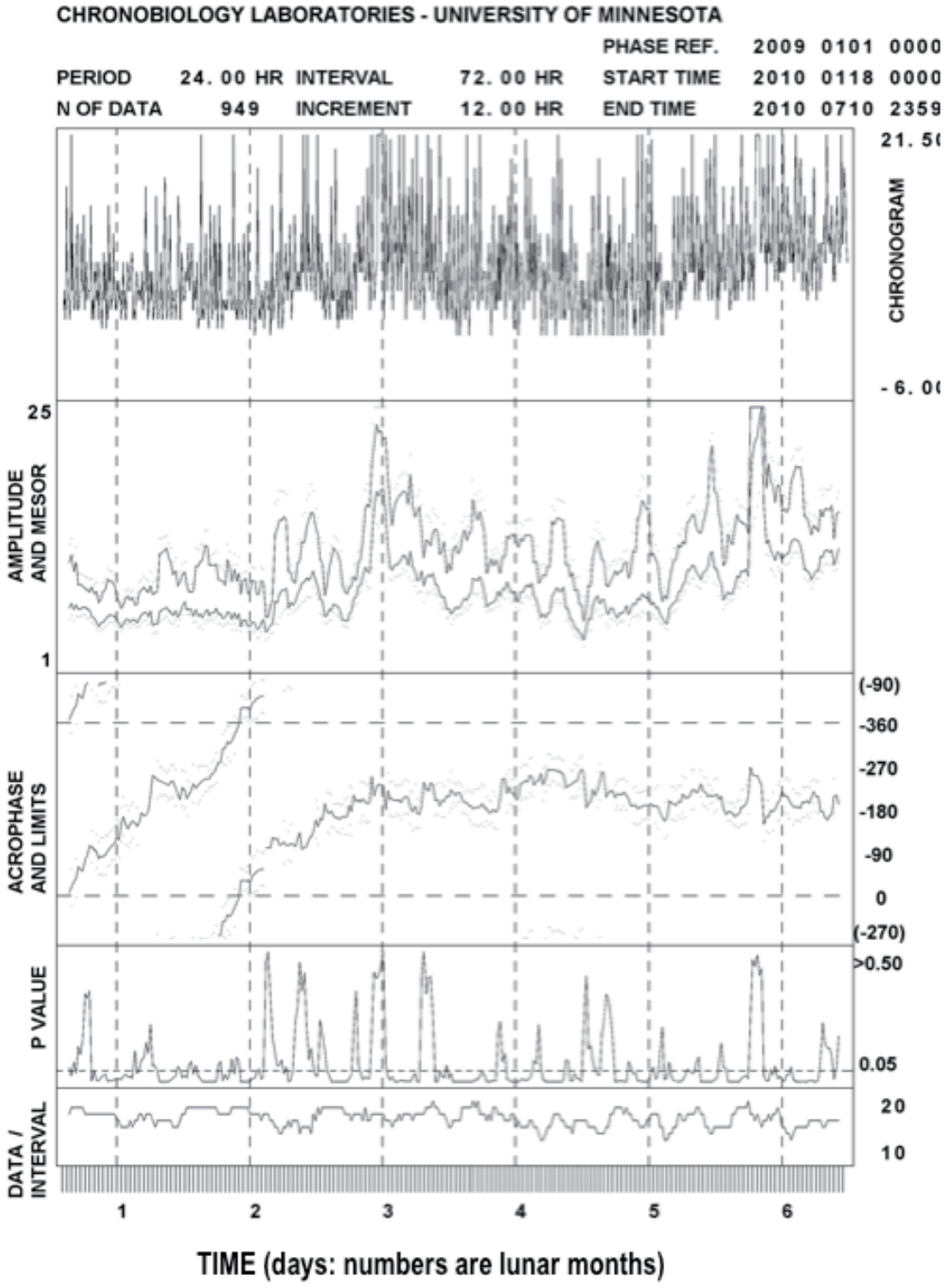

Figure 1. Chronobiologic serial section of salivary cortisol in JF showing, in the third row, initial circadian desynchronization by an oblique time course of acrophases and subsequently, starting in cycle 3, 24-hour synchronization, apparent from the horizontal time course of acrophases. Note in row 4 that with the 72-hour intervals the zero-amplitude assumption can be rejected, more often than not by P-values under the horizontal dashed 5% line. See Figure 10 for most P-values at or below 1% with 1-week intervals used for analysis. © Halberg.

Figure 2: JF: DHEA

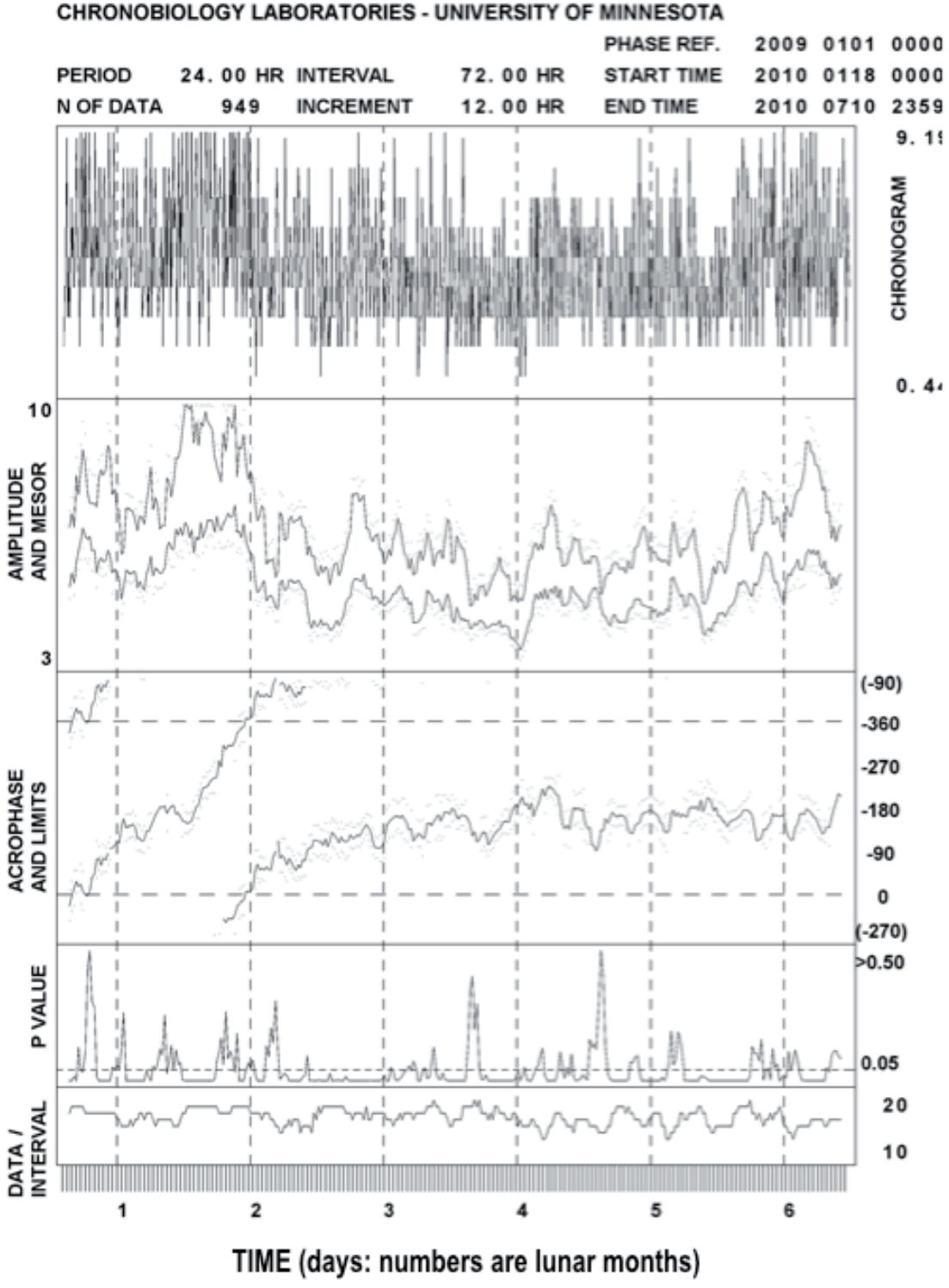

Figure 2. Chronobiologic serial section of salivary dehydroepiandrosterone (DHEA) in JF showing, in the third row, initial circadian desynchronization by an oblique time course of acrophases and subsequently, starting in cycle 3, 24-hour synchronization, apparent from the horizontal time course of acrophases. Note in row 4 that with the 72-hour intervals the zero-amplitude assumption can be rejected, more often than not by P-values under the horizontal 5% line. Most P-values are at or below 1% with 1-week intervals for analysis (not shown). © Halberg.

Figure 3: JF melatonin

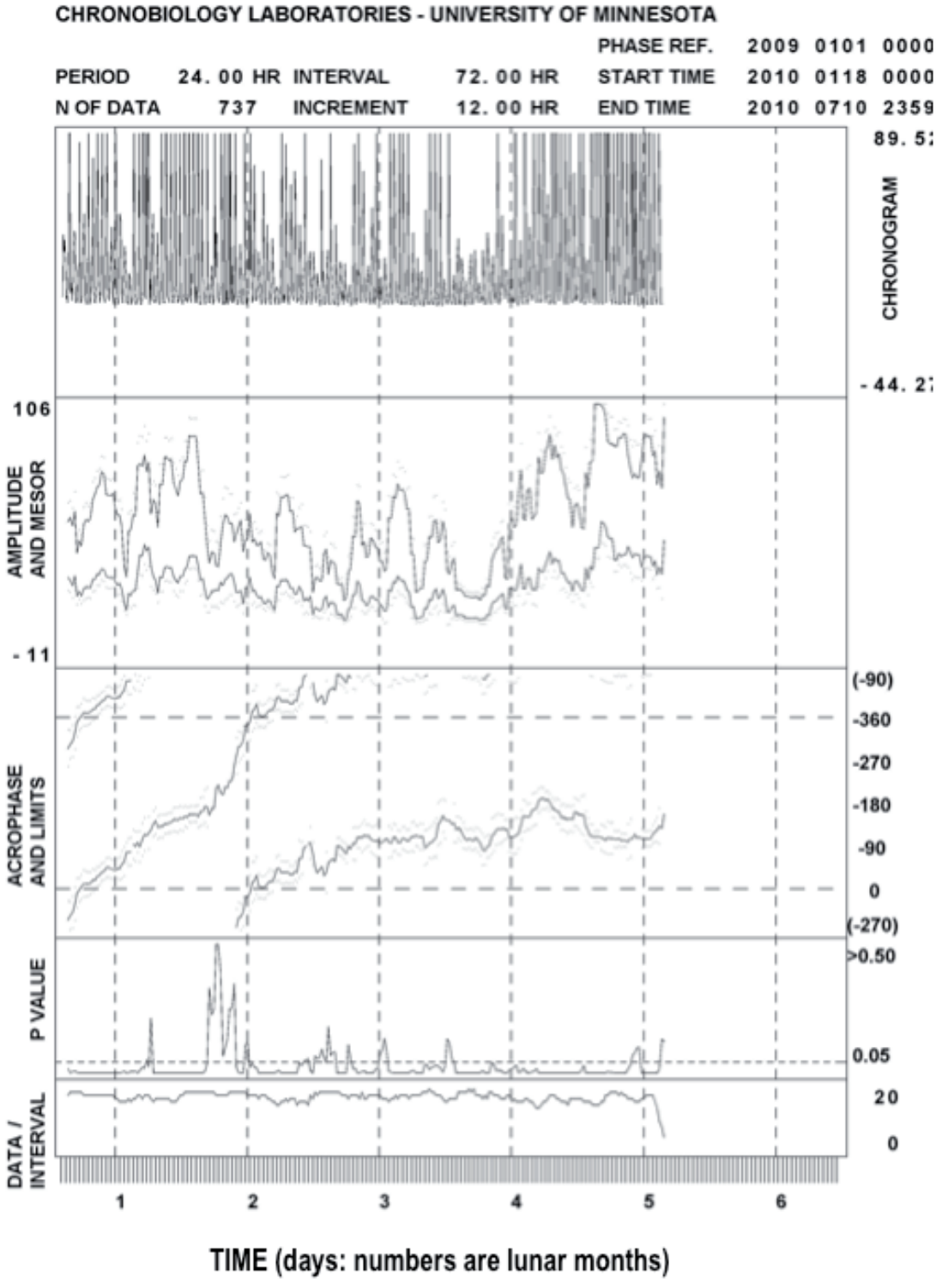

Figure 3. Chronobiologic serial section of salivary melatonin in JF showing, in the third row, initial circadian desynchronization by an oblique time course of acrophases and subsequently, starting in cycle 3, 24-hour synchronization, apparent from the horizontal time course of acrophases. Note in row 4 that with the 72-hour intervals the zero-amplitude assumption can be rejected, more often than not by P-values under the horizontal 5% line, mostly at or below the 1% or lower bottom line. © Halberg.

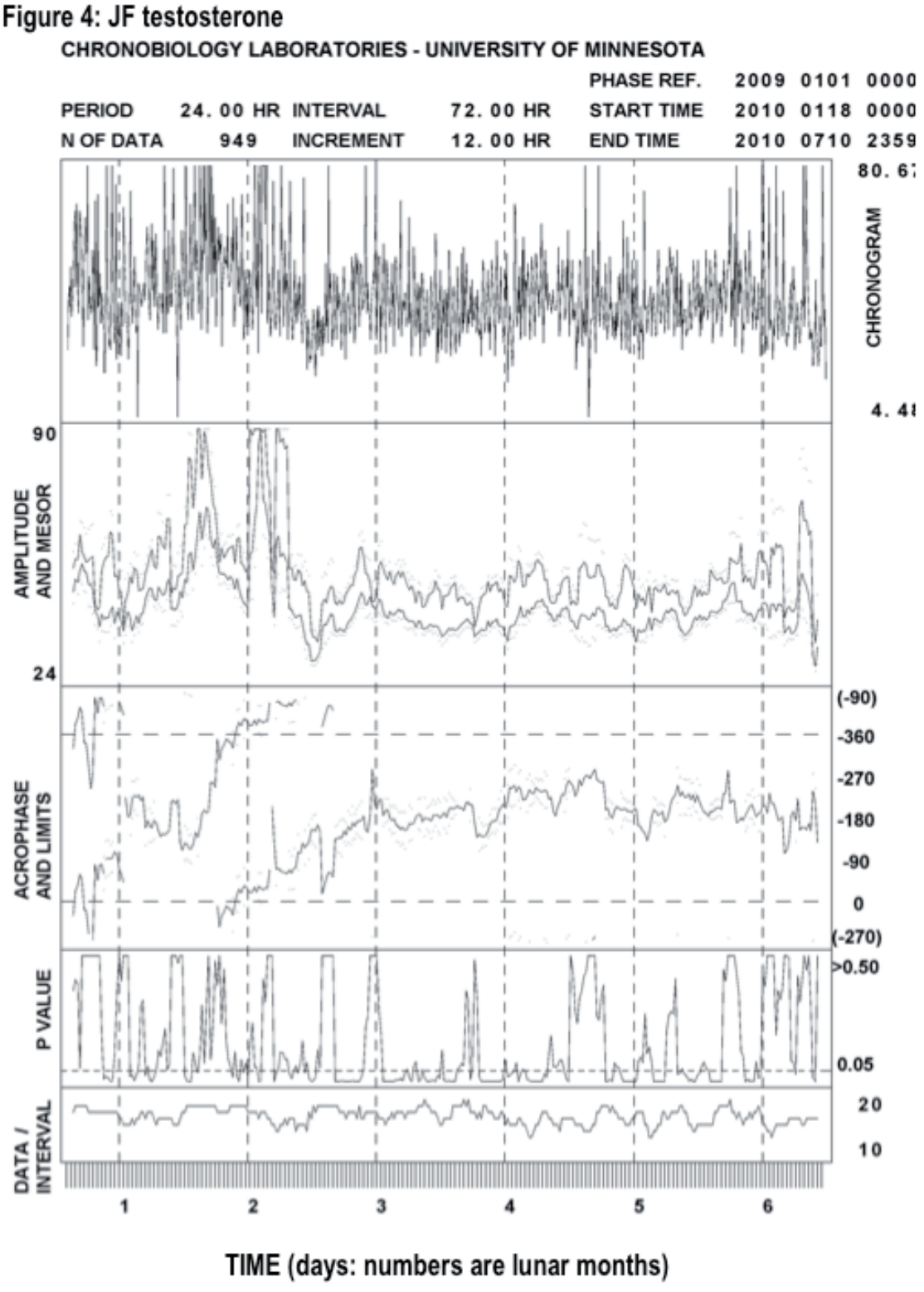

Figure 4. Chronobiologic serial section of salivary testosterone in JF showing often that the zero-amplitude assumption cannot be rejected, but covering 360˚ in the first two cycles, but not thereafter. © Halberg.

Figure 5: JF estradiol

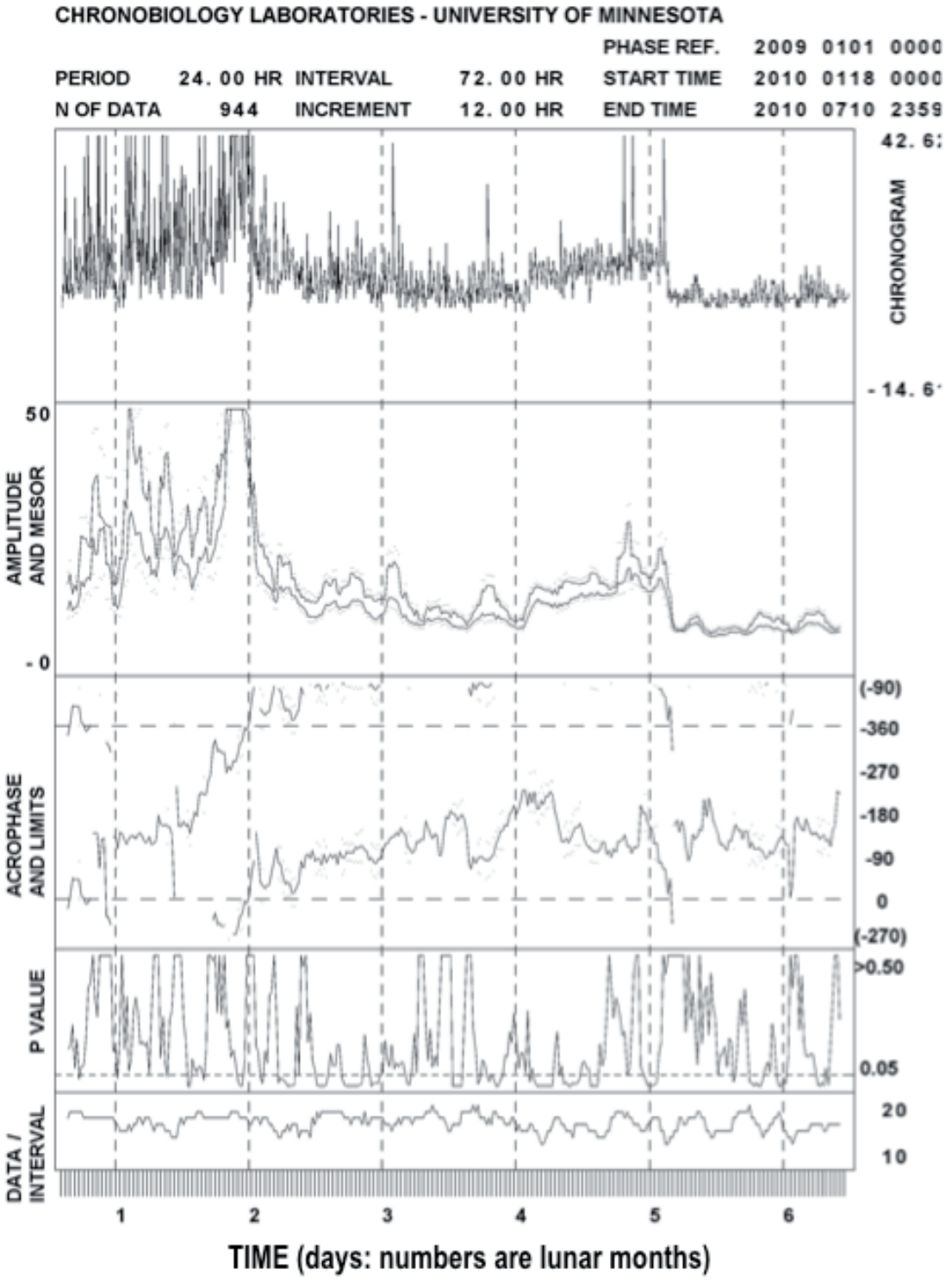

Figure 5. Chronobiologic serial section of salivary estradiol in JF showing often that the zero-amplitude assumption cannot be rejected with the 3-day (72-hour) interval analyzed. The difference in phases scanning the 24-h span in cycles 1 and 2, but not thereafter, is nonetheless apparent. © Halberg.

Figure 6: JF: aldosterone

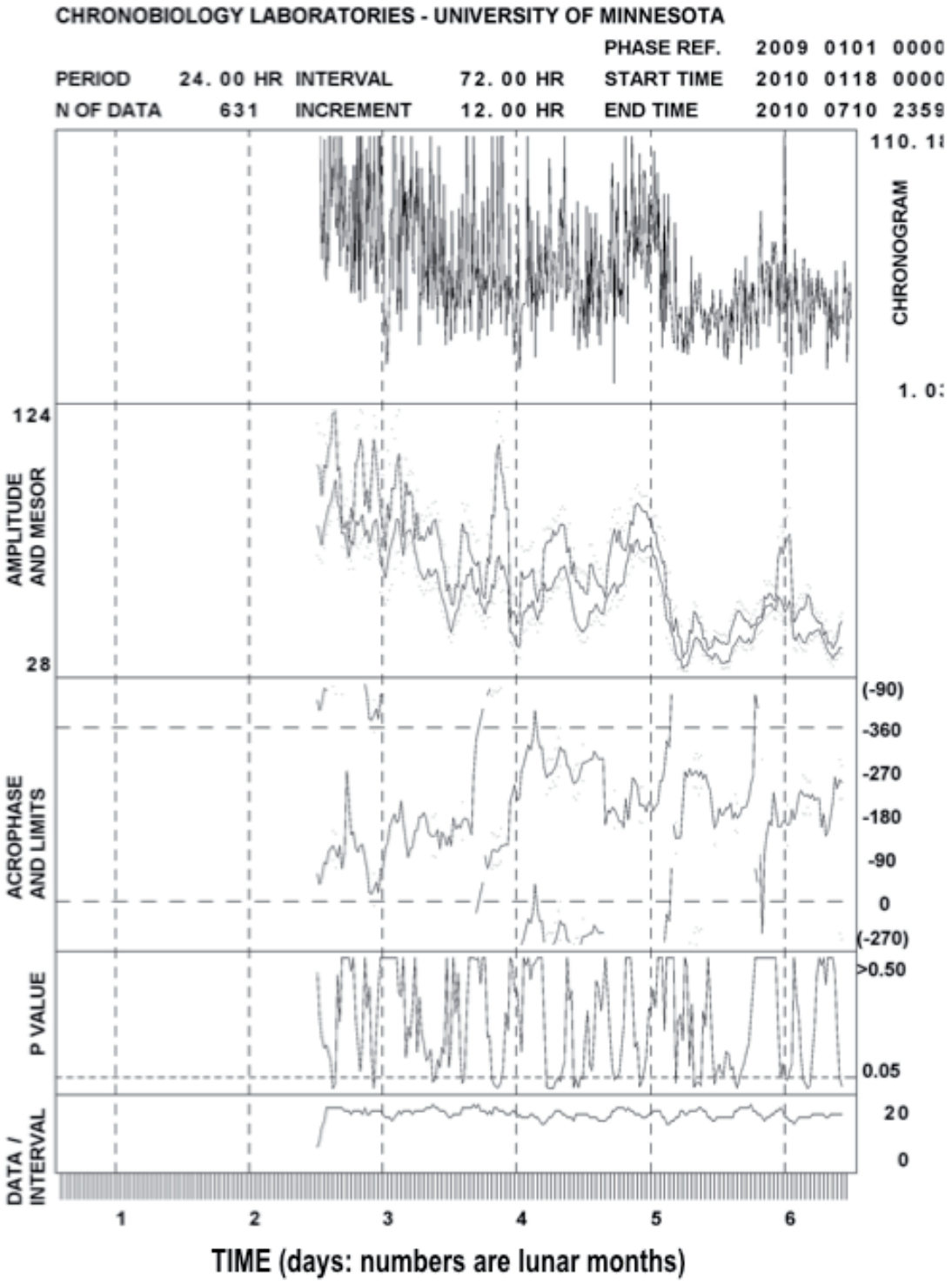

Figure 6. Chronobiologic serial section of salivary aldosterone in JF showing often that the zero-amplitude assumption cannot be rejected and suggesting a phase jump rather than a drift. © Halberg.

Figure 7: JF estradiol (interval lengthened to 1 week)

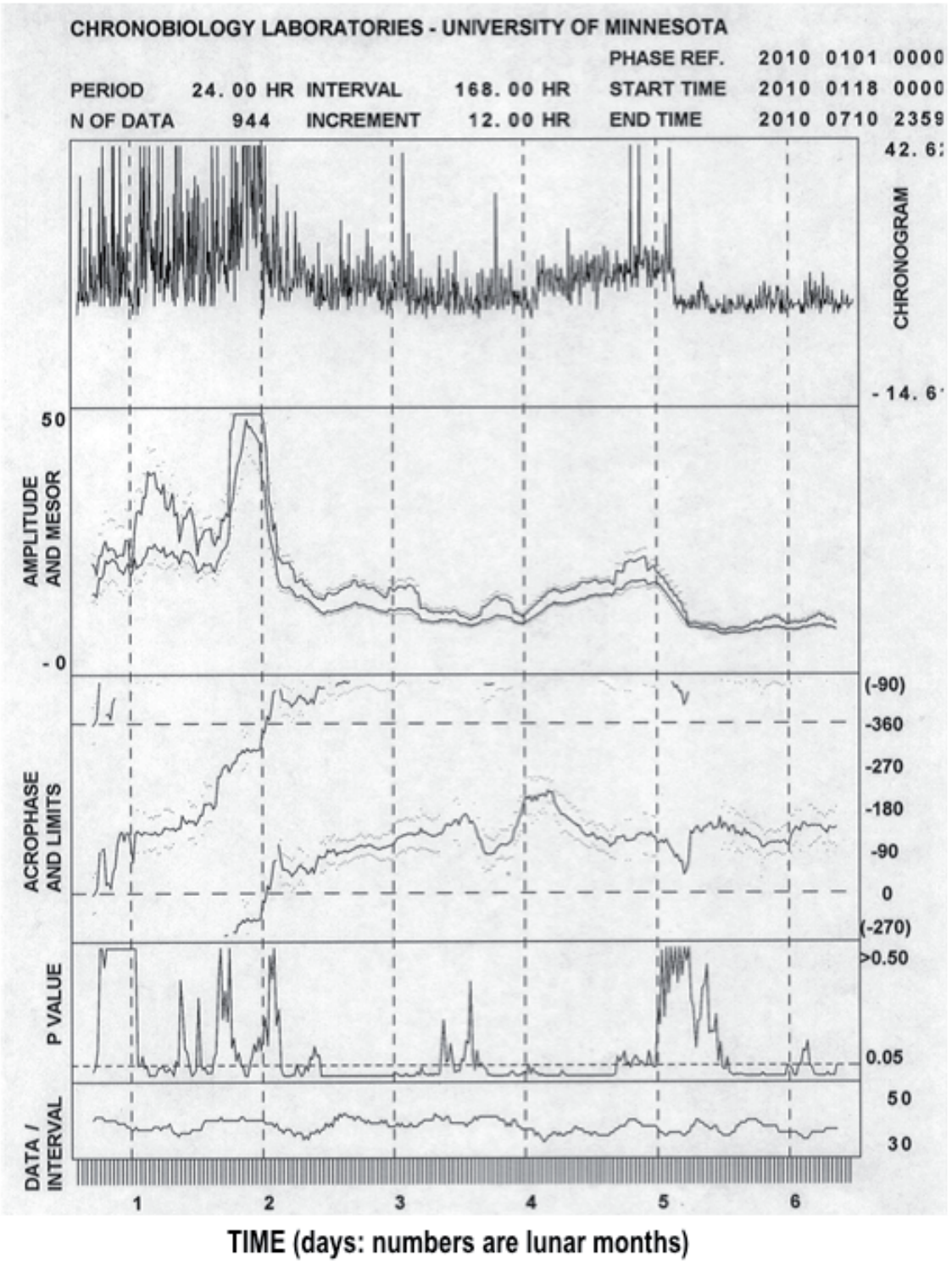

Figure 7. Often statistical significance is gained with a lengthening of the interval used for analysis. Results with an interval of 168 hours are in keeping with initial desynchronization followed by resynchronization of salivary estradiol. © Halberg.

Figure 8: JF testosterone (interval lengthened to 1 week)

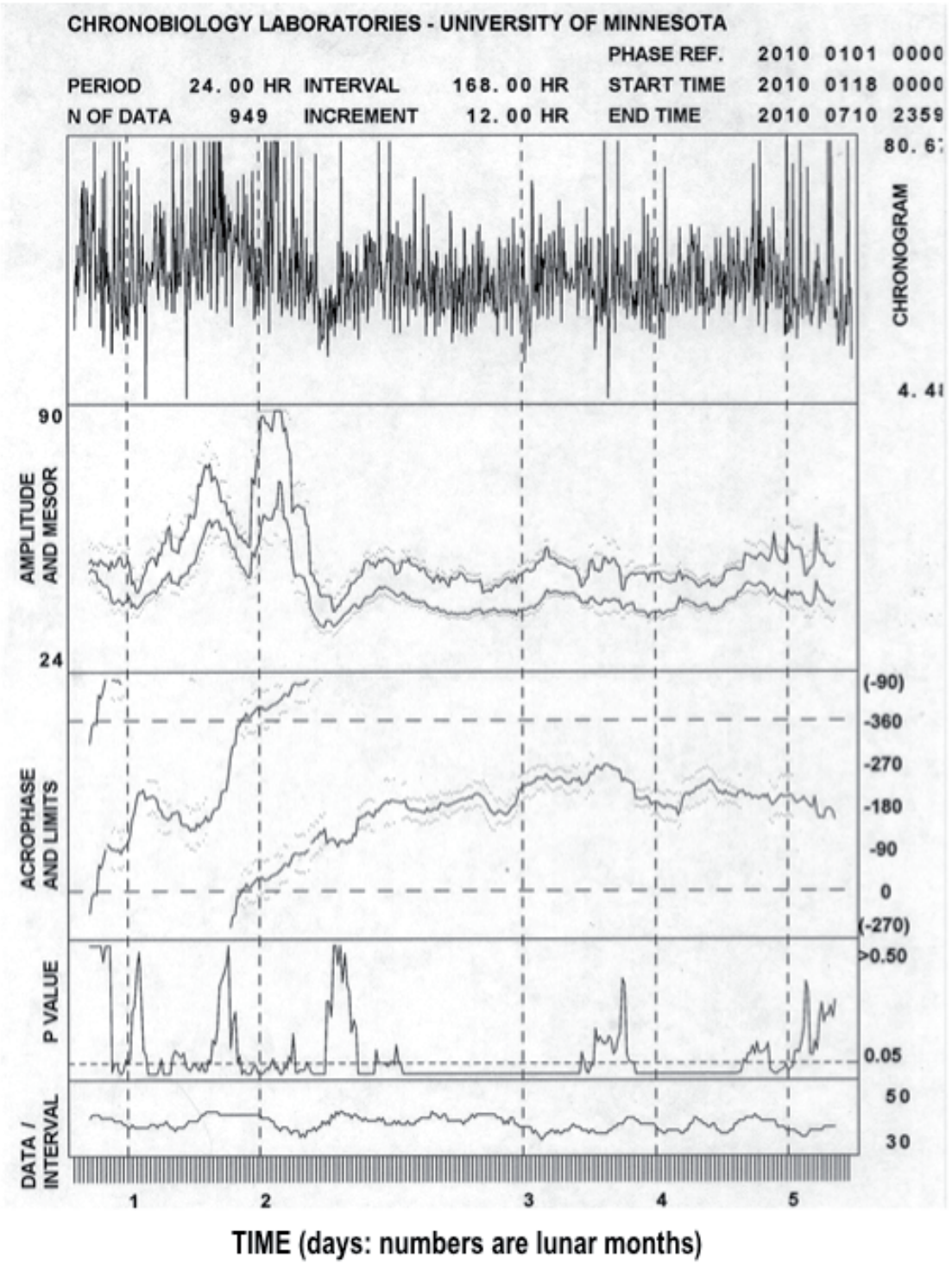

Figure 8. Analyses with a 168-hour interval are in keeping with initial desynchronization followed by resynchronization of salivary testosterone. © Halberg.

Figure 9: JF aldosterone (interval lengthened to 1 week)

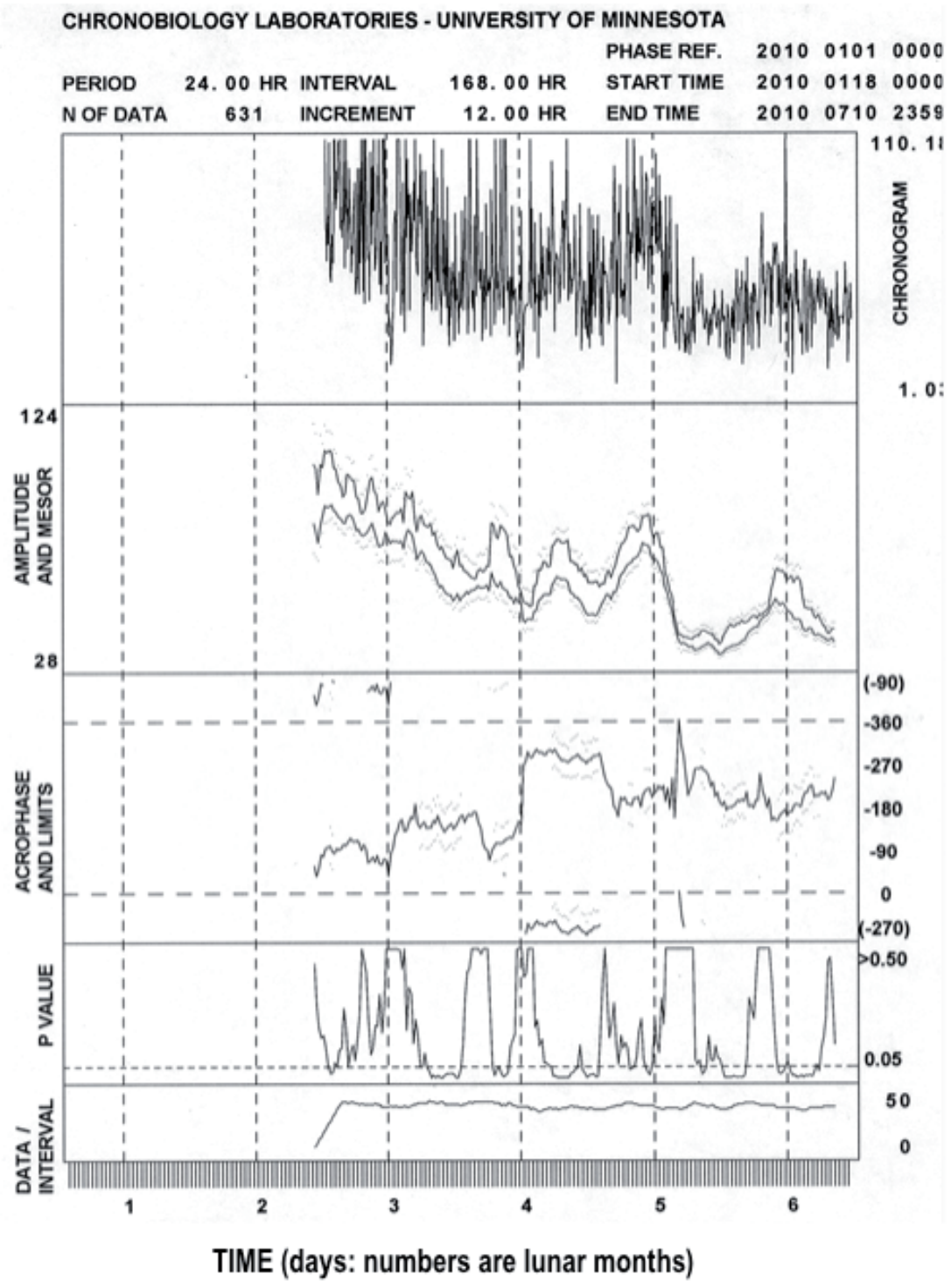

Figure 9. For the case of aldosterone, with intervals of 1 week used for analysis, phase jumps are more clearly apparent from cycles 3 to 4 and from 4 to 5. © Halberg.

Figure 10: JF cortisol (interval lengthened to 1 week)

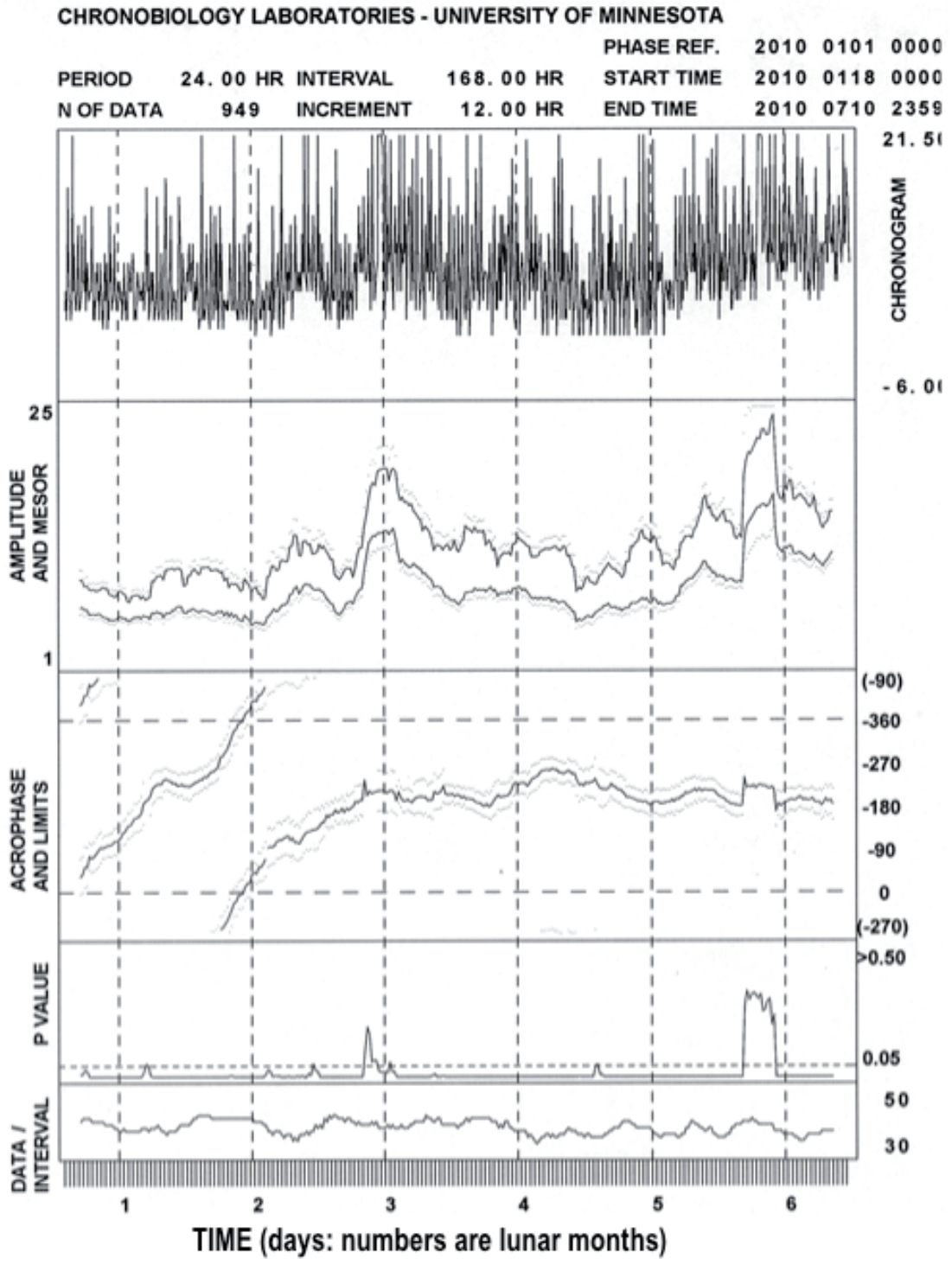

Figure 10. Lengthening the interval for analysis also provides statistical significance at or below the 1% level for dysfrequentia revealed by the time course of salivary cortisol. © Halberg.

Figure 11: JF: aldosterone (interval lengthened to 2 weeks)

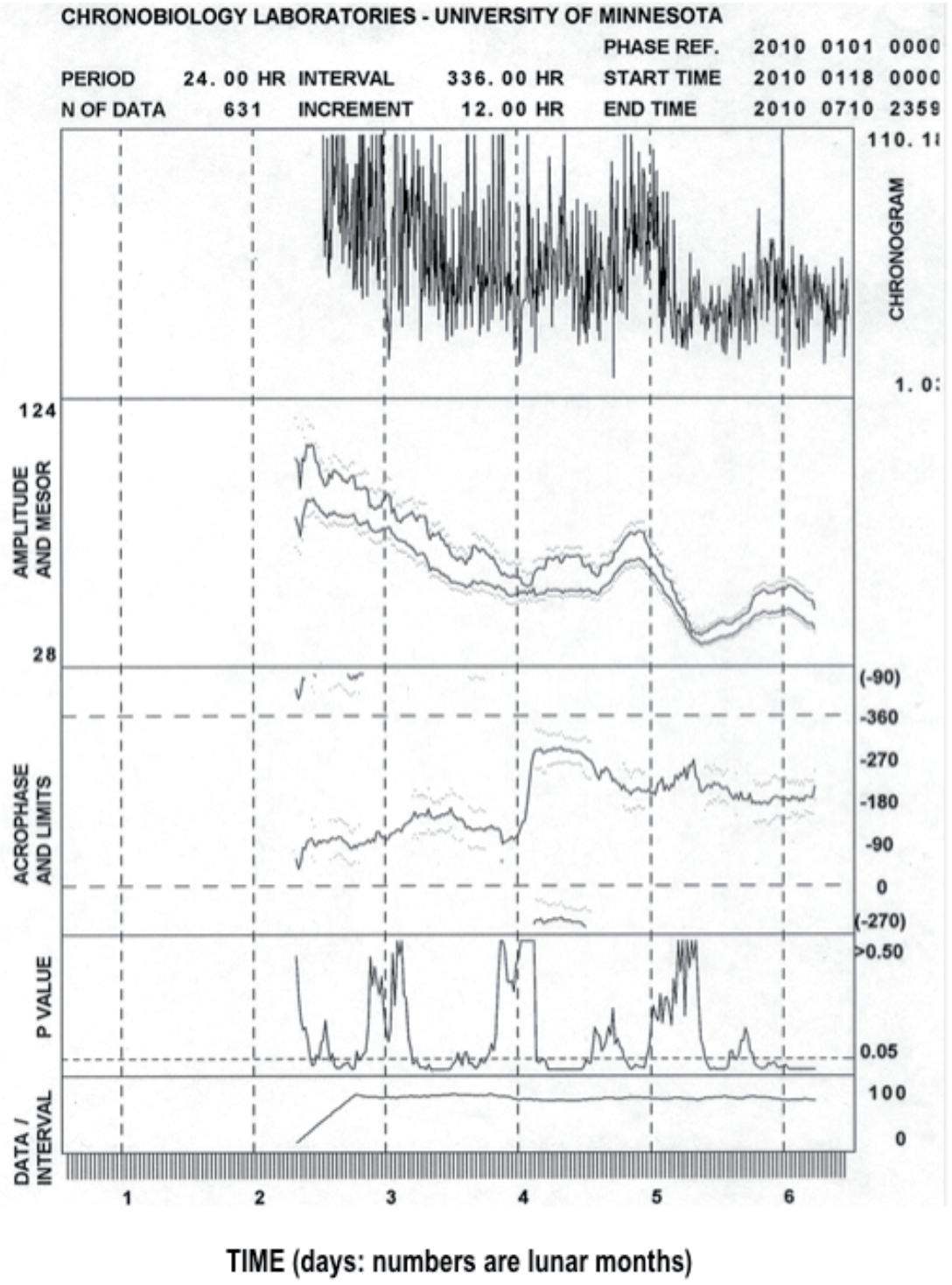

Figure 11. Lengthening the interval to two weeks smooths the record further, but changes one of the phase jumps into a shift for salivary aldosterone. Smoothing beyond a desideratum may obscure details. © Halberg.

THE MOON'S AND THE GENES' TIDES AND DOUBLE TIDES PULLING THE BIOSPHERE

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Abstract.

The average period of the principal lunar (M2) semidiurnal constituent of the tide is 12.42 hours (h); accordingly the lunar day is 24.84 h. While time series analyses have been carried out on data notably from intertidal organisms, the results are usually point estimates at best. We herein present tidal or double tidal periods with their CIs (95% confidence intervals) in an archaeon (a primeval unicell microorganism) and in humans. We found a 24.8-h period in the longest time series available to us for a human under conditions of isolation from society comfortably in an Underlab for 267 consecutive days. Apart from the documented molecular basis of circadian rhythms, and a possibly also built-in circatidal cyclicity, it seems likely that perhaps through gravity-triggered telluric currents that reach the earth-air interface, the moon also exerts a pull detectable as periods longer than 24 h, not only in caves and isolation chambers, but also in particularly magneto-seleno-sensitive persons.

Physiological variables undergo changes with periods, τ, of a day and half a day. In blood eosinophil cell counts or core temperature of certain strains of mice, the intrinsic τ is usually shorter than 24 h, on the average by about 30 minutes, as found originally after blinding (1). In contrast, the human τ is usually longer than 24 h. A partly built-in τ that differed from precisely 24 h led to the coining of "circadian" (2). The analogy of a free-running oscillator, provided by Earl E. Bakken (3) of the implantable cardiac pacemaker fame, served to emphasize partial endogenicity. Periods found under conditions of isolation from the 24-h schedule of society in individual (4-6) or grouped (7) human beings in caves or bunkers (8), usually longer than 24 h, also have been called "free-running". In 135 subjects studied by Rütger Wever in two underground isolation chambers (i.e., "the Bunker") in Germany under conditions described as constant (i.e., continuous overhead lighting, stable room temperature, soundproof, total absence of time cues from the outside environment), the mean "free-running" τ was reported as 25.0 ± 0.5 h and the median free-running τ was 24.73 h with a 95% range of 24.85 to 25.01 h and a 99% range of 24.82 and 25.04 h. Some free-running periods in some subgroups were precisely 24.8 h, but most had longer τs. In some cases, τs were shorter than 24 h and changed during isolation (8). As a young man, one of us (RBS) experienced free-running first-hand during isolation for 19 days in the bunker mentioned above, with a body temperature rhythm estimated at τ = 25.0 h (9).

A τ of 24.8 h reported by Miles et al. (10) in a blind subject "could not be significantly distinguished from the period of the lunar day (24.84 hours)". Furthermore, throughout the ad-lib phase of ths sleep study, there was a remarkable coincidence between his sleep onset and a local tide. Miles et al. (10) deserve credit for studying the patterns along the 24-h scale of serum cortisol throughout days 12, 17, 22, 28 and 35 (during the ad-lib phase of their sleep study) and on day 78, the last day of their entrainment study. These strategically placed samplings allowed them to indirectly suggest a free-run

of cortisol, since the rhythm was apparent to the naked eye in data stacked along a scale of 24.9 h, but not along the scale of 24.0 h. Miles et al. (10) align their case with our interpretation (4) of data on late blind subjects by Remler (11), and a meta-analyzed case by Bryson and Martin (12) as features of adrenocortical desynchronization, also noted by Orth et al. (13) in a blind subject.

The desynchronization from society can be established by CIs (95% confidence intervals) of the τ that do not overlap precisely 24.0 h (1-6). In human data, as a rule a 24-h synchronized component and a precise 12-h component dominate the spectrum (Figure 1) with the 12-h component, apart from being a descriptor of any nonsinusoidality in the waveform, possibly constituting a component in its own right, gauging, for instance, the slow adjustment during transmeridian travel by ship (14,15). Biological evidence for spectral components approximating lunar periodicities exists especially in marine organisms that appear to track the 12.42-h period of the principal lunar (M2) semidiurnal constituent of the ocean tide.

Under presumably aquatically tideless laboratory conditions, a tidal τ of 12.47 h with a CI extending from 12.46 to 12.48 h, not covering 12.0 h, characterizes an intertidal fiddler crab's *(Uca minax)* locomotor activity (Figures 2A and B and Table 1) (16). Miroslav Mikulecky, professor of medicine at Bratislava, deserves credit for a series of monographs on human beings affected by their cosmos (17-19), including a special volume on the moon (17), skeptics (20) notwithstanding. “Earth tides” have also been documented with periodicities similar to ocean tides, as a result of the effects of gravitational and centrifugal forces that change with the movements of the Earth and moon, and thus may also contribute to and/or help to synchronize lunar periodicities observed in various life forms (cf. 21).

The controversy as well as skepticism concerning lunar associations with human physiology, reviewed in (20), is reminiscent of 1950, when the senior author’s (FH) coining of “circadian” for the then diurnal variations was called paranoia (1). It seems thus pertinent that a tidal τ has been noted by our meta-chrono-analysis of data on an archaeon (22) (Figure 3), along with a free-running circadian τ of about 21.0 h, very close to that first demonstrated as an average for the bacterium *E. coli* (23), but found to change as a function of time (Figures 4A and 4B) (24, 25), as perhaps did the archaeon’s time structure. It seems pertinent that 440 million years ago, the length of the day was estimated to be 21.5 h, estimated by rings secreted daily by corals. “The width of the rings ... depends on the amount of sunlight received, which in turn depends on the season of the year. The fossils show that there were ... 407 days per year 440 million years ago” (26). As background information, due to the gravitational effect of the moon since its formation when the Earth was only about 50 million years old, the Earth’s day length has been slowly becoming longer, from an estimated 6.0 h and 1461 days/yr 4.5 billion years ago (bya), to 13.5 h and 649 days/yr 4.0 bya (the Archeon Eon is estimated to have begun about 3.465 bya), to 23.5 h and 373 days/yr 100 million years ago (during the age of the dinosaurs), to today’s 24.0 h and 365.25 days/yr (see Essay 2.2 and Tables 2.5 and 3.5 in 27, 28).

The average circadian τ was 24.79 h in juvenile crayfish (29). A 24.8-h τ has also been recorded in the telemetered core temperature of rats kept in continuous light of low intensity (30) in the presence (Figure 5A), but not in the absence of the suprachiasmatic nuclei (SCN) (Figure 5B) (31). Any effect of the moon's gravity stressing and inducing telluric currents in the Earth's crust as stress-activated positive holes (defect electrons in the oxygen anion sublattice, equivalent to O^- in a matrix of O^{2-}) that are dormant electronic charge carriers as peroxy links where two O^- are tightly bound together (32, 33) or piezoelectrically (34) that reach the earth-atmosphere boundary may be mediated by the SCN.

As to humans, tidal and double tidal τs, with their uncertainties not overlapping 12.0 h, have not been noted repeatedly by us, i.e., not (yet) in any consecutive two intervals of 270 about 1-week long sections of human blood pressure or heart rate series of a clinically healthy 54-60 year old woman (Figure 6) (35), or in other time series obtained in a project on The Biosphere and the Cosmos

(BIOCOS) or in the literature available to us. When found coexisting with a 24.0-h peak in the spectral window of a man's half-hourly systolic blood pressure, before an episode of delayed sleep phase syndrome (DSPS), a small component of 24.7 h in Figure 7 is overshadowed by the 24-h synchronized circadian component (36).

Figures 8A and B, concerning JF, a 61-62-year-old woman (35), are hence the more noteworthy for their dominant ~24.8-h components. They are each based on one month of around-the-clock data, except for urine volume involving 3 weeks of sampling at spontaneous voidings; blood pressure and heart rate were measured automatically at 60min intervals by an ambulatory monitor from Spacelabs (provided by Jon Clark of that company); and more densely, activity was monitored on the wrist with Actiwatches from Respironics by JF during the initial month of the third investigated episode of adynamia. This condition, to the point of occasional inability to get out of bed and unwellness, had recurred half-yearly over the previous 20 years (Table 2) (35). By linear-nonlinear extended cosinor analysis (37-39), heart rate, urine volume and activity had two circadian and two circasemidian spectral components, with the major circadian components having CIs overlapping the double tidal τ or adjacent to it and the circasemidian τ's CI adjacent to or overlapping 12.4 h in Figure 8A. Systolic and diastolic blood pressure had no tidal τ and a single circadian peak, again with the CI of the τ covering 24.8 h but not 24.0 h, where the amplitude estimate showed a valley (Figure 8B). There was no circadian peak in estimates of vigor in a summer episode in 2010, which was milder than previous ones, while in the first month of two previous episodes there were estimates of 24.8 h, found nonlinearly and demonstrated by an oblique delaying time course of acrophases (Figure 9). There is also a 24.8-h τ in one of two week-long profiles of diastolic blood pressure of 4-year old LT, JF's granddaughter (Table 3). JF, FT (JF's daughter and LT's mother) and LT's behavior all suggested that they are selenosensitive.

Figure 10 shows that the longest study of comfortable human isolation in a cave for over 260 days also had the 24.8-h indication of the moon as the dominant spectral component, which was opposite to the amplitudes of prominence of the 24-h component in Figure 7 and in keeping with Figure 8. Desynchronization, if not free-running from societal 24-h schedules with τs longer than 24 h but shorter than 24.8 h, may imply lunar pull, as seen during prolonged isolation in a cave (4: Table 4; cf. 4-7, 40-44), as do JF's periods during the second episode investigated (Table 5) (35). τs with CIs overlapping 24.8 h indicate seleno- (lunar) synchronization, while intermediate periods may indicate lunar pull. Some τs slightly longer than 24.8 h or shorter than 24.0 h could be transients. An average period slightly longer or shorter than 24.8 h could be built-in by the same tides to which life has been exposed since its origin. Answers are certainly required as to the mechanisms underlying de-, re-, rede- and re-resynchronization with our 24-h society, and why these recur with a half-yearly periodicity in JF, notably when desynchronization from 24 h during life in society (Figure 11) is accompanied by extreme fatigue, as in JF. Methodologically, it seems particularly relevant that in the case of changes in τ, multiple τs characterize spectral windows in different spans which, when analyzed separately, reveal just one circadian τ. A consistently "glocal" analysis of time series as a whole (globally) and in sections (locally) is indicated (Table 6) and helps to avoid artifacts (Figures 12 and 13).

Insofar as blood circulation is concerned, an altered period (or frequency), i.e., ecfrequentia is a vascular variability anomaly (VVA) that can become a vascular variability disorder (VVD) in its own right. As postulated with meta-analyses of available data by 1968 (4) and subsequently investigated by Kripke et al. (45), Emens et al. (46) and others cited herein, dysfrequentia was eventually documented with >5100 ELISAs pointing to the hypothalamic-pineal-pituitary-adrenal network, with circadian acrophases of cortisol, DHEA, melatonin and sex steroids scanning obliquely (delaying) more than the entire 24-h scale during desynchronization associated with an adynamic episode. The endocrine acrophases change to a horizontal time course after resynchronization (Figure 11).

Take-home message

~24.8-h and ~12.4-h periods are in keeping with a genetically-anchored resonance of living matter with earth-air and moon, as well as sea tides, among other critical periodicities of our solar system and from beyond it. A lunar pull may also act when periods happen to be intermediate between 24.0 h and 24.8 h. Two round (not flat), moving (not fixed) and heterogeneous magnets -- sun and earth with its moon -- interact, as seen along an evolutionary scale from an archaeon to a healthy person in isolation from society for 267 days and in a number of dominant 24.8-h periods in a selenosensitive grandmother and her granddaughter. The pull of the moon in a magneto-sensitive person may lead to an alteration of period (ecfrequentia) that may become a vascular variability disorder (dysfrequentia) associated with the circulation, cortisol and other endocrines all getting out of sync with society and, with an accompanying loss of vigor, a half-yearly recurring adynamia lasting 2-3 months. The alternative of purely endogenous free-running is "simpler", perhaps only in the sense of making things as simple as possible but not simpler, as phrased by Einstein (47) "*... the supreme goal of all theory is to make the irreducible basic elements as simple and as few as possible without having to surrender the adequate representation of a single datum of experience.*" The tidal and double tidal periods each are such data of experience.

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Table 1: Rhythm characteristics and their 95% confidence intervals (CI) for locomotor activity of a female crab *(Uca minax)* from Buzzards Bay, MA

Component	Period (in hours) (CI)	Amplitude (of „activity“ hour) (CI)
1	12.47 (12.46, 12.48)	1.46 (1.10, 1.83)
2	24.05 (23.95, 24.15)	0.59 (0.22, 0.95)
3*	25.94 (25.79, 26.09)	0.44 (0.07, 0.81)

*Beat frequency of components 1 and 2 is 25.40 h; 25.95 h is the beat between component 1 and a period of 24.00-h length.

Table 2: Recorded recurrent adynamia (A), overall self-rated vigor spectrum (B), lunar-cycle-related summaries (C) and endocrines during part of an adynamic episode (D)*

A. Start-end dates, lunar phase (f: date of full moon; n: date of new moon) and length (weeks) of spans of adynamia when recorded in winter (W) and summer (S)

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

*90 and 95% prediction intervals in 2010, computed from dates listed, are May 26-June 10 (90% PI) and May 22-June 29 (95% PI), respectively.

Table 3: Familial selenosensitivity in JF's family is supported by the moon's 24.8-hour image in circadian aspects of the circulation of a 3-year-old in the diastolic blood pressure on one of 3 spans (of hourly around-the-clock measurements for ~15, ~9 and ~7 days) investigated#

Variable (unit)	Period (hours) (CI*)	Double amplitude, 2A (CI)
2009: 08/03 - 08/18		
Diastolic blood pressure (mm Hg)	24.85 (24.04, 25.66)	13.50 (6.00, 21.09)
Systolic blood pressure (mm Hg)	24.40 (23.30, 25.51)	14.39 (2.77, 26.01)
Heart rate (beats/min)	24.20 (23.14, 24.67)	27.92 (18.08, 32.74)
2010: 05/07 - 05/16		
Diastolic blood pressure (mm Hg)	23.99 (23.34, 24.64)	14.07 (7.94, 20.19)
Systolic blood pressure (mm Hg)	23.85 (23.19, 24.51)	17.94 (9.92, 25.96)
Heart rate (beats/min)	23.88 (23.57, 24.20)	30.19 (23.71, 36.67)
2010: 07/26 - 08/02		
Diastolic blood pressure (mm Hg)	23.67 (21.89, 25.44)	4.20 (0.18, 8.21)
Systolic blood pressure (mm Hg)	23.94 (22.96, 24.93)	10.86 (5.57, 16.14)
Heart rate (beats/min)	24.01 (23.44, 24.58)	17.38 (12.63, 22.13)

*95% confidence interval

#Lunar period in diastolic blood pressure with no overlap of the 24-h period on one of three occasions investigated seems noteworthy in that LT was observed to be unusually energetic, talkative and somewhat resistant to parental guidance at new moons. The incidence rate of a point estimate corresponding to the double tidal period of 24.8 h was less than 1% of 270 ~7/24 records of DBP of a 54-60-year-old woman and was also low in hundreds of 7/24 records obtained half-hourly around the clock in Urausu, Japan.

Table 4: Free-running or pulled circadian cardiovascular and thermal rhythms in social isolation for >90 days*

Parameter		MESOR	Period (τ)	Amplitude
System	Variable	95% confidence limits		
Cardiovascular	SBP	102.5 (101.6, 103.4)	24.57 (24.53, 24.60)	2.8 (1.6, 4.2)
	MAP	78.5 (77.7, 79.2)	24.60 (24.59, 24.61)	2.4 (1.3, 3.5)
	DBP	61.7 (61.0, 62.2)	24.56 (24.49, 24.62)	1.3 (0.5, 2.2)
	HR	60.6 (59.3, 61.7)	24.59 (24.56, 24.60)	6.9 (5.3, 8.7)
Thermal	Sub	36.65 (36.58, 36.72)	24.56 (24.53, 24.59)	0.22 (0.14, 0.33)
	Axi	36.16 (36.10, 36.22)	24.60 (24.57, 24.62)	0.22 (0.13, 0.31)

*27-year-old woman. SBP: systolic blood pressure; MAP: mean arterial pressure; DBP: diastolic blood pressure (all in mm Hg); HR: heart rate (beats/min). Sub: sublingual and Axi: axillary temperature (˚C). Data analyzed by linear-nonlinear least squares rhythmometry. Period given in hours. The number of hourly means analyzed was 1632 for SBP, 1634 for MAP, 1635 for DBP and 1747 for HR; the corresponding total number of 26,403 original values stems from 6363 for SBP; 6295 for MAP; 6298 for DBP; 6777 for HR; and 335 for each Sub and Axi temperature. From ref. 5.

Table 5: Societal (24-h) and lunar asynchronization of circadian blood pressure (BP), heart rate (HR) and adrenocortical function (with possible lunar pull*), and lunar synchronization of vigor of JF during 41 days (of a longer span) of adynamia and unwellness for which cortisol data are available (N: 236; 2010/01/18-2010/03/01)

Variable (unit)	Period, τ_1 (CI) (hours)	Amplitude, A_1 (95% CI)	τ_2 (days)	A_2	A_2/A_1
Vigor/wellness rating*	24.71 (24.10, 25.32)	**2.01 (0.00, 5.66)**	16.21	12.60 (8.98, 16.23)	**6.27**
Systolic BP† (mm Hg)	24.55 (24.44, 24.66)	10.83 (7.21, 14.45)	15.77	5.18 (1.43, 8.94)	0.48
Diastolic BP† (mm Hg)	24.63 (24.50, 24.77)	6.07 (3.63, 8.50)	14.06	**2.05 (0.38, 4.47)**	0.34
Heart rate† (beats/min)	24.36 (24.24, 24.49)	4.08 (2.52, 5.65)	18.41	3.45 (1.82, 5.09)	0.85
Cortisol (nmol/L)	24.57 (24.44, 24.70)	2.97 (1.82, 4.12)	14.73	**0.23 (0.00, 1.35)**	0.08
DHEA (ng/ml)	24.56 (24.46, 24.67)	3.21 (1.18, 5.25)	7.48	**0.73 (0.09, 1.36)**	0.23

*Note that only vigor‘s CI overlaps 24.84 h, the double tidal τ, which τ was found in an analysis (wherein the period was allowed to vary as a parameter) of the first two of JF's investigated adynamic episodes.

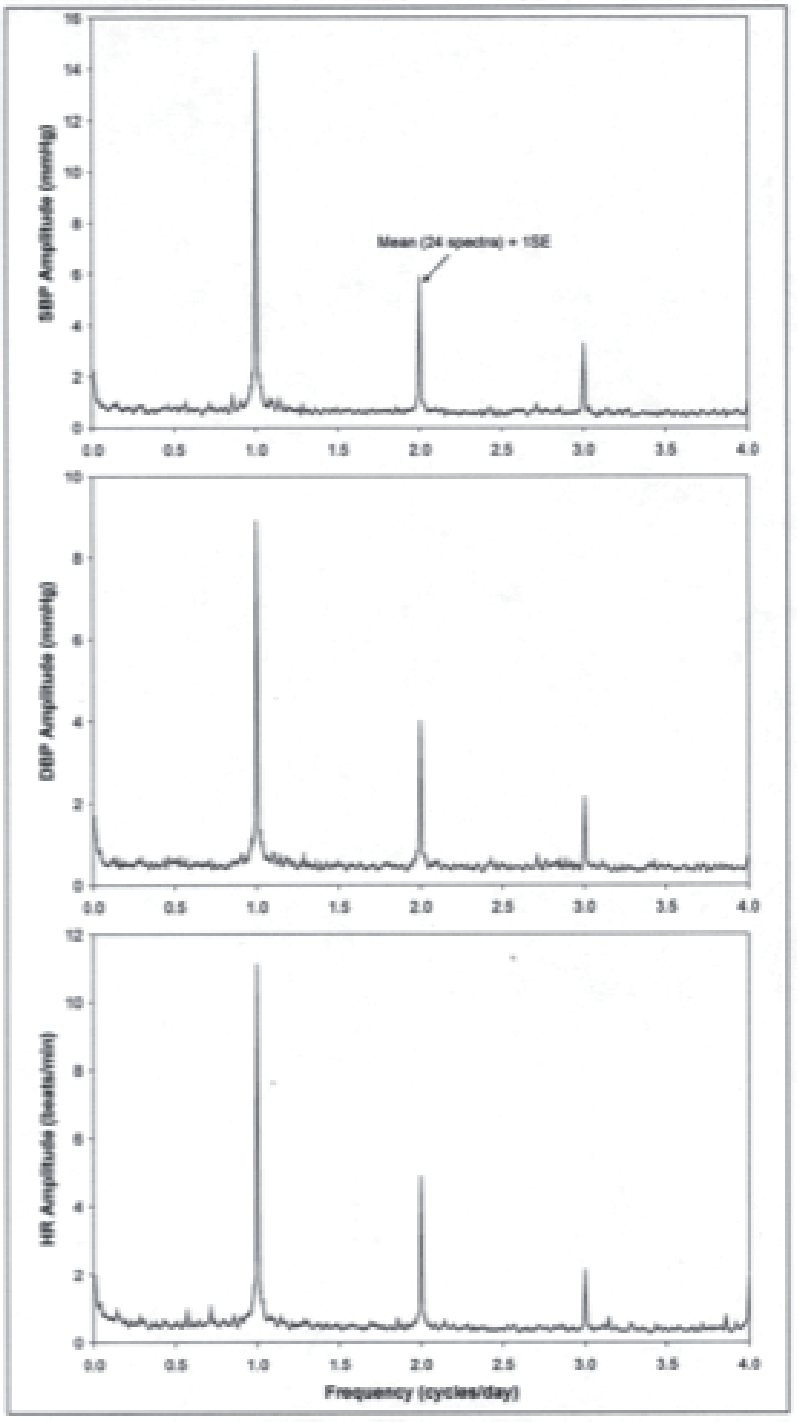
Table 6: Two distinct neighboring spectral components of JF's hormones may indicate a change in the period of just one*

Analysis	Cortisol		DHEA	
	Period	Amplitude	Period	Amplitude
Whole series	24.05 (23.95, 24.14)	2.29 (1.71, 2.87)	24.04 (23.97, 24.12)	0.97 (0.38, 1.55)
	24.66 (24.55, 24.76)	2.06 (1.40, 3.72)	24.60 (24.52, 24.68)	1.02 (0.43, 1.61)
Part 1	24.69 (24.52, 24.86)	2.89 (0.65, 5.12)	24.62 (24.47, 24.77)	1.69 (0.75, 2.63)
	—	—	25.43** (25.13, 25.72)	0.96 (0.03, 1.89)
Part 2	12.02 (11.97, 12.07)	2.58 (0.48, 4.67)	12.04 (11.99, 12.09)	0.59 (0.13, 1.05)
	24.08 (23.96, 24.19)	4.54 (2.51, 6.57)	24.10 (24.02, 24.18)	1.54 (1.08, 1.99)

*When a **glocal** analysis of a series dealing with salivary determinations of two adrenocortical hormones at 4-hour intervals around the clock covering 2 months was analyzed as a whole, it revealed, in each case, two circadian periods, τ, one τ_1 with the CI (95% confidence interval) of τ overlapping 24.0 h, the other τ_2 with a CI overlapping neither 24 h nor the CI of τ_1 as seen in the top row of the table for each cortisol and dehydroepiandrosterone, in a global analysis. Chronobiologic serial section then revealed first desynchronization with a longer than 24-h period, with an oblique time course of acrophases, ϕ, followed by 24-h synchronization with a horizontal sequence (not here shown), and delineated two different intervals of the time series for a local scrutiny. When the series were thus separated into two parts with the separation based on the change of the time course of ϕs in the serial sections and each part was analyzed separately, each of two endocrine data sets revealed only one or the other about 24-h circadian component (locally in time) rather than the 2 found globally (in the series as a whole).

**Probably another indication of a change in period that requires scrutiny in a serial section to find out whether separation needs to be done again, a task remaining, and if so where.

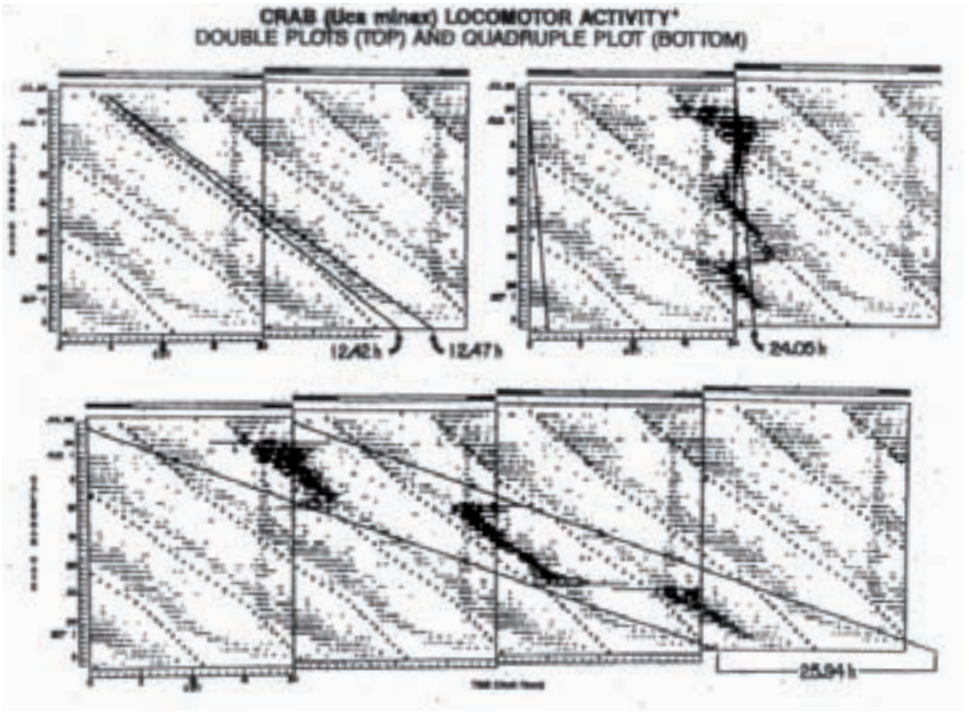
Average Least Squares Spectra of Systolic (S) and Diastolic (D) Blood Pressure (BP) and Heart Rate (HR) of GC (F, 54-60 years of age during 2004-2010) *



* Data collected around the clock, mostly at ~30-minute intervals (with short interruptions) with an ambulatory monitor (TM-2430) from A&D (Tokyo, Japan).

Figure 1. Prominent 24-h synchronized period and its harmonics in the circulation of GC, a clinically healthy woman 54-60 years of age, under conditions of life in society. © Halberg.

A



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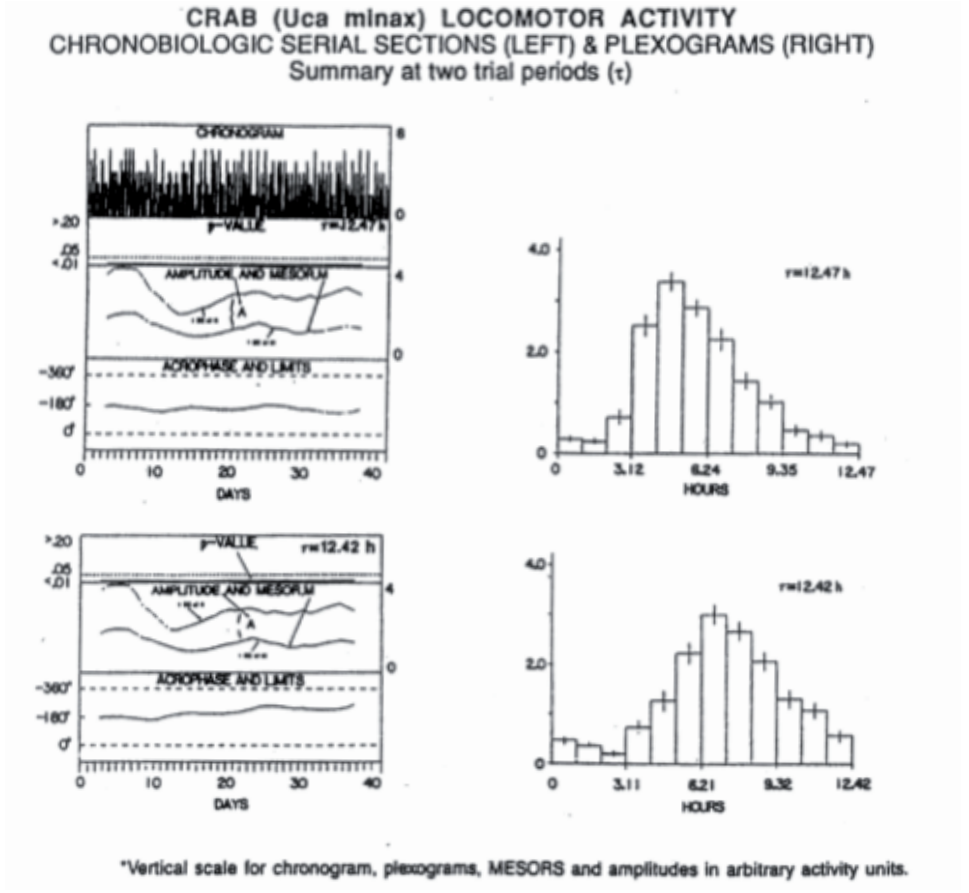


Figures 2A and B. Circatidal and circadian periods in *Uca minax,* an intertidal fiddler crab: original data (A) and acrophase charts from chronobiologic serial sections (B), showing a horizontal time course with the best-fitting period of 12.47 h. The time course of acrophases in the bottom chart is obliquely delaying in keeping with the assumption that the period is longer than that fitted. © Halberg.

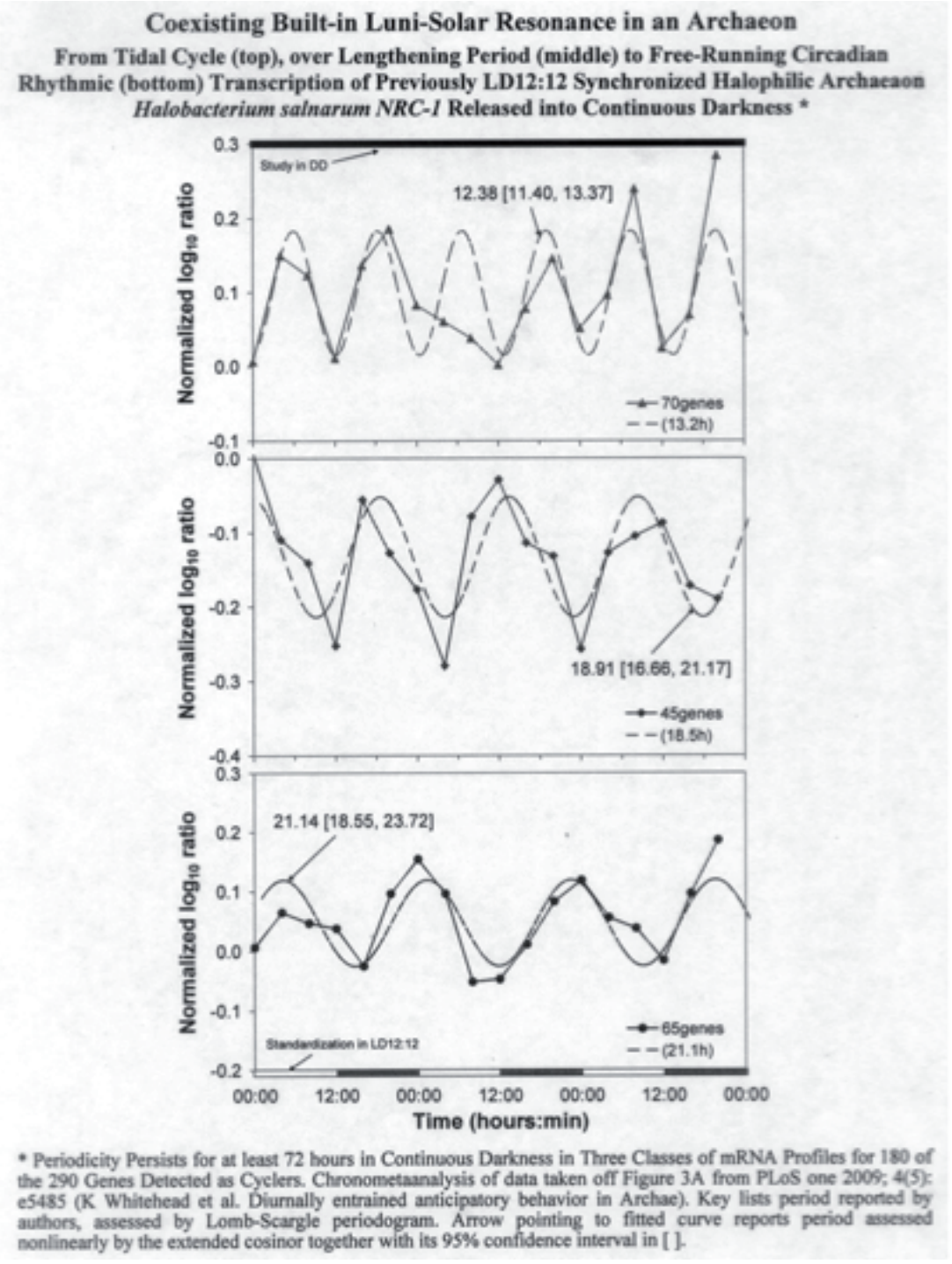


Figure 3. Earliest life may well be characterized by a lunar (tidal, top), lengthening (middle) and solar (circadian, bottom) average period, which in their turn must be analyzed for changes as a function of time when given appropriately long time series (see Figure 4B). © Halberg.

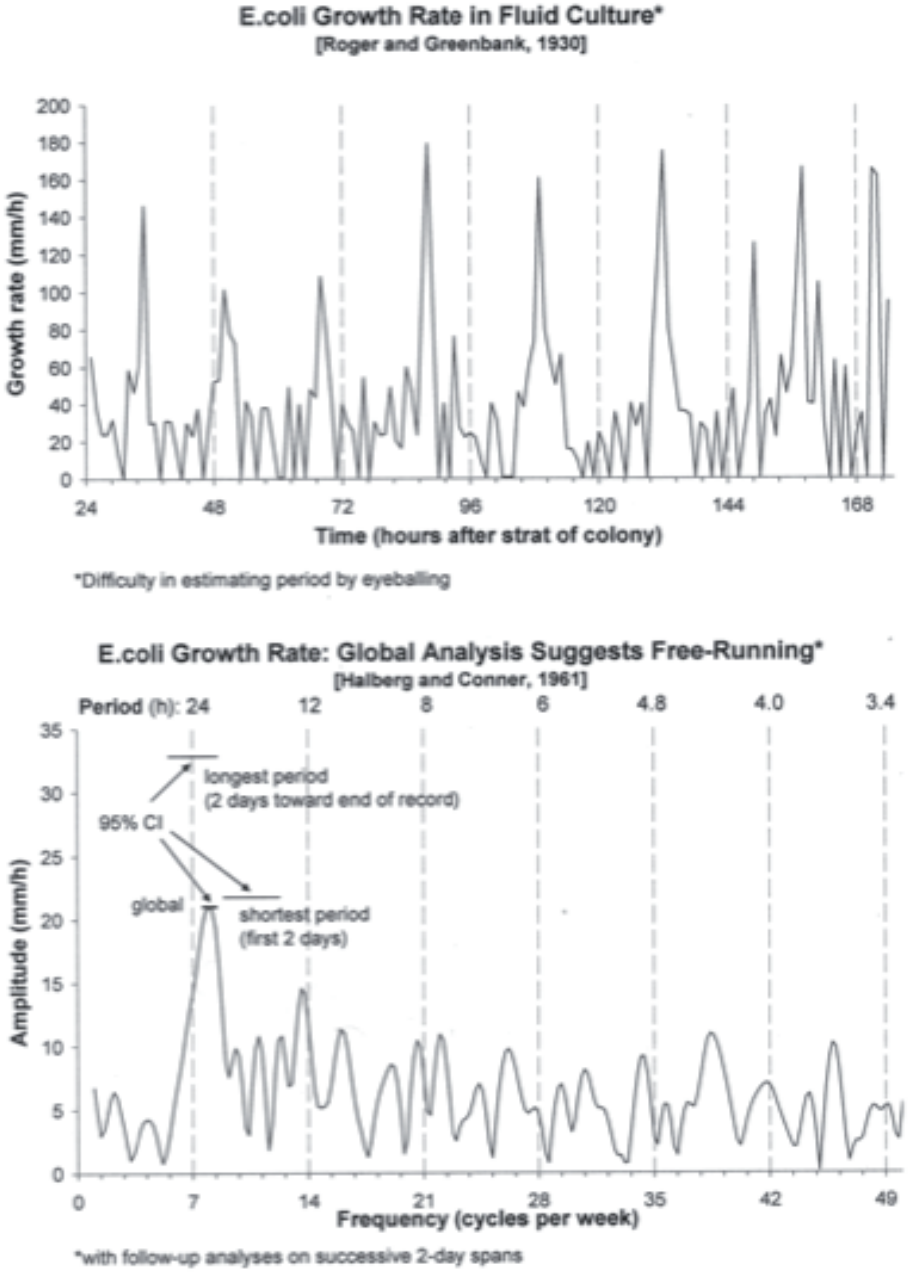


Figure 4A. Time plot of the 1930 data of Lore Alford Rogers and G.R. Greenbank, a noted bacteriologist described by a Cosmos Club (Washington, DC) Vignette of December 1967 as "the bright star in the [US Department of Agriculture] scientific horizon before World War II". In 1961, the data on growth rate (actually colony advance) of *E. coli* assessed at hourly intervals for slightly over 6 days were taken off the graph published by Rogers and Greenbank in 1930. Some regularity in the time series is apparent from the spikes in colony growth occurring at intervals shorter than 24 h, as seen by reference to the vertical dashed lines drawn at daily intervals, yet eyeballing can hardly serve for an estimate of a period and certainly forestalls any evaluation of uncertainties. Rogers and Greenbank wrote: "Fig. 1 [on top], which is representative of a number of experiments, shows that there is a considerable degree of periodicity to the alternation of rapid and slow growth." In considering this graph, it should be kept in mind that the curve represents not extent of growth, but rate of advance of growth for definite time periods. The number of bacteria in the different periods could not be determined. © Halberg.

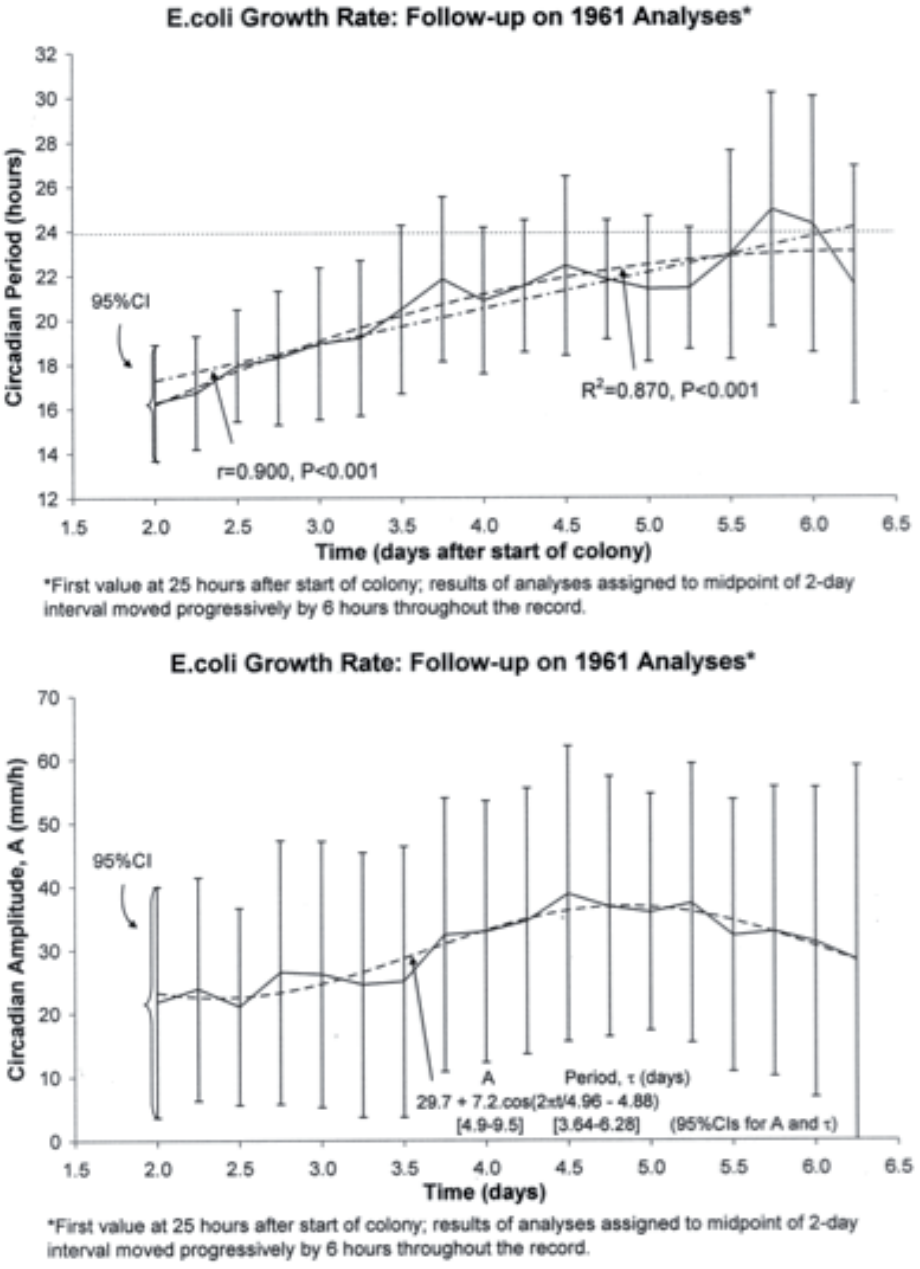
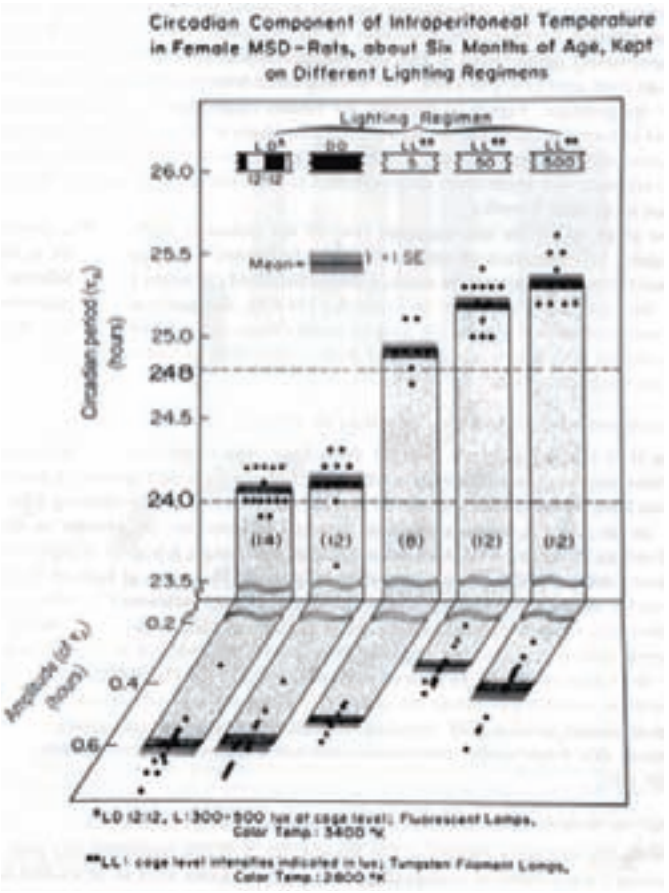


Figure 4B. Periods and corresponding 95% CIs characterizing the data shown in Fig. 4A are here estimated for intervals of 2 days progressively moved throughout the time series by 6 h. An interval of 2 days was selected to have at least one replication to secure a more reliable estimate of the period while also allowing the investigation of any change in period length with time. Separate, non-overlapping 1-day intervals analyzed similarly yield acceptable similar estimates. The period is seen to lengthen as a function of time. As a first approximation, the dash-dotted line is in keeping with a linear increase. This increase is only of about 18 h at the beginning of the series, but approaches 24 h by the end of the first week of monitoring. With the qualification that consecutive estimates are not independent, the lengthening of the period has an ordering $P < 0.001$ ($r = 0.90$). The fit of a second-order polynomial (solid line) suggests that the period levels off. In this model, the quadratic term significantly reduces the residual variance (ordering $P < 0.02$) beyond the linear term. The results could be interpreted as an originally free-running circadian component that may be pulled by (if not become synchronized with) the 24-h day. © Halberg.

A



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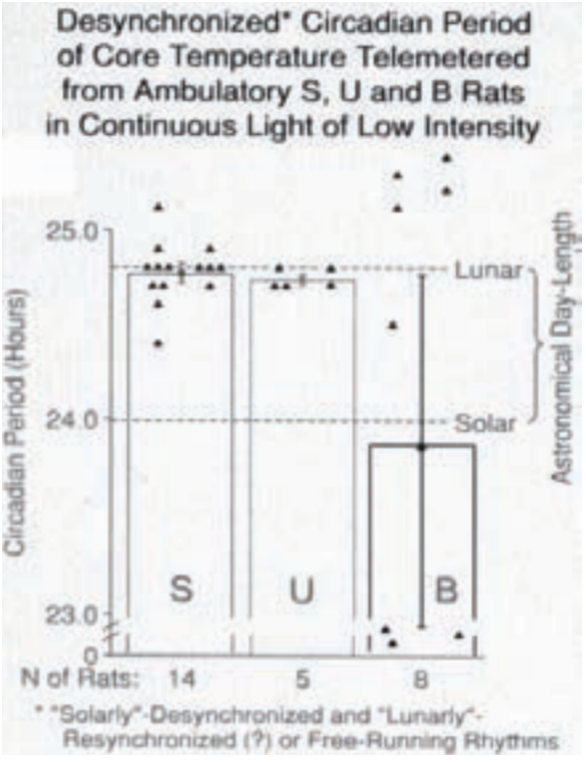


Figure 5A and B. The double tidal period of telemetered core temperature of rats kept in continuous light of low intensity in the presence (A) but not in the absence (B) of the suprachiasmatic nuclei. © Halberg.

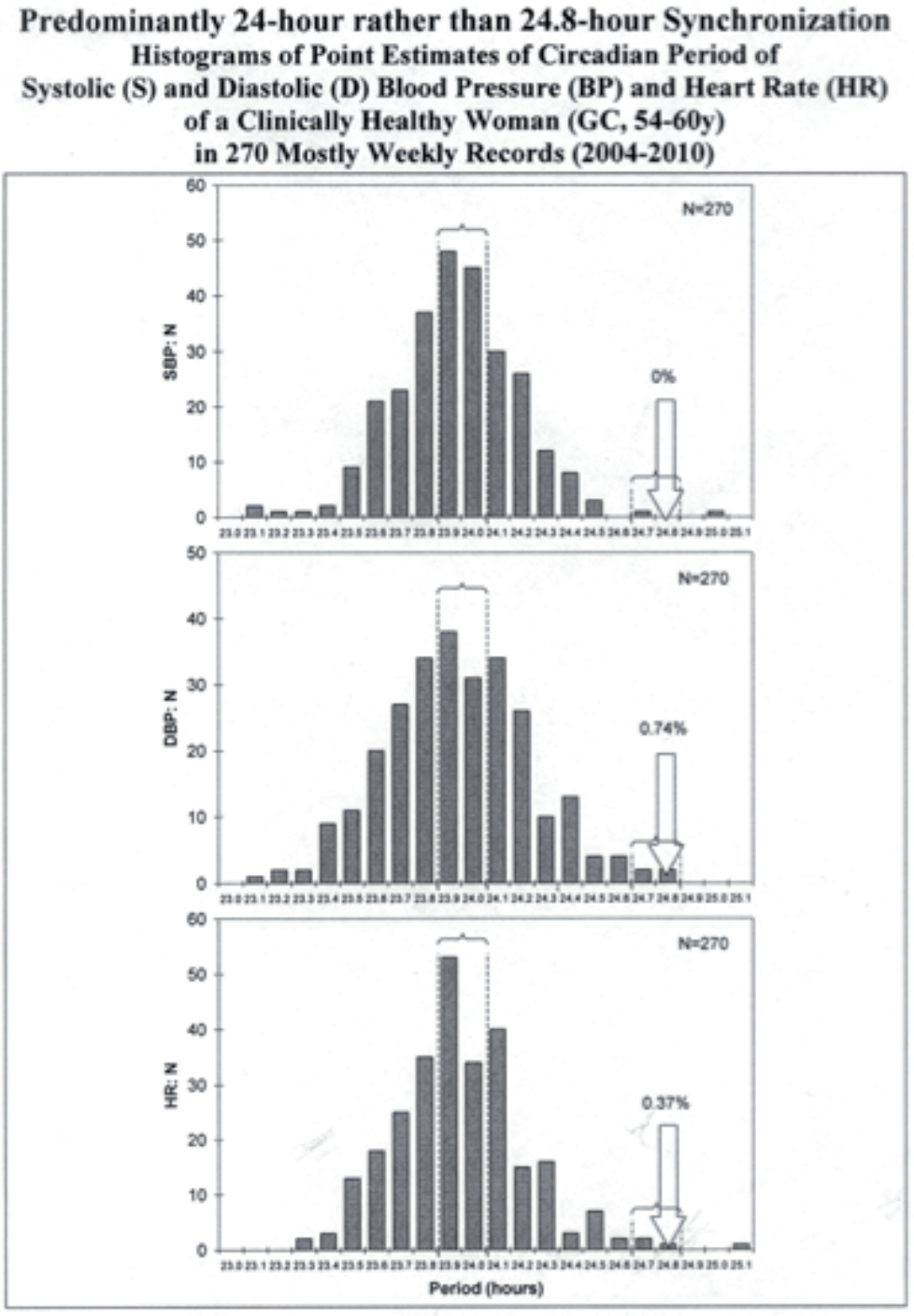


Figure 6. Periods encountered in mostly consecutive acceptable 270 ~7-day sections of vascular variables of GC, a clinically healthy woman. The incidence of a double tidal period varies from zero to less than 1% in the three variables investigated. © Halberg.

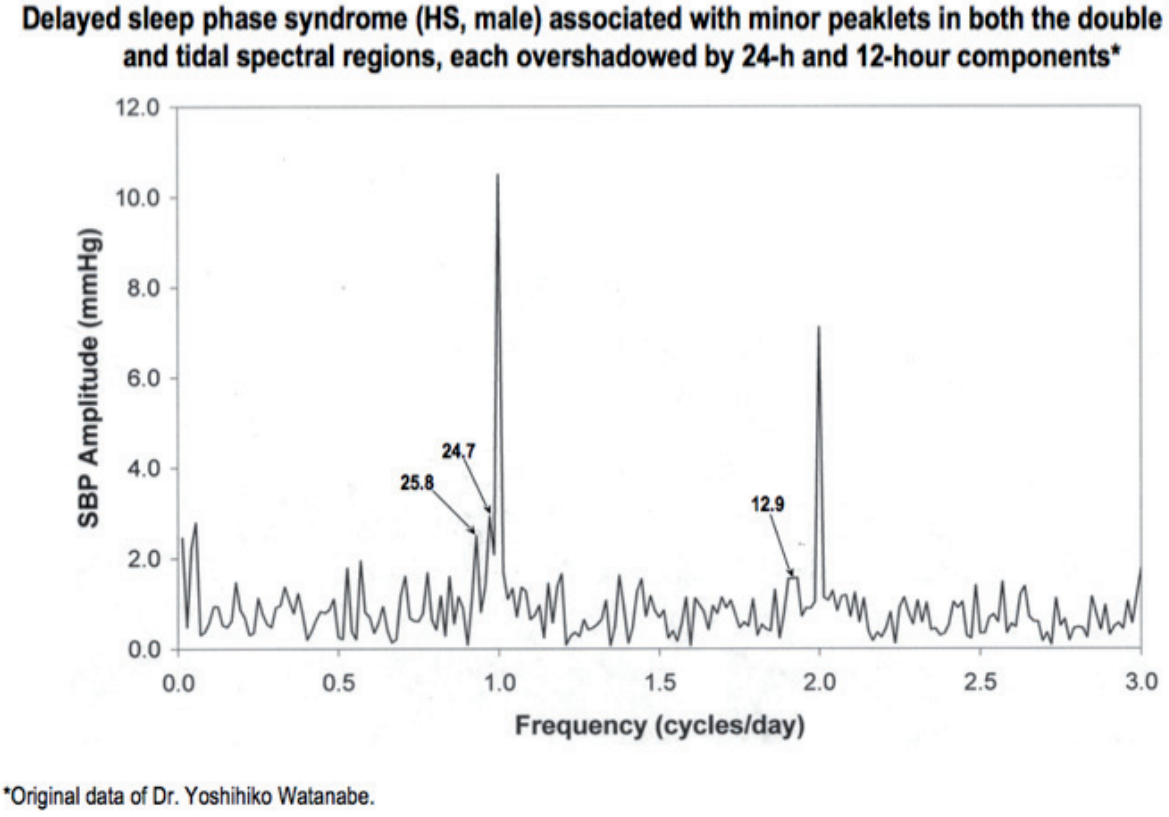
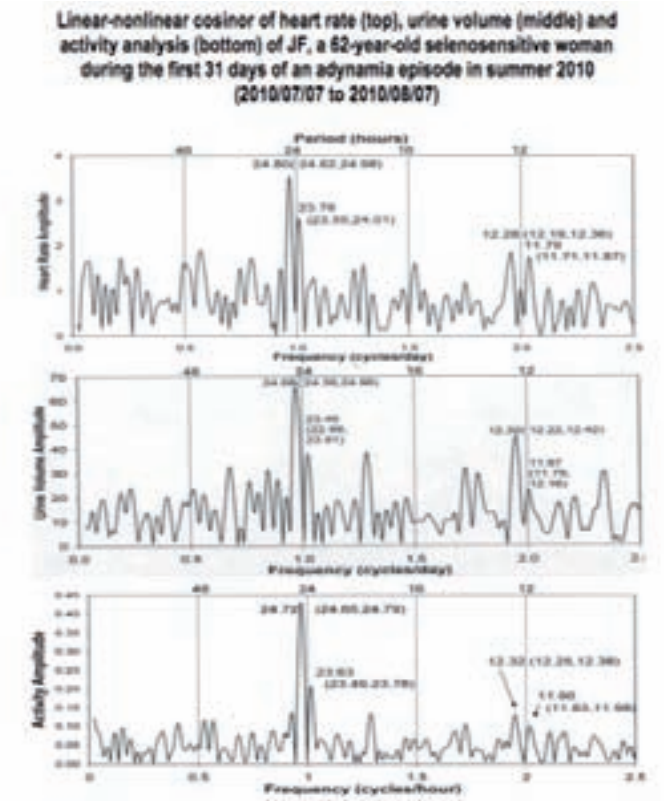
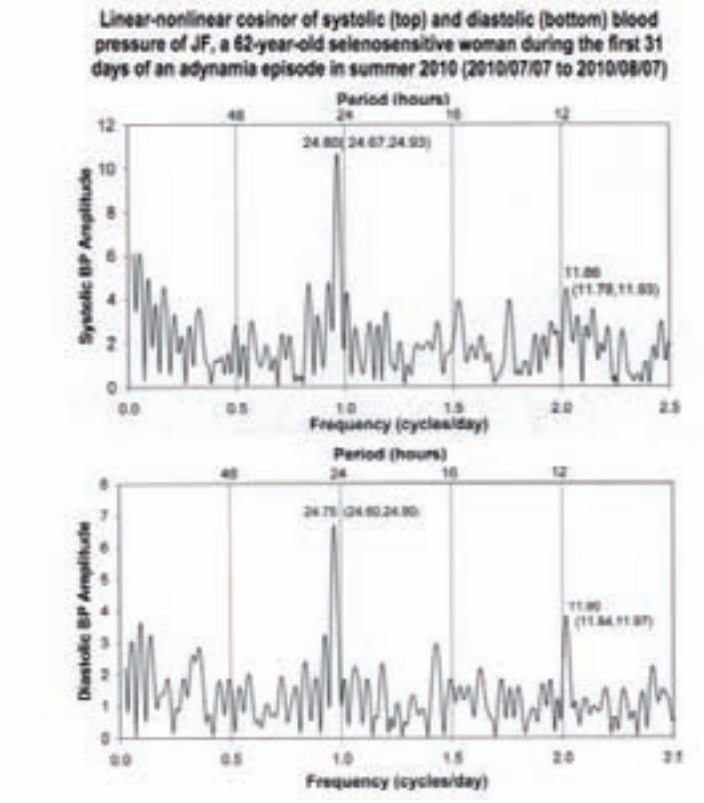


Figure 7. A 24.7-hour peaklet (encountered adjacent to a dominant 24-h synchronized circadian) and a 12.9-h peaklet (next to a dominant 12-h component) are minuscule in the spectrum of systolic blood pressure of a clinically healthy physician prior to an episode of delayed sleep phase syndrome (DSPS). © Halberg.





Figures 8A and B. Objective indications of the moon are mirrored in a case of a circadian and circasemidian dysfrequentia (circadian frequency desynchronization from the societal 24-h routine and possible lunar synchronization) of some of the variables investigated in a 62-year-old subjectively seleno-sensitive grandmother during the first month of an adynamic episode in the summer of 2010. © Halberg.

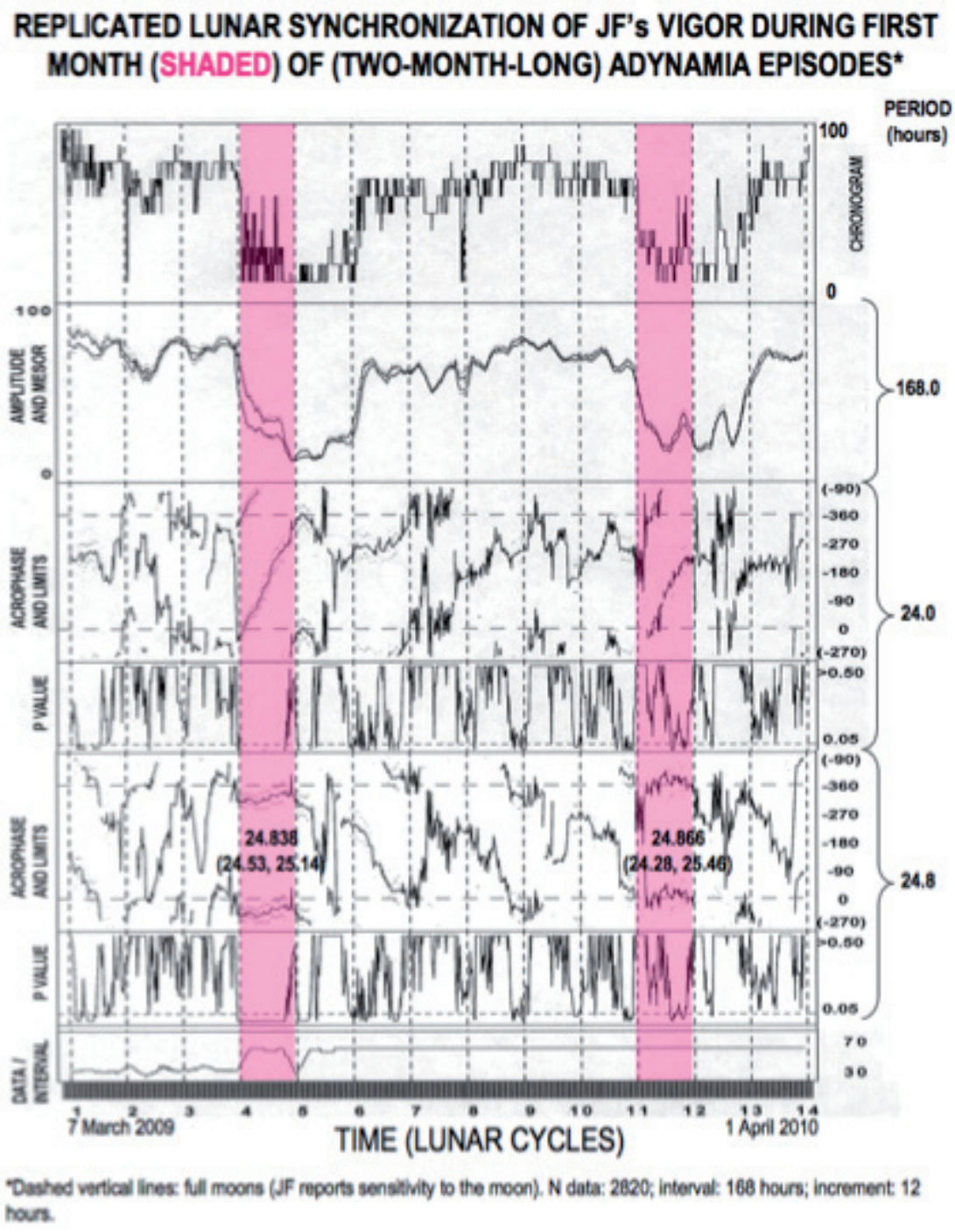


Figure 9. The double tidal period in self-ratings of vigor by the subject described in Figure 7 during the first month of two investigated summer and winter episodes, just preceding the summer episode in Figure 7. © Halberg.

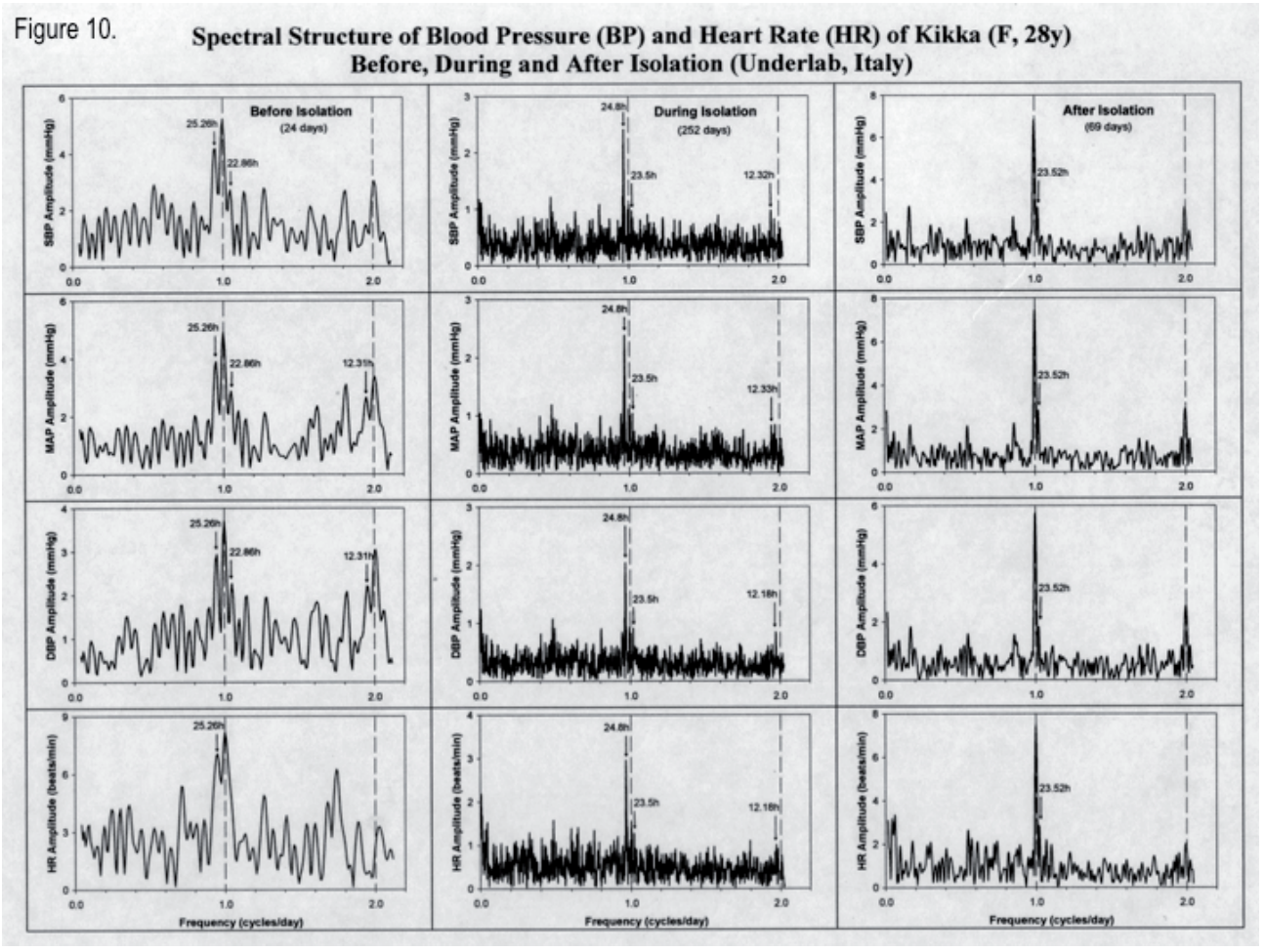


Figure 10. During the longest span of comfortable isolation from a 24-h schedule of a healthy young woman in a special underground laboratory, but not before or thereafter, a period of 24.8 h characterizes her blood circulation upon meta-analysis of original data as a whole and by serial sections (5). © Halberg.

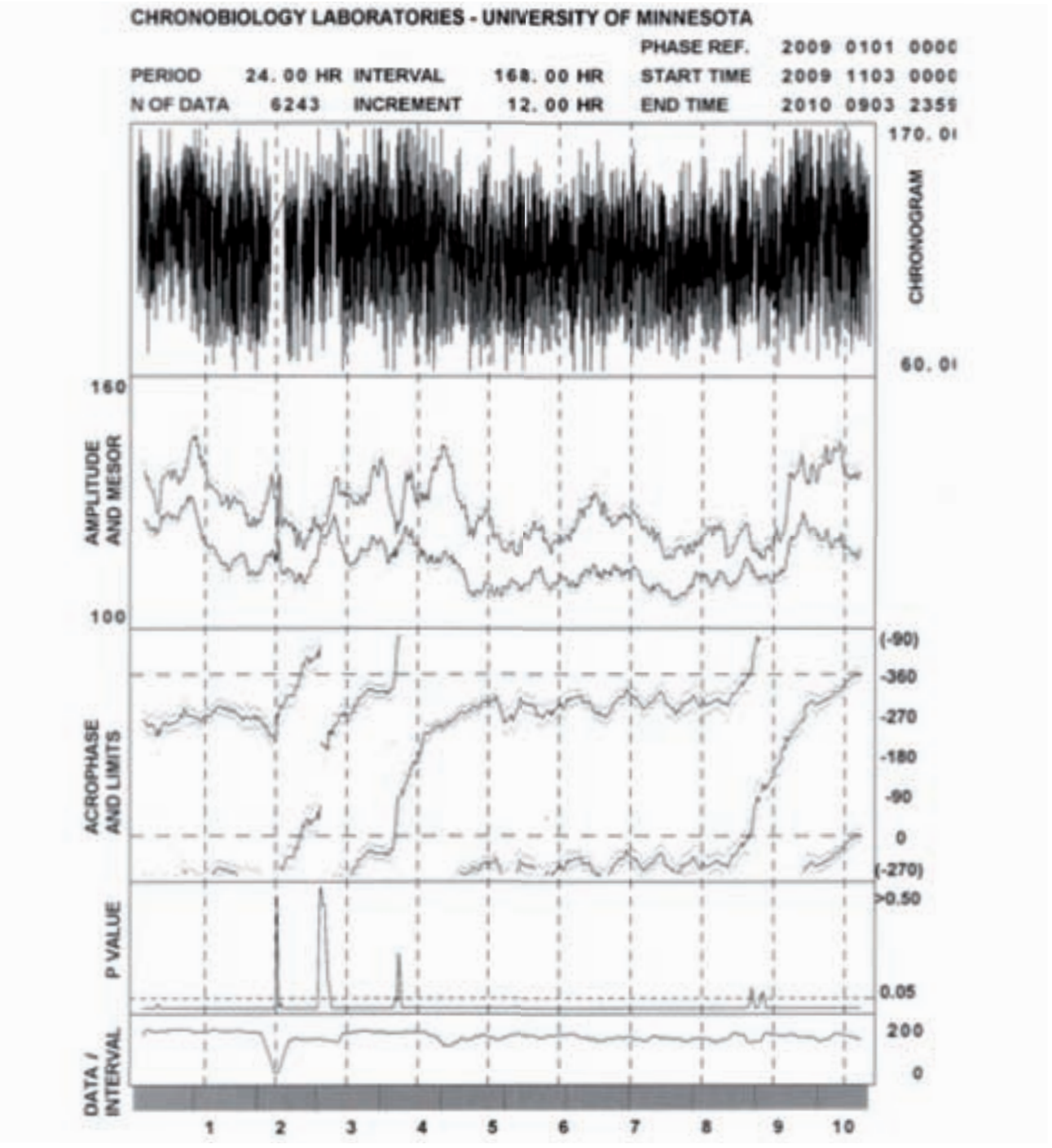


Figure 11. Circadian synchronization with the societal 24-h routine for 2 lunar months is followed by desynchronization, resynchronization and another desynchronization of the systolic blood pressure (and of diastolic blood pressure and heart rate, not shown) in JF. Numbers on the abscissa are lunar months. © Halberg.

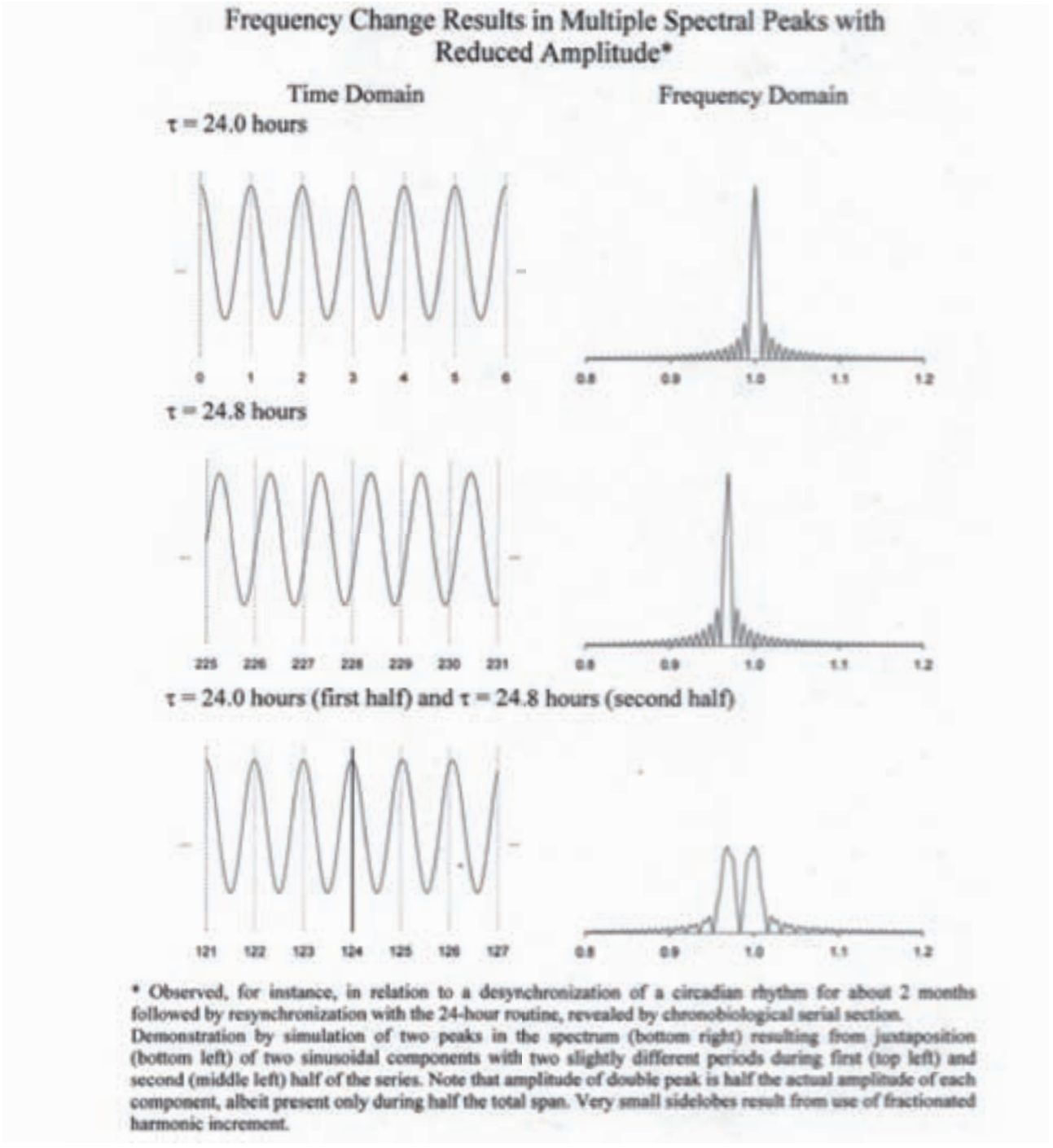


Figure 12. Artificial two major peaks resulting from a change in period. © Halberg.

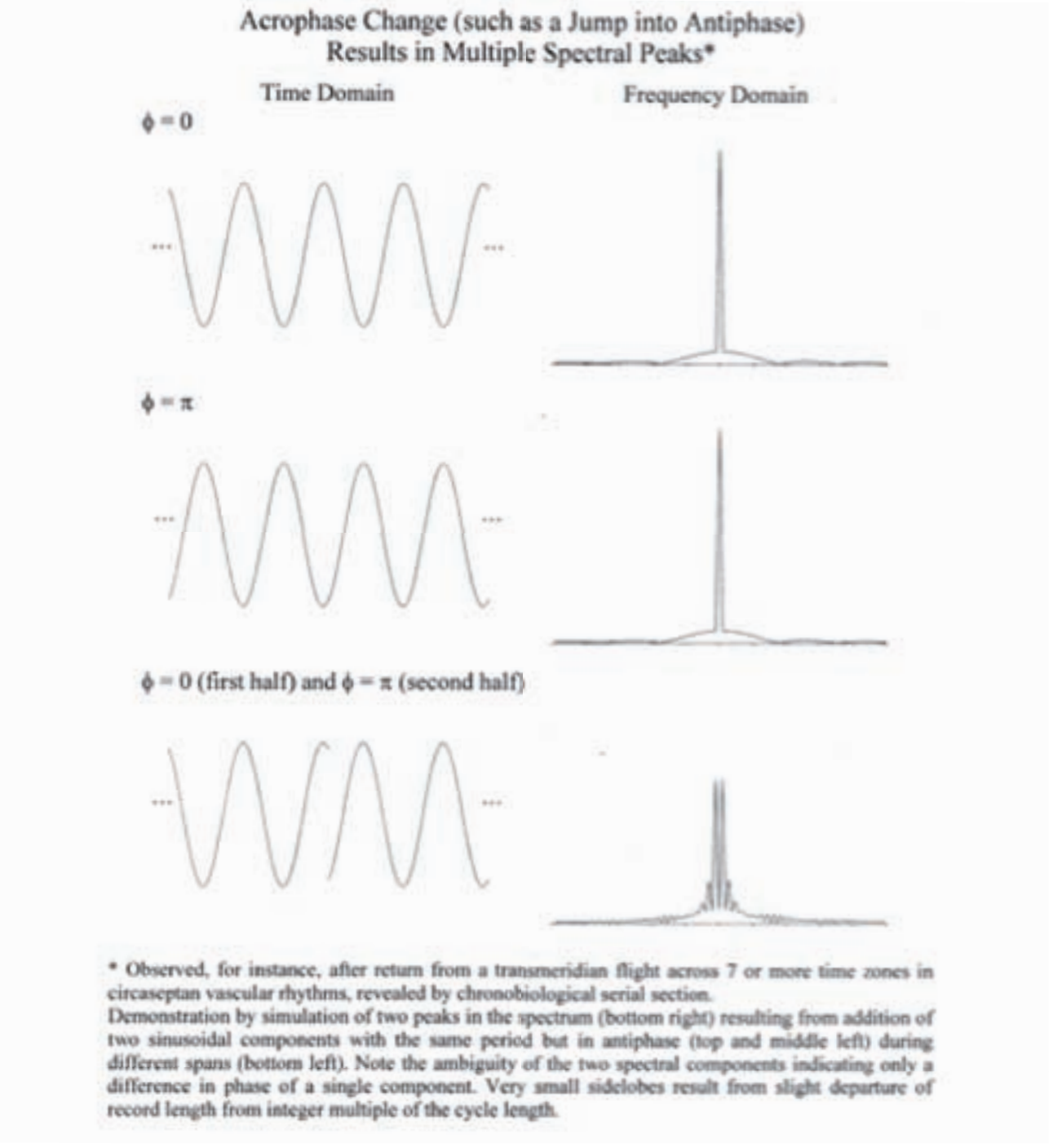


Figure 13. Artifical two major peaks resulting from a change in phase. © Halberg.

GENDER DIFFERENCES IN THE CHRONOME OF SUDDEN CARDIAC DEATH INCIDENCE IN THE ABSHERON PENINSULA, AZERBAIJAN

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Aim. To explore genetic and/or epigenetic associations of the sex chromosome with photic and non-photic cycles in the incidence patterns of sudden cardiac death in Baku and the Absheron Peninsula (Azerbaijan).

Materials and methods. The daily incidence (on most days) of sudden cardiac death (SCD WHO code ICD-10, classification I46.1) in the Absheron Peninsula, including the capital city Baku (Azerbaijan, > 3 million inhabitants) was obtained from 21 emergency and first medical aid call stations and a central station between 15 Nov 2002 and 30 Jun 2009. The date and time of occurrence was recorded together with gender and age (only cases in age range between 25 and 80 years were considered). There were 401 cases of SCD in women and 1,786 in men. For circadian analyses, the SCD incidences were stacked over an idealized 24-hour day and the number of cases per hour was counted separately for men and women. The data were analyzed by cosinor, involving the fit of cosine curves with periods of 24 hours and harmonic terms separately or jointly (1-3). Parameter tests (4) served to examine any gender difference in the circadian patterns of SCD. Daily incidences were also analyzed by least squares spectra to identify major spectral components, further resolved by nonlinear least squares to obtain point and 95% confidence intervals (CIs) for the period in addition to the MESOR, amplitude and acrophase, using Marquardt's algorithm (5).

Results. Overall, the circadian pattern of SCD incidence can be modeled by a two-component model consisting of cosine curves with periods of 24 and 12 hours (24-hour: PR=48%, P<0.001; 12-hour: PR=28%, P=0.001; composite model: PR=76%, P<0.001). In men, as expected, the fundamental amplitude is the largest (24-hour: PR=48%, P<0.001; 12-hour: PR=20%, P=0.011; composite model: PR=68%, P<0.001). In women, however, the opposite is true (24-hour: PR=24%, P=0.003; 12-hour: PR=47%, P<0.001; composite model: PR=71%, P<0.001), Figure 1. The difference in circadian pattern between men and women is statistically significant and consists primarily of a larger 12-hour harmonic in women as compared to men, Figure 2.

Apart from long-term trends not assessable on the basis of the relatively short records, the daily incidence of SCD in women is characterized by a circannual component, Figure 3. Using as initial periods 1.0 and 0.5 year, nonlinear estimates of 1.016 [CI: 0.936, 1.095] and 0.517 [CI: 0.493, 0.541] year are obtained, overlapping the anticipated respective photic and geomagnetic environmental counterparts. Among others, a far-transyear with a period of 1.65 [1.43, 1.86] year is also detected, as is a cis-half-year with a period of 0.388 [0.377, 0.398] year, slightly shorter than the about 0.42-year component characterizing solar flares (6), also reflected in physiology (7). An about-yearly component of much smaller amplitude is also found for men, Figure 4. Among others, a cis-half-year with a period of 0.375 [0.363, 0.387] year, similar to that seen in women, is also detected, as is a relatively prominent cis-year with a period of 0.763 [0.736, 0.790] year not found in women.

Discussion and conclusion. Larger databases will be needed to investigate putative reasons underlying the larger prominence of the 12-hour versus 24-hour component characterizing the incidence of SCD in women, to determine whether the difference relates to no more than a difference in circadian waveform, or whether it may involve a separate mechanism more specifically related to the 12-hour component, as discussed elsewhere in this issue. Gender differences were also observed in the number of cases, with much fewer cases in women than in men. Gender differences observed in the time structure of SCD incidence have also been reported for the incidence patterns of suicide in Minnesota and in Australia (8, 9). Solar activity reportedly affects the gender ratio and modulates lifespan (10), among a host of other effects (11). Some critical environmental-biospheric associations occur primarily at non-photic para-annual and para-semiannual frequencies, including SCD which is further characterized by geographic differences (12, 13). Further systematic assessment of gender differences in spectral features and exploration of putative underlying physiological mechanisms may help understand how space weather exerts its influence on biota.

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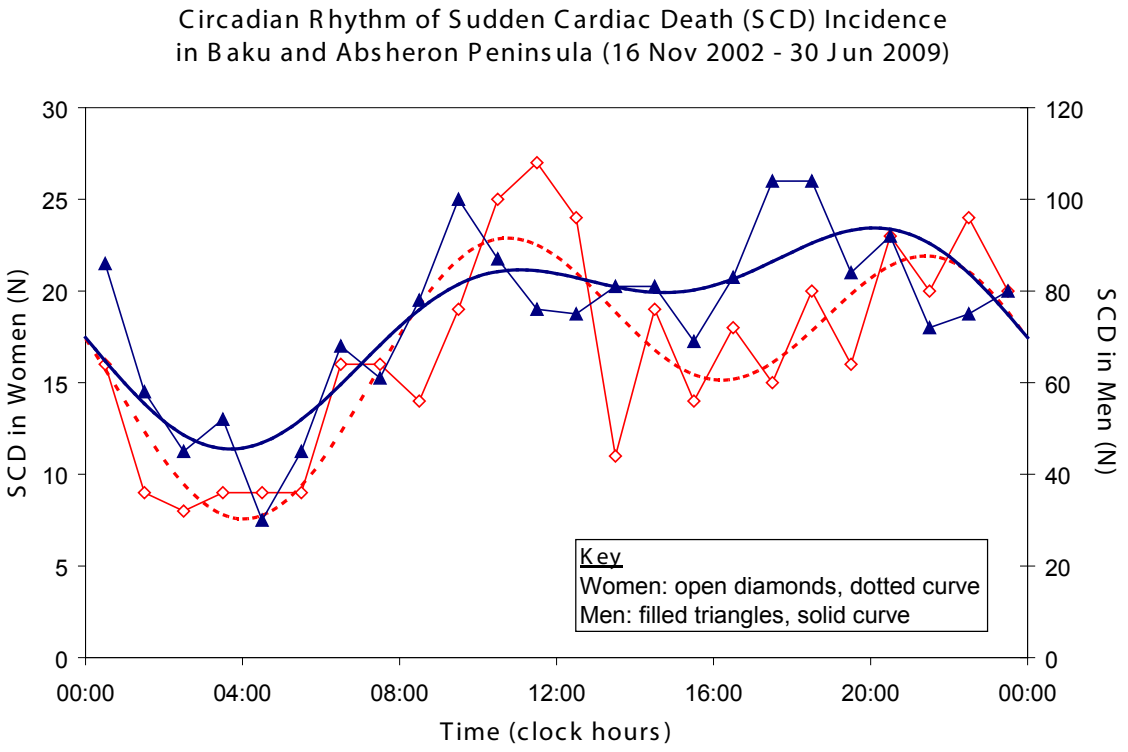
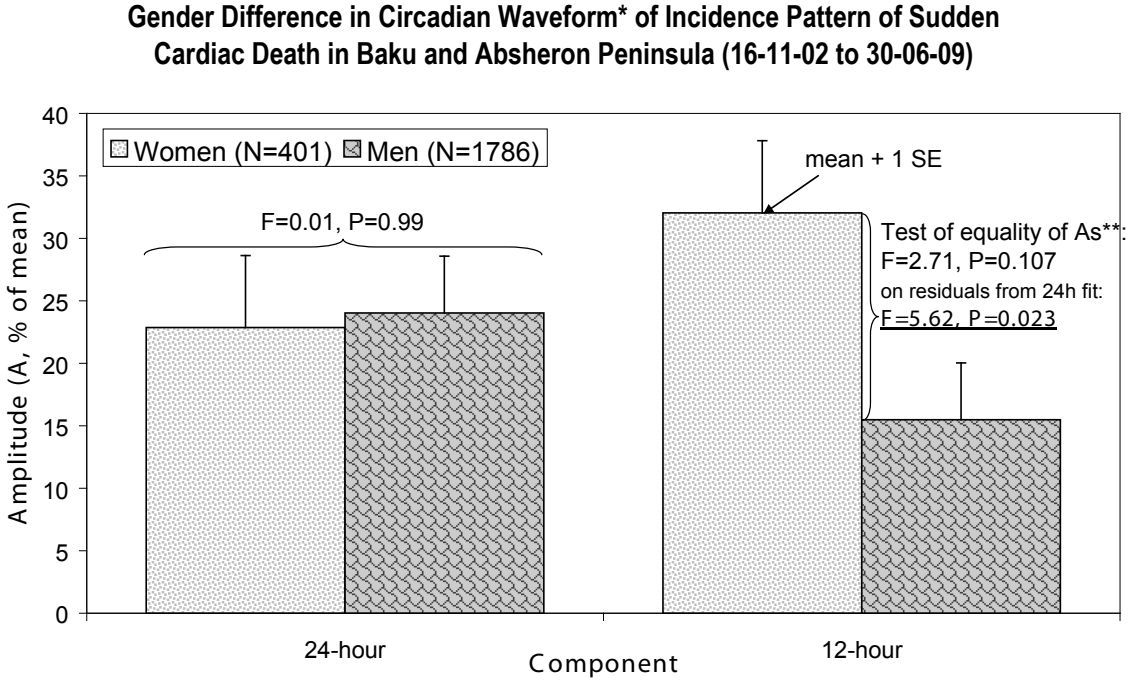


Figure 1



Data are hourly counts pooled over entire span, expressed as a percentage of the 24-hour mean (N=24)
* 12- vs. 24-hour A ratio; ** Bingham C et al. Chronobiologia 1982; 9: 397-439.

Figure 2

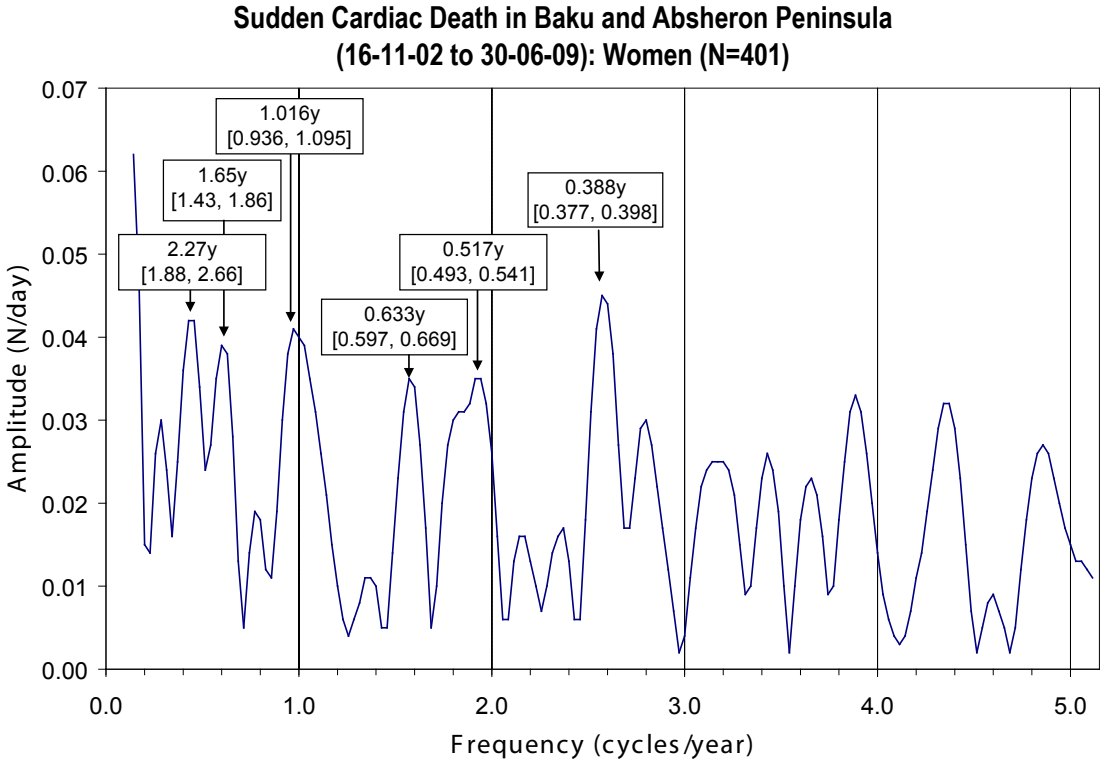


Figure 3

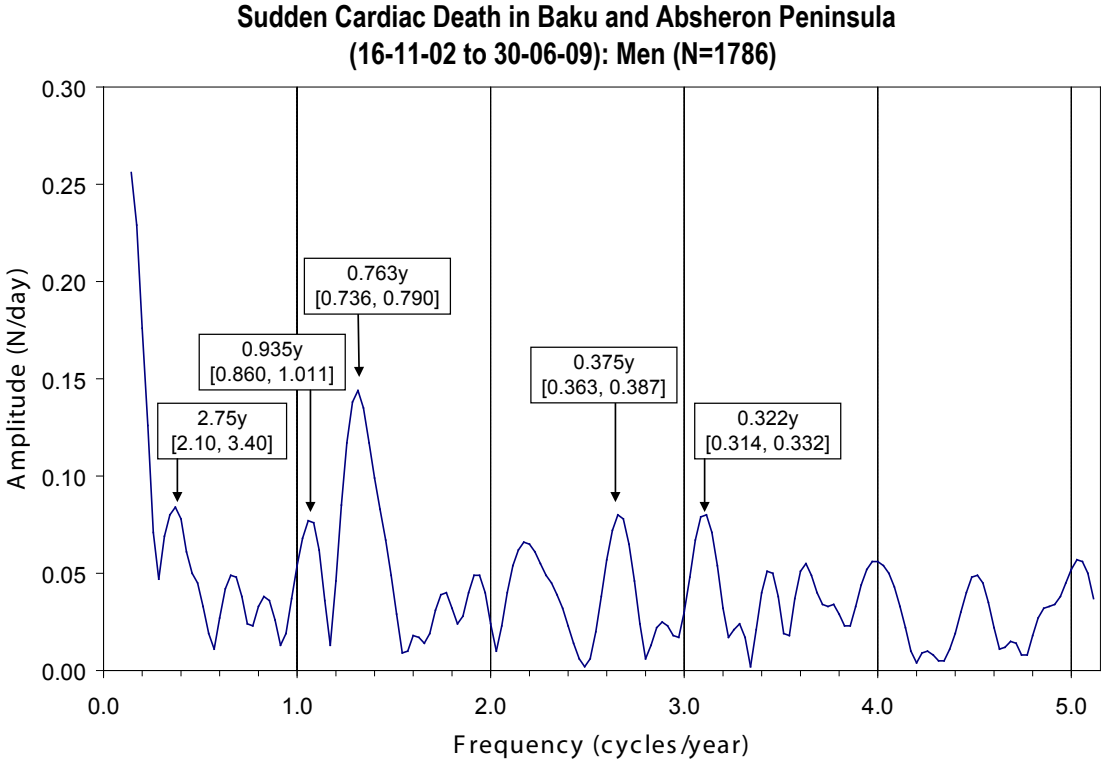


Figure 4

GROUNDING OR EARTHING: GLIMPSES AT PHYSIOLOGY AND PATHOLOGY

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Aim. To assess whether "earthing" (connecting the body to the earth by grounding) affects physiology and pathology in selected volunteering investigators.

Background. Based primarily on anecdotal stories, a book on "earthing" advocates that connecting with the Earth can alleviate a number of symptoms, such as inflammation, sleep quality and energy/vigor, presumably by neutralizing positive ions (free radicals) (1). One published study (2) reports an effect of "earthing" on circulating cortisol from 12 subjects sampled at 4-hour intervals for 24 hours before and after sleeping on Earthing pads for up to 8 weeks, yet explicitly without detecting a statistical significance of the observation. Our re-analysis of the data by means of circadian parameter tests (3) also did not find any change in MESOR, circadian amplitude and/or acrophase (P>0.20), Figure 1. The authors' finding, however, related to a "normalization" of the circadian cortisol rhythm (2), could be qualified by a comparison by paired t-test of inter-individual changes among circadian profiles (differences of individual time-specified values versus their corresponding timepoint means: t=3.169, P=0.025), Figure 2. "Normalization" may be no more than a regression to the mean, i.e., the observation that a variable that is extreme in a first series of measurements may be closer to the center of the distribution in follow-ups. The present investigation examined whether an effect of grounding could be documented for the individual rather than on a group basis.

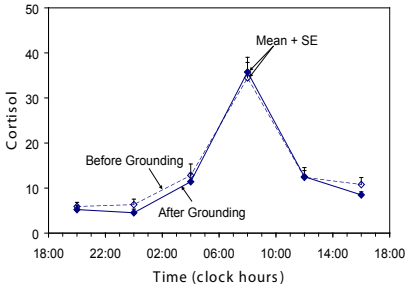

Figure 1 (adapted from 2)

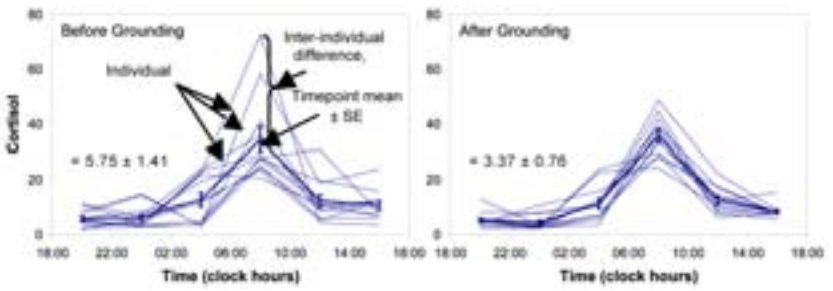

Figure 2 Chrono-meta-analysis of (2) © *Halberg*

Subjects and Methods. Self-measurements of blood pressure (BP) and heart rate (HR) during waking, followed by automatic around-the-clock data at 1-hour intervals were available from JF (F, 62 years) for over one year. Effects of grounding focused on data from May 2010 when hormonal determinations in saliva (4 to 6 per day) had been obtained, including 9 days of grounding by night. For about 5 weeks, 4 other volunteering investigators automatically recorded their BP and HR around the clock at 30-minute intervals with an arm cuff (FH, M, 90 years MESOR-hypertensive when untreated but MESOR-normotensive thanks to current treatment; OS, F, 86 years; and GC, F, 60 years) or every 15 minutes during the night with a BP monitor on the wrist (FG, M, 62 years). The participants slept grounded during weeks 1, 3 and 5, unplugging the grounding sheet during weeks 2 and 4. The nightly data from FG were averaged daily. Daily data from the other 4 subjects were analyzed by cosinor (3)

to obtain daily estimates of the MESOR, 24-hour amplitude and acrophase. The daily endpoints were compared by Student t-test between days when each subject was or was not grounded.

Results. Table 1 summarizes results for the five investigators, each individual serving as his/her own control. No statistically significant differences in blood glucose concentration or in daily insulin requirements (P>0.15) were found for FG who has insulin-dependent diabetes mellitus. Nightly means of FG's systolic (S) BP were higher during grounding (110.6 vs. 104.9 mmHg, t=2.745, P=0.010), as were those of his pulse pressure (48.0 vs. 44.2 mmHg, t=2.716, P=0.011). By contrast, FH's pulse pressure was lower during grounding (58.1 vs. 61.6 mmHg, t=2.138, P=0.040). In the case of FH, grounding was also associated with a higher MESOR of HR (63.4 vs. 58.8 beats/min, t=4.413, P<0.001) and a larger circadian double amplitude (7.8 vs. 4.5 beats/min, t=3.136, P=0.004). In the case of GC, grounding was associated with a slight increase in body weight measured daily upon awakening (143.3 vs. 142.9 lbs, t=2.428, P=0.019) but it had no statistically significant effect on activity (P>0.10), assessed by step counts with a pedometer). Grounding was also associated with a lower MESOR of HR (72.9 vs. 76.1 beats/min, t=3.309, P=0.002) and with a decrease in the double circadian amplitude of diastolic (D) BP (17.9 vs. 21.7 mmHg, t=2.563, P=0.015), Figure 3. A similar decrease in the circadian double amplitude of DBP was observed for OS (13.1 vs. 17.5 mmHg, t=2.143, P=0.045), Figure 4.

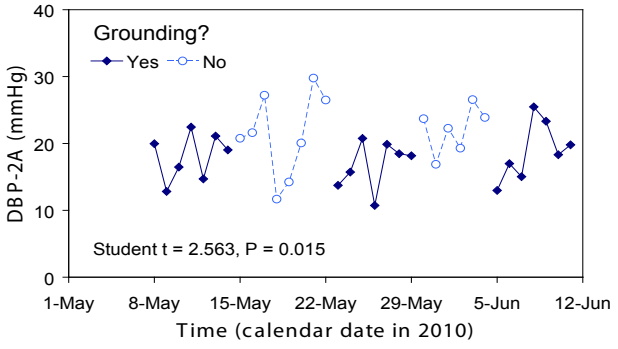

Figure 3 © *Halberg*

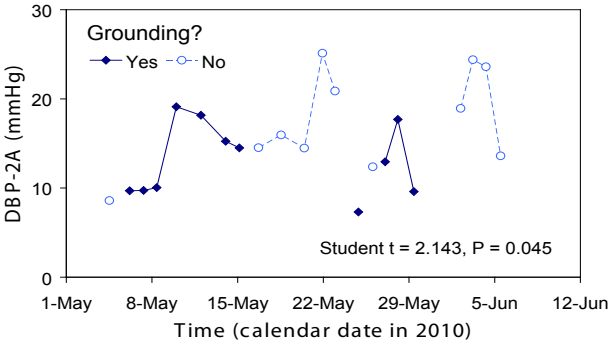

Figure 4 © *Halberg*

No effect of grounding was found on the BP and HR of JF (P>0.20). Grounding also had no statistically significant effect on JF's cortisol (P>0.30). Grounding was associated, however, with an increased circadian amplitude of salivary testosterone (15.1 vs. 9.3 pg/ml, t=2.466, P=0.020), Figure 5, and a decrease in DHEA MESOR (4.0 vs. 4.6 ng/ml, t=2.958, P=0.006), Figure 6.

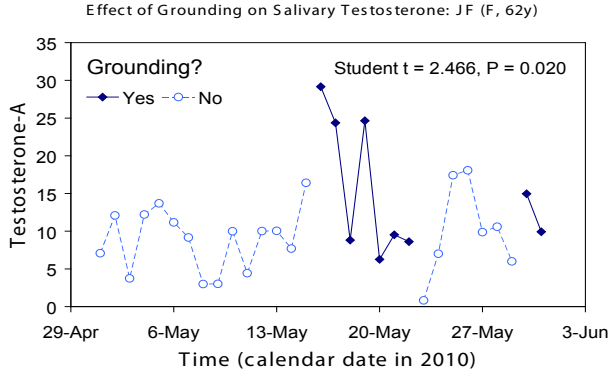

Figure 5 © *Halberg*

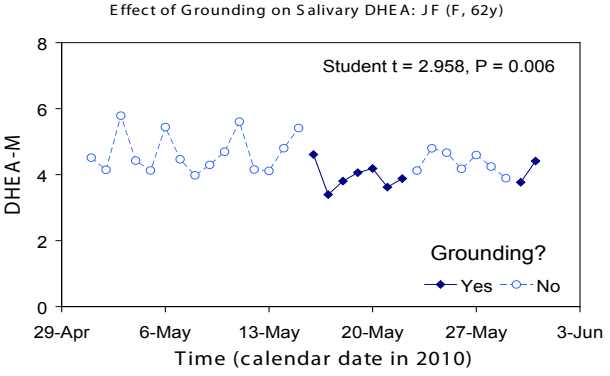

Figure 6 © *Halberg*

An increase in vigor/wellness ratings of JF during grounding (72.5 vs. 60.7 AU, t=2.126, P=0.042), Figure 7, is noteworthy as JF has suffered for the past 20 years from adynamia episodes that can last 2-3 months and recurred twice yearly thus far, usually involving frequency desynchronization of her circadian system, a Vascular Variability Disorder (VVD). Grounding seems to have been associated with a later onset of adynamia in the summer of 2010 and perhaps also with an episode of shorter duration, Figures 8 and 9, albeit results on the duration of the summer 2010 episode of adynamia remain uncertain at the time of this writing. Prediction intervals for the date of onset and for the duration of adynamia episodes were computed from records kept over the past 10 years. The onset of the summer 2010 episode occurred later than the upper 90% and even 95% prediction limit, and the duration was presumably less than the lower 90% (but not lower than the 95%) prediction limit, but the ending date of the episode is being debated as the recovery may have been followed by a return to adynamia.

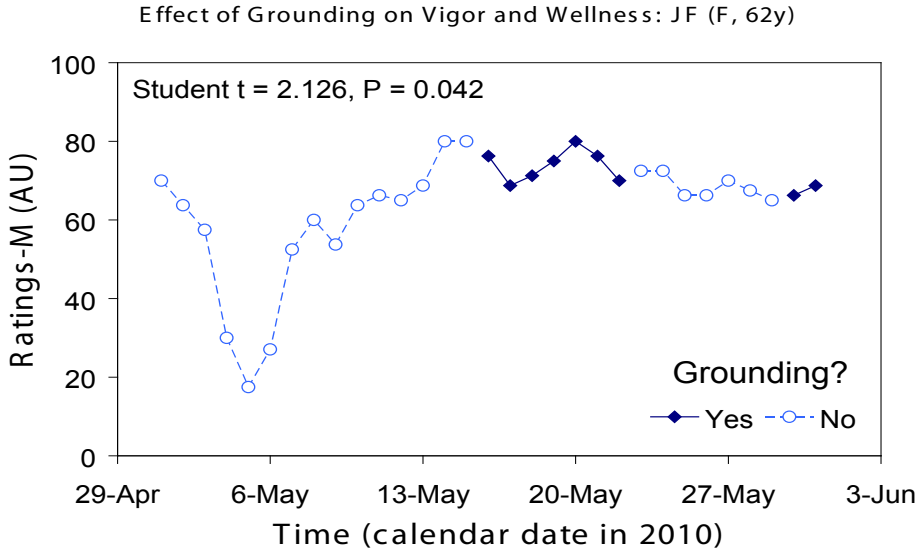

Figure 7 © *Halberg*

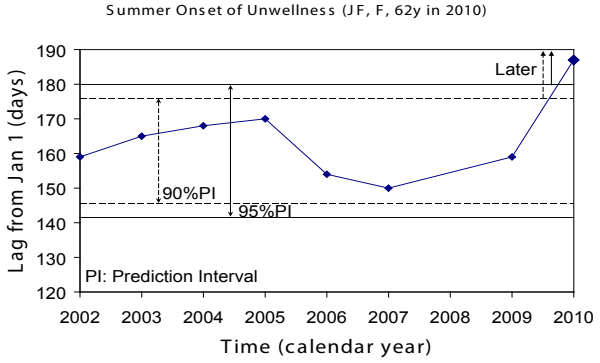

Figure 8 © *Halberg*

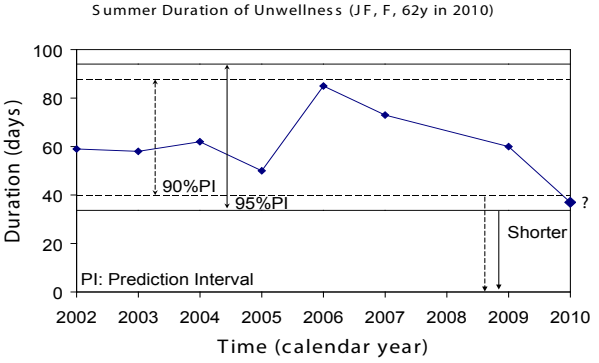

Figure 9 © *Halberg*

Discussion and Conclusion. Whereas grounding was found to affect some BP and/or HR endpoints, the results are not consistent among the participants who differ in BP-MESOR when untreated. N-of-1 studies are complicated by the fact that a multitude of other factors may have contributed to the effects detected herein, beyond any effect of grounding. For instance, GC and FG had a head cold during this investigation, which may account in part for GC's lowered body weight in the absence of grounding. FH suffered a painful foot.

Interestingly, an observation made by the authors of the book (1) that earthing may be associated with an increase in the INR of patients treated with coumadin was confirmed in the case of FH, Figure 10, albeit not (yet?) in that of OS (not shown). The range of variation of the INR was determined by computing 90% and 95% prediction limits based on data obtained before earthing started. An increase in the INR above the upper 95% prediction limit is found in association with earthing for FH, Figure 10. An increasing trend of borderline statistical significance (P=0.062) in the INR of FH after the initiation of earthing is also noteworthy, Figure 10.

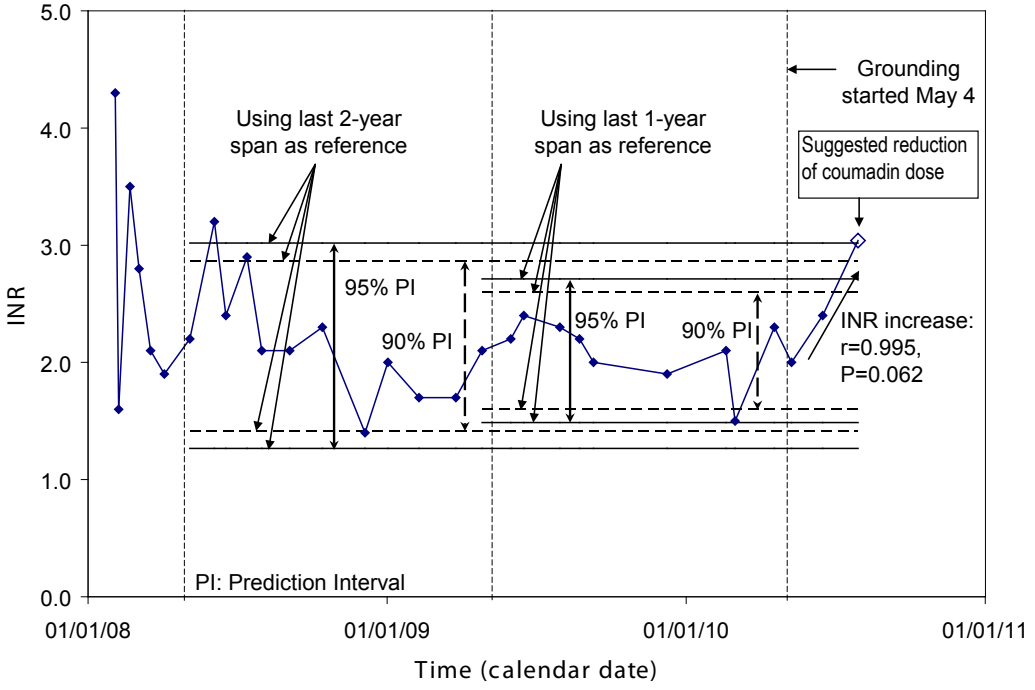

Figure 10 © *Halberg*

The design of this ongoing study will eventually allow the checking for consistent findings on an individual basis by examining whether differences observed within a 2- to 4-week span are reproducible over time. A placebo effect also needs to be considered and may require conducting double-blind studies.

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Table 1. Sometimes opposite inter-individual variability of differences found in the presence versus absence of earthing in the subjects investigated *

		SBP-M	SBP-2A	DBP-M	DBP-2A	PP	HR-M	HR-2A	HR-SD	Glucose	Insulin	BW	steps
FH (M, 91y)													
Grounding?													
Yes	(21days)	130.3	39.93	72.2	32.91	58.1	63.4	7.82	8.30				
No	(14 days)	133.6	38.83	72.0	29.19	61.6	58.8	4.49	6.85				
Student t		1.412	0.324	0.121	1.505	2.138	4.413	3.136	1.486				
P		0.167	0.748	0.905	0.142	0.040	<0.001	0.004	0.147				
		Decr	NS	NS	*Incr*	Decr	Incr	Incr	*Incr*				
FG (M, 62y)													
(nightly) Grounding?													
Yes	(20/19days)	110.6		62.5		48.0	72.4		5.10	130.8	33.2		
No	(14/11 days)	104.9		60.6		44.2	72.3		4.44	141.0	30.5		
Student t		2.745		1.971		2.716	0.083		1.074	1.325	0.748		
P		0.010		0.057		0.011	0.934		0.291	0.196	0.461		
		Incr		***Incr***		Incr	NS		NS	NS	NS		
OS (F, 86y)													
Grounding?													
Yes	(11days)	118.3	15.71	67.2	13.09	51.1	64.1	9.26	12.38				
No	(11 days)	122.1	21.71	69.1	17.50	52.9	62.4	10.04	11.50				
Student t		1.283	1.946	1.700	2.143	0.711	1.420	0.344	0.719				
P		0.214	0.066	0.105	0.045	0.485	0.171	0.734	0.481				
		NS	***Decr***	*Decr*	Decr	NS	*Incr*	NS	NS				
GC (F, 60y)													
Grounding?													
Yes	(21days)	117.9	29.12	69.4	17.90	48.6	72.9	21.98	11.22			143.3	10335
No	(14 days)	118.0	32.85	69.1	21.74	48.9	76.1	21.91	11.33			142.9	10982
Student t		0.079	1.447	0.518	2.563	0.444	3.309	0.037	0.193			2.428	1.602
P		0.937	0.157	0.608	0.015	0.660	0.002	0.970	0.848			0.019	0.116
		NS	*Decr*	NS	Decr	NS	Decr	NS	NS			Incr	*Decr*
JF (F, 62y)													
Grounding?													
Yes	(9 days)	113.5	32.56	63.9	17.79	49.6	62.4	14.51	8.71				
No	(22 days)	113.1	31.43	64.0	14.57	49.1	62.3	14.88	9.62				
Student t		0.163	0.184	0.081	1.089	0.222	0.091	0.111	0.798				
P		0.871	0.855	0.936	0.286	0.826	0.928	0.912	0.432				
		NS	NS	NS	NS	NS	NS	NS	NS				

		Mood-M	Mood-A	Cort-M	Cort-A	DHEA-M	DHEA-A	Mel-M	Mel-A	Test-M	Test-A	Estr-M	Estr-A	Aldo-M	Aldo-A
JF (F, 62y)															
Grounding?															
Yes	(9 days)	72.5	3.96	5.83	4.16	3.97	1.55	40.5	55.8	39.7	15.14	15.55	5.69	54.8	16.62
No	(22 days)	60.2	6.58	6.39	5.10	4.57	1.91	31.2	45.2	39.5	9.25	13.90	3.77	60.9	15.28
Student t		2.126	1.448	0.832	0.924	2.958	1.320	1.986	1.674	0.105	2.466	1.834	1.377	1.250	0.382
P		0.042	0.158	0.412	0.363	0.006	0.197	0.057	0.105	0.917	0.020	0.077	0.179	0.221	0.705
		Incr	*Decr*	NS	NS	Decr	NS	***Incr***	*Incr*	NS	Incr	***Incr***	*Incr*	NS	NS

* SBP: Systolic Blood Pressure (mmHg); DBP: Diastolic Blood Pressure (mmHg); PP: Pulse Pressure (= SBP-M – DBP-M); HR: Heart Rate (beats/min); Glucose (mg/dl) by finger prick; Insulin (IU): daily requirement to treat IDDM; BW: Body Weight (lbs); steps (N): daily pedometer count; Mood: ratings (arbitrary units on 0-100 scale); Cort: Cortisol (μM); DHEA: Dehydroepiandrosterone (ng/ml); Mel: Melatonin (pg/ml); Test: Testosterone (pg/ml); Estr: Estradiol (pg/ml); Aldo: Alsosterone (pg/ml); all hormones determined in saliva; M: MESOR (Midline Estimating Statistic Of Rhythm, a rhythm-adjusted mean); A (or 2A): 24-hour (or double) amplitude (half or full extent of predictable change within a day assessed by least squares fit of 24-hour cosine curve to data in 1-day intervals); Incr, Decr or NS: Earthing associated with Increase, Decrease or No (statistically Significant) effect.

AEOLIAN CHANGES AND GENDER IN THE INCIDENCE OF CARDIAC ARRESTS IN MINNESOTA (1979-2008)

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

Abstract

This paper updates earlier reports on the topic of solar wind cycles in the incidence patterns of diseases involving the heart and extends evidence concerning their aeolian nature with reference to both myocardial infarction (MI) and sudden cardiac death (SCD). It also summarizes physiological data that reflect their cosmos in some aspects of the human circulation in health. In addition to, or apart from, calendar-yearly components, blood pressure and heart rate can be characterized by a period, τ, longer than a year (y) -- the far-transyear, trans (beyond 1-y length) by several months (1.20 years [τ - CI {95% confidence interval}] < [τ + CI] < 1.90 years) -- that have been distinguished from near-transyears (1.00 year < [τ - CI < [τ + CI] < 1.20 years). Both kinds of transyears can coexist for a while with a calendar-yearly component and, in some locations, can even transiently replace the latter.

Data base

The dates of deaths from cardiac arrest in Minnesota were obtained for the span from 1979 to 2008 (30 years). Additional information included date of birth and gender. From 1979 to 1998, cardiac arrest was diagnosed according to the ICD9 classification of diseases, whereas ICD10 was used for data collected starting in 1999. Cardiac arrest in a patient with an MI was an exclusion criterion in ICD10 while it was included under SCD in ICD9.

Time series were formed separately for males and females (ages at death spanned the range from early after birth to centenarians). Least squares spectra by cosinor (1-3) were performed for the series overall and for the shorter 10-year span of diagnoses made under the ICD 10 classification. In the latter case, the data were further subdivided according to codes I46.1 and I46.9. Chronobiologic serial sections were obtained at the trial period of I year and at periods corresponding to the spectral peak around the year for the 30-year series. Gliding spectra were obtained for both the overall 30-year series (all cardiac arrests, irrespective of gender) and for the last 10-year series (ICD10 I46.1 and I46.9, irrespective of gender).

Over 30 years, there were 11,302 deaths from cardiac arrest in Minnesota, equally distributed between males (N=5,905) and females (N=5,397). From 1979 to 1988, there was an increase in mortality from cardiac arrest, followed by an abrupt decline in 1989. From 1990 to 1996, the average daily incidence of cardiac arrests remained stable. It was also stable from 1999 to 2008, albeit slightly less than during the previous decade.

In view of the large trends in mortality, the least squares spectra had inflated low-frequency amplitudes. Overall, a spectral peak is centered on the year. An additional smaller peak is observed at a period of about 1.35 or 1.05 years for females and males, respectively. Least squares spectra of the last 10 years (ICD 10) show multiple peaklets that are not consistent between males and females, except for a weak about 0.32-year component. Least squares spectra of consecutive 5-year spans corroborated the earlier detection of a transyear with a period of about 1.4 years (4), contributed primarily by females, males having a peak

around 1.04 years during the 1999-2003 span analyzed earlier. A cis-half-year is also corroborated for this particular 5-year span. The corresponding spectra for 2004-2008 are markedly different.
Because earlier analyses were restricted to the incidence of sudden cardiac deaths (ICD10 146.1), the cardiac arrests from 1999 to 2008 were further analyzed specifically for I46.1 and I46.9. Again, the about-1.4-year transyear observed earlier is contributed primarily by females and is not reproduced during the next 5 years when a calendar year component is prominent, albeit contributed by females. The about 1.4-year transyear detected during 1999-2003 for females characterizes both deaths classified as I46.1 or I46.9.
Chronobiologic serial sections at a trial period of 1.00 year reveal a relatively stable acrophase in winter, as anticipated. This is the case overall as well as for females or males considered separately. In the case of females, a disruption in the acrophase sequence is observed shortly after the transition from ICD9 to ICD10, during which span the yearly component cannot be detected with statistical significance. Thereafter, the acrophase seems to undergo a slight drift indicative of a period longer than 1 year, but it only reaches statistical significance at the end of the record when the acrophase seems to have stabilized, albeit around a slightly later time as compared to the timing at the beginning of the record. A similar situation applies to the results of males, but the disruption in the acrophase sequence occurs earlier, toward the middle of the record, and the acrophase drift during the last 10 years is more readily apparent. A trend toward stabilization of the acrophase at a slightly later time as compared to that observed at the beginning of the record is also observed in this case.
Chronobiologic serial sections at periods of 1.15 years, 1.05 years, or 1.02 years, periods corresponding to spectral peaks for females, males, and overall incidence (irrespective of gender), show a relatively stable acrophase sequence during the last 10 years when the ICD 10 classification was used for both males and females. In the case of females, such a stable acrophase sequence is also observed during other earlier spans when the acrophase can assume a similar or a different value. No consistent drift in acrophase is seen. In the case of males, a drift in acrophase suggesting the presence of a component with a period shorter than the one used for analysis is seen during the first half of the record (before the disruption in acrophase sequence also observed when using 1 year as trial period). The fact that a period of 1.05 years was considered for males, closer to 1 year than the 1.15-year trial period used for females, may account for the visual acrophase drift seen for males but not for females. In the overall analysis, the drift in acrophase is milder as the trial period is even closer to 1 year. It also lasts longer, practically until the switch from ICD9 to ICD10. A reversal from a shorter-than-1 year to a longer-than-1 year seems to occur in association with the ICD9 to ICD10 switch.
Gliding spectra, Figure 2, corroborate the above impressions. A relatively strong yearly component is weakened already once the daily incidence of cardiac arrests starts declining, probably because the amplitude diminishes in keeping with the decreased average daily incidence. Of particular interest is the observation that a transyear is present intermittently, even before the institution of ICD 10. The same applies to cis-half-years that are particularly prominent during the first few years of the record. The transient presence of a transyear as well as of cis-half-years during the last 10 years is readily apparent, as is the more consistent detection of a circannual component. Whether the about 0.3-year component also detected during most of the last 10 years is an independent signal or the third harmonic of the year contributing to the circannual waveform remains to be elucidated.
The bracketed section of Figure 3 shows the broad range of periods found in individual time series covering years or decades as well as some wide uncertainty estimates (CIs). This spread led to the very broad definition of the range of far-transyears (4-6) based on a similar span also encountered in the geographic variation of Table 1 (7; cf. 11), also reflected in Figure 4. While the proposition of transyears has been confirmed in other variables in our laboratory and elsewhere (8-11), their aeolian nature must be emphasized.

Conclusion

A number of pathological and physiological cycles drift in period and wax and wane in amplitude to the point of bifurcation, disappearance (or drawning in noise) and reappearing and requiring a global analysis of the series as a whole and in local analyses, the latter here initiated for SCD and MI as a follow-up on an earlier investigation (4, 12; cf. 5-11).

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

Sudden Cardiac Death (SCD)[1]							
Site	Span	T, Δt, N	SCD (N)	Period (y) (95% CI)	Amplitude (95% CI)	A (% MESOR)	P-value[2]
				- - - - - Transyear (TY) or Candidate Transyear (cTY) Detected - - - - -			
Minnesota	1999-2003	5y, 1d, 1826	343	1.392 (TY) (1.173, 1.611)	0.042 (0.00, 0.09)	22.0	0.014
Arkansas	1999-2003	5y, 1d, 1826	273	1.095 (0.939, 1.251)	0.032 (0.00, 0.07)	21.1	0.040
				1.686 (cTY) (1.293, 2.071)	0.031 (0.00, 0.07)	20.7	0.044
Czech Rep.	1999-2003	5y, 1d, 1826	1006	0.974 (0.856, 1.091)	0.078 (0.00, 0.16)	14.2	0.007
				1.759 (cTY) (1.408, 2.110)	0.077 (0.00, 0.15)	13.9	0.01
	1994-2003	10y, 1d, 3652	1792	1.726 (TY) (1.605, 1.848)	0.074 (0.02, 0.13)	15.1	<0.001
				1 (0.944, 1.056)	0.052 (0.00, 0.10)	10.6	0.01
				- - - - - Candidate Transyear Not Detected - - - - -			
North Carolina	1999-2003	5y, 1d, 1826	752	0.929 (0.834, 1.023)	0.069 (0.00, 0.14)	16.9	0.007
Tbilisi, Georgia	Nov 99-2003	4.1y, 1d, 1505	130	0.988 (0.862, 1.114)	0.035 (0.00, 0.07)	40.7	0.007
Hong Kong	2001-2003	3y, 1m, 36	52	0.843 (0.651, 1.036)	(NS)	44.9	0.077
Myocardial Infarction (MI)							
Site	Span	T, Δt, N	MI (N)	Period (y) (95% CI)	Amplitude (95% CI)	A (% MESOR)	P-value[2]
				- - - - - Coexisting Year (Circannual) and Transyear (TY) - - - - -			
Czech Rep.	1999-2003	5y, 1d, 1826	52598	1.014 (0.989, 1.038)	2.85 (2.22, 3.48)	9.88	<0.001
				1.354 (TY) (1.252, 1.456)	1.35 (0.69, 2.02)	4.68	<0.001
	1994-2003	10y, 1d, 3652	115520	0.998 (0.988, 1.009)	3.03 (2.47, 3.60)	9.58	<0.001
				1.453 (TY) (1.417, 1.489)	1.91 (1.34, 2.49)	6.04	<0.001
				1.15 (TY) (1.116, 1.184)	1.23 (0.64, 1.82)	3.88	<0.001
Minnesota	1968-1996	29y, 1d, 10593	129205	1.049 (1.035, 1.062)	0.30 (0.11, 0.49)	2.46	<0.001
				1.232 (1.207, 1.258)	0.18 (0.02, 0.35)	1.48	0.013
				1.001 (0.998, 1.004)	1.04 (0.89, 1.20)	8.53	<0.001

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

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

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

From Halberg F, Cornélissen G, Otsuka K, Fiser B, Mitsutake G, Wendt HW, Johnson P, Gigolashvili M, Breus T, Sonkowsky R, Chibisov SM, Katinas G, Siegelova J, Dusek J, Singh RB, Berri BL, Schwartzkopff O. Incidence of sudden cardiac death, myocardial infarction and far- and near-transyears. Biomedicine & Pharmacotherapy 2005; 59 (Suppl 1): S239-S261.

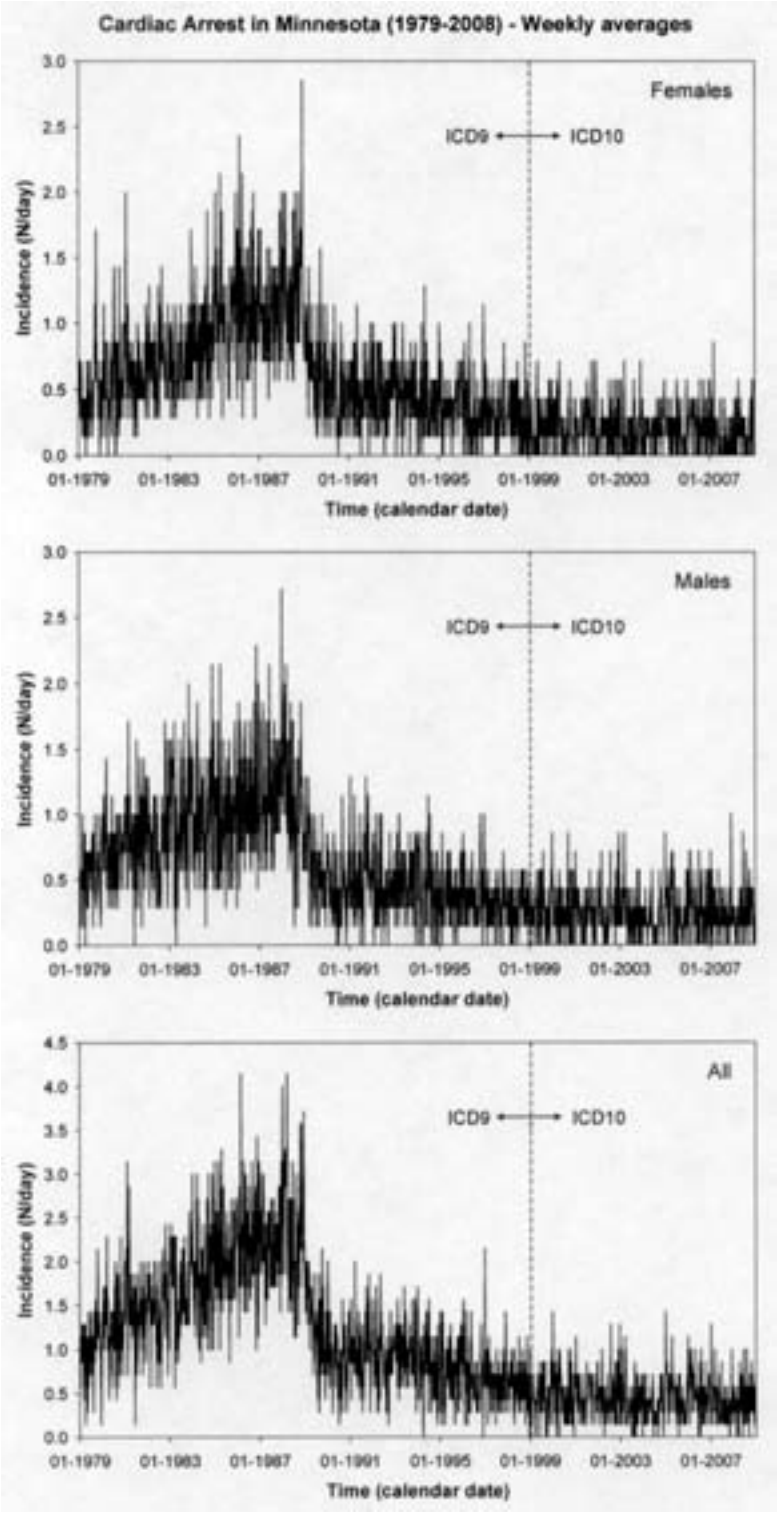

Figure 1. Cardiac arrest before and after a change in the International Classification of Diseases (ICD), indicated by a vertical line in females (top), males (middle) and a pool of both genders (bottom). © Halberg.

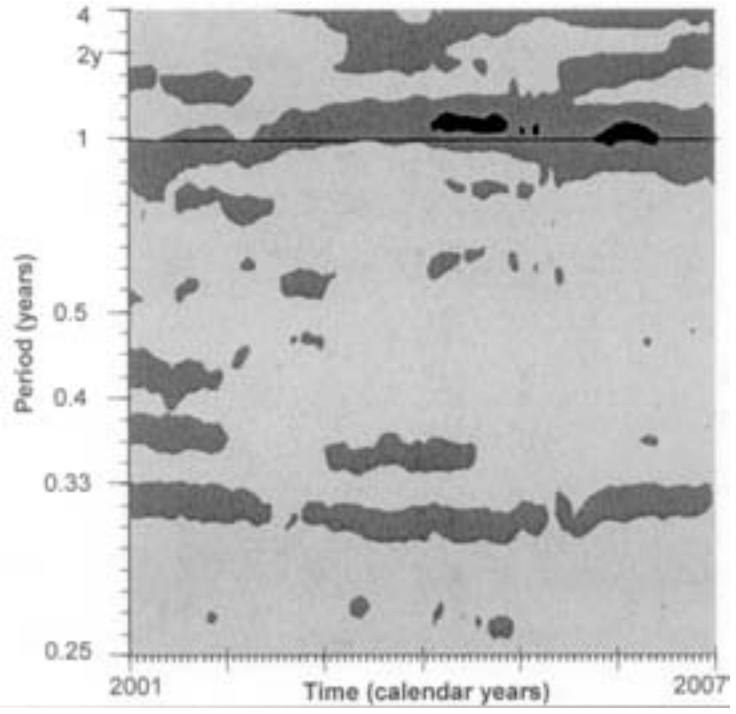

Figure 2. Gliding spectral windows in the range of periods from 0.25 years (y) to 4 y of cardiac arrest in Minnesota. © Halberg.

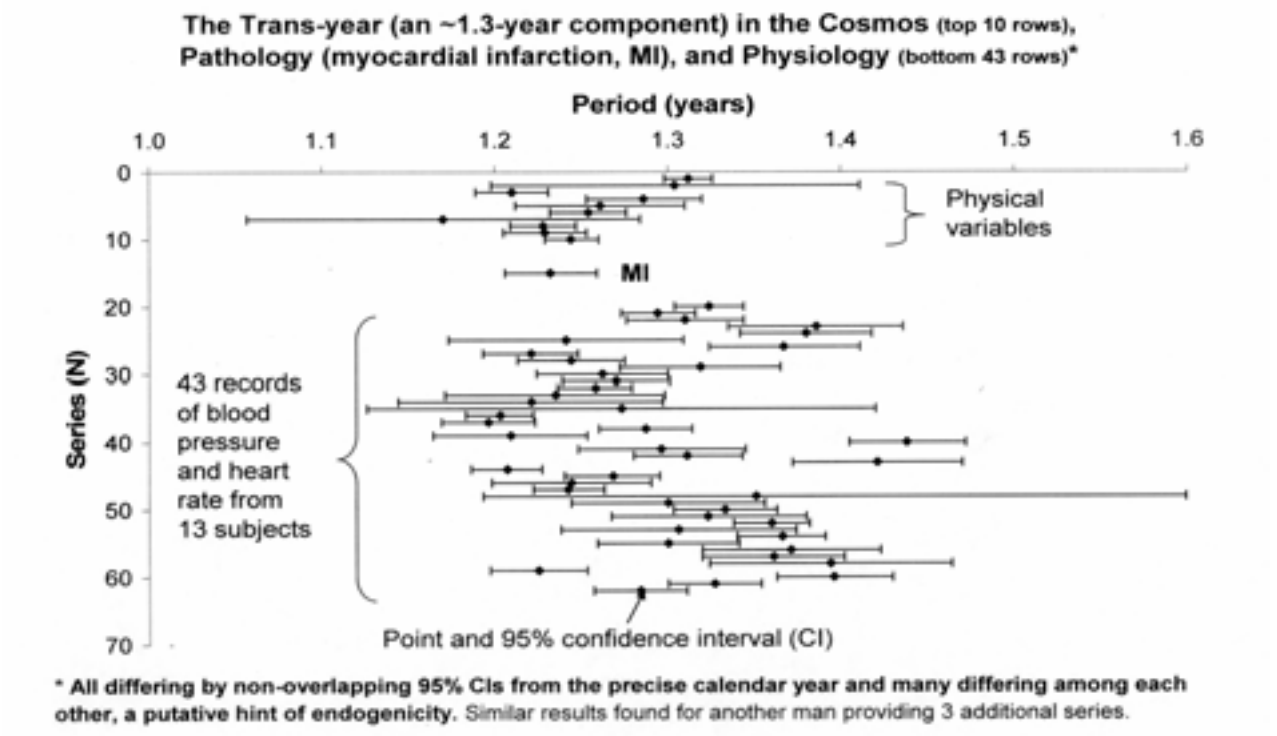

Figure 3. Transyears found in physics, in the incidence pattern of myocardial infarctions (MI), and in each physiological time series examined thus far. Note that broad 95% confidence intervals of the period extend to shorter than 1.2-y estimates, violating this lower limit of a far-transyear. Hence, we refer to transyears in these cases, rather than coining another term. All limits remain tentative. © Halberg.

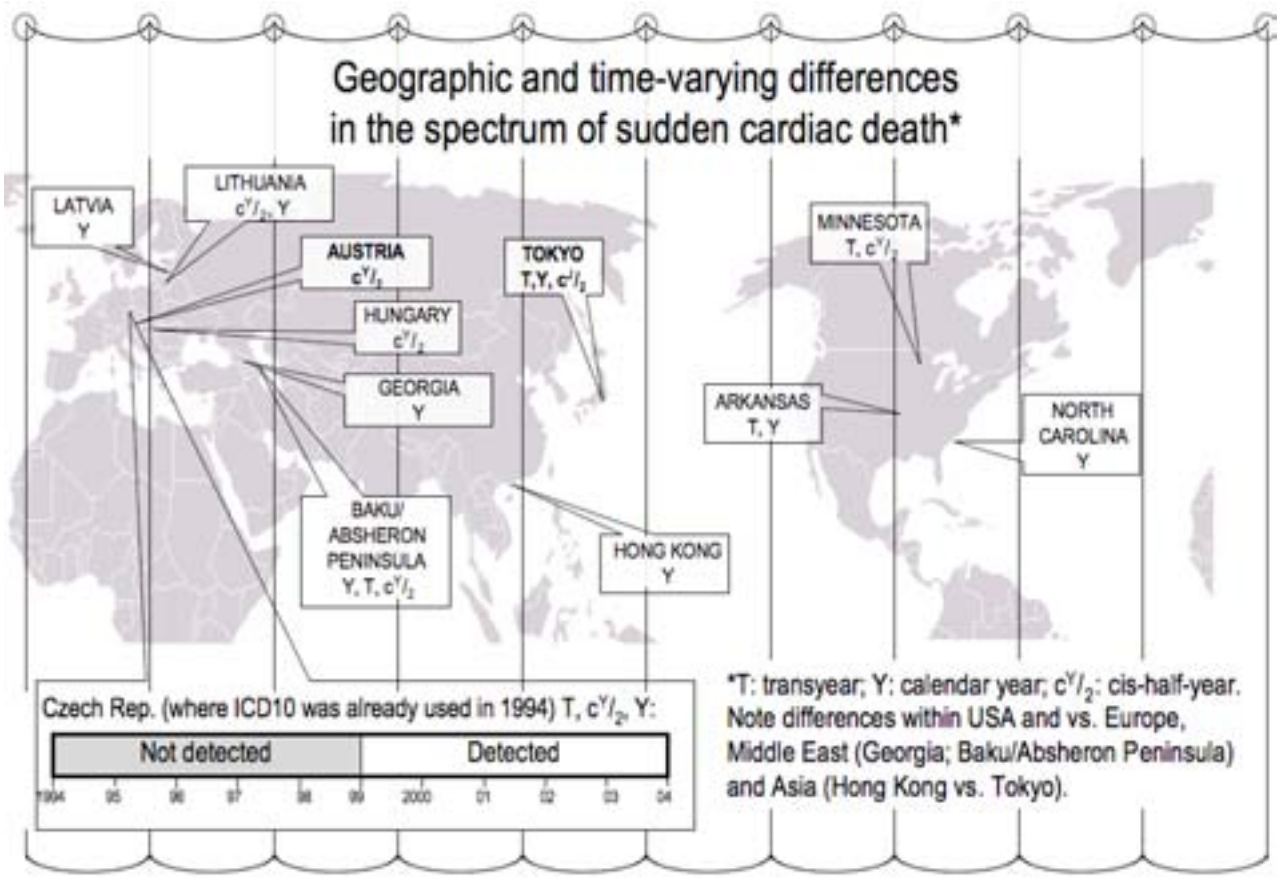

Figure 4. Geographic differences in the presence (and prominence) of a far-transyear (T) vs. that of a calendar year (Y) component during the span investigated. For the incidence in bracketing data, see Figure 2. Table 1 cannot be generalized. © Halberg.

FEASIBLE AMBULATORY BLOOD PRESSURE AND HEART RATE MONITORING IN AMERICAN SECONDARY SCHOOLS TO ASSESS CHRONOMES IN CLINICALLY HEALTHY ADOLESCENTS

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Aims. To demonstrate the feasibility of prolonged monitoring of blood pressure (BP) and heart rate (HR) in high school students and to illustrate how it can address some interesting physiological questions while also providing reference values for the time structure of BP and HR at an important stage of life.

Background. Teaching how to measure BP and HR in secondary education (1-4) has a long history in the context of chronobiology education (1-7). Before ambulatory monitors became available, students had to be taught how to listen to Korotkoff sounds to measure systolic (S) and diastolic (D) BP and how to take their pulse. Despite great limitations related to this approach, notably in young children, these early school projects were first to reveal a difference in the circadian amplitude between students with a positive versus negative family history of high BP and related cardiovascular problems (8-11). BP and HR monitoring in schools, even with ambulatory monitors, as a rule has been limited to 24 or at most 48 hours (8). The data collected around-the-clock for up to 5 weeks from 14 adolescents in this award-winning school project (12) are reanalyzed herein to assess the time structure (chronome) of BP and HR.

Subjects and Methods. As part of a secondary school project focusing on effects of exercise on BP and HR (12), 14 clinically healthy adolescents measured their BP and HR around-the-clock at 30-minute intervals for up to 5 weeks, with few and short interruptions. They used the TM-2421 ambulatory monitor from A&D (Tokyo, Japan). The students (7 girls and 7 boys) were between 15 and 17 years of age. The data were edited prior to analysis to remove obvious outliers and bad data. Criteria for data editing were values for the pulse pressure (SBP – DBP) less than 10 or greater than 100 mmHg. Least squares spectra (13-15) were computed for each edited data series in the frequency range of one cycle in 35 days (5 weeks) and three cycles per day. Amplitudes at each trial period were averaged over the 14 students to obtain an average least squares spectrum for each variable. Population-mean cosinor spectra (13-15) were also computed to test the zero-amplitude (no rhythm) assumption of anticipated components with periods of 24, 12 and 8 hours (circadian rhythm and harmonic terms) and of 168 and 84 hours (week and half-week components). Their amplitudes and the MESOR were compared between boys and girls by means of the two-tailed Student t-test assuming equal variances.

Results. Twelve of the 14 students mostly completed the scheduled monitoring. Since shorter records might yield spuriously elevated amplitudes of the low-frequency components, average least squares spectra were computed on the basis of these 12 students only, Figure 1. The average amplitude with its standard error (SE) is shown for each trial period (between 5 weeks and 8 hours). The two major spectral peaks have periods of 24 and 12 hours, as expected since the circadian system is usually very prominent and ubiquitous. As the circadian variation of BP and HR is not necessarily sinusoidal, being characterized by a steeper fall of shorter-than 12 hours duration during the night, a relatively sharp rise in the morning and a slower decrease in the evening hours, it is likely that the 12-hour peak reflects the second harmonic of the circadian rhythm, accounting for the non-sinusoidal waveform.

Least Squares Spectra of Systolic (S) and Diastolic (D) Blood Pressure (BP) and Heart Rate (HR) of 12 Adolescents

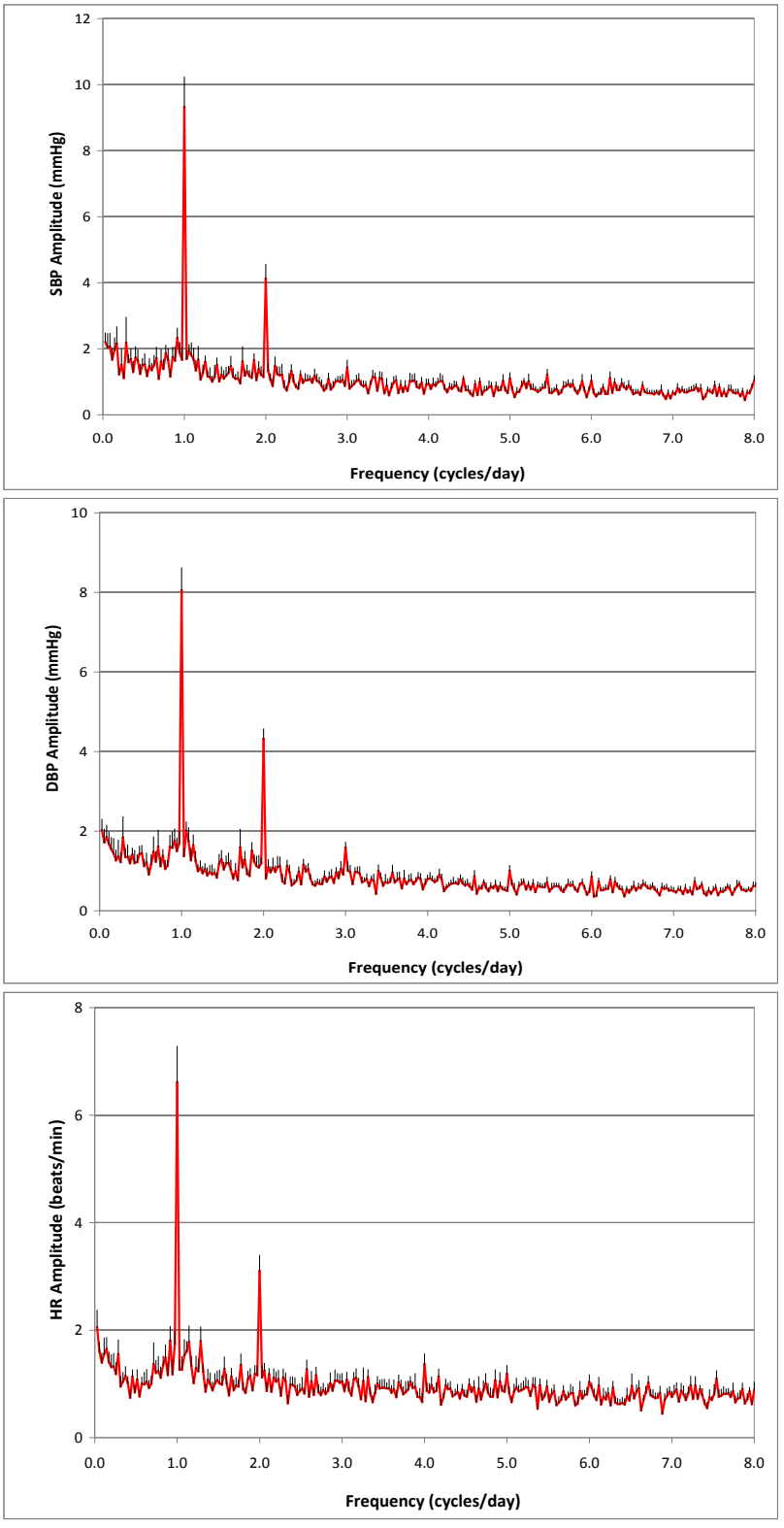

Figure 1

The 24-hour and 12-hour components are invariably statistically significant by population-mean cosinor (P<0.001) for all three variables. In addition, the 7-day and 3.5-day components of HR are also statistically significant (P<0.05), as are harmonic terms of the circadian variation with periods of 6.0 and 4.8 hours, Figure 2.

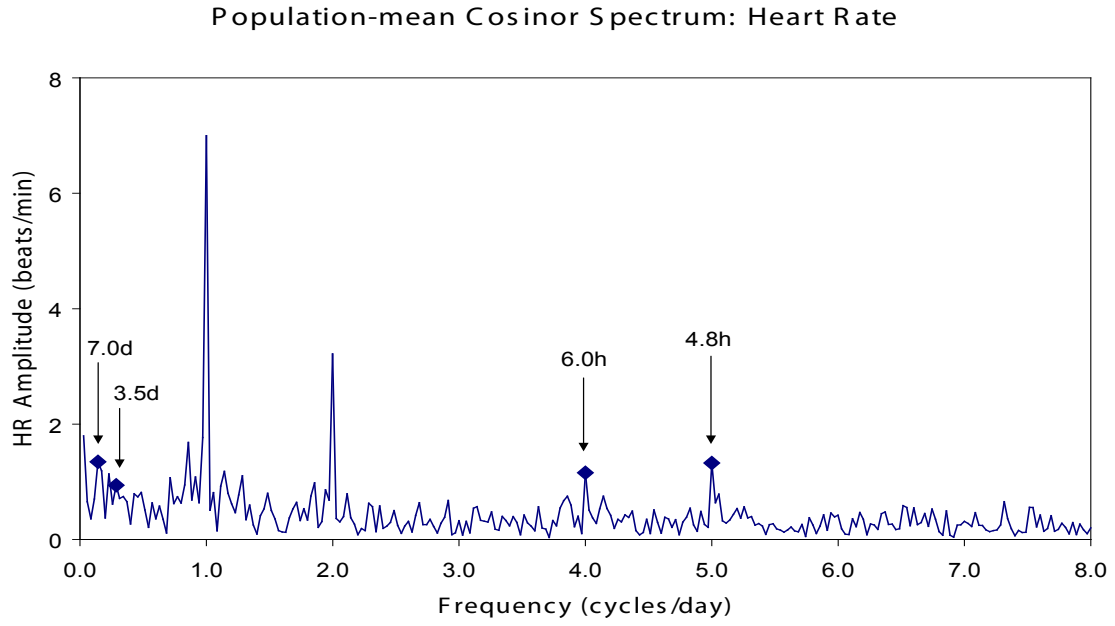

Figure 2. Population-mean cosinor of HR. In addition to the prominent 24-hour and 12-hour components, statistically significant harmonics of 6.0 and 4.8 hours also contribute to the circadian waveform of HR, and the week and half-week components are detected with statistical significance.

On an individual basis, the circadian component is invariably statistically significant for all three variables (P<0.001). The second harmonic with a period of 12 hours is also invariable statistically significant for DBP, and it is statistically significant in 13 of the 14 students for SBP and HR, while reaching borderline statistical significance (P<0.10) for the other student in the case of SBP. In the case of SBP, the circaseptan component reaches statistical significance for 2 girls and 5 boys, and borderline statistical significance for 3 girls and 1 boy. The half-week is statistically significant for 5 girls and 3 boys and reaches borderline statistical significance for 2 boys. In the case of DBP, the circaseptan component is statistically significant for 3 girls and 3 boys and reaches borderline statistical significance for 1 girl and 1 boy. The circasemiseptan component is detected with statistical significance for 3 girls and 4 boys and with borderline statistical significance for 1 girl and 1 boy. In the case of HR, statistical significance of the circaseptan component is reached for 4 girls and 5 boys and that of the circasemiseptan component for 6 of the 7 boys but for none of the girls.
As seen from Table 1, boys have a slightly higher MESOR of SBP as compared to girls (P=0.086),, in keeping with earlier studies. The two genders do not differ in terms of their circadian or circaseptan systems of SBP, however (P>0.20). No gender difference is found for the MESOR of DBP or for the double amplitudes of components with a period of 7 days, 3.5 days or 24 hours in the spectrum of this variable, but boys show a larger double amplitude of the 12-hour component than girls (P=0.030), Table 1. As expected, girls have a higher MESOR of HR than boys (P=0.035). Whereas the two genders do not differ in terms of their circadian system of HR, boys are found to have a more prominent half-weekly component than girls (P=0.005), Table 1.

Table 1

	Systolic Blood Pressure					Diastolic Blood Pressure					Heart Rate				
Girls	**MESOR**	**168h-2A**	**84h-2A**	**24h-2A**	**12h-2A**	**MESOR**	**168h-2A**	**84h-2A**	**24h-2A**	**12h-2A**	**MESOR**	**168h-2A**	**84h-2A**	**24h-2A**	**12h-2A**
02_	110.8	5.38	19.67	27.65	12.35	66.9	1.89	14.03	21.87	8.73	77.2	3.77	3.28	11.05	3.79
05_	118.4	14.00	9.99	36.67	22.19	68.8	2.69	1.13	14.61	7.69	79.0	11.84	4.24	28.79	12.27
07_	111.2	0.29	1.45	27.95	3.28	64.8	2.79	2.19	22.07	5.37	73.7	1.57	1.61	9.97	3.22
08_	113.4	9.32	0.68	13.56	7.56	60.9	7.73	1.45	14.84	7.82	73.5	2.04	1.97	10.55	5.55
10_	114.2	1.92	3.02	12.86	8.30	61.1	0.54	3.04	10.57	6.71	73.6	2.41	1.78	9.90	5.24
11_	121.0	3.47	3.91	18.02	9.72	66.9	4.70	2.59	19.92	9.44	73.3	6.34	1.21	10.13	4.25
14_	109.9	1.16	3.16	25.41	9.10	64.0	2.16	2.64	18.11	8.69	74.4	2.83	0.73	11.19	5.86
Mean	114.1	5.08	5.98	23.16	10.36	64.8	3.21	3.87	17.43	7.78	75.0	4.40	2.12	13.08	5.74
SE	1.7	2.03	2.75	3.56	2.40	1.2	0.96	1.85	1.74	0.56	0.9	1.49	0.50	2.84	1.24
Boys															
01_	120.7	4.38	9.68	20.43	7.27	71.9	2.71	7.20	17.62	9.28	77.1	2.06	6.42	15.22	5.93
04_	119.4	2.12	0.52	9.94	3.86	67.1	0.49	1.52	13.06	8.19	70.3	3.78	1.95	18.94	7.22
06_	108.5	3.68	2.65	20.47	11.09	59.2	2.12	1.89	16.22	11.93	72.3	5.60	3.72	20.64	10.57
09_	118.5	9.34	7.04	29.53	12.88	62.1	8.00	7.79	19.67	11.75	70.8	9.15	5.26	18.40	9.86
12_	116.2	4.05	2.35	10.98	8.40	65.3	4.70	3.05	11.06	8.55	72.1	3.45	4.18	10.94	6.83
13_	127.1	6.99	2.92	21.95	12.55	72.2	4.67	3.25	13.57	10.87	71.3	4.00	5.31	21.64	7.88
15_	135.4	4.46	2.21	14.41	5.50	66.6	2.47	1.27	14.34	8.06	70.7	1.56	5.09	8.43	7.95
Mean	120.8	5.00	3.91	18.25	8.79	66.4	3.59	3.71	15.08	9.81	72.1	4.23	4.56	16.32	8.03
SE	3.5	0.98	1.32	2.82	1.43	1.9	1.00	1.10	1.20	0.69	0.9	1.04	0.59	2.05	0.67
Student t	***-1.871***	0.036	0.734	1.169	0.604	-0.745	-0.298	0.078	1.198	**-2.468**	**2.376**	0.102	**-3.422**	-0.999	-1.758
P	***0.086***	0.972	0.477	0.265	0.557	0.471	0.771	0.939	0.254	**0.030**	**0.035**	0.920	**0.005**	0.338	0.104

MESOR: Midline Estimating Statistic Of Rhythm; 2A: double amplitude, a measure of the extent of predictable change within one cycle. SE: standard Error. Systolic and Diastolic MESORs and 2As in mmHg, Heart Rate MESOR and 2As in beats/min.

Discussion and Conclusion. This study clearly demonstrates the feasibility of ambulatory monitoring of BP and HR in adolescents as part of a school project, not only for just a day or two but for a prolonged span of up to 5 weeks. It shows that students can be motivated to learn about themselves while also having an opportunity to experience first-hand how their physiology is affected by a variety of factors such as exercise, the original topic of the project (12, 16). The data thereby collected are amenable to checking for a number of physiological results, such as important gender differences documented herein. They also provide a valuable reference standard in the light of which future monitoring can be interpreted for an individual assessment of change. Such an assessment was obtained by sphygmochron (17) for consecutive weeks of monitoring for all study participants. This analysis compares each subject's circadian (parametric and non-parametric) endpoints with time-specified reference values that are qualified by gender and age, by contrast with current practice that relies on the same threshold for all adults 18 years and older. The results herein clearly indicate the need to account for the prominent circadian variation and for gender differences in interpreting BP and HR data, even though the age range of the participants did not allow for an examination of changes as a function of age.

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THE MOON'S IMAGE IN PROLONGED HUMAN ISOLATION

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Abstract: An alternative hypothesis to the usual assumption of mere circadian desynchronization merits consideration in interpreting data collected during isolation from society, whether in buildings at or near the earth's surface or in caves underground (1, 2). Around-the-clock blood pressure (BP) and heart rate (HR) data collected during 267 days of isolation in a special habitat (like Lunar Base) known as Underlab in the Frasassi caves near Ancona, Italy, by a 28-year old woman show a stable and robust about 24.8-hour "lunar" component with a residual weaker near 24.0-hour synchronized cycle. Before as well as after isolation, only a strong 24.0-hour synchronized circadian rhythm is detected.
Aim: To assess the time structure of BP and HR in a clinically healthy woman under conditions of prolonged isolation, with focus on the circadian system and a possible lunar pull.
Background: Circadian was coined to account for a partly endogenous circadian system, when the period was found to differ slightly but statistically significantly from 24 hours in the absence of environmental synchronizers such as the alternation of light and darkness (3). The "circa" in "circadian" also implies that there is an inherent uncertainty in the determination of the period, due to measurement errors and primarily to the finite duration of the span during which a given variable is observed, not accounting for the added possibility that the period itself may not necessarily remain constant over time (1). The demonstration of free-running in the experimental laboratory relied on telemetry over prolonged spans on large numbers of animals. Lessons learned therefrom included a measure of the extent of inter-individual variability in the free-running period as well as inter-species differences in the average free-running period. In rats kept in continuous light of low intensity, the desynchronized circadian period of core temperature telemetered from ambulatory sham-operated animals averaged 24.8 hours, close to the lunar period (4). By contrast, the average period of animals after bilateral lesioning of the suprachiasmatic nuclei was close to 24 hours, albeit with a much larger inter-individual variation in period length. Unilaterally-lesioned animals, like sham-operated rats, also had an average period close to 24.8 hours (4). Human studies conducted in caves and in bunkers, while also documenting circadian desynchronization in the absence of major environmental clues, had to rely at first on self-measurements rather than automatic monitoring. Many studies in isolation also tended to be of shorter duration. Against this background, we analyze the about 1-year record of BP and HR measured automatically around-the-clock by a clinically healthy woman who spent 267 days in isolation.
Subject and Methods: K is a 28-year old clinically healthy woman. She used an ambulatory monitor (ABPM-630) from Colin Medical Instruments (Komaki, Japan) to automatically measure systolic (S), mean arterial (MA) and diastolic (D) BP and HR, mostly at 20-min intervals around-the-clock with few interruptions. She spent 267 days in the isolation of a laboratory near Ancona, Italy, from 26 July 1994 to 20 April 1995. Monitoring started 24 days prior to isolation and proceeded for another 69 days after completion of the isolation span. The original analysis of these data had revealed the presence of a circadian period longer than 24 hours but slightly shorter than 24.9 hours by chronobiologic serial sections. The circasemiseptan component (half-week) of heart rate was also found to be congruent with that of the geomagnetic disturbance index Kp (5).

The recent finding of desynchronized circadian rhythms assuming a period close to 24.8 hours discussed elsewhere in this volume prompted a re-analysis of these data to determine whether the free-

running rhythm of K also was close to the lunar period of 24.8 hours. The data were averaged over consecutive 3-hour intervals for association with environmental variables (local K, Kp, and cosmic rays) and analyzed by least squares spectra, separately before, during ad after isolation. The data collected during the first week of isolation were omitted to reduce any artifacts related to the transition from society to isolation. Spectra were computed in the frequency range from one cycle in 24, 252, or 69 days (before, during and after isolation, respectively) to slightly more than two cycles per day. The periods of components corresponding to spectral peaks were further assessed by nonlinear least squares according to Marquardt's algorithm (6). In order to examine whether the desynchronized circadian period varied with time, nonlinear analyses were also carried out in 8-week intervals displaced by 1 week during the isolation span, using a two-component model consisting of cosine curves with initial periods of 24.8 and 24.0 hours.

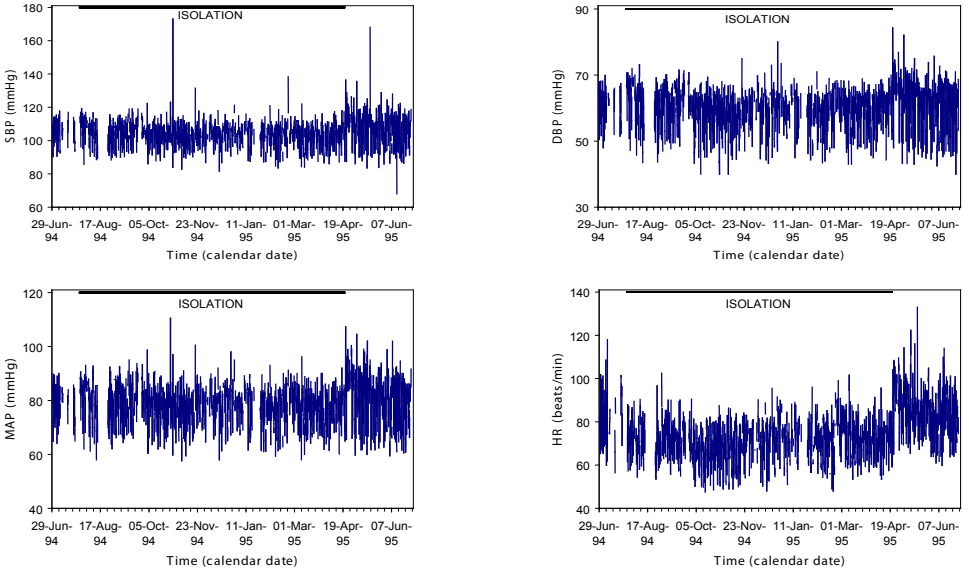

Figure 1. Time plots of systolic blood pressure, mean arterial pressure, diastolic blood pressure and heart rate of K (F, 28y) before, during and after isolation.

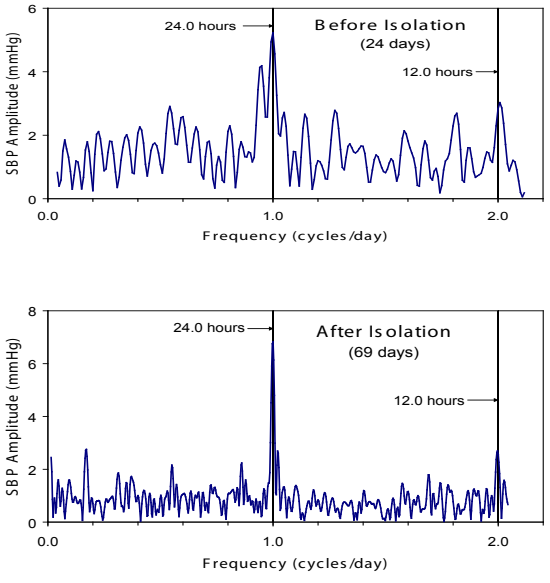

Figure 2. Least squares spectra of systolic blood pressure before and after isolation reveal the prominence of a 24.0-hour synchronized component as well as the presence of its second harmonic.

Results: The 3-hourly mean data for SBP, MAP, DBP and HR are plotted as a function of time in Figure 1. Except for an overall decrease in HR during isolation, the naked eye cannot discern the underlying time structure of these variables.

As expected, least squares spectra before and after isolation indicate the prominence of a 24-hour synchronized circadian component, as illustrated in Figure 2 for SBP. By contrast, during isolation the major spectral peak corresponds to a period of about 24.8 hours, as shown in Figure 3 for SBP. A much smaller spectral peak is also observed at 24.0 hours. Another spectral peak corresponding to a period of 12.32 hours is validated nonlinearly for BP but not for HR. Its period has a narrow 95% confidence interval (CI) extending from 12.31 to 12.33 hours.

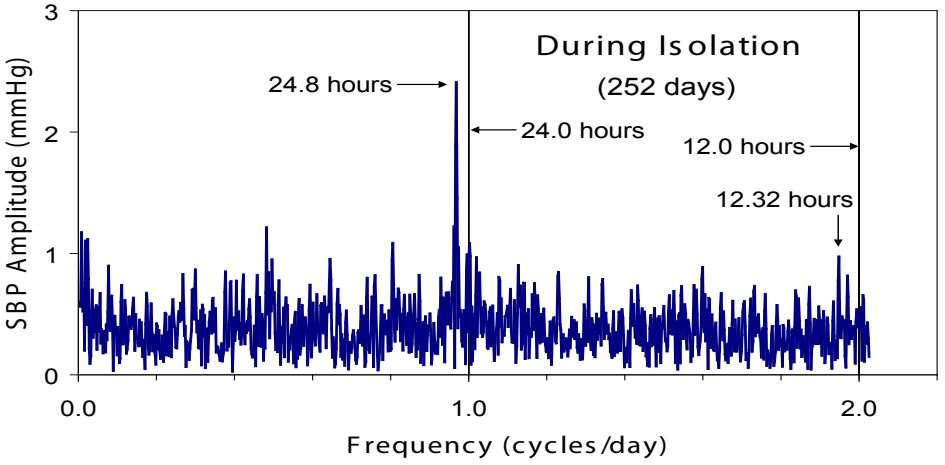

Figure 3. Least squares spectrum of systolic blood pressure during isolation (omitting data collected during the first week of isolation) reveal an about 24.8-hour component.

A model consisting of two cosine curves with trial periods of 24.8 and 24.0 hours was fitted nonlinearly to each variable during isolation. As seen from Table 1, both components are detected with statistical significance as the CIs of their respective amplitudes do not overlap zero, with the exception of the 24.0-hour component of DBP. The nonlinearly estimated period is invariably 24.80 hours for BP and 24.82 hours for HR, its 95% CI covering 24.8 hours. The period of the second component is invariably close to 24.0 hours, albeit the 95% CI does not cover 24.0 hours for SBP and MAP, Table 1.

Table 1	SBP		MAP		DBP		HR	
M	103.4		77.9		59.5		70.90	
95%CI	[102.7	104.1]	[77.23	78.60]	[58.9	60.1]	[70.0	
24.8h	24.80		24.80		24.80		24.82	
95%CI	[24.77	24.82]	[24.77	24.82]	[24.77	24.82]	[24.8	
A1	2.45		2.42		2.02		3.05	
95%CI	[1.44	3.45]	[1.45	3.39]	[1.18	2.85]	[1.79	
24.0h	23.93		23.92		24.01		23.96	
95%CI	[23.88	23.98]	[23.88	23.97]	[23.94	24.09]	[23.92	
A2	1.13		1.08		0.58		1.51	
95%CI	[0.13	2.12]	[0.11	2.04]	[-0.26	1.41]	[.25	

This global two-component model remains applicable throughout most of the isolation span, as seen from local nonlinear analyses carried out over an 8-week interval progressively displaced by

1 week. The desynchronized circadian component assumes a period close to 24.8 hours most of the time, except for the first interval that may still be influenced by the transition from society. The 95% CI that does not cover 24.0 hours, as illustrated in Figure 4A for SBP. Similar results are obtained for MAP, DBP and HR (not shown). Despite the much shorter (8-week) spans, the 24.8-hour component is detected with statistical significance most of the time, as seen from the non-overlap of zero by the 95% CI of the about 24.8-hour amplitude, shown in Figure 4B for SBP.

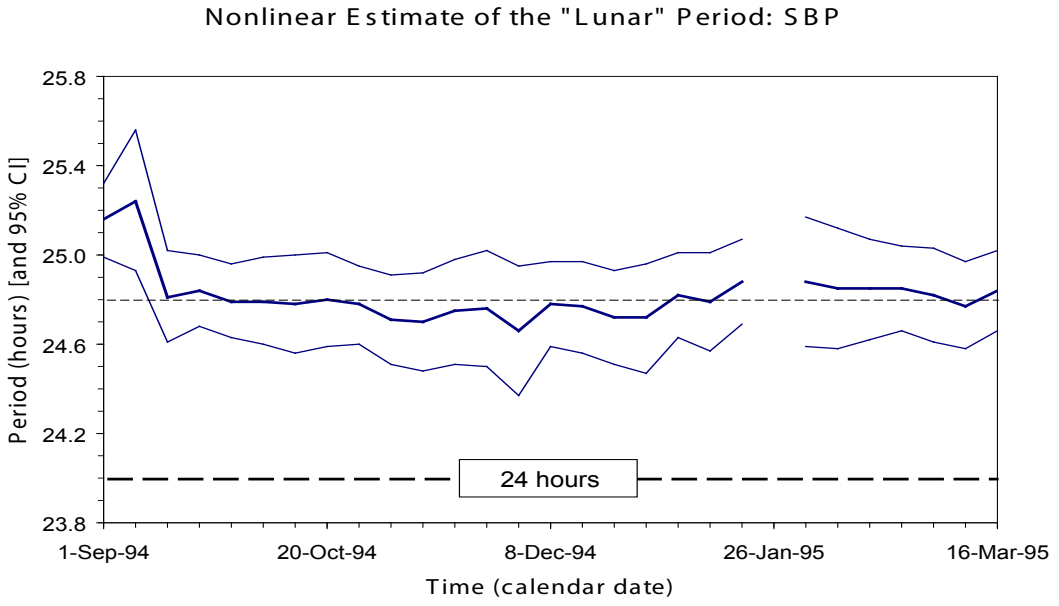

Figure 4A. The desynchronized circadian period of SBP remains close to 24.8 hours throughout isolation, its 95% confidence interval not covering 24.0 hours.

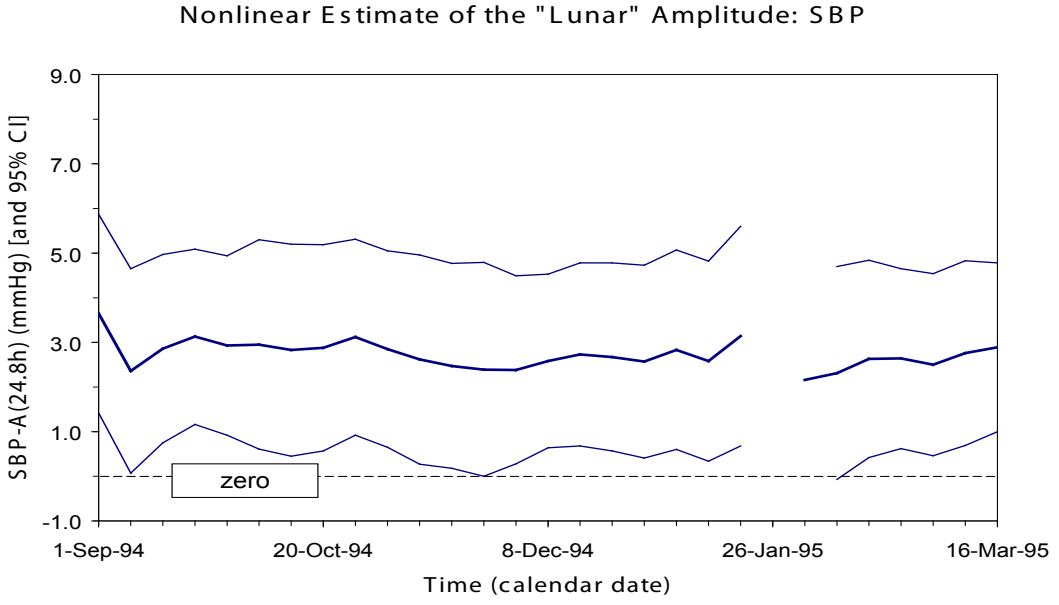

Figure 4B. Time course of the about 24.8-hour amplitude of systolic blood pressure, assessed nonlinearly, indicates the statistical significance of this component most of the time during isolation. Similar results are obtained for the three other variables (not shown).

Whereas the about 24.0-hour component also has a relatively stable period that remains close to 24.0 hours during isolation, as seen in Figure 4C for SBP, it is only detected with statistical significance in a few but not in the majority of the intervals considered, illustrated for SBP in Figure 4D. Similar results apply to MAP, DBP and HR (not shown).

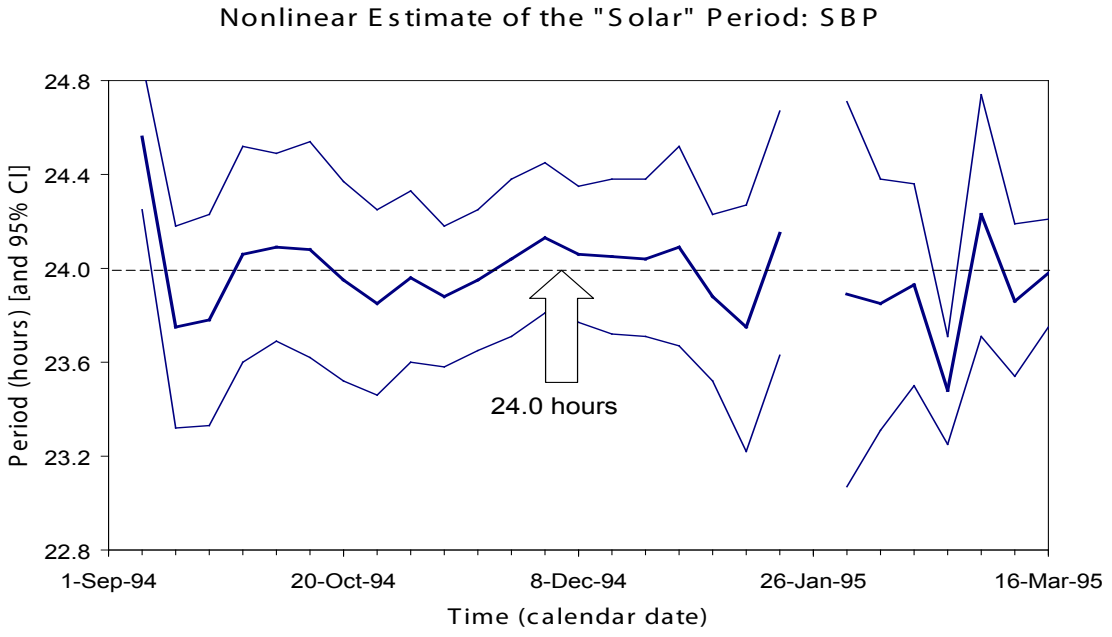

Figure 4C. Time course of the about 24.0-hour period of systolic blood pressure, assessed concomitantly with the about 24.8-hour component by nonlinear least squares during isolation, indicates relative stability over time, the 95% CI remaining shorter than 24.8 hours, except for the first interval likely influenced by the transition from society.

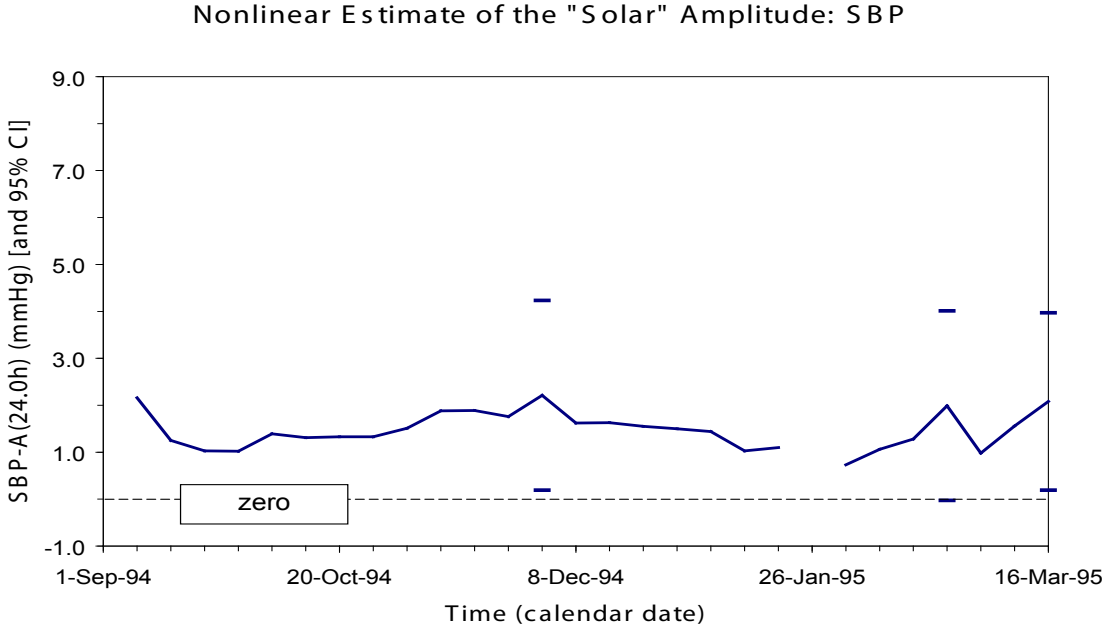

Figure 4D. Time course of the about 24.0-hour amplitude of systolic blood pressure during isolation only shows occasional statistical significance by the non-overlap of zero by the 95% CI.

Discussion and Conclusion: For the entire 267 days of social isolation, the BP and HR of K were characterized by a strong and stable about 24.8-hour component, whereas a much weaker about 24.0-hour rhythm remained demonstrable overall but only in a few of the 29 8-week intervals examined. Desynchronization from 24.0 hours in human isolation studies is not new, but this thoroughly examined case raises the question whether deviation from 24.0 hours preferentially assumed a period of 24.8 hours, close to twice the tidal period. Evidence reviewed elsewhere in this issue suggests that it may not necessarily be only a chance event. The possibility of a pull by the moon in the absence of strong 24.0-hour synchronizers deserves further investigation. For this purpose, the dense and automatically collected data of K represent a great asset amenable to additional analyses from a fresh new perspective.

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Dedicated to the memory of Maurizio Montalbini (1953-2009) who had “hoped it [the study chrono-meta-analyzed herein] would provide valuable insight into the natural cycles of the body”. Indeed, he achieved more; he demonstrated natural solar and lunar cyclicities and their continued response (resonance with) geomagnetism through which the lunar effect might be mediated.

URINARY OUTPUT AND GEOMAGNETISM REVISITED

Germaine Cornélissen[1], Franz Halberg[1], Judy Finley[1], Faithe Thomas[1], Jarmila Siegelova[2], Jiri Dusek[2], Bohumil Fiser[2]

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In 1989, Payne et al. (1) concluded that urinary metabolite retention is periodic in nature insofar as in 815 patients presenting as emergency admissions in two hospitals in Great Britain, a higher incidence of urinary retention was observed during the new moon in comparison with the other phases of the lunar cycle, a finding prompting our chrono-meta-analysis herein. No association was found by the original authors between urinary retention and circadian, monthly and seasonal periodicity.
We confirm Payne et al.'s (1) negative finding only when we test for a circannual component separately. When in turn we use a combined linear-nonlinear approach to concomitantly fit a year and a half-year by the nonlinearly extended cosinor (2-4), we find, Figure 1, that the combined model is statistically significant ($P<0.02$). Both tested components are present, and with this model, the geomagnetic half-year matches the contribution of the seasons.
The half-year has been associated with geomagnetism by Chapman (5) as reviewed (6) with biospheric associations (7). That it may influence human water metabolism is suggested by a study of nocturia of a 54-year-old man with benign prostatic hypertrophy, who recorded for about 4 years the number of times he awoke each night to urinate (8). These data have been reanalyzed by the methodology of chronomics, the mapping of time structures (chronomes), involving the computation of least squares spectra of the urinary record and of environmental variables recorded during the same 4-year span. In addition to the previously reported monthly variation (8), other periodicities have been documented, including two separate components with periods of one week and of a near-week, Figure 2 (9). The precise 7-day component may be a mainly exogenous resonance with external influences such as a weekly social schedule, whereas the near-week may be a resonance with natural changes in geomagnetics, reflecting in part changes in other non-photic natural environmental factors. Table 1 shows congruent periods in nocturia and geomagnetic activity (9), and Figure 3 congruence between geomagnetics and heart rate of a woman isolated from society in a cave specially designed for studies of natural periods in and around us (10). Congruence is also apparent for nocturia in Figure 4, all extending the scope of Figure 1.

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

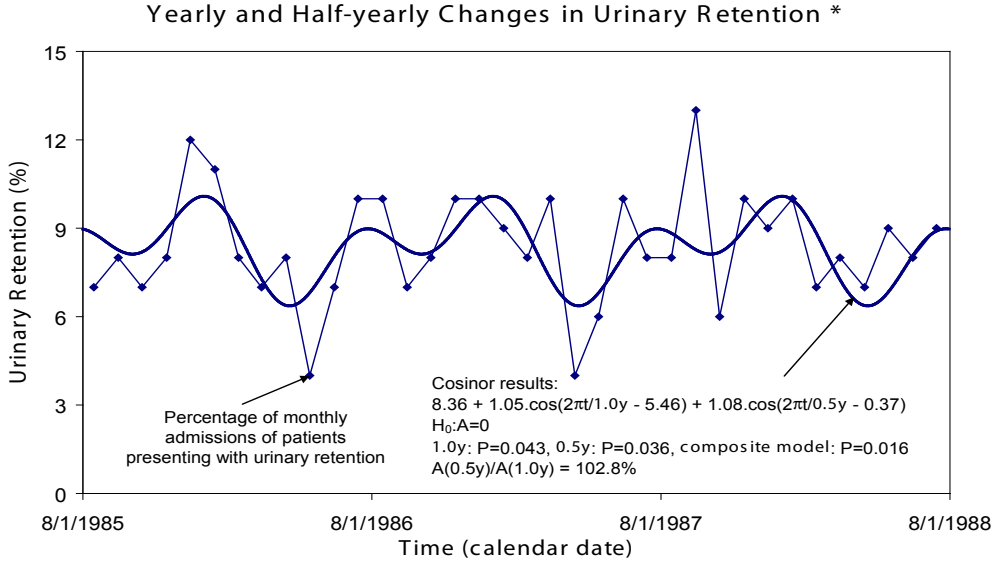
Table 1. Major periods of nocturia and geomagnetic activity*

	Nocturia			Kp		
Trial Period (days)	Period	(95% CI)	Amplitude	Period	(95% CI)	Amplitude
			Different Behavior			
365	349.8		0.15	432.2		0.11
	(320.7; 378.9)		(0.05; 0.25)	(363.3; 501.2)		(0.0; 0.23)
182.5	—		—	181.8		0.3
				(177.3; 186.3)		(0.19; 0.42)
			Similar Behavior			
26	26.22		0.13	26.42		0.17
	(26.03;26.40)		(0.03; 0.23)	(26.24; 26.59)		(0.05; 0.28)
7 **	7.007		0.14	7.021		0.15
	(6.992; 7.022)		(0.02; 0.27)	(7.004; 7.038)		(0.00; 0.29)
6.85 **	6.87		0.11	6.879		0.14
	(6.849; 6.889)		(0.00; 0.22)	(6.862; 6.895)		(0.00; 0.29)

** Assessed concomittantly

* CI: Confidence Interval. Although the 95% CIs of the circannual periods of nocturia and Kp partly overlap, the behavior of the two variables differs in that for nocturia, the period is not statistically significantly different from one year, but for Kp it is statistically significantly longer than one year (when series longer than 4 years are analyzed). The difference in behavior also related to the fact that nocturia is characterized primarily by an about-yearly variation, whereas Kp has a much more prominent half-yearly variation, which is not detected for nocturia.

Chrono-meta-analysis revealing that in a population of 685 patients, resonance with the geomagnetic half-year more than matches resonance with the seasons, as gauged by the 0.5-year/1.0-year amplitude ratio



* Payne SR, Deardon DJ, Abercrombie GF, Carlson GL. BMJ 1989; 29: 1560-1562.

Figure 1. Chrono-meta-analysis of Table II from (1) on the number of patients per month presenting with acute urinary retention in Portsmouth. © Halberg.

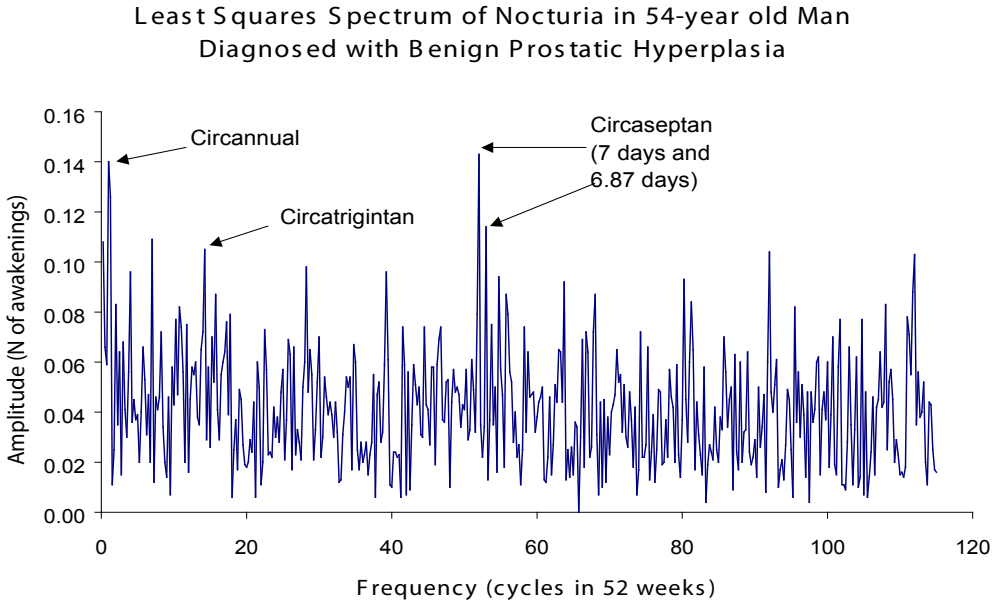
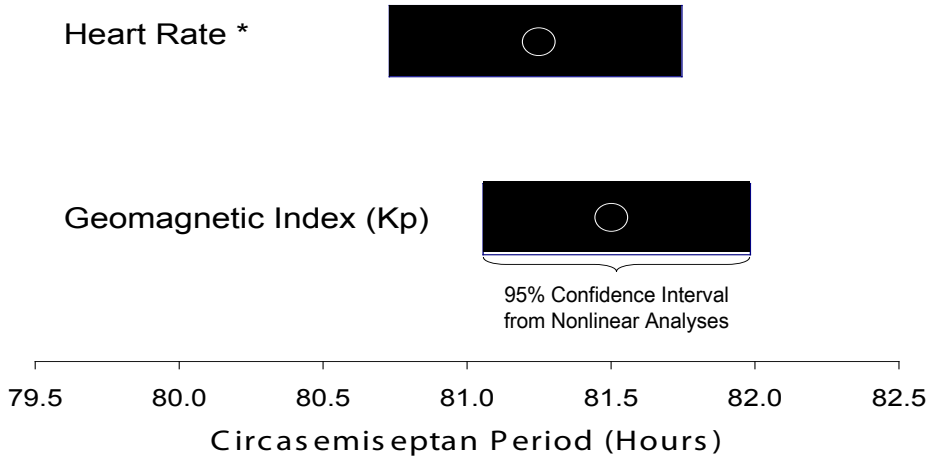


Figure 2. Anticipated spectral peaks resolved with their uncertainties by linear-nonlinear rhythmometry (2-4). In particular, two separate components in the circaseptan range deserve further study. Their relative prominence, gauged by the amplitude difference in nocturia, may be aligned with a similar difference in geomagnetic activity. The 6.87-day period is similar to the natural geomagnetic activity and the 7-day period is probably anthropogenic, yet in each case there is only a frequency and no phase synchronization, pointing to resonance without phase lock-in. By contrast to Figure 1, a half-year could not be demonstrated for nocturia in this patient. © Halberg.

DO GEOMAGNETIC DISTURBANCES AFFECT HUMAN PHYSIOLOGY?



* 28-year old woman (K) during 267 days of isolation from society (26 July 1994 to 20 April 1995).

Figure 3. Even if temporal relations are not necessarily causal, a possible influence of geomagnetics on human HR is suggested by closeness of circasemiseptan period reached nonlinearly for HR (monitored automatically around the clock for 267 days of isolation from society) and Kp, a global geomagnetic disturbance index (recorded every 3 hours during the same span) (10). © Halberg.

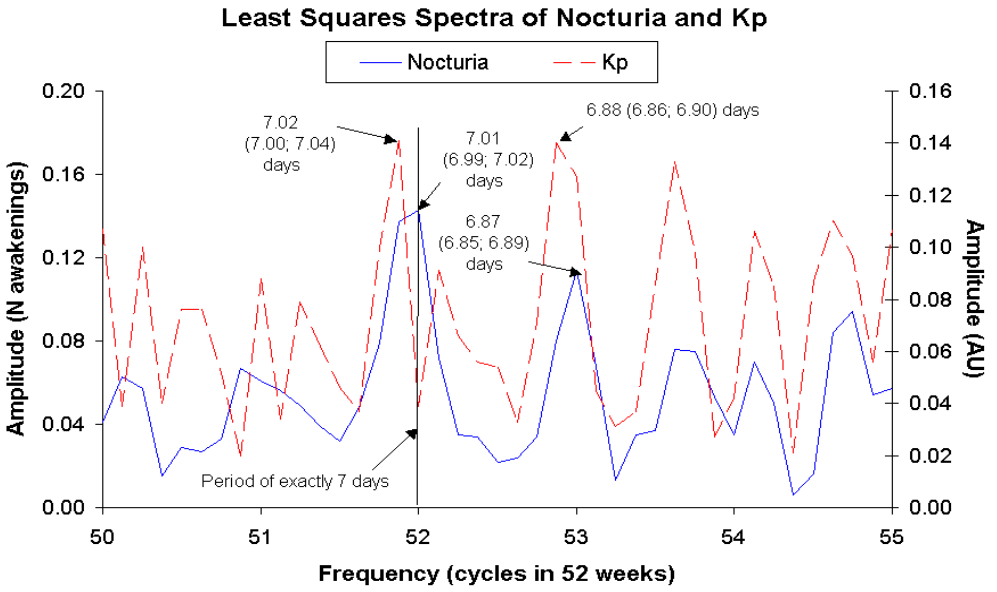


Figure 4. Similarity in the circaseptan range of spectra on nocturia and the planetary geomagnetic index Kp, both with more than a single about 7-day component. One component in nocturia corresponds to the social week. It is almost certainly societal, of anthropogenic origin. It is close to a spectral peak for the geomagnetic index Kp, which in this record happens to be characterized by a period slightly but statistically significantly longer than precisely 7 days (52 cycles in 52 weeks, vertical line), as gauged by its 95% confidence interval. The next peak to the right corresponds to a component with a period of 6.87 (nocturia) or 6.88 (Kp) days, also resolved by nonlinear least squares. The about 6.88-day component in Kp, albeit wobbly, is almost certainly natural environmental, as reported earlier (11, 12), and may pull, if not synchronize, a built-in component of similar period length in nocturia.

CIRCASEMIDIAN AND CIRCASEMISEPTAN GAUGES OF VASCULAR ADJUSTMENT AFTER TRANSMERIDIAN CROSSING OF THREE TIME ZONES

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A temporal microscopy (microchronometry, a term suggested by the senior author, or perhaps microbiochronometry) applied by the cosinor (1-3) to consecutive intervals of a time series is the counterpart of serial sections used in histology. It serves to reveal rhythms as the counterpart of cells, with the anticipation that some rhythm alterations may precede cellular change and could thus provide useful harbingers for preventive action. This approach can be used for analyses revolving around the abundant literature dealing with transmeridian dyschronism (jet lag) and related problems (4-15) by considering mainly the 24-hour component, usually without parameter estimation after prior hypothesis testing, with only exceptional concern with circaseptans (16-19), circasemiseptans (19, 20) and circannuals (21), and without consideration of other non-photic (22) components. It seems the more important to include an assessment of second harmonics of both the circadian and circaseptan components (with periods of 12 and 84 hours, respectively). We herein consider circasemidians and circasemiseptans with circadians and circaseptans, the former two components considered in their own right and as second harmonics accounting for non-sinusoidality. With certain interval lengths chosen for analysis by chronobiologic serial sections on data involving flights across only a few (here three) time zones and a return trip by ship rather than air, these harmonic terms happen to be sensitive and the only gauges of adaptation.

Systolic (S) and diastolic (D) blood pressure (BP) and heart rate (HR) were automatically measured with a TM-2421 monitor (A&D, Tokyo, Japan) at half-hour intervals before, during and after an arctic tour from 20 July to 4 August 2005. Serial sections on these and bracketing data, extending until 22 August 2005 were performed by the separate fit of cosine curves with trial periods (τs) of 168, 84, 24 and 12 hours. Departure from the USA was on July 18 to Anchorage, Alaska, USA, and from there to Anadyr, Russia (64˚44'N, 177˚20'W). Return was from Resolute, Nunavut, Canada, 74˚42'N, 95˚10'W, on August 4, 2005. Intervals were chosen to cover by their length 4 to 8 cycles in the case of circadian and circasemidian analyses, or 2 to 4 cycles in the case of circaseptan and circasemiseptan analyses. They were displaced by increments of 12 or 24 hours for the case of circadian-circasemidian and circaseptan-circasemiseptan analyses, respectively. The circadian and circaseptan rhythms remain environmentally synchronized, as apparent from the horizontal time course of their acrophases, Figures 1-3. By contrast, their second harmonics show the major phase adjustments for each of the variables examined. Whether we deal with changes in the waveform of the circadian system or with an ~12-hour oscillation in its own right (23) remains to be determined and cannot be inferred from their different behavior during adjustments.

Analyses by sphygmochron (24) of 7-day/24-hour records of BP and HR routinely consist of the concomitant fit of cosine curves with τs of 24 and 12 hours to account for the traditional

approximation of the usually non-sinusoidal circadian waveform of these variables. Determining the time of maximum of such a composite model (orthophase) with an estimate of uncertainty (95% confidence interval) was achieved in the context of cancer chronotherapy with adriamycin (25, 26). The addition of harmonic terms to describe the circadian waveform was illustrated for the case of inter-beat intervals (27). Analyses of such R-R intervals to derive the correlation dimension as a measure of fractal scaling indicated the critical role of the 12-hour component to separate healthy men from patients with coronary artery disease (28). Harmonic terms indeed may be more sensitive gauges, notably for adjustments after flights over a few time zones: a 3-hour shift as in the case here reported corresponds to a 90˚ change in phase by the 12-hour component, but only to a 45˚ change in phase by the 24-hour component. The 12-hour and 24-hour components could be routinely included in the study by 24- and 168-hour cosinor analyses of transmeridian or shiftwork-related adjustments. *Conclusion.* Harmonic terms could be routinely used to study adjustments to changes in schedule, provided they contribute with statistical significance to the waveform of the fundamental rhythm(s) of interest and, much more generally, for studies in health and disease.

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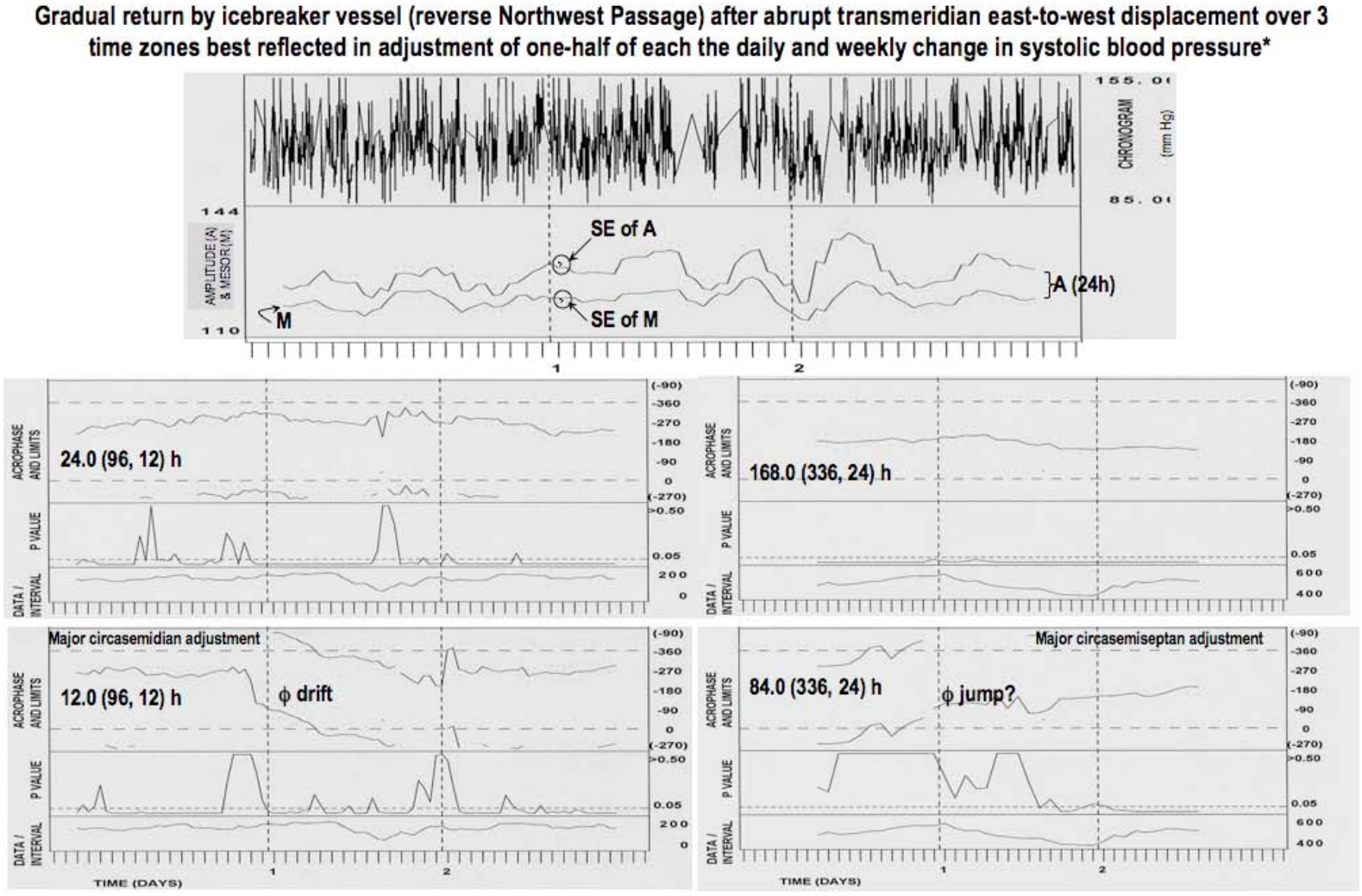

Figure 1. For systolic blood pressure (SBP), with the intervals chosen for analyses, the major adjustment along the 24-hour scale is gauged by the 12-hour cosine fit (bottom left). The 84-hour component suggests, but does not validate, a jump in phase since it is statistically significant too briefly before the return home and thereafter. © Halberg.

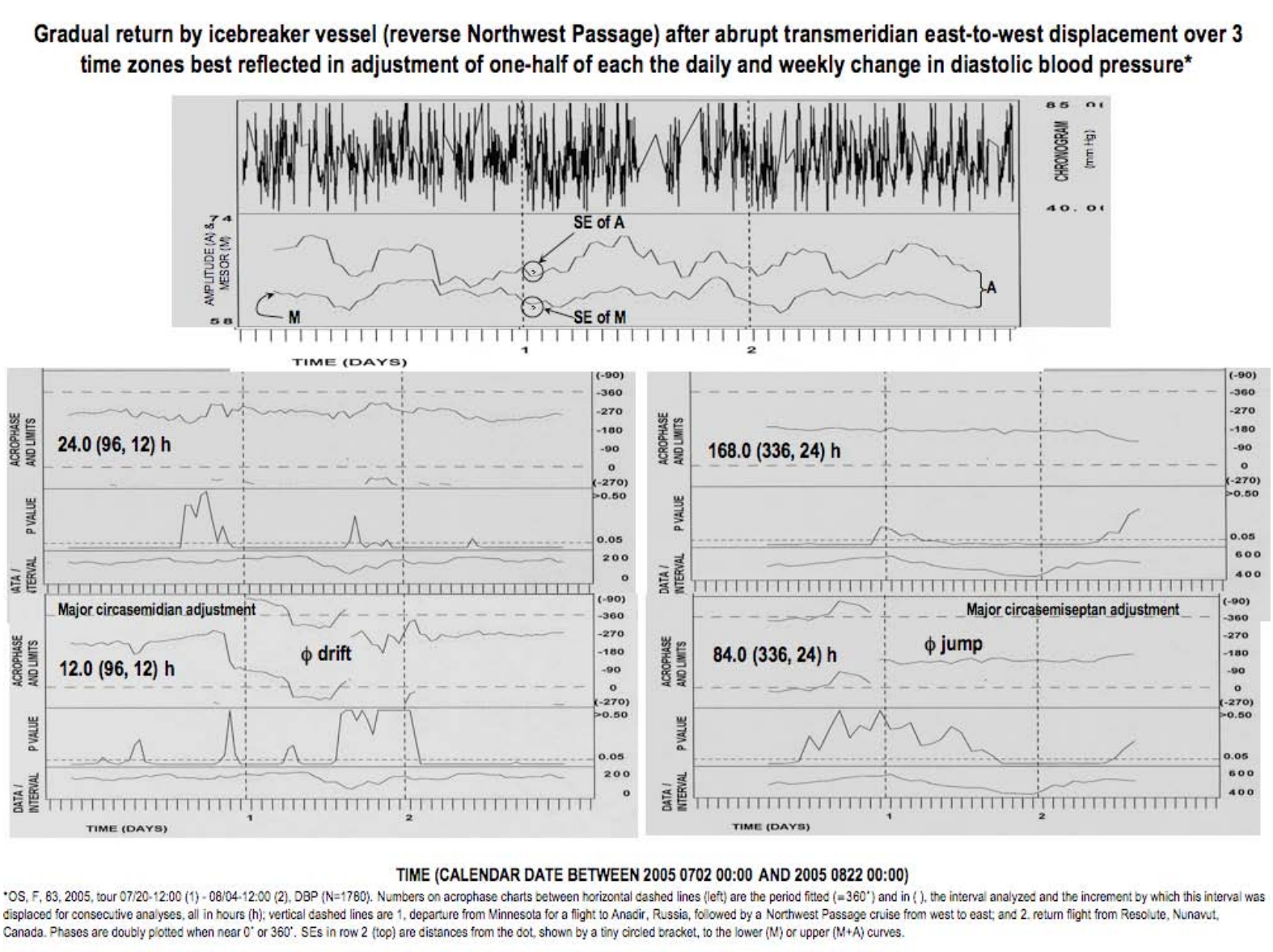

Figure 2. For diastolic (D), as for systolic (S) blood pressure (BP), the 24- and 168-hour components with the intervals chosen for analyses show a steady course of their acrophases while their harmonics jump in phase, even when inference is limited to the statistically significant sections analyzed. © Halberg.

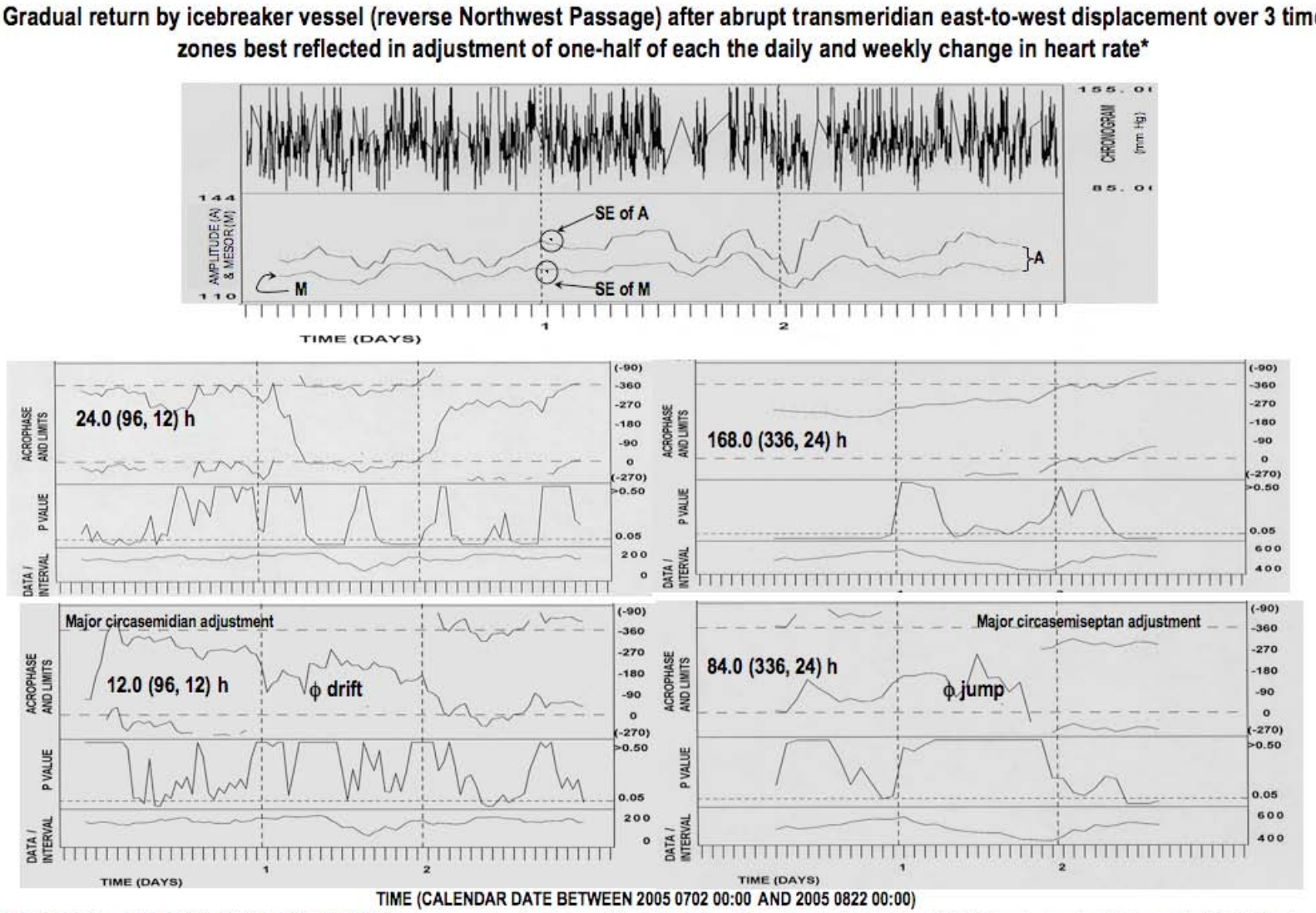

Figure 3. For heart rate (HR), noise clouds acrophase behavior and the acrophases of components that are not statistically significant cannot rigorously distinguish a gradual shift from a sudden jump. © Halberg.

A FAR-TRANSYEAR IN THE BLOOD PRESSURE OF A 17-YEAR-OLD MALE

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While a father (YW) self-monitored blood pressure (BP) and heart rate (HR) automatically half-hourly for decades, FW, his clinically healthy boy, has self-measured these variables as a follow-up on dense neonatal monitoring (1-14). This paper updates an earlier report on a far-transyear, a spectral component with a period, τ, longer than a year by several months (11). With Figure 1, we here document again, with added data, that in both systolic (S) and diastolic (D) BP FW has, during ages 8-17, a far-transyear, defined broadly as a spectral component with a τ longer than a year (y) -- trans = beyond (1 year length) -- by several months (1.2 years $\leq [\tau$ - CI {95% confidence interval}] < $[\tau$ + CI] < 1.9 years), to be distinguished from a near-transyear (1.00 year < $[\tau$ - CI {95% confidence interval}] < $[\tau$ + CI] < 1.20 years) (15). The far-transyear is the major peak in the para-annual region for both SBP and DBP, even when a peaklet is present at a trial period of precisely 1 year, notably for DBP. By contrast for HR, Figure 1 shows a peak at the calendar year that is numerically slightly larger in amplitude than that of the also-present far-transyear.

Discussion. A transyear (T) characterizes decades-long series of blood pressure and heart rate from 13 adults, mimicking, by the range of CIs (95% confidence intervals) of its periods, τ, the range of CIs of τs of several physical variables, and further the incidence pattern of myocardial infarctions (MIs) (15, 16). A transyear can coexist for a while with a calendar-year component (Y) in the same and/or in different geographic locations in sudden cardiac death (16, 17), and is found in terrorism (18), natality (19, 20), epilepsy (21) and stroke (22), among other conditions. A selective assortment of biospheric-environmental congruences in period is often encountered in the infradian spectral range as already noted in this case (11) and others (23).

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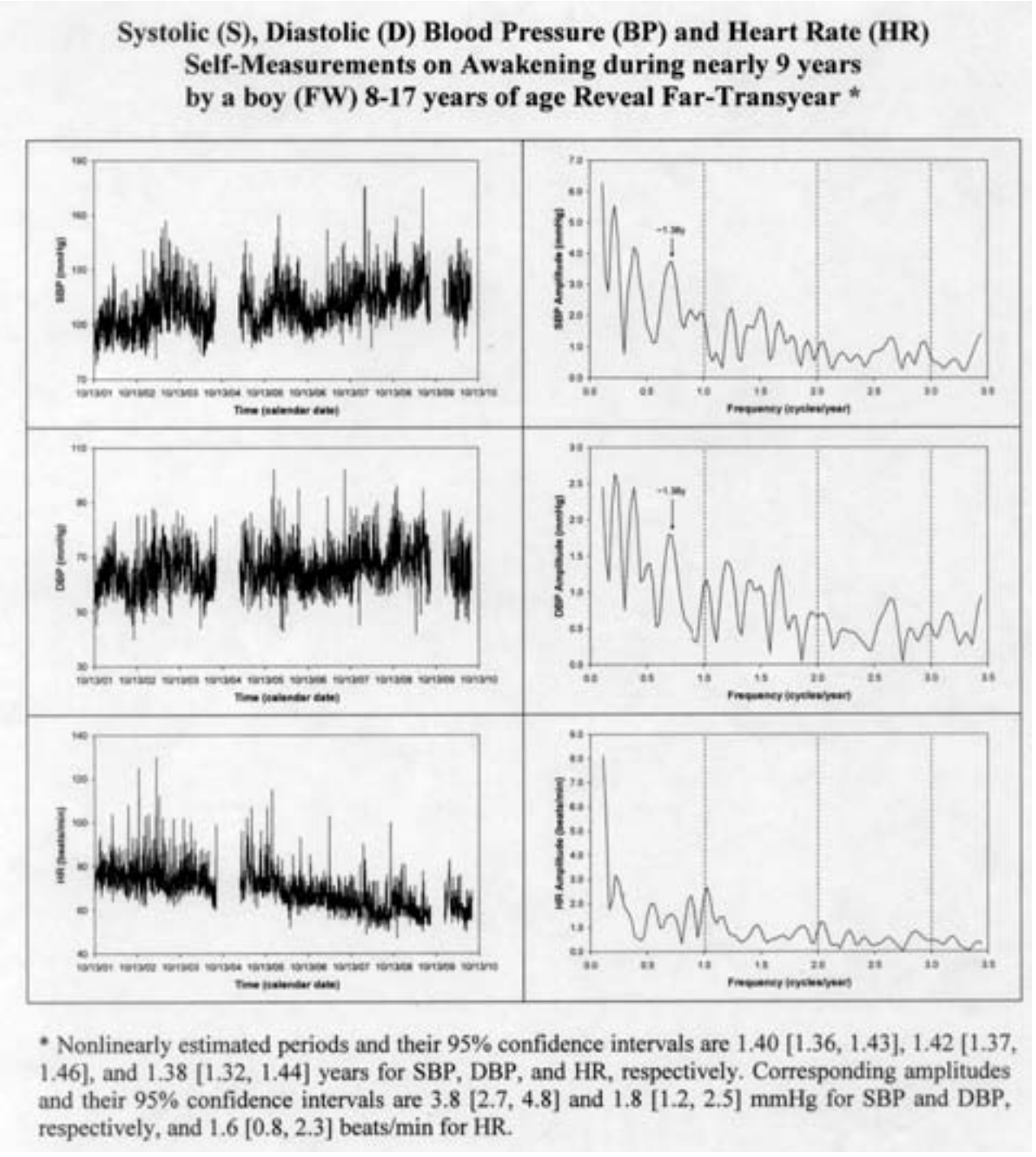

Figure 1. Prominence of 1.38-year far-transyear, gauged by amplitude, A, exceeds the A estimate at the trial period of a calendar year in systolic and diastolic blood pressure. Heart rate has a slightly more prominent calendar-yearly component. © Halberg.

CHRONOBIOLOGICALLY INTERPRETED ABPM (C-ABPM) IN DELAYED SLEEP PHASE SYNDROME

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We here introduce chronobiologically interpreted blood pressure (BP) and heart rate (HR) monitoring with analyses of the time series as a whole (globally) and/or in sections of the data (locally), i.e., glocally, to study a delay in the timing of the habitual sleep span usually uninterpreted for biospheric and environmental interactions, the topic of chronomics. A chronomic analysis aligning physiological data with environmental ones remains to be carried out.

Case reports

HS. Suddenly, patient HS (M, 41 y) could not go back early in the morning to work at his company, where he made drawings. He came to our hospital with a relatively severe to absolute inability to advance his sleep time (phase) to earlier hours by enforcing conventional sleep-wake times. He was diagnosed with a delayed sleep phase syndrome (DSPS) because of his sleep-wake logs, kept for 3 prior weeks, documenting a consistent habitual pattern of sleep onset, later than 3 am, and lengthy sleeps. He monitored his BP and HR around the clock at 30-minute intervals before and after bright light (5000 lux for 2 hours [h]/day) therapy administered first in the afternoon, then progressively earlier in the day, with the rate of advance being 1 h/week. Monitoring started on 26 Feb 1998 and lasted until 10 Jul 1998. Treatment started on 2 Apr 1998 and succeeded in allowing the patient to sleep and work on the regular societal activity schedule.
YW. For a while, patient YW (M, 35 y) could not go to his office early in the morning because his sleep phase was delayed toward early morning. He could not go to bed before 3 am. He understood that something was happening in his body. Every day when he got up, he felt general fatigue. Some days, he did not retire until nearly 4:30 am. In spite of this unacceptable condition, he had worked hard in his office from morning to midnight. One day, he did not leave his office until the sun was rising. As a physician, he realized that he had a sleep disorder and knew about treatment methods that claimed to adjust the time of retiring. He tried to do a sort of chronotherapy by will power, not a chronotherapy by bright light. Forcing himself to go to bed before 1 am was very difficult on his ordinary routine, but he eventually succeeded in advancing his bedtime to that of his society.

Method

The data were analyzed by chronobiologic serial sections. In this approach, a cosine curve with a given period is fitted by cosinor to data in a given interval progressively displaced in increments throughout the time series. Least squares spectra were also obtained to provide an overall assessment of the time structure of BP and HR during specified spans. Periods corresponding to spectral peaks were used as initial values in nonlinear analyses that estimate the period as well as the MESOR, amplitude and acrophase, each parameter with its CI (95% confidence interval). The extended cosinor (1-3) with Marquardt's algorithm was used, with several models that allowed all periods to vary, or

only some of them, with or without harmonic constraints.

Results

In the case of HS, chronobiologic serial sections, obtained using a 7-day interval displaced with 1-day increments, indicate that treatment (starting at the vertical dashed line) was associated with a gradual advance of the 24-h acrophase in systolic (S) and diastolic (D) BP, Figures 1 and 2, as well as HR, Figure 3. The circadian rhythm was invariably the most prominent component in the least squares spectra in all data, Figure 4, in the section before treatment, Figure 5, and in that summarizing data after the start of light therapy, Figure 6. A summary at a trial period of 24 h confirms that for all three variables, the CIs of the acrophase after start of treatment did not overlap the corresponding CIs before treatment (Table 1). For SBP and DBP but not for HR, the 24-h amplitude increased on treatment.

A two-component model consisting of cosine curves with trial periods of 24 and 12 h (with no constraint of harmonicity) was fitted by nonlinear least squares to data in each of the 5 spans (before treatment and to 4 separate spans after start of treatment). In each case, the model was found to be statistically significant, each component contributing to the overall variability in the data with statistical significance (Table 2). In all instances, estimated periods were close to 24 and 12 h and their CIs covered 24 and 12 h, respectively.

Least squares spectra, computed over the entire about 4-month span, over the about 1-month span before treatment, and over the entire about 3-month span on treatment, all had the two major spectral peaks corresponding to frequencies of one and two cycles per day (Figures 4-6). Only before treatment had the circasemidian component a period slightly longer than 12 h in the case of SBP and DBP but not HR (Figure 5). The period of 12.3 h is very close to the tidal period. In the case of all three variables, there was then another smaller spectral peak in the circadian region corresponding to a period of about 26.4 h (Figure 5), no longer detected after the start of treatment (Figure 6).

Accordingly, a model consisting of a cosine function with a fixed 24.0-h period and of cosine functions with trial periods of 26.4 and 12.3 h was fitted to data before the start of bright light therapy. All components are found to contribute with statistical significance to the model, except for the about 12.3-h component of HR (Table 3), in keeping with the results of least squares spectra. When a slightly different model was used in which the trial period of 24.0 h was allowed to vary, similar results were obtained, the estimated circadian period being very close to 24.0 h with a CI overlapping 24 h.

These results indicate that for patient HS, DSPS was associated with the presence of a second circadian component that had a period longer than 24 h, albeit of lesser prominence than the concomitantly present 24.0-h synchronized component. DSPS was also associated with a desynchronization of the 12-h component of BP but not of HR. Bright light therapy restored a 12-h synchronized circasemidian component and amplified the 24-h synchronized circadian amplitude of BP but not that of HR. The secondary circadian component with a period of about 26.4 h was no longer detected with statistical significance after the start of bright light therapy.

Figure 7 shows acrophases before, during and after YW's DSPS. Non-overlapping CIs of acrophases indicate the statistical significance of the phase delay in all three variables investigated (not shown). Figure 8 shows the very great prominence of the 24- and 12-h components. Therefore, these two components were fixed for follow-up extended cosinors, to prevent them from interfering with the estimation of any 24.8- and 12.4-h components. These data were fitted by four models in all of which the periods of the two dominant components (24 and 12 h) were fixed. In model 1, the 24.8- and 12.4-hour components were allowed to vary without constraint; in models 2 and 3, only the 24.8 h or the 12.4 h component was added to the fixed 24-h and 12-h cosine curves; and in model 4, both were allowed to vary, but constrained to be harmonically related. Model 2, fixing the 24.0 and 12.0 components and allowing the 24.8-h period to vary, was found to fit the data well before and during

DSPS. Before the span with DSPS (1 Jan-12 Mar 1988), the period of SBP was estimated as 24.70 h [CI: 24.59, 24.82] and its double circadian amplitude was 4.88 [2.06, 7.70] mmHg by comparison with double amplitudes of 20.62 and 14.16 mmHg for the 24.0 h and 12.0 h components, respectively. The DBP period was 24.65 h [24.53, 24.76] with a double amplitude of 4.04 [1.82, 6.28] mmHg by comparison with double amplitudes of 16.14 and 11.38 mmHg for the 24.0 h and 12.0 h components, respectively. In the case of HR, the period was 24.69 h [24.55, 24.83] with a double amplitude of 3.50 beats/min [1.16, 5.86] by comparison with double amplitudes of 14.56 and 9.94 beats/min for the 24.0 h and 12.0 h components, respectively. During DSPS (13 Mar-25 Aug 1988), the SBP period was 24.75 h [24.66, 27.84] with a double amplitude of 1.74 mmHg and a CI slightly overlapping zero [-.04, 1.77]. The period of DBP was 24.72 h [24.66, 24.78] and its amplitude 2.10 mmHg [0.62, 3.58]. For HR, the period was 24.76 h [24.68, 24.83] with an amplitude of 1.84 beats/min [0.20, 3.50]. After the DSPS (18 Sep-31 Dec 1988), the more complete model 4 allowed the demonstration of both ~24.8 h and ~12.4 h components for BP but not HR. The estimated fundamental periods were 24.75 h [24.69, 24.80] and 24.75 h [24.70, 24.80] for SBP and DBP, respectively, with corresponding double amplitudes of the ~24.8 h component of 1.88 [-.04, 3.78] and 1.36 [-.04, 2.78] mmHg and of the second harmonic of 2.16 [0.24, 4.08] and 1.70 [0.28, 3.10] mmHg, respectively.
The decimals in all of these results are given only to indicate, in the case of periods, the presence or absence of overlap by CIs of 24.8 and 24.0 hours and in the case of double amplitude, the absence or presence, and in the latter case the extent of an overlap of zero. No quantitative importance beyond the foregoing considerations is attached to the decimals.

Discussion

Elsewhere, we show that an actual frequency change in a time series results in multiple peaks, as does a phase change. Therefore, a glocal analysis is recommended in dealing with any ecfrequentia that has been found in blind individuals by Emens et al. (5), who have reviewed the literature on circadian clocks and free-running, terms and concepts coined by analogy to a free-running oscillator in the early 1950s (6, 7). The finding of a 26.4-h period could be simply a free-running desynchronized period with the 24-h period masking it (5). An earlier finding of a 24.7h period (only) in the SBP and reported without a confidence interval in 1973 (in a blind boy for, one year after a bilateral retinoblastomectomy during 14 days at home), was not analyzed in the circasemidian region of the spectrum (8; cf. 9).
The finding of a near-tidal period of 12.3 h in BP but not in HR of HS during DSPS and in YW only after DSPS lets us question the pertinence of a tidal period (10) to the DSPS. More generally, tidal components deserve consideration since the double tidal 24.8-h period was found in a selenosensitive woman (9); it certainly cannot be generalized, but it provides an objective basis for lunar effects when the double tidal period (10) appears in her self-ratings of vigor in two untreated adynamic episodes and the 24.8 h period is also found in SBP and HR (and a 24.75-h period in DBP in the third desynchronized episode as the dominant components with the largest amplitudes). Whether a lunar cycle occurs in some others is a possibility with a precedent in the longest study in isolation from society for 267 days in a cave (11, 12).
In the circaseptan spectral region, a selective pull of geomagnetics is documented for a physiological variable, HR, but not for BP which remained societally 7-day synchronized (13). A selective assortment characterizes environmental-biospheric congruences of periods (14). Gravity may act by inducing currents piezoelectrically (15) or via positive holes (16) that reach the earth-air interface. From this viewpoint, the presence of a longer-than-12-h semidian component in HS and after DSPS in YW deserve attention. Whether we deal with free-running, also from the moon in the case of

24.8-h periods, is also at variance with data on rats that show an average 24.8-h period in continuous light of low intensity, in keeping with lunar synchronization (17). A second circadian component in subjects with and without DSPS with a period longer than 24 h and the presence of a trans-semidian (trans = beyond, i.e., longer than a 12-h) component remain to be investigated on added subjects. If the methodologic aspect of this paper introduces a glocal approach, i.e., the analysis of time series as a whole, globally and in sections, it will have served its purpose, but any effects of the moon remain a challenge.

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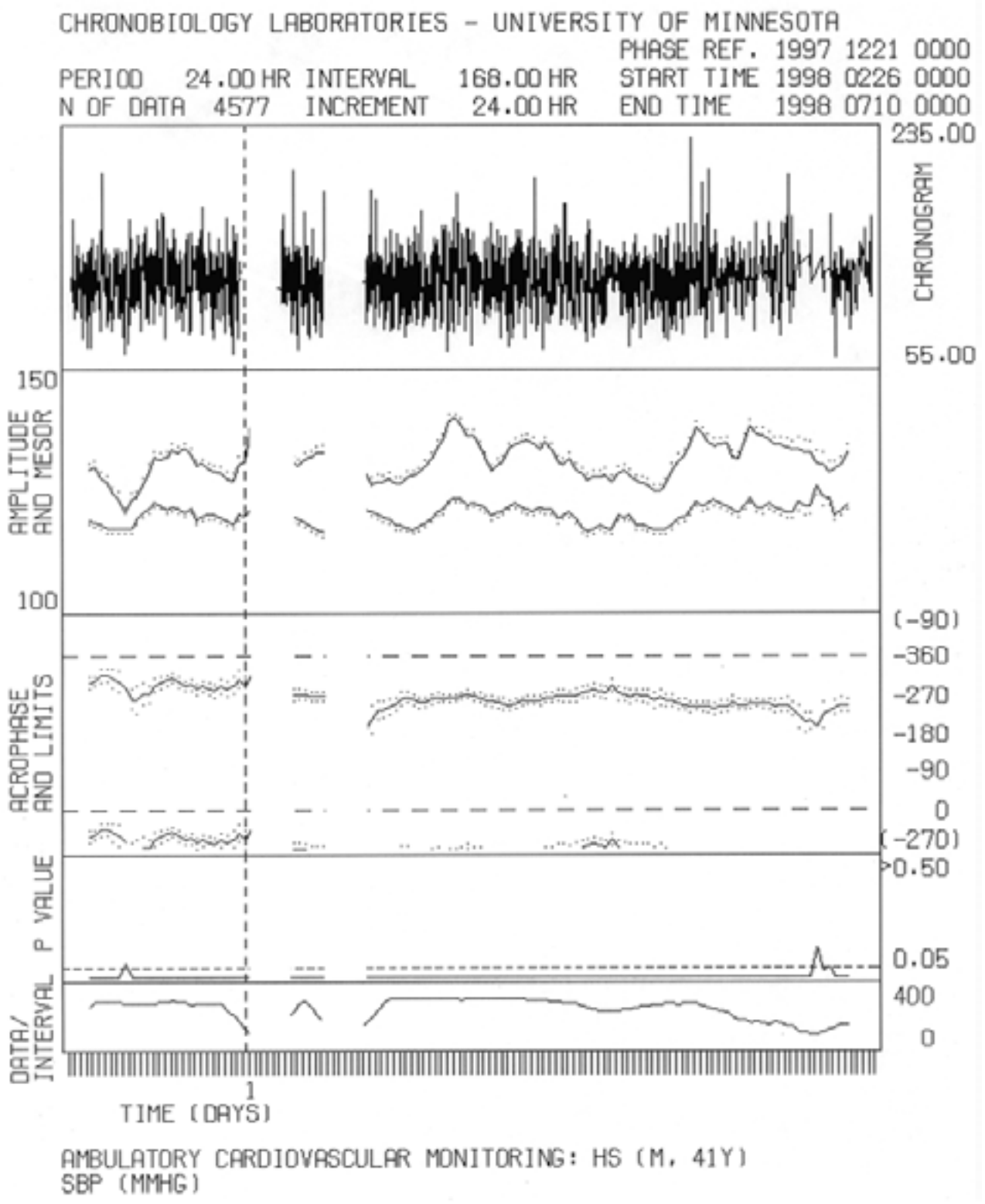

Figure 1. Chronobiologic serial section of systolic blood pressure (SBP) in a patient (HS) with delayed sleep phase syndrome (DSPS). © Halberg.

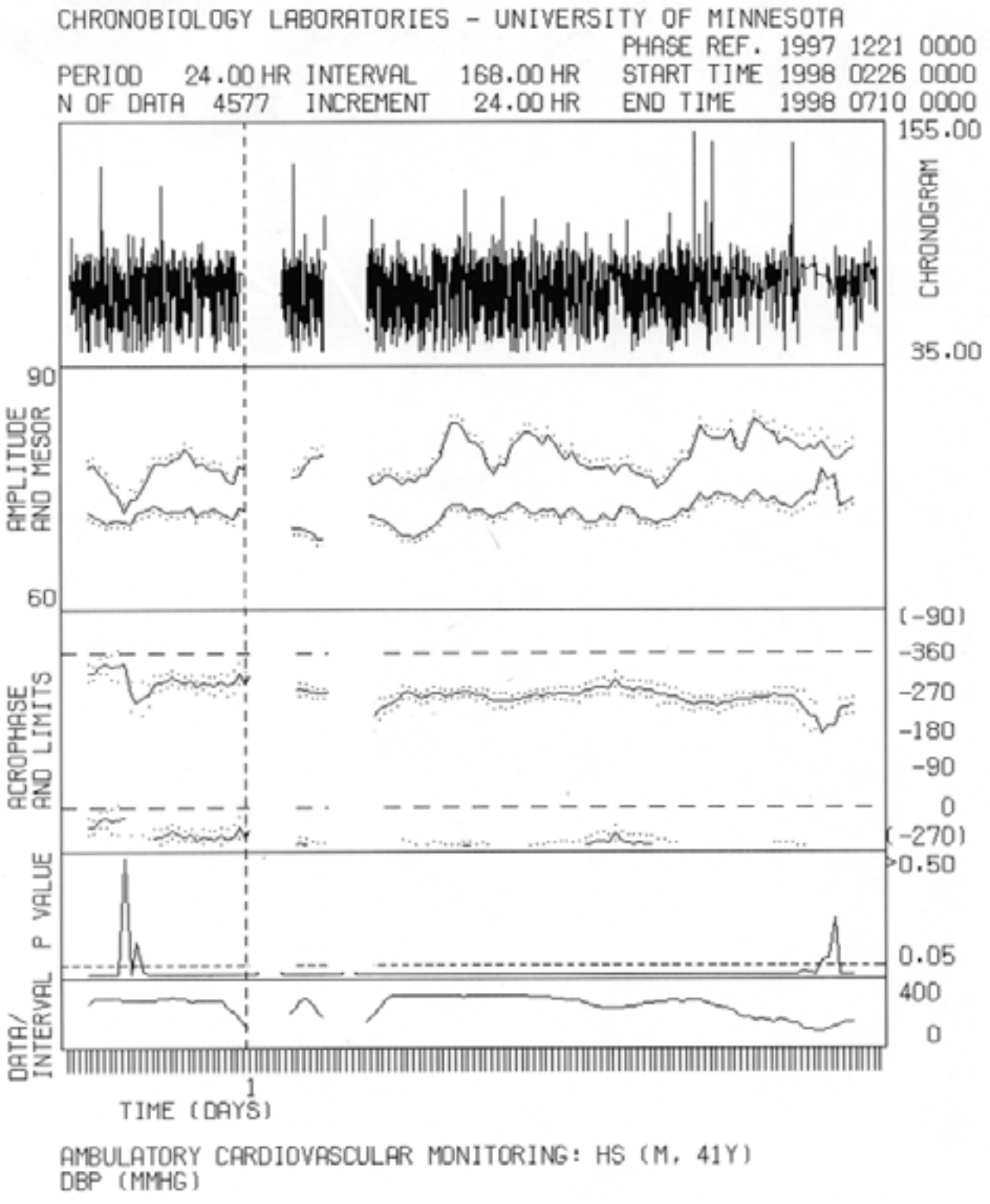

Figure 2. Chronobiologic serial section of diastolic blood pressure (DBP) in a patient (HS) with delayed sleep phase syndrome (DSPS). © Halberg.

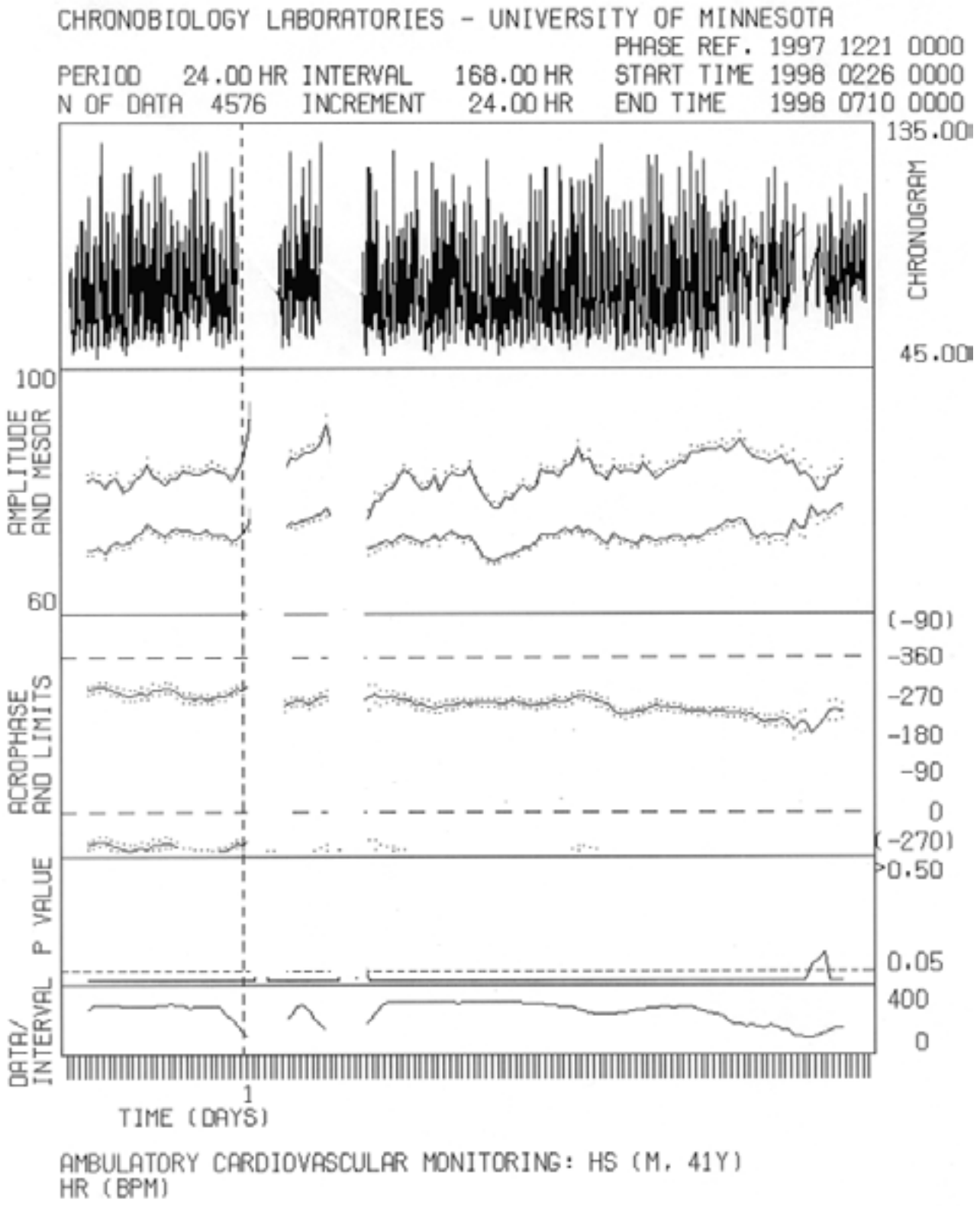

Figure 3. Chronobiologic serial section of heart rate (HR) in a patient (HS) with delayed sleep phase syndrome (DSPS). © Halberg.

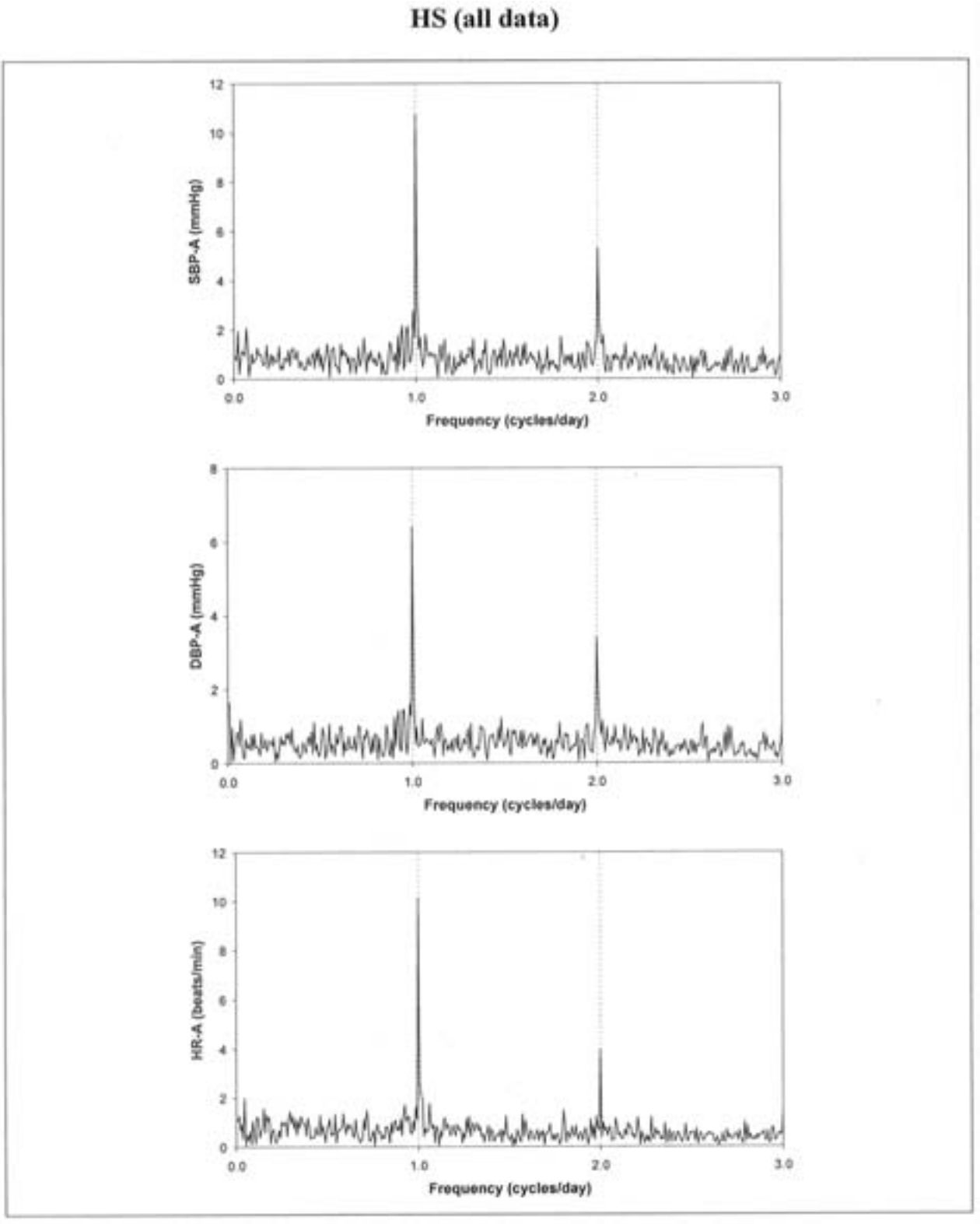

Figure 4. Least squares spectrum: all data of systolic (S) and diastolic (D) blood pressure (BP) and heart rate (HR) in a patient (HS) with delayed sleep phase syndrome (DSPS). © Halberg.

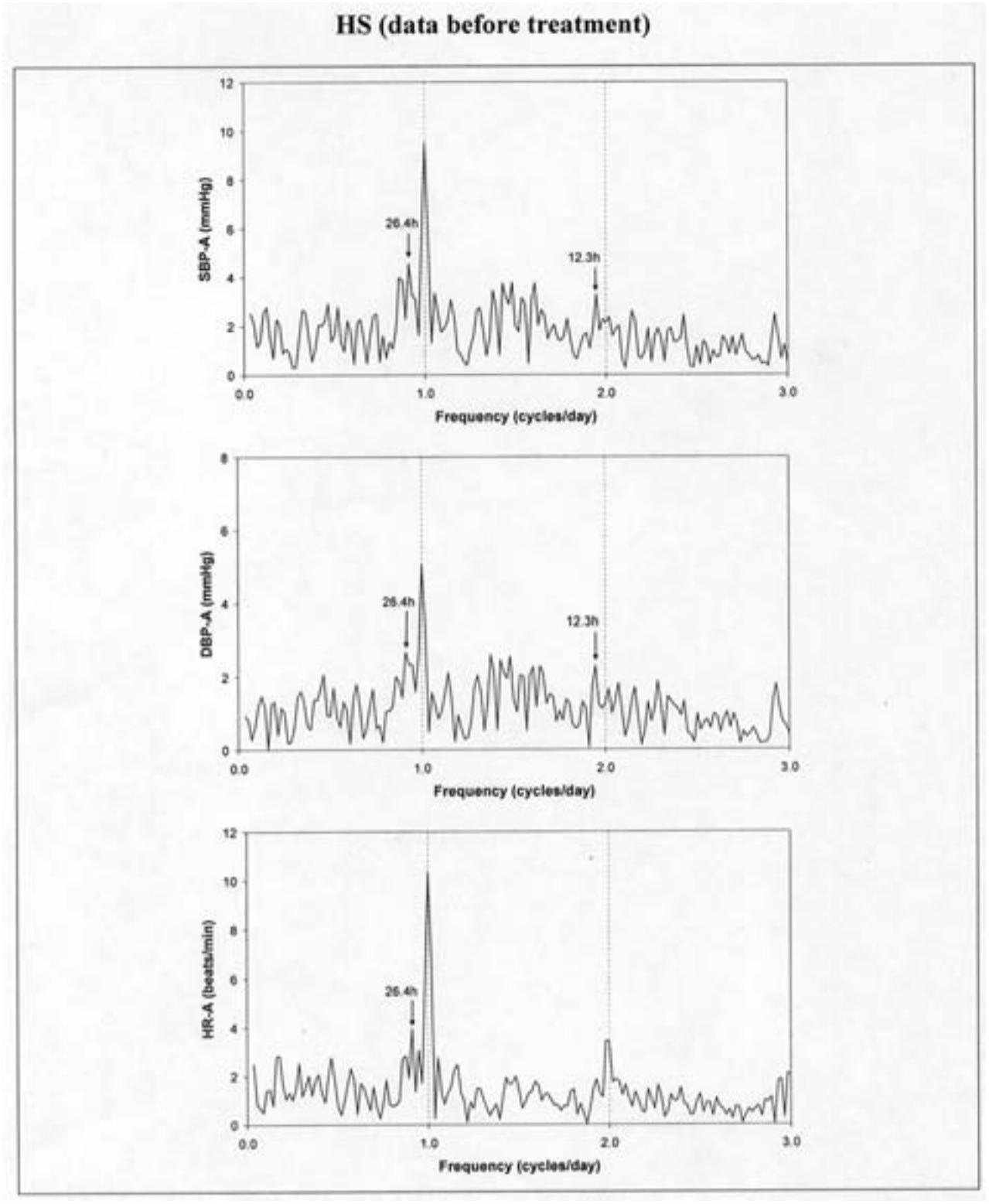

Figure 5. Least squares spectrum of HS: pre-treatment data of systolic (S) and diastolic (D) blood pressure (BP) and heart rate (HR). © Halberg.

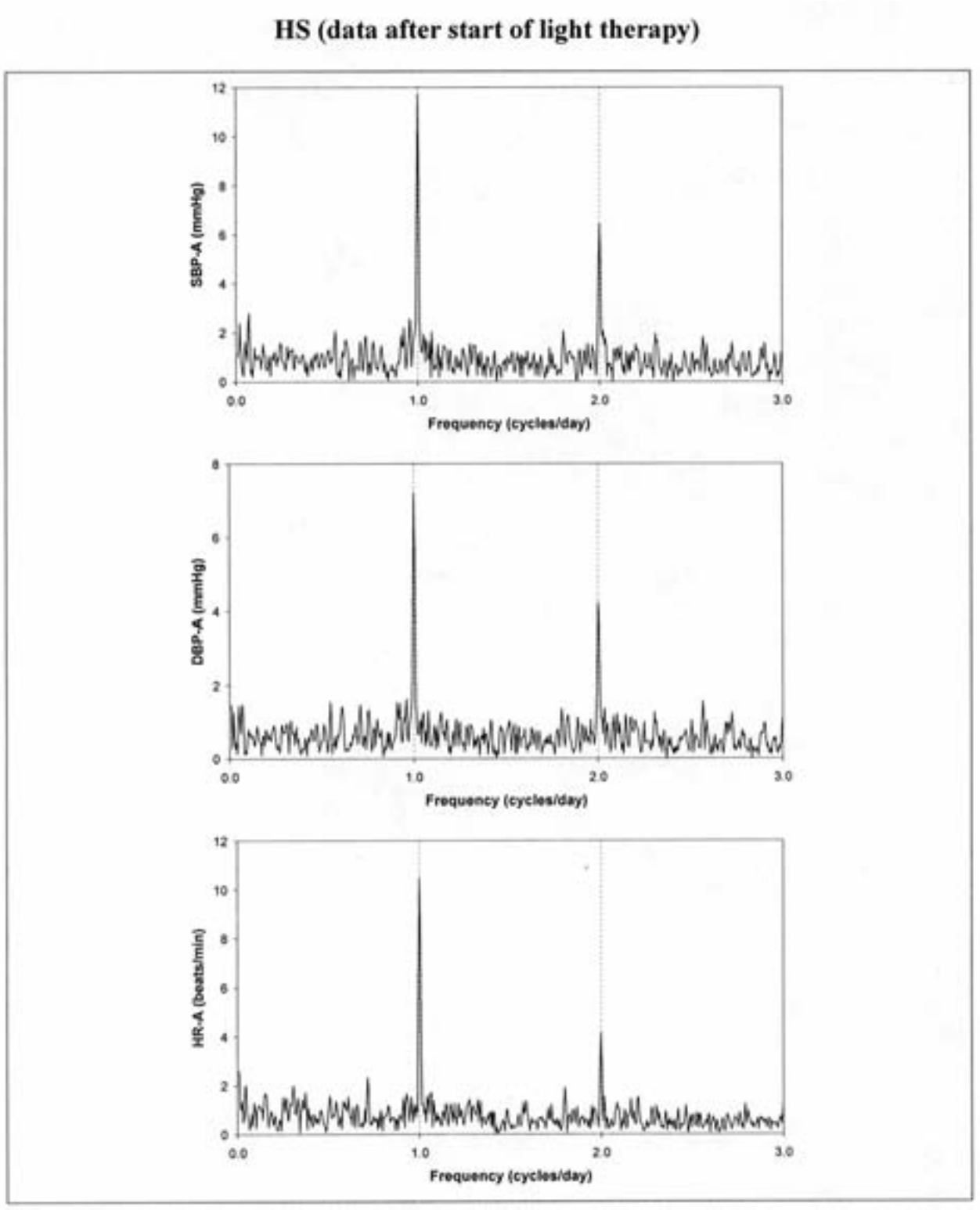

Figure 6. Least squares spectrum of HS: data after start of treatment of systolic (S) and diastolic (D) blood pressure (BP) and heart rate (HR). © Halberg.

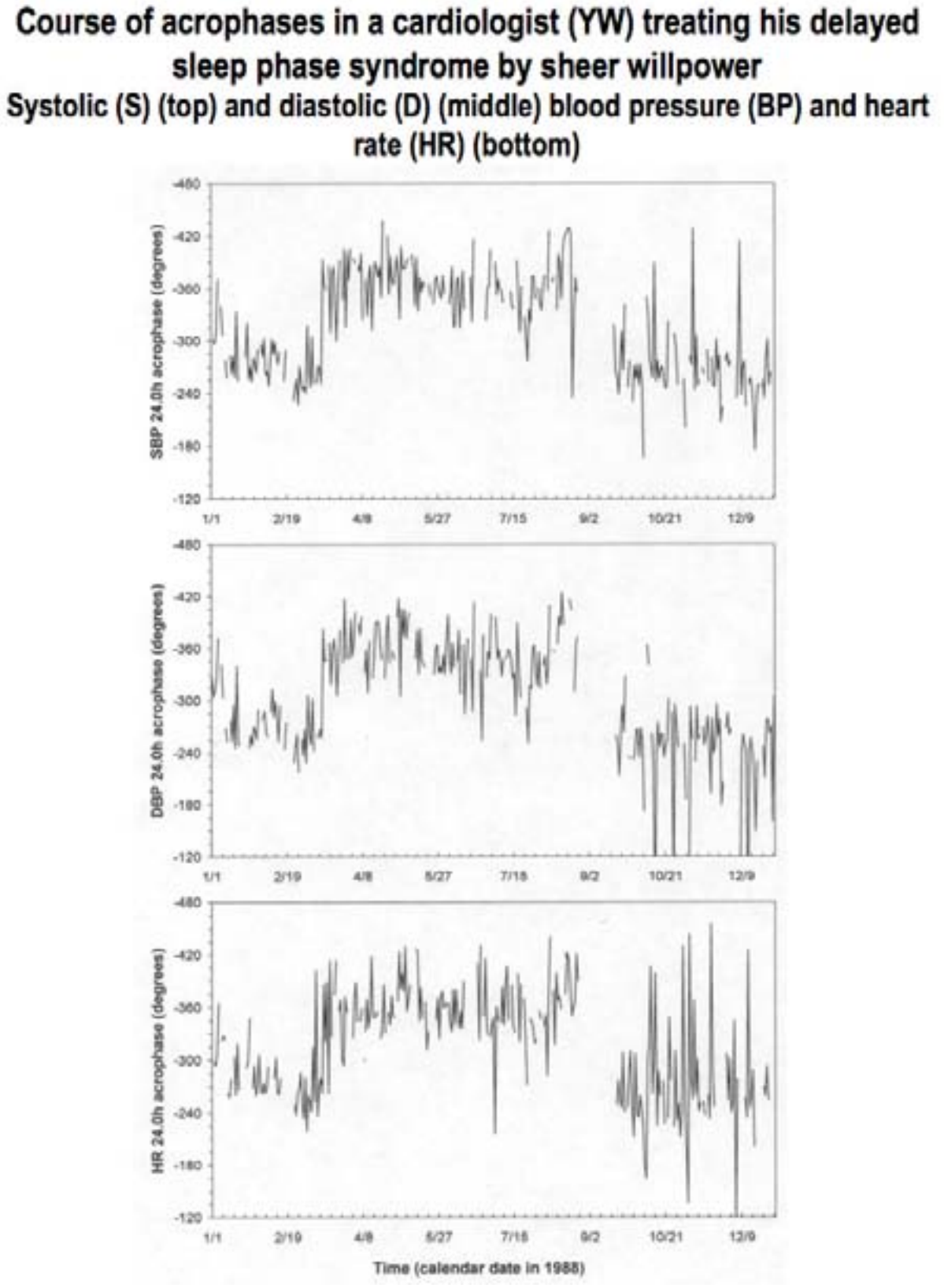

Figure 7. Acrophase of YW before, during and after delayed sleep phase syndrome. © Halberg.

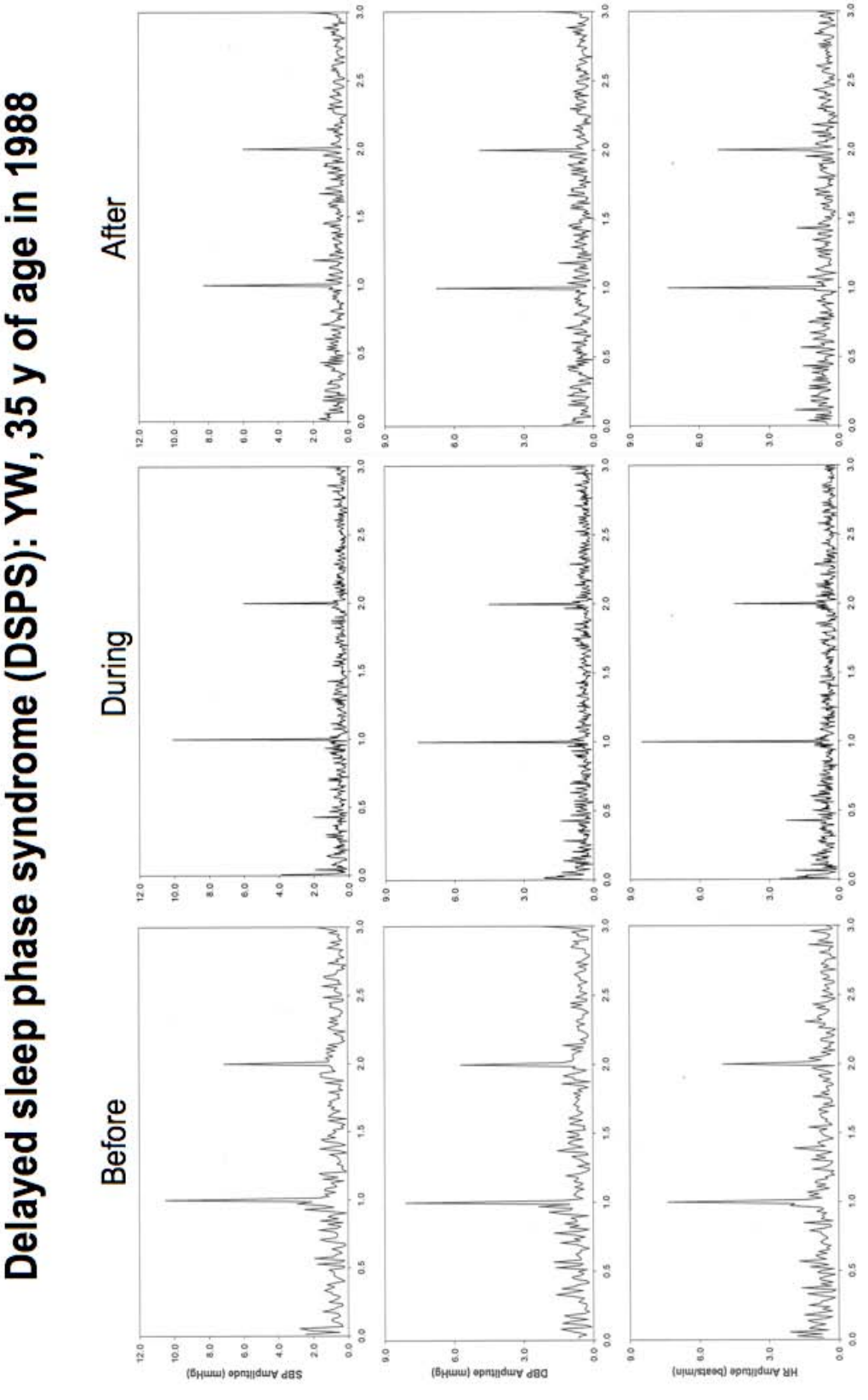

Figure 8. Dominant 24-h and 12-h components in YW with added 24.7- and 12.9-h components. © Halberg.

Table 1

Bright Light Therapy (Rx) Advances 24.0-hour Acrophase of Blood Pressure (BP) and Heart Rate (HR) in Patient with Sleep-Delayed Phase Syndrome (HS, M, 41y) *

Span	SBP			DBP			HR		
	PR (%)	A (mmHg)	ϕ (95% CI)	PR (%)	A (mmHg)	ϕ (95% CI)	PR (%)	A (bpm)	ϕ (95% CI)
Before Rx	14	9.5	-294 (-287,-302)	9	5.1	-298 (-288,-309)	26	10.4	-278 (-272,-283)
Rx (span 1)	20	11.2	-258 (-250,-265)	16	7.1	-263 (-254,-271)	22	9.4	-257 (-251,-264)
Rx (span 2)	24	12.4	-264 (-258,-270)	18	7.8	-264 (-257,-271)	30	10.8	-257 (-252,-262)
Rx (span 3)	21	11.9	-252 (-245,-259)	14	6.6	-255 (-246,-265)	35	12.7	-235 (-230,-241)
Rx (span 4)	22	11.4	-236 (-226,-246)	16	6.5	-243 (-231,-255)	22	9.2	-217 (-207,-228)

* SBP: Systolic BP; DBP: Diastolic BP; PR: Percentage Rhythm (proportion of overall variance accounted for by fit of 24.0-hour cosine curve); A: 24.0-hour amplitude (half the extent of predictable change within a day); ϕ: 24.0-hour acrophase (measure of the timing of overall high values recurring each day, expressed in negative degrees, with 360°=24 hours and 0°= local midnight); CI: Confidence Interval.

Table 2

Nonlinear Estimate of Circadian and Circasemidian Periods of Blood Pressure (BP) and Heart Rate (HR) in Patient with Sleep-Delayed Phase Syndrome (HS, M, 41y) Receiving Bright Light Therapy (Rx) *

Span	Systolic BP		Diastolic BP		HR	
	24h Trial Period [95% CI]	12h Trial Period [95% CI]	24h Trial Period [95% CI]	12h Trial Period [95% CI]	24h Trial Period [95% CI]	12h Trial Period [95% CI]
Before Rx	24.00 [23.88,24.13]	12.05 [11.93,12.17]	23.96 [23.79,24.12]	11.91 [11.79,12.04]	23.98 [23.90,24.06]	12.05 [11.99,12.10]
Rx (span 1)	23.95 [23.85,24.05]	11.97 [11.93,12.01]	23.96 [23.85,24.07]	11.96 [11.92,12.01]	23.98 [23.89,24.08]	11.97 [11.93,12.02]
Rx (span 2)	24.03 [23.94,24.12]	12.02 [11.98,12.05]	24.05 [23.94,24.15]	12.01 [11.97,12.05]	24.03 [23.95,24.11]	12.00 [11.94,12.06]
Rx (span 3)	23.94 [23.80,24.09]	11.96 [11.90,12.02]	23.91 [23.73,24.10]	11.97 [11.89,12.04]	24.03 [23.93,24.14]	11.98 [11.92,12.04]
Rx (span 4)	24.00 [23.85,24.15]	12.02 [11.94,12.10]	23.94 [23.76,24.11]	12.01 [11.92,12.10]	24.07 [23.91,24.22]	12.00 [11.93,12.06]

* Period (in hours); CI: (conservative) Confidence Interval.

Table 3

Model Consisting of Circadian Component with Fixed 24.0-hour Period, Desynchronized Circadian Component with Trial Period of 26.4 hours, and Desynchronized Circasemidian Component with trial Period of 12.3 hours Assessed Concomitatntly by Nonlinear Least Squares for Blood Pressure (BP) and Heart Rate (HR) of Patient with Sleep-Delayed Phase Syndrome (HS, M, 41y) Before Receiving Bright Light Therapy *

Variable	Fixed 24h C	Desynchronized ~26.4h C		Desynchronized ~12.3 C	
	A [95% CI]	Period [95% CI]	A [95% CI]	Period [95% CI]	A [95% CI]
Systolic BP (mmHg)	9.28 [6.54,12.02]	26.14 [25.70,26.59]	3.38 [0.66,6.09]	12.34 [12.24,12.43]	3.53 [0.80,6.25]
Diastolic BP (mmHg)	5.03 [3.08,6.97]	25.94 [25.45,26.42]	2.22 [0.31,4.14]	12.35 [12.25,12.44]	2.51 [0.58,4.44]
HR (beats/min)	10.09 [8.04,12.13]	26.44 [26.01,26.88]	2.61 [0.59,4.63]	12.41 [12.27,12.54]	NS

C: Component; Period (in hours); CI: (conservative) Confidence Interval; NS: Not Statistically Significant.

INFRADIAN MODULATION OF THE DEVELOPMENT OF HUMAN TRUE WHITE-COAT MESOR-HYPERTENSION

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Running title: MESOR-hypertension: strain test,

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

Abstract

Objective. To explore any changes in blood pressure (BP) and heart rate (HR) with age by **c**hronobiologically interpreted (C-) **a**mbulatory **b**lood **p**ressure **m**onitoring (ABPM) for a continuous electronically implemented self-surveillance. C-ABPM is now a cost-effective alternative to spotcheck BP measurements in office visits and to spotchecks *(sic,* because of day-to-day variability) by 24-hour ABPM; the latter is not only limited to a single circadian cycle but also only to a minuscule fraction of infradian cycles, with periods in months, years and decades as well as days, an endeavor comparable to taking the pulse for a minuscule fraction of a second.
Design. Data from automatic ambulatory instruments collected for 23 years at 30-minute intervals are subjected to a cosine model-based and a complementary stacking-based assessment of results from inferential statistical approaches by the linear-nonlinear cosinor and gliding spectral windows and/or chronobiologic serial sections.
Setting. Everyday clinical practice by a cardiologist (YW).
Results. Circadian and infradian rhythms characterize a busy cardiologist's (YW) systolic (S) and diastolic (D) BP and HR, and infradians are mapped tentatively including components with a period length exceeding the limits of the series' length.
Main findings. The rare opportunity of following the development of human as yet transient insofar as professional work-related MESOR-hypertension, MH, shows that it can differ in three different, each several months-long consecutive records of the same individual. Hence, continued self-surveillance should become routine, unless people who should be treated are not and vice versa, and should be implemented in the population as a whole. Such dense and long around-the-clock records along the age scale covered by YW allow the detection of decadal and tentatively even of transtridecadal and other infradian spectral components. In the development of human MH, a recurrent increase in A with infradian periods preceded the increase in M, as it does only once, with a shorter lag, in laboratory models of MH, in the stroke-prone spontaneously hypertensive Okamoto rat and with a lag of only a few days in the rat's salt and DOCA-induced hypertension.

Conclusion. A spotcheck evidence-based health care awaits replacement by one based on continued inferential statistical surveillance of the individual. The P-values and 95% confidence intervals that are currently indispensable in publications of research are applicable to the individual, in whose care they are equally indispensable. Moreover, with automatic analyses of data required by self-surveillance, this approach is cost-effectively practical, providing much more information at a much lesser cost.

Introduction

Half-hourly around-the-clock BP and HR values, surveilled over 7 days or preferably over longer spans, are 24-hour synchronized in most time series. Hence, one can fit a 24-hour cosine curve to the data, preferably with the 12.0-hour harmonic, to obtain model-based estimates of the midline-estimating statistic of rhythm, i.e., the MESOR, M; the amplitude, A, and acrophase, φ, measures of the extent of rhythmic change and of its timing, respectively. The data can also be stacked along the 24-hour scale without model-fitting for comparison with time-specified reference values from clinically healthy peers matched by gender and age. Measures of the extent of abnormality, if any, are thus obtained by the hyperbaric (or hypobaric) indices, summarizing BP excess (or deficit). These indices consist of the integrated area between the time-varying prediction limits and any part of the BP curve where the latter lies outside the limit. All endpoints of a given subject can be compared with those of clinically healthy peers of the same gender and age group for a circadian and any broader infradian as well as ultradian (in dense data) chronobiologic assessment, separately of systolic (S) and diastolic (D) BP and of HR.
YW, a clinically healthy chrono-cardiologist/scientist, 57 years of age, is in the 23rd year of continued chronobiologically-interpreted automatic half-hourly around-the-clock, ambulatory as well as resting monitoring (C-ABPM) (with relatively few interruptions) of his BP and HR. His father died of renal failure with malignant hypertension associated with a pheochromocytoma at the age of 47 years. At the age of 55 years in an about (~) 7.5-month section of his record, YW had by cosine fitting (of a 2- component model, consisting of cosine curves with periods of 24 and 12 hours) and by stacking, both compared with reference standards of clinically healthy peers matched by gender and age, a complete (model-based and non-model-based) SBP-MESOR (M)-hypertension (S-MH) and an incomplete (model-based, but not stacking-derived) DBPM-hypertension, D-MH. In an immediately following ~5-month record at the age of 56 years, he has incomplete (only model-based) S-MH and DBP MESOR-normotension, MN (D-MN) (1).
Months-long records in everyday life can differ as a function of professional and other loads. For YW, this assumption is in keeping with the finding that, during 4 days of vacation at home away from work, there is complete S-MN and D-MN, due to a statistically significant lowering of the BP-M and only a slight numeric increase in the hyperbaric index of DBP. Thus, the monitoring during as well as before and after a vacation constituted a professional strain test. His varying complete vs. incomplete (both model-based and stacking-derived vs. only model-based) S-MH or his incomplete (only model-based) vs. absent D-MH can be interpreted as an occupational MESOR-hypertension. We are dealing with a reversible D-MH that can be readily "treated", e.g., that is eliminated by a change in routine.

Method

YW wears an automatic monitor from A&D (Tokyo) around the clock with few interruptions. His summary a year ago (1) serves as a reference standard for the data accumulated in the interim of ~7 months. YW's chronobiologic reference summaries at ages 55 and 56 years include a sphygmochron carried out with both a model-based approach, from the fit of a two-component model (consisting of

cosine curves with periods of 24 and 12 hours) and one by stacking, both interpreted by comparison with clinically healthy peers matched by gender and age, Figure 1, as done routinely in the project on The BIOsphere and the COSmos, BIOCOS (2).

Results

Figure 1 shows the original data, that involve gaps, a change in the instrumentation used for monitoring, an episode of a delayed sleep phase disorder and trips, among other "noise" (not here identified). Figure 2 stacks the data along an idealized 24-hour scale from the span summarized by the sphygmochron in Figure 3. Thus, the first of the 48 dots in the top row of Figure 2 is the average of all values collected between 00:00-00:30 during ~7 months; the next dot summarizes all data collected between 00:30-01:00, etc. The ~7-month recordings caught a glimpse of an interesting time span when many SBP clock-time mean values are slightly above the time-specified limit of peers matched by gender and age, while, with no exception from 48 clocktime mean values, the DBPs are near but just below or at the upper 95% prediction limit, but none exceeds that limit.

The diagnosis made 2 years earlier at age 55 differed from that in the sphygmochron in Figure 3 at age 57, inferentially statistically but hardly clinically. At age 55, it was a complete (model- and stacking-based) systolic MH (S-MH) and an incomplete (model- but not stacking-based) diastolic MH (D-MH). All abnormality of BP or HR had been absent during 4 vacation days, summarized in Table 1. Moreover, the blood pressure M on Sundays had been lower than on other days of the week, as seen in Figure 4 (cf. summary in Table 2). No diastolic abnormality was found in the last sphygmochron in Figure 3. A stacking excess during 24 hours above 50 mm Hg x h, as found for SBP, is not acceptable. Thus, the diagnosis of 2008 changed by early 2009 to an incomplete model-based but not stacking-based S-MH and (complete) DBP MESOR-normotension, while in 2010, it is now a complete S-MH with complete diastolic MESOR-normotension.

In this case at this time a systolic abnormality occurred in the absence of the previous but not lasting diastolic MESOR-hypertension. Thus, parameters of consecutive spans, each of at least 5 months, reveal statistically significant differences. The desirability to assess and compare diagnoses with their uncertainties in inferential statistical terms cannot be overemphasized, yet a statistically significant difference in itself does not imply clinical or scientific signification (3, 4), notably if we realize that we are modulated by our cosmos.

The main findings on infradians can account for the foregoing differences; they are summarized in the variabilities of over 231,277 measurements/variable analyzed in two preliminary steps by serial sections, involving the fit of a 24-hour period in Figure 5 and that of a 7-day (168-hour) cosine in Figure 6. Infradians are apparent to the naked eye, which, however, is unable to assess the periods involved (and their uncertainties) or the extent to which they may contribute to the changing diagnoses in the development of MH and in its course. The data are dense with few gaps as seen in Figure 1. In the top rows of Figures 5 and 6, for each variable the lower curve is the MESOR, M, a **m**idline-**e**stimating **s**tatistic **o**f **r**hythm, and the distance from this to a dot below is the standard error (SE) of M. The distance between the two curves in the top row is the amplitude, A, and the distance from the upper curve to the dot above it is the SE of A. The second rows show acrophases, ϕ, of the cosine curve best fitting the data; dots above and below the ϕ bracket 95% confidence intervals of ϕ, which is doubly plotted whenever it approaches midnight, i.e., 0° or 360°. The acrophases are reasonably consistent for both the circadian and the circaseptan component.

The bottom rows of each section of Figures 5 and 6 are the results of the tests of the "no-rhythm", i.e., zero (circadian or circaseptan) amplitude assumption, and are overwhelmingly below the dashed horizontal line representing the 5% level of significance. The rhythms can be demonstrated, most of the

time at or below the 1% level, but with the weekly intervals used in Figure 5 only with interruptions, with fewer interruptions when much longer intervals are used, as in Figure 6 for the fit of the 1-week cosine. Figures 5 and 6 suffice to discern modulations of both M and A but for an estimate of the periods involved, and certainly for the uncertainty of the periods. Figures 5 and 6 are imputations leading to Table 3 and Figures 7 and 8.

Figures 7 and 8 and Table 3 show some of the infradian modulations of the M and the A for systolic and diastolic blood pressure. The M is modulated for both blood pressures by a circadecadal component and, in addition, tentatively, in the case of diastolic blood pressure, by a transtridecadal component, the latter qualified by the relative brevity of the series. The A of each variable shows a circaseptennian modulation and, in addition, a didecadal component for systolic and a tentative transtridecadal component for diastolic blood pressure with the uncertainties and double amplitudes of some of the periodic components given in Table 3. Both Figures 7 and 8 reveal more than one circadian double amplitude increase in a clinically healthy subject with a positive family history of vascular disease. Whether these amplitude increases are harbingers of a vascular variability disorder, VVD, or are physiological will eventually have to be clarified with the study of other longitudinally investigated subjects and in the light of long-term outcomes. YW has tried non-drug approaches, but no drug therapy.

Discussion

From studies consisting of 24-hour spotchecks in the stroke-prone spontaneously MESOR-hypertensive Okamoto rat, it was learned that a circadian A-increase precedes an M-increase (5). This finding was extended to humans with a cross-sectional design (6) with an A-increase preceding an M-increase around an M of ~140 mm Hg along a scale of the left ventricular mass index. Cugini et al. (7) found a higher A & M around an M of ~120 mm Hg in patients with minimal change retinopathy vs. those without this condition. Table 3 shows that the double amplitude of about (~) 5.34 mm Hg, associated with an ~10-year periodicity, is small, yet other periodic components may add to that difference. For diastolic BP, a tentative transtridecadal period has a double A of 11.32 mm Hg, sufficient to account for the difference between the diagnosis of an acceptable double amplitude vs. CHAT, **c**ircadian **h**yper-**a**mplitude-**t**ension (8). Likewise, the infradian modulation of the diastolic blood pressure MESOR can, at critical MESORs, account for the difference between MH and MESOR-normotension. There is an opportunity in YW's data and in other longitudinal records to account for both circadian and infradian variability in following the development of MH or CHAT, lessons learned in Figures 7 and 8 and Table 3.

Further analyses in others' time series, covering decades, may answer the question about the degree of generality with which a deviation (e.g., an elevation) in A alone or concomitantly with M (7) or in M alone leads to MH or CHAT (8). Consecutive sphygmochrons to pursue in more detail the development of a VVD remain to be computed. In the laboratory, the sequence of a 2A elevation preceding an elevation of M also occurs for BP and other telemetered variables, albeit with a lag of only a very few days, in the saline and desoxycorticosterone-induced hypertension of the rat (unpublished studies by John Osborn), mimicking findings in the spontaneously-hypertensive stroke-prone rat (SHR-SP) (5). Likewise, a higher BP-A is associated with intermediate values of the left ventricular mass index (LVMI), whereas a higher BP-M (above 140 mmHg) is seen only for larger LVMI values in humans (6). This chronobiologic pre-hypertension around an M of 140 mm Hg and the finding of an increase in both 2A and M around a SBP-M of 120 mmHg associated with minimal change retinopathy, discovered by Pietro Cugini and interpreted by him as constituting a pre-hypertension (7, 8) can be reconciled by the operation of genetically anchored infradians. Similarly, pre-diabetes has been documented by focus upon the detection of circadian VVDs (9, 10). More than single subjects will

have to be longitudinally investigated by systematic monitoring as newborns (2, 3) and at school age to explore any sequences in the development of incomplete to complete S-MH and D-MH, started in adulthood, now in the perspective of decades in YW.
The removal of the load of professional activity can normalize BP in certain individuals: this should be explored further with replications in YW's vacations and work-free Sundays as contrasted to workdays in YW and other individuals. We here present evidence that an ~30-40-year Brückner-Egeson-Lockyer (BEL) transtridecadal cycle (11) and a ~21-year Hale cycle in the bipolarity of sunspots are mirrored in YW's circulation as noted earlier for 3 of 3 others examined (11), one MESOR-normotensive, the other two MESOR-hypertensive, one of them with complicating CHAT. There is also evidence in YW's son FW of an ~5-month cycle in his SBP, putatively related to solar flares, as he aged from 8 to 17 years (12).
The frequency and sequence of alternations between incomplete or complete D-MH and/or S-MH probably also depend on factors like pain (JF has a history of lumbago), grief or conflict during the daily routine, problems to be explored with diaries in decades-long time series like that of YW. It will be interesting to find out from the entire 23-year and still accumulating record whether professional loads are associated with differences not only in circadian summaries but also in certain infradian cycles' A and/or φ (e.g., by comparing infradian characteristics at certain frequencies from data collected only during weekdays vs. only from weekends and holidays). Also to be further explored is the sequence, if any, in which SBP vs. DBP stacking-based endpoints, such as the hyperbaric index (HBI), change, by comparison to changes in their A, φ and M, if they do not alter concomitantly, as seems to have been the case for YW. The exploration of sequences in which the foregoing changes occur in any longitudinal records of others collected systematically with diaries depends on the development of affordable, unobtrusive instrumentation for continuous automatic BP and HR monitoring.

Conclusion

In current practice, under the assumption of homeostasis, it may appear that diagnoses based on monitoring spans of 5 or more months are superfluous and the 24-hour profile is the platinum standard. Pre-hypertension is conventionally defined as a systolic pressure of 120 mm Hg or higher. As earlier (5-8), others and we here describe pre-hypertension as increases in circadian double amplitude that can (and do in YW) undergo infradian variations in their own right, for years, before an increase in M occurs. We must not fly blind (13) to a cosmically influenced physiology when "seeing" may enter the state of the art in terms of both affordable, unobtrusive hardware and software on a website for automatic analysis (14, 15).
Support: GM-13981 (FH), University of Minnesota Supercomputing Institute (GC, FH), MSM0021622402

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Table 1: Comparison of 3 vascular profiles: 1 and 2 based on months of monitoring; 3 based on weekends and holidays

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

A: Amplitude; ϕ: Acrophase, expressed in (negative) degrees, with 360˚ ≡ 24 hours, 0˚ = 00:00. Results from parameter tests (Bingham C, Arbogast B, Cornélissen Guillaume G, Lee JK, Halberg F. Inferential statistical methods for estimating and comparing cosinor parameters. Chronobiologia 1982; 9: 397-439). For this time-microscopic assessment, the data during the 4 days of vacation in span 3 were removed from span 2 prior to analysis.

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

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

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

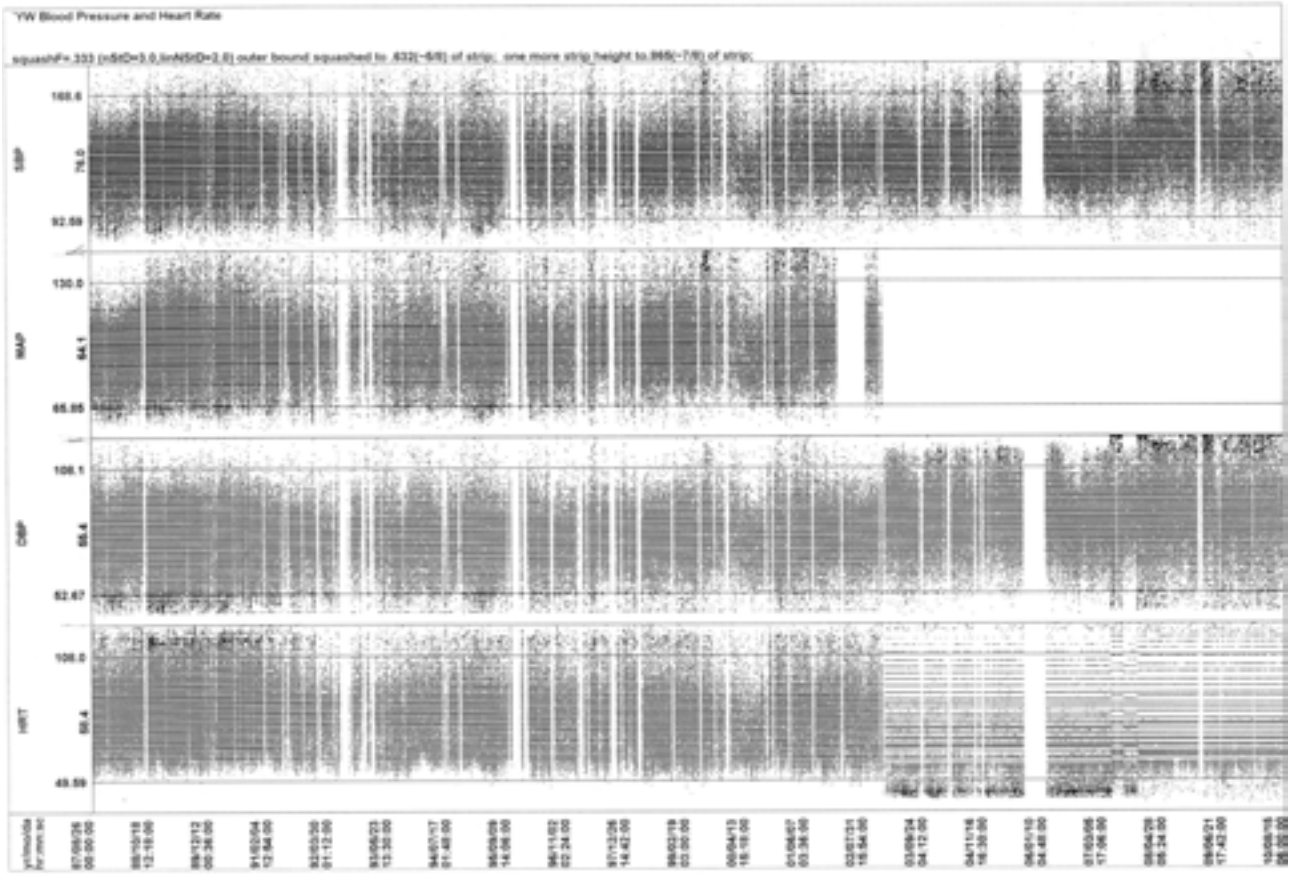


Figure 1. Plot of original measurements of YW, M, 57 years of age. Data between + and -2 standard deviations from the mean are plotted linearly within the proximal horizontal lines. Beyond these lines, in lesser intervals between the proximal and distal upper and lower borders, data are compressed for an exponential approximation of the upper and lower extremes representing + or - infinity. Location: 3 SD at ~5/8, and 4 SD at ~7/8 of strip width. © Halberg.

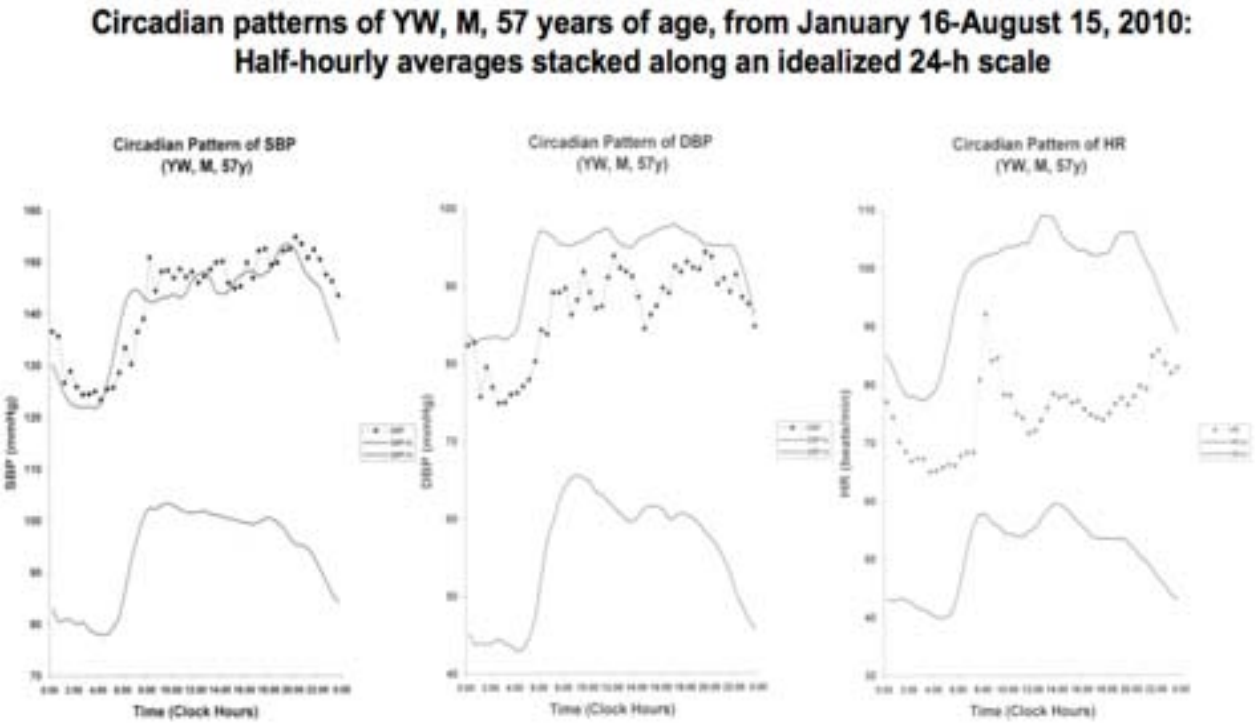
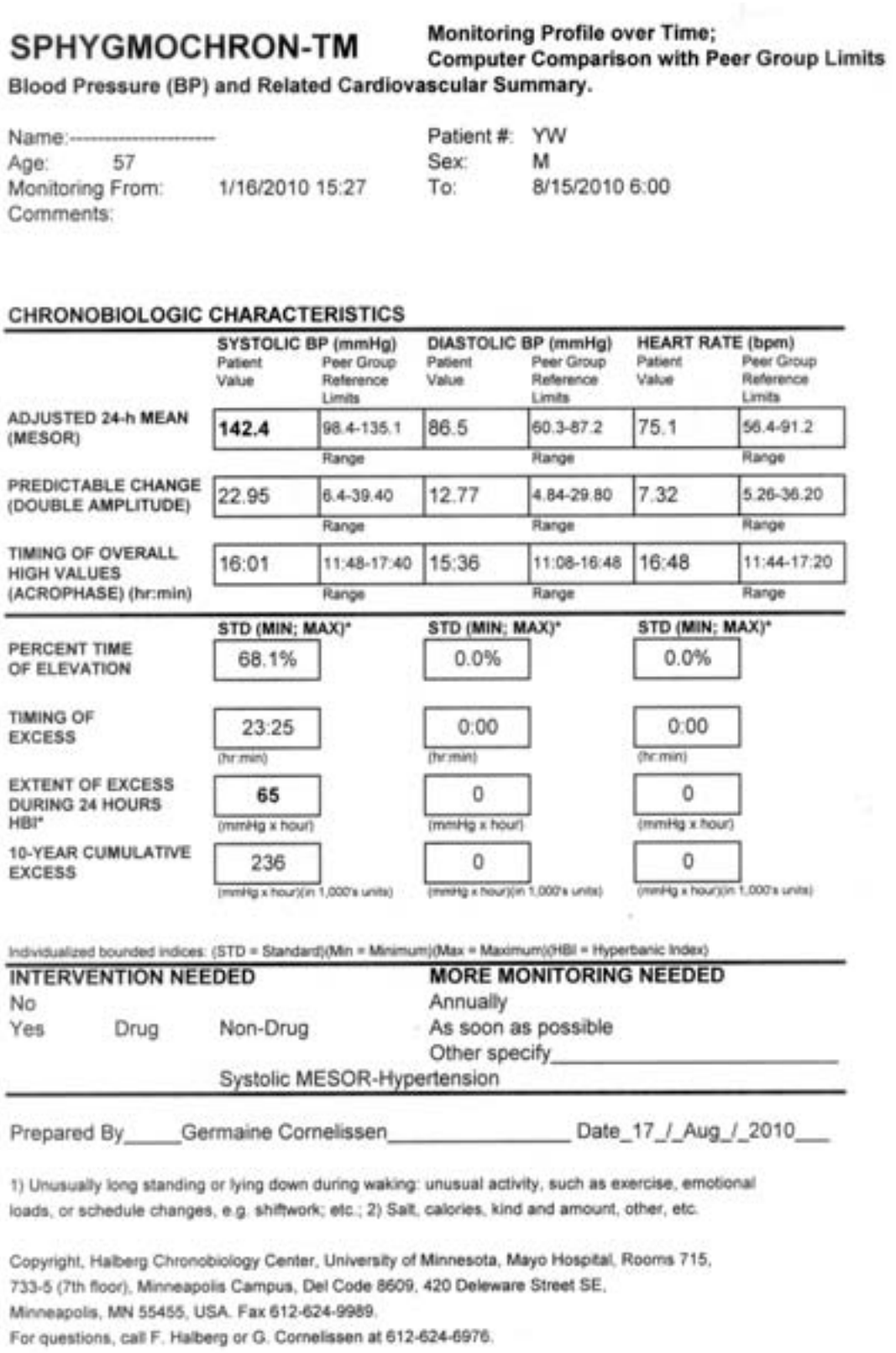


Figure 2. Summary by stacking of half-hourly around-the-clock means along an idealized 24-hour day at age 57 years for blood pressure (BP) and heart rate (HR) during regular professional life. © Halberg.



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

Blood Pressure (BP) and Related Cardiovascular Summary.

Name:---------- Patient #: YW
Age: 57 Sex: M
Monitoring From: 1/16/2010 15:27 To: 8/15/2010 6:00
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)	**142.4**	98.4-135.1 Range	86.5	60.3-87.2 Range	75.1	56.4-91.2 Range
PREDICTABLE CHANGE (DOUBLE AMPLITUDE)	22.95	6.4-39.40 Range	12.77	4.84-29.80 Range	7.32	5.26-36.20 Range
TIMING OF OVERALL HIGH VALUES (ACROPHASE) (hr:min)	16:01	11:48-17:40 Range	15:36	11:08-16:48 Range	16:48	11:44-17:20 Range
	STD (MIN; MAX)*		**STD (MIN; MAX)***		**STD (MIN; MAX)***	
PERCENT TIME OF ELEVATION	68.1%		0.0%		0.0%	
TIMING OF EXCESS	23:25 (hr:min)		0:00 (hr:min)		0:00 (hr:min)	
EXTENT OF EXCESS DURING 24 HOURS HBI*	**65** (mmHg x hour)		0 (mmHg x hour)		0 (mmHg x hour)	
10-YEAR CUMULATIVE EXCESS	236 (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 = Hyperbaric Index)

INTERVENTION NEEDED
No
Yes Drug Non-Drug

MORE MONITORING NEEDED
Annually
As soon as possible
Other specify_____

Systolic MESOR-Hypertension

Prepared By_____Germaine Cornelissen_____ Date_17_/_Aug_/_2010___

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 mostly half-hourly around-the-clock data, stacked and averaged for 48 consecutive (half-hourly) bins of an idealized 24-hour day, for a man (YW) in everyday professional life as a cardiologist at age 57 years. © Halberg.

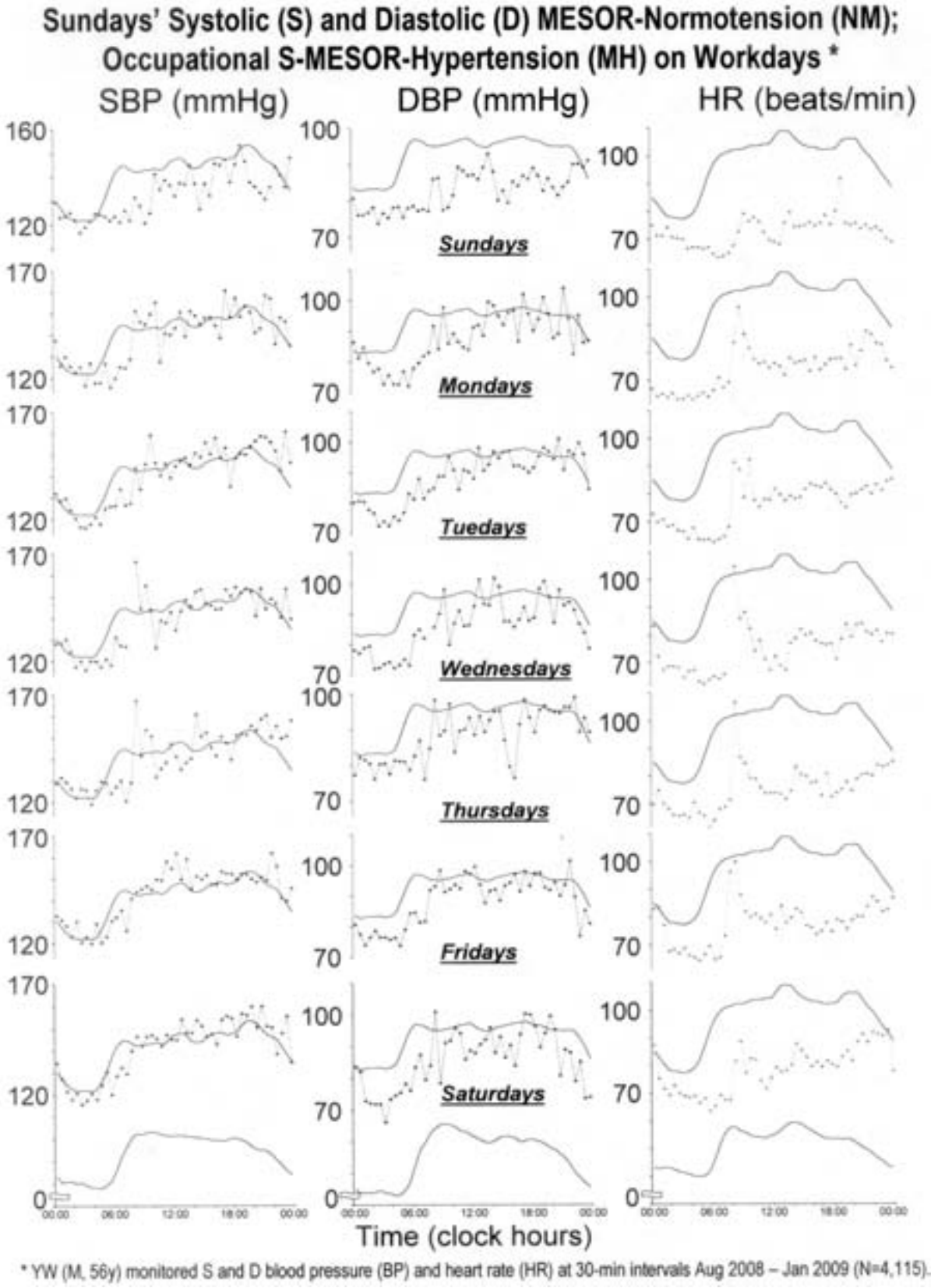


Figure 4. Weekend blood pressures and heart rates differ from those on weekdays. See also Tables 1 and 2. © Halberg.

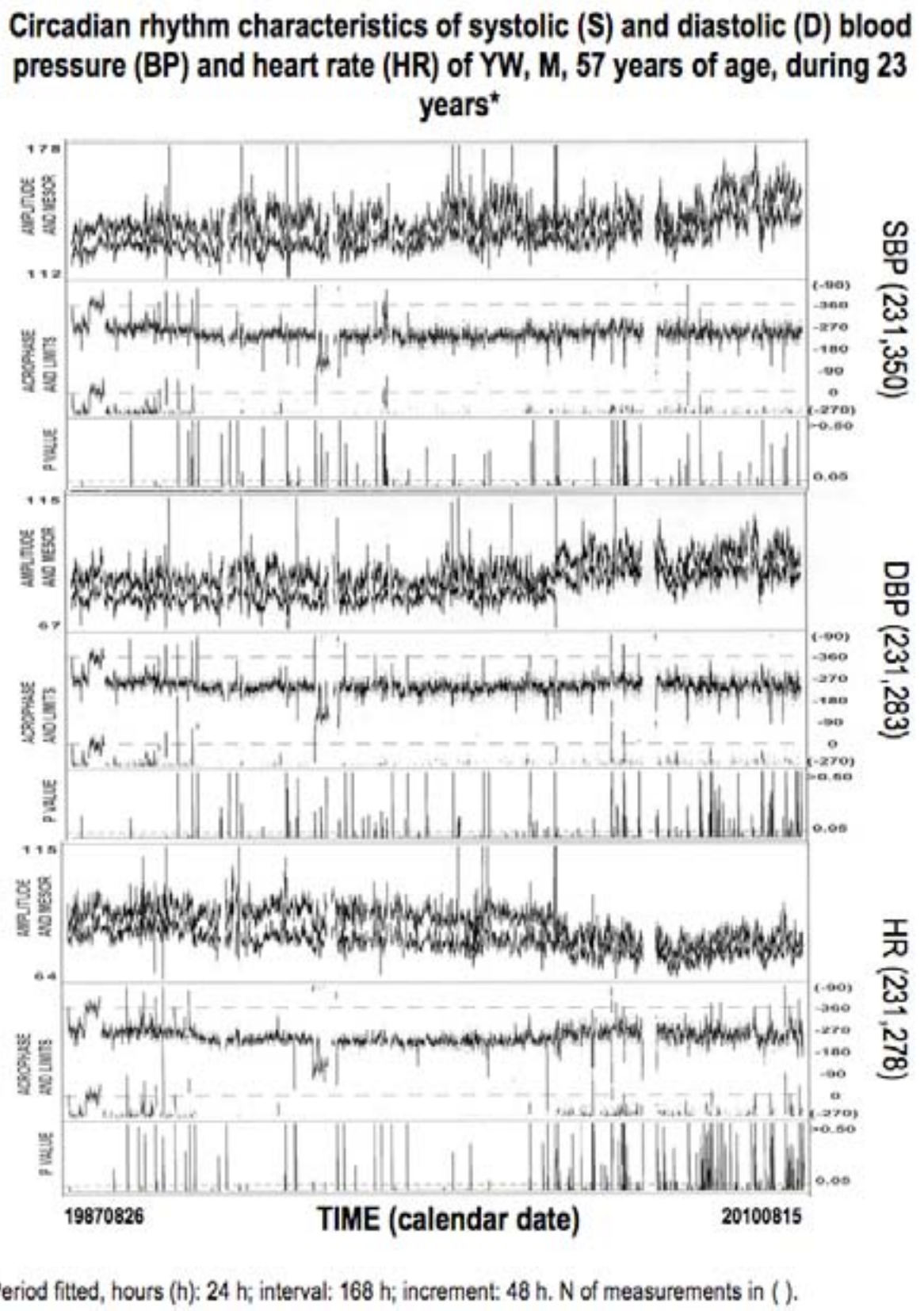


Figure 5. Chronobiologic serial sections of YW's systolic (A) and diastolic (B) blood pressure and heart rate with the fit of a 24-h cosine curve to consecutive intervals of 1 week, displaced in 48-hour intervals. © Halberg.

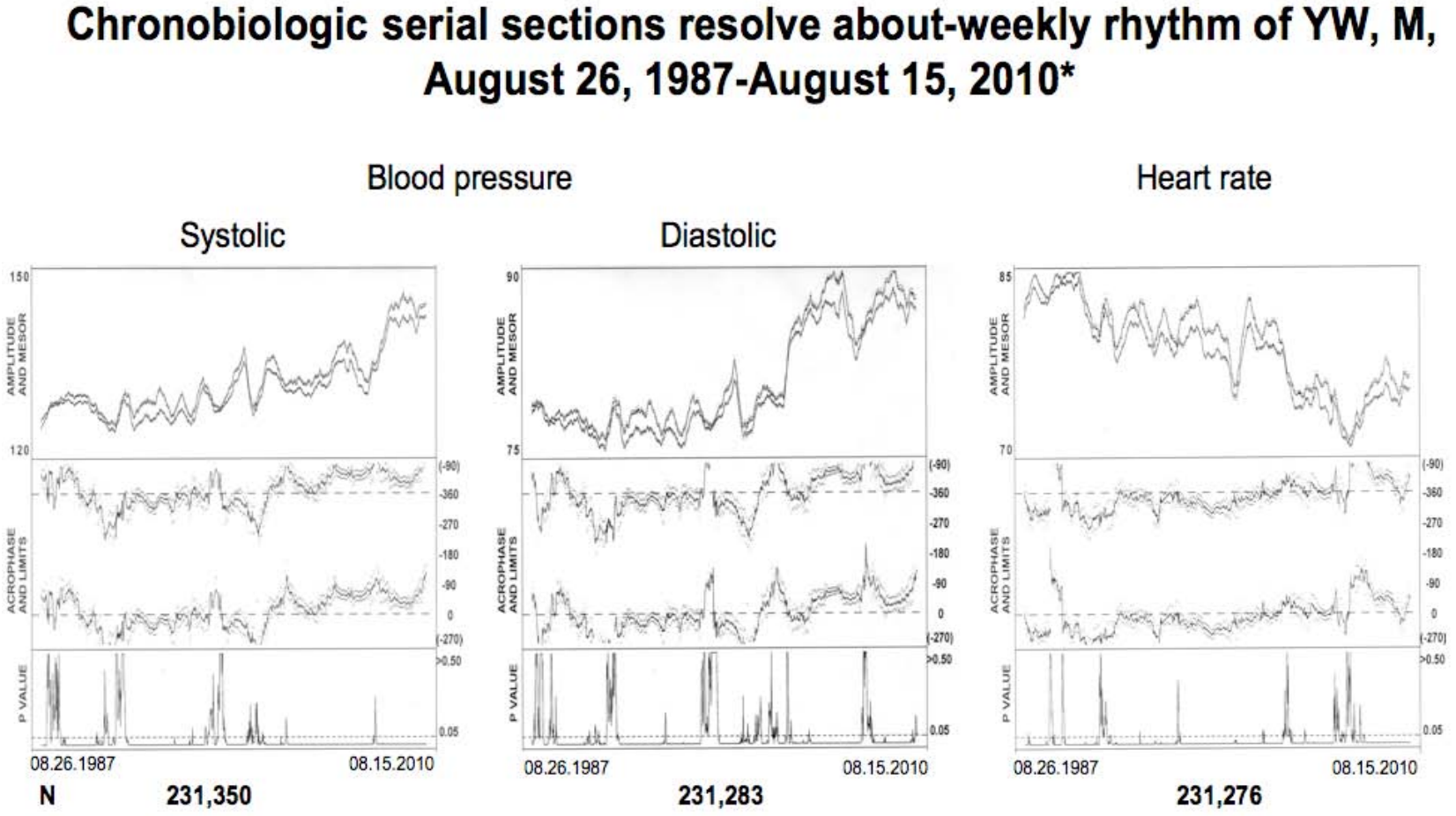


Figure 6. Chronobiologic serial sections of YW's systolic (A) and diastolic (B) blood pressure and heart rate with the fit of a 1-week cosine curve to 280-day intervals displaced in 1-week increments. © Halberg.

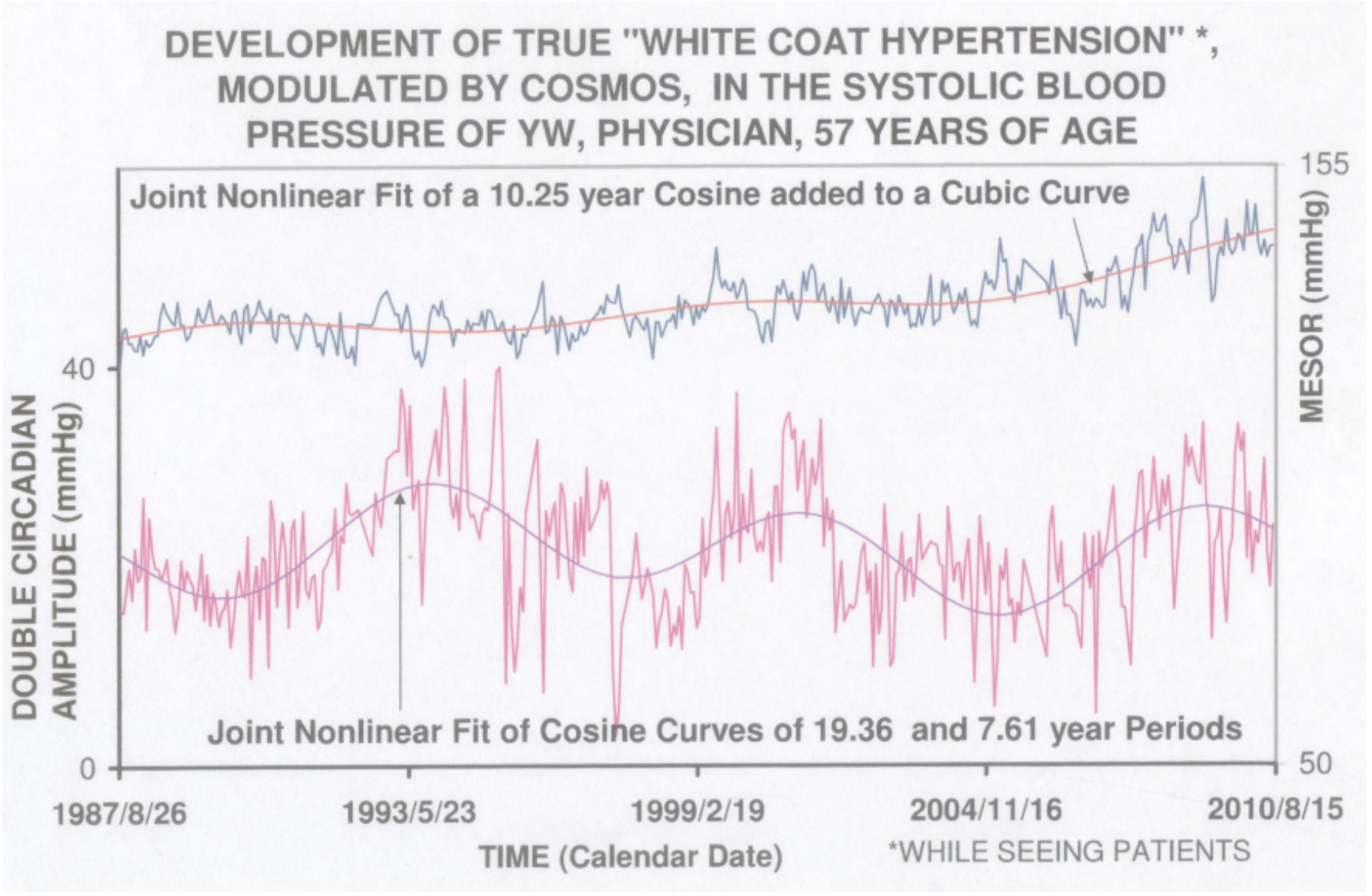


Figure 7. Infradian fit by linear-nonlinear cosinor of MESOR (top curve) and circadian amplitude (bottom curve) of systolic blood pressure of YW. A decadal modulation of the MESOR (top curve) coexists with a didecadal and circaseptennian modulation of the double circadian amplitude (bottom curve). © Halberg.

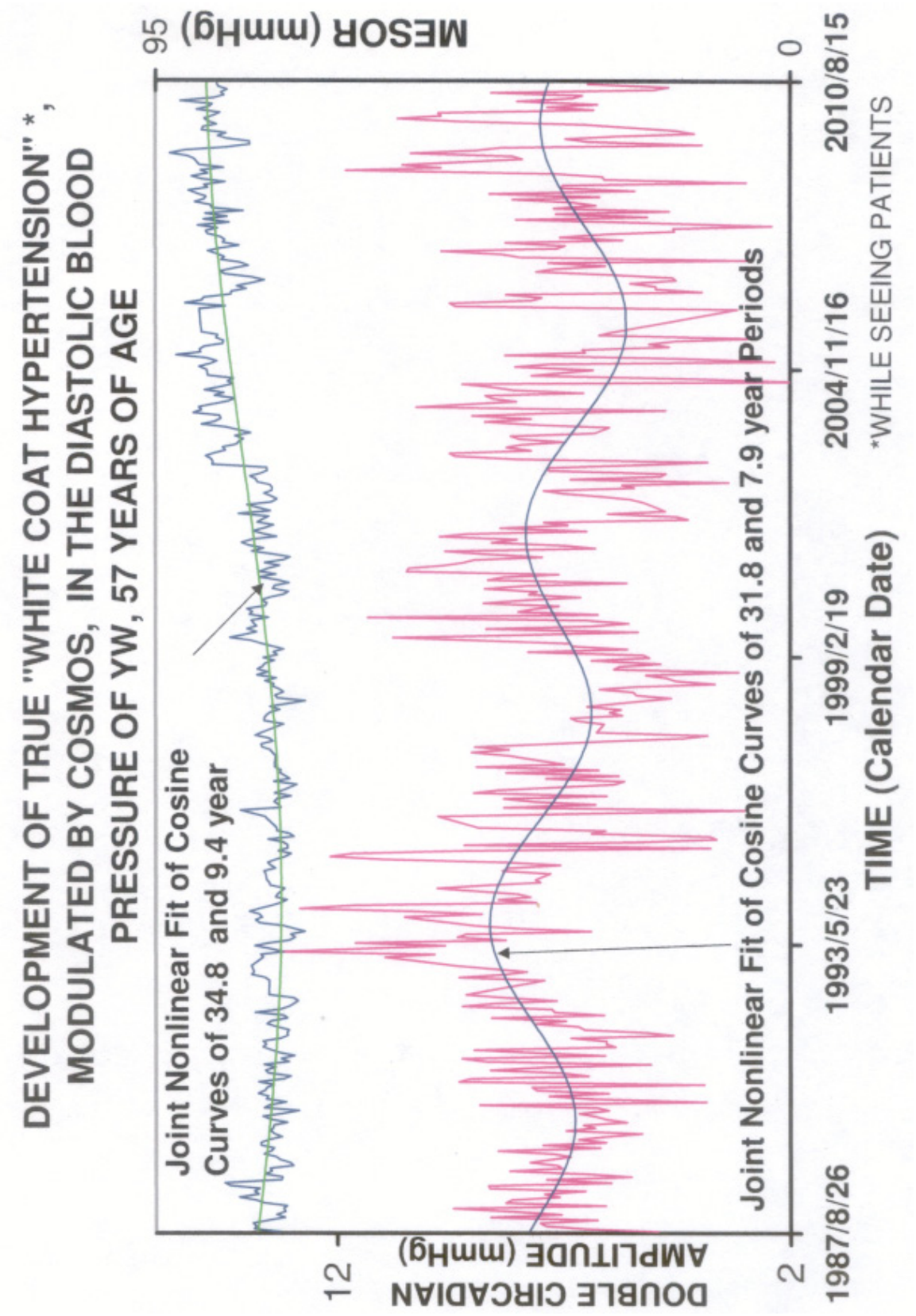


Figure 8. Infradian fit by linear-nonlinear cosinor of MESOR (top curve) and circadian amplitude (bottom curve) of diastolic blood pressure of YW. A transtridecadal component modulates both the MESOR and the double amplitude in addition to a decadal component in the case of the MESOR and a circaseptennian component for the double circadian amplitude. © Halberg.

COMPLEMENTARY YET DIFFERING RHYTHMIC ASPECTS OF A MAN‘S MOOD AND VIGOR IN VARIOUS SPECTRAL REGIONS

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Abstract. Using the most recent subspan of 8 months from a more than 4-decade-long self-measurement project, we report a statistically significant difference in the circadian phase of mood (M) and vigor (V) self-rated by a clinically healthy man (RBS, age 62y) about 6 times a day, mostly between awakening and bedtime. Analyses involving 24-hour cosine fitting confirm statistically significant circadian rhythms in each variable and quantify the subject’s awareness that his vigor peaked during mid-activity (acrophase, ϕ = 15:42), while his mood peaked late in the evening (ϕ = 00:16). Oral temperature (OT) measured simultaneously verified synchronization to his sleep-wake schedule (ϕ = 16:34). Chronobiologic serial sections confirmed the stability of each variable's circadian acrophase over the 8-month span. Additional cosinor analyses for periods up to 30 days revealed statistically significant periodicities between 12 and 16 days in V, but no circaseptan rhythm, while M showed periodicities between 11.5 and 19.0 days, plus a 27.5-day cycle and a possible free-running circaseptan component with a period of 6.5 days. Gliding spectral windows between 0.7 and 2.5 years showed further infradian differences between M and V that can be compared with the infradian time course of OT during the entire four decades of monitoring. Differences in circadian timing, and changing amplitudes and drifting infradian frequencies in M and V describe diverse rhythmic patterns in subjective assessments of what superficially seem to be interdigitated aspects of psychology.

Background. By separating positive from negative affect with their PANAS scale (1), Watson, Clark and Tellegen enabled the demonstration of a prominent about 7-day (circaseptan) cycle in negative affect (NA) versus a 24-hour (circadian) prominence in positive affect (PA) in 196 clinically healthy subjects (2). The circaseptan amplitude was larger than the circadian amplitude for NA, whereas the circadian amplitude was larger for PA. The broader spectrum of rhythms includes a circadecadal modulation, i.e., an about 11.5-year variation (3) in a 30-year-long record of M and V self-ratings carried out on average about 5 to 6 times a day with only a few interruptions by the same subject (RBS) of this current report. Information on the time structure of M provides endpoints to be considered in any attempt to optimize psychological well-being by making sleeping, dietary, and/or other lifestyle adjustments. The 8-month series of M and V self-ratings examined herein by chronobiologic analyses served as clinically healthy control data for a magneto-labile family who self-monitored over the same time span that covered 8 lunar cycles.

Subject. A healthy male biomedical scientist (RBS), age 62y at the start of the current 8-month self-ratings span, used a slightly modified version of 7-point scales proposed in 1972 (4) for M and V (summarized in Table 1), although in actuality he only rated V between 1-5. Self-rating on each M and V rating scale separately (3) has its justification, as documented herein, in assessing different aspects of psychology.

Table 1: Mood and Vigor Ratings modified from (4) used by RBS

Mood		Physical Vigor
Very depressed, „blue“	1	Very tired, very sleepy, no energy
Somewhat depressed, „down“	2	Somewhat tired, sleepy, inactive
Slightly less cheerful than usual	3	Slightly less active than usual
Usual state, „average mood“	4	Usual state, „average vigor“
Slightly more cheerful than usual	5	Slightly more active than usual
Quite cheerful, feel good	6	Quite active, full of pep
Super cheerful, happy	7	Super active, „hyper“

The subject performed 1,450 self-measurements between Mar 7 and Nov 4, 2009. After removal of 84 values during 2 weeks with an upper respiratory infection in March, the remaining „healthy“ M, V and OT data (N = 1,366) were analyzed for rhythm characteristics by the least-squares fit of cosines between 24 hours and 30 days, which included a precise 7-day (168-hour) fit (4). Serial sections (4) with 7-day intervals were then used for the fit of a 24-hour cosine, and intervals covering 6 or 12 weeks for the fit of a 168-hour cosine. The intervals used for analysis were advanced through the time series to derive moving estimates of amplitudes, acrophases, statistical significance and percentage rhythm (coefficient of determination) of the components investigated.

Results. A highly significant circadian rhythm ($P<0.001$) was found in each variable measured by RBS, with acrophases (Ø) located at night for M (00:16) and during the day for V (15:42) and OT (16:34) (Figure 1). The fit of a 7-day cosine did not reach statistical significance for M ($P = 0.160$), V ($P = 0.136$) or OT ($P = 0.541$). When looking at rhythm stability over the 8-month time span, chronobiologic serial sections show a particularly tight circadian acrophase in the early afternoon for V (row 3 of Figure 2), in keeping with a consistent statistically highly significant rejection of the zero-amplitude assumption in row 4 in which all P-values are well below the dashed horizontal line marking $P=0.05$ (arrow). In row 2 of Figure 2, the lower curve represents the rhythm-adjusted mean (MESOR) and dots below it its standard error, while the distance between the two curves represents the amplitude and dots above the upper curve represent its standard error. The 95% confidence intervals of the acrophase bracket the dark row of acrophases and show a more or less horizontal (stable) circadian timing even though the MESOR and amplitude exhibit infradian modulations. The fit of a 168-hour cosine curve to the same data set for V (not shown) do not allow the consistent demonstration of circaseptan rhythmicity.

In turning to Figure 3, a 24-hour-synchronized circadian rhythm is demonstrated more often than not in M, as apparent from the fourth row of P-values ($P<0.05$ mostly). Row 2 of Figure 3 shows that the infradian modulation of both the circadian MESOR and amplitude of M is much more pronounced than that of V, and its acrophases hovering around midnight are clearly different from the time course in early afternoon of the acrophases for V. From the fit of a 7-day cosine (Figure 3, rows 5 and 6), for parts of its time course, the circaseptan phase for M (row 6), at the start and particularly at the end of the record, is outwardly advancing, and thus not synchronized with the societal week, suggesting a shorter than 7-day period. Indeed, the period of the best-fitting cosine in the circaseptan region was 6.5 days ($P<0.001$) compared with $P = 0.160$ for a 7-day cosine. RBS, the subject uniquely self-investigated, apparently can show a 24-hour-synchronized cycle in M in the presence of a 7-day socially-desynchronized cycle in M. The circaseptan component, however, was the third most prominent in a list of several candidate infradian periods up to 30 days that were detected for M, which includes (in order of prominence): 16.5, 19.0, 6.5, 27.5, 11.5 and 14.0 days, all of which were significant at $P<0.001$ (P-values not corrected for multiple testing). No infradian components were found in OT, but several candidate periods were found for V, including 14.0 days ($P=0.005$), 16.0

days (P=0.023) and 12.0 days (P=0.046). Of note, results from 7 months of data collected in 1971 by this same subject when he was 24 years of age found a statistically significant 16.0-day component in M and a 7.0-day periodicity in V, but no infradians in OT (5).

Using previously published findings, further differences between M and V, also versus OT, in the spectral region extending from 0.7 to 2.5 years can be seen in a gliding spectrum (6) in Figure 4 for the same subject, in whom, among others (7), an about 33-year transtridecadal cycle was also demonstrated for his heart rate (8) and in data collected at certain times of day for his estimation of 1 minute (9).

Discussion. Without extrapolating beyond the scope of a single subject, the extensive data herein analyzed in the circadian and infradian regions, covering 8 months and nearly 8 lunar cycles, each from one full moon to the next full moon as indicated by vertical dashed lines in Figures 1 and 2, are presented as control information for other data from subjects presumably sensitive to the moon. The data in the para-annual region of the spectrum of 3 variables studied in Figure 4 over 4 decades also show differences in time structure. In the case of M, all results in Figures 1-4 could possibly benefit further from a separation of positive from negative affect (1, 2).

Conclusion. The inclusion of a simple-to-perform and fast mood and vigor self-rating separately throughout the day is recommended for the study of individuals' and groups' behavior over time, whereby circadian and other rhythm characteristics can be consistently assessed by cosinor, including chronobiologic serial sections (4) and gliding spectra (5). The data in hand warrant the construction of a device in which all self-ratings could be recorded in a form electronically downloadable to a computer.

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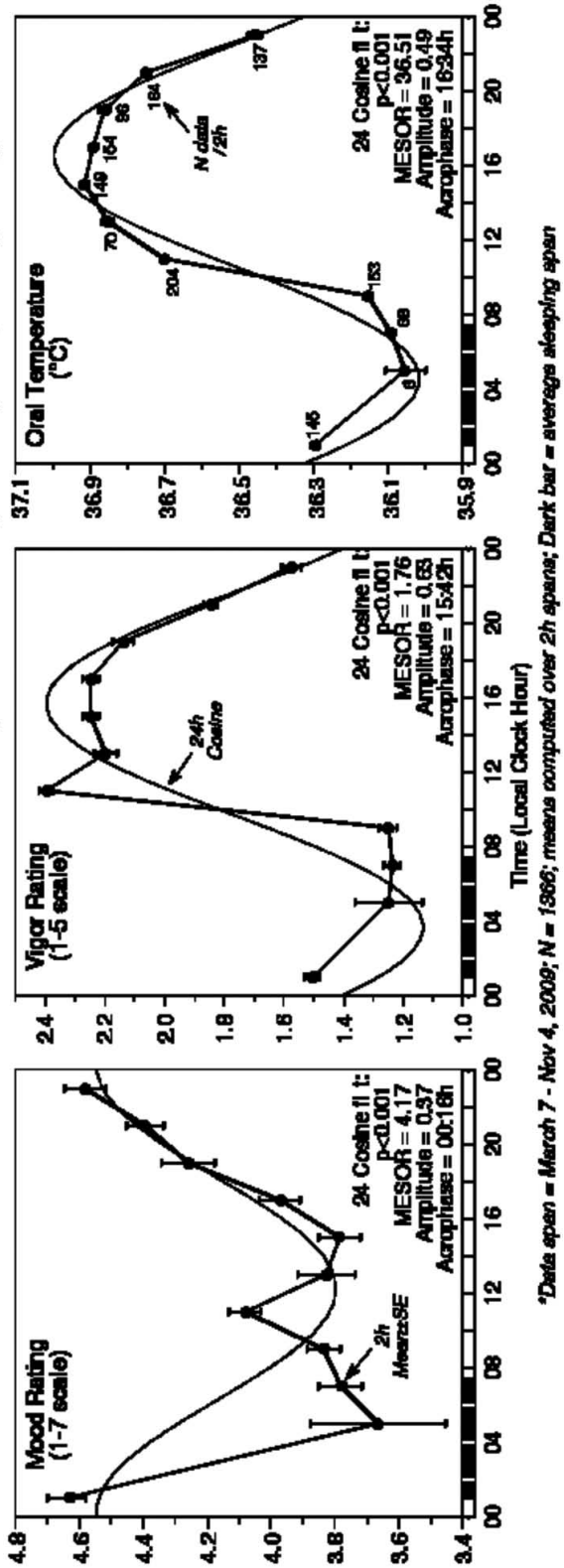

Figure 1. Circadian patterns show peaks in the afternoon for vigor and oral temperature and in the evening for mood in self-measured data by a clinically-healthy man, Two-hourly means±SE (assigned to midpoint) shown with best-fitting 24-hour cosine. N data per 2 hours, P-value from zero-amplitude (no-rhythm) test and rhythm parameters are listed.

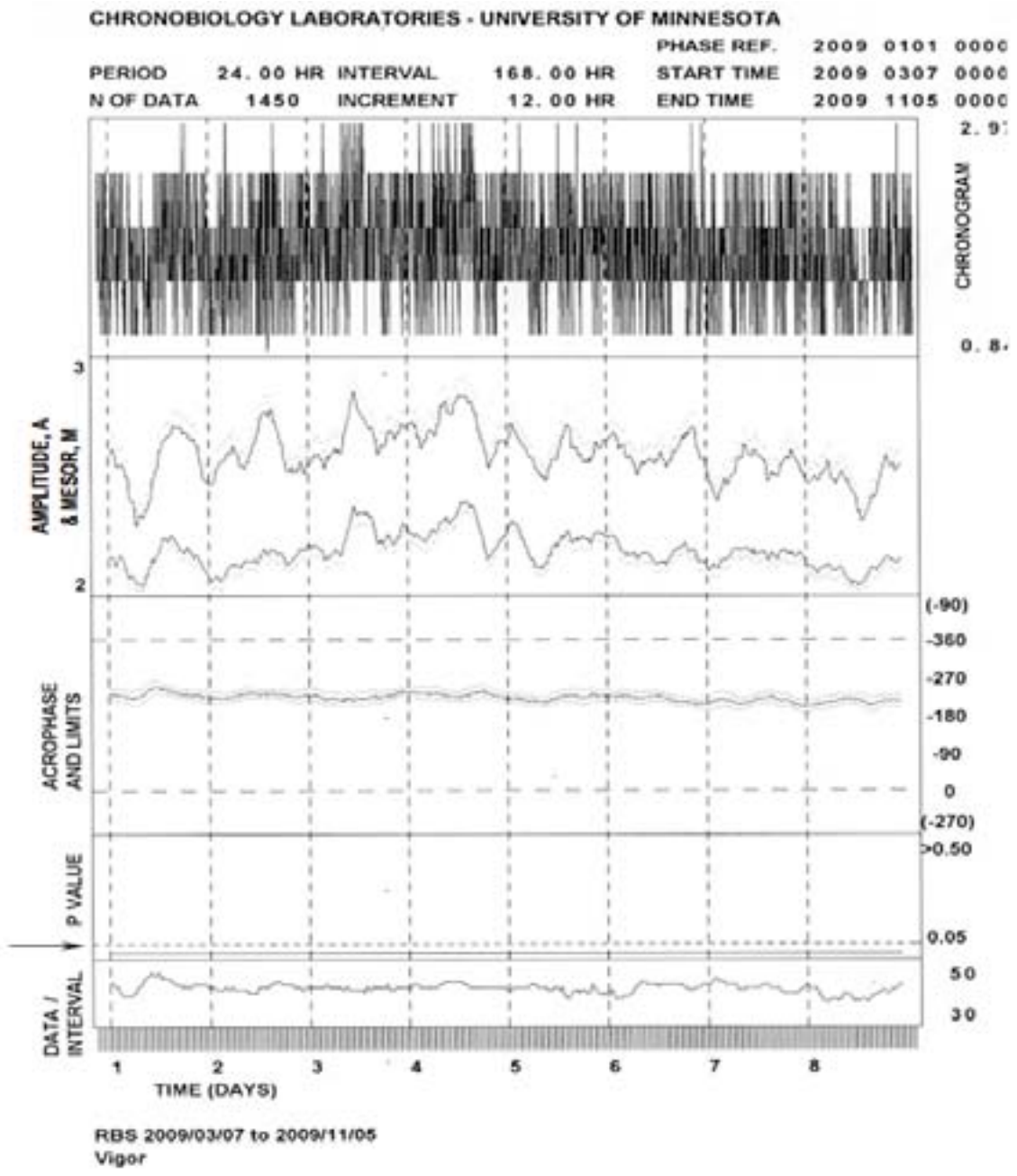

Figure 2. Serial section of 8 months of vigor ratings by RBS showing results from the fit of a 24-hour cosine. Acrophase units: 0° and -360° = 00:00, -90° = 06:00, -180° = 12:00, -270° = 18:00. © Halberg.

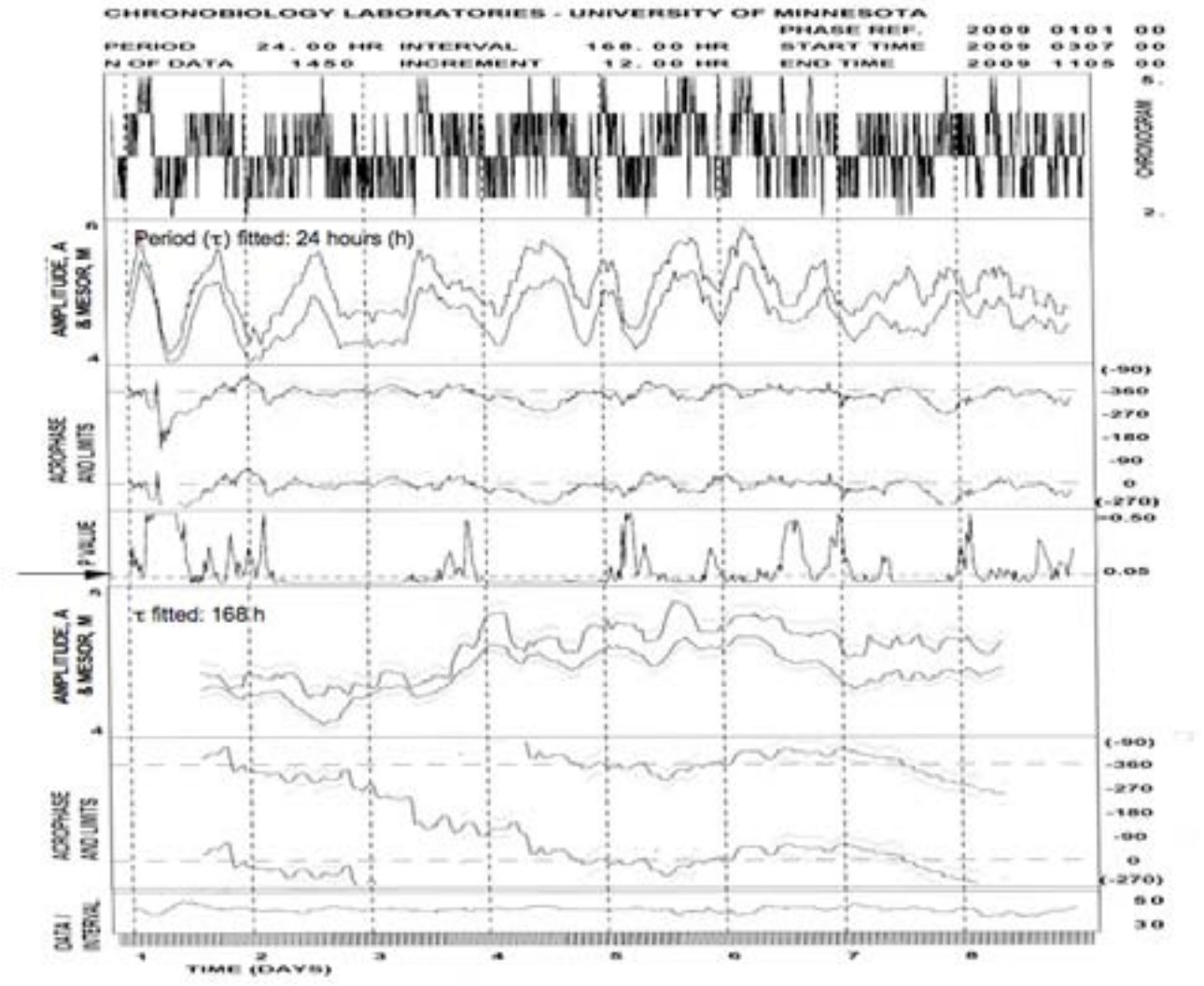

Figure 3. Serial section of 8 months of mood ratings by RBS showing results from the fit of a 24-hour cosine in rows 2-4 (see Fig 2 legend for acrophase units) and of a 7-day cosine in rows 5 and 6 (acrophase reference: 0° = Thur, Jan 1 00:00). © Halberg.

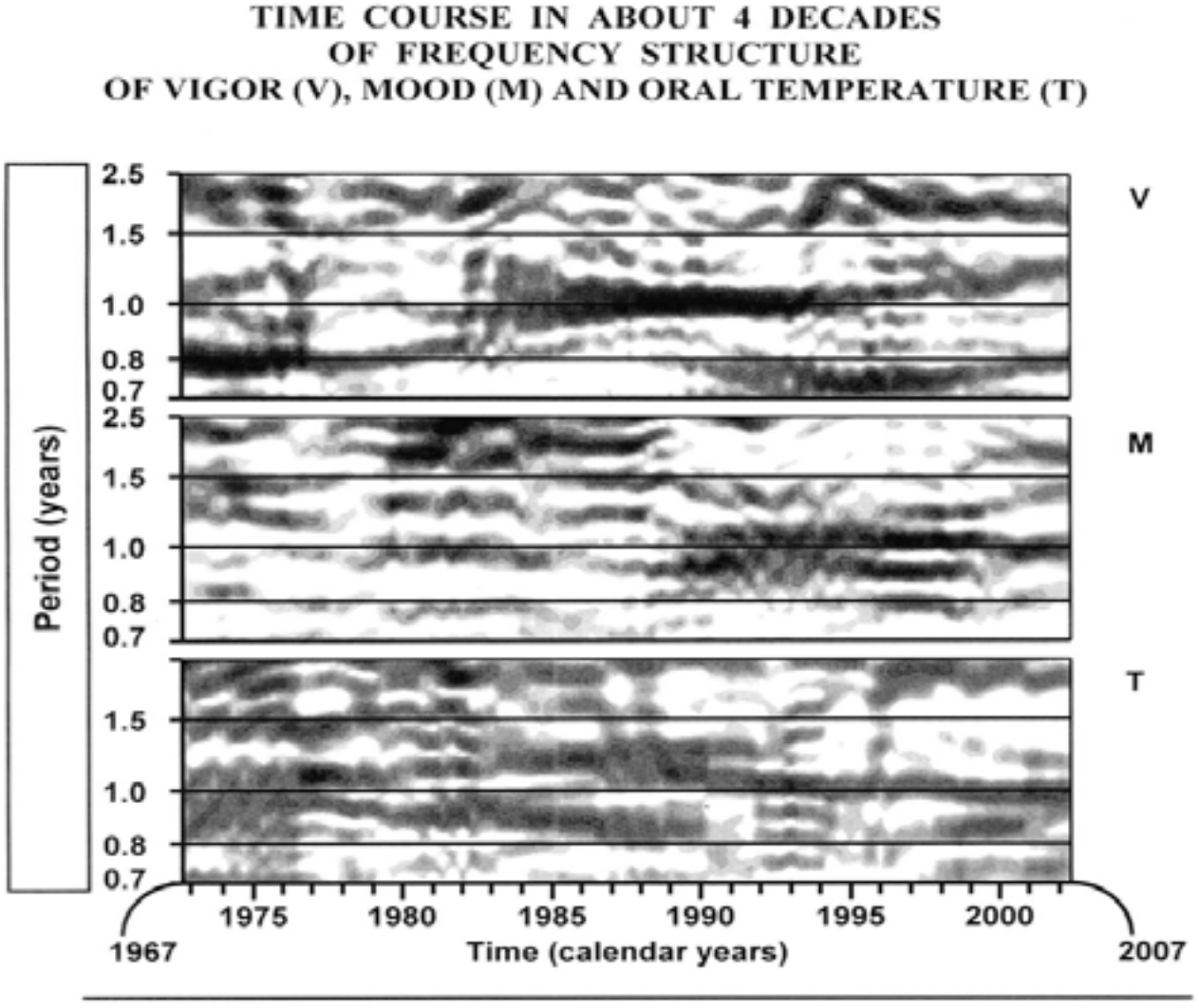

Figure 4. Gliding spectral window showing frequency structure of mood (M), vigor (V) and oral temperature (T) investigated in RBS over 40 years. © Halberg.

NIGHT-TO-DAY BLOOD PRESSURE RATIO DURING SEVEN-DAY AMBULATORY BLOOD PRESSURE MONITORING

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From 1988, when O`Brien and colleagues reported that an abnormal circadian blood pressure profile with a less marked decrease in night-time blood pressure led to an increased risk for stroke, the clinical significance of night-to-day blood pressure ratio is known (1). Subsequent studies confirmed the prognostic significance of night-to-day blood pressure ratio for prediction of a higher rate of cardiovascular complications (2-8). One of large-scale studies based on International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes was published in 2007 (9). The investigators did 24-hour blood pressure monitoring in 7458 people (mean age 56.8 years) from Denmark, Belgium, Japan, Sweden, Uruguay and China. Median follow-up was 9.6 years. They found that night-to-day ratio of systolic and diastolic blood pressure adjusted for cohort, sex, age, body-mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, and antihypertensive drug treatment predicted total mortality, non-cardiovascular mortality and cardiovascular mortality. In fully adjusted models night-to-day ratio was additionally adjusted for 24-hour blood pressure. The results for fully adjusted night-to-day ratio were similar except systolic blood pressure and cardiovascular mortality where the hazard ratio 1.08 (0.99- 1.17) was not statistically significant. After the patients were, according the night-to-day ratio, divided in 4 categories with night-to-day ratio >1.0 (reverse dippers), 0.9-1.0 (non-dippers), 0.9-0.8 (dippers) and <0.8 (ultra-dippers), the total mortality was increased in non-dippers and reverse-dippers in comparison to dippers. Cardiovascular mortality was significantly increased in reverse dippers, as well as incidence of all cardiovascular events.

Although the prognostic significance of night-to-day blood pressure ratio was proved in a large group of patients, the clinical significance of this value depends on variation of repeated measurement in individual patients.

The evaluation of night-to-day blood pressure variability during 7 days of ambulatory blood pressure measurement was the aim of the present study.

Methods

Thirty subjects (18 males, 12 females), twenty one years to seventy three years old, were recruited for seven-day blood pressure monitoring. Colin Medical Instruments (Komaki, Japan) were used for ambulatory blood pressure monitoring (oscillation method, 30-minute interval between measurements) (10). One-hour means of systolic and diastolic blood pressure were evaluated, when night-time was considered from midnight to 0600 h and day time from 1000 to 2200 h, avoiding the transitional periods. Mean day-time and mean night-time systolic and diastolic pressures were evaluated every day (11).

Dipper status was evaluated every day. Dippers were defined as those individuals with a 10-20 % fall in nocturnal blood pressure. Non-dipping was defined as a less than 10 % nocturnal fall, and those with no fall in blood pressure were defined as reverse-dippers (12).

Results

The patients were ordered according mean 7-day SBP (patient No 1: 107 mmHg, patient No 30: 131 mmHg; median value: 123 mmHg).
Variability of night-to-day ratio during 7-day monitoring is seen in Fig. 1 for SBP and in Fig. 2 for DBP.
Only 4 subjects (13 %) were found which could be classified as SBP dippers or ultra-dippers every day. Most of the subjects were classified on various days differently, even 8 subjects (27 %) were one day classified as ultra-dippers and the other day as reverse-dippers.
Similarly no subject classified as DBP dipper or ultra-dipper every day was found. Four subjects (13 %) were one day classified as ultra-dippers and the other day as reverse-dippers.
The day-to-day variability of night-to-day ratio is large. The dipping status classification in individual patient is not reliable.

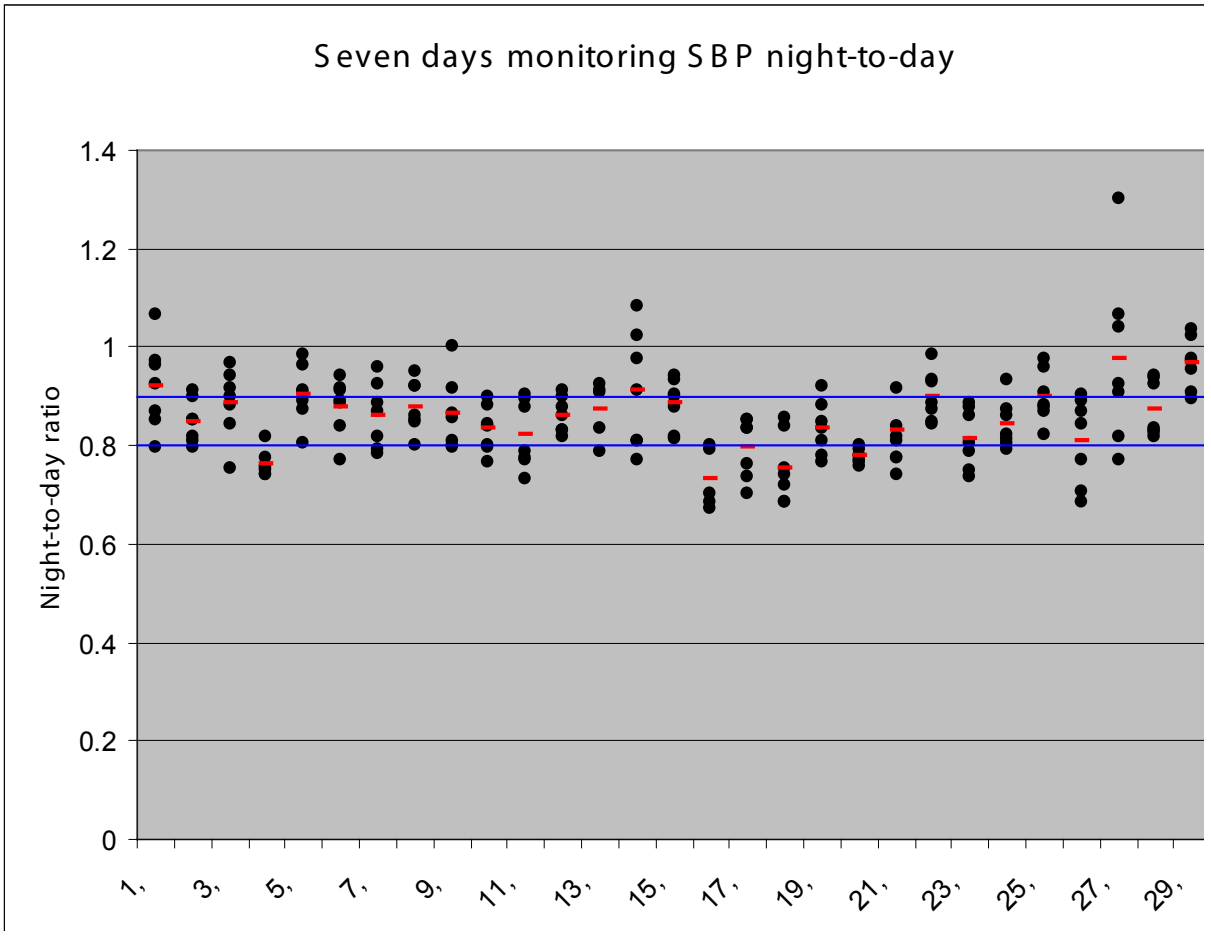

Fig. 1
Variability of night-to-day SBP ratio during 7-day monitoring. Patients were put to order according mean 7-day SBP (patient No 1: 107 mmHg, patient No 30: 131 mmHg; median value: 123 mmHg). One-day mean values (point) and 7-day mean values (dash) are indicated.

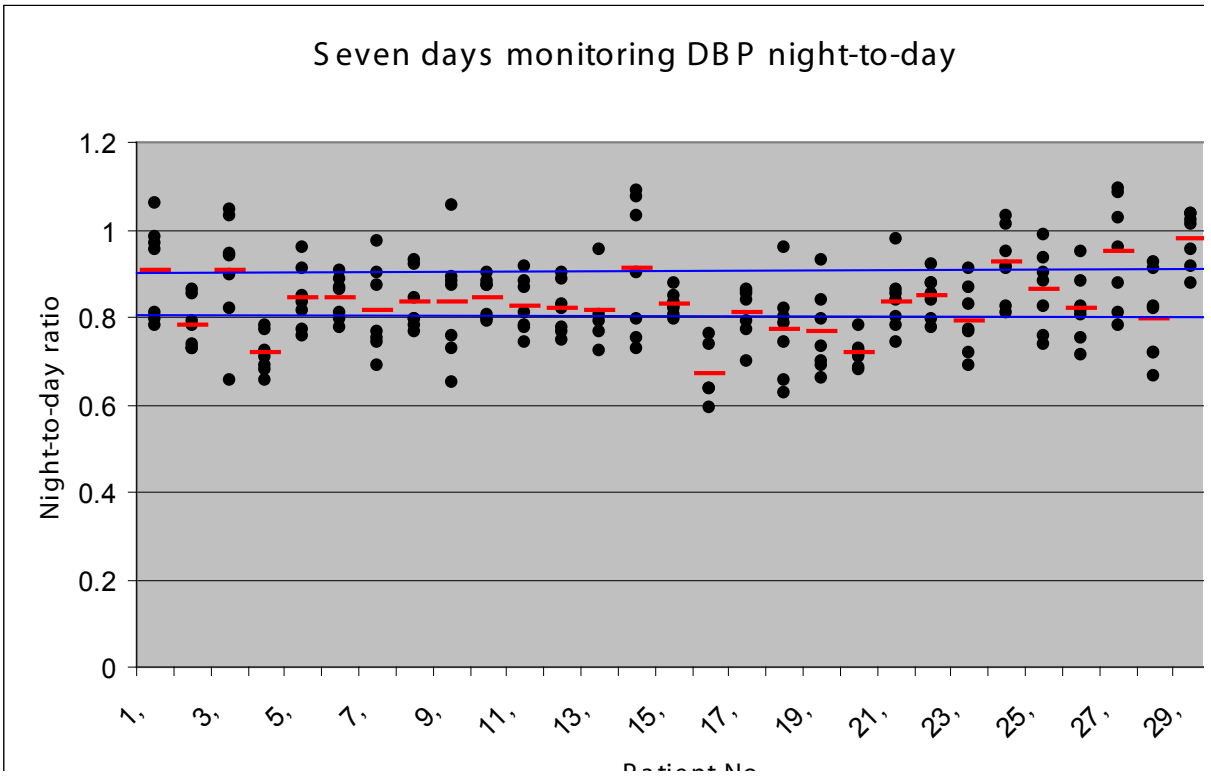

Fig. 2
Variability of night-to-day DBP ratio during 7-day monitoring. Patients were ordered according mean 7-day SBP (patient No 1: 107 mmHg, patient No 30: 131 mmHg; median value: 123 mmHg). One-day mean values (point) and 7-day mean values (dash) are indicated.

Discussion

Our finding of large night-day ratio variability in individual subjects corresponds to the results of other studies. The night-to-day blood pressure ratio is subject to regression-to-the mean (13).
Dipping status has also a low reproducibility, with up to 40 % of individuals from Europe (14) and Asia (15) changing status between repeat recordings.
In our former study we demonstrated that the relation between night-to-day ratio and risk of cardiovascular events is not linear as it is in the case of mean 24-hour systolic and diastolic pressure (16). We observed at low circadian double amplitude which roughly corresponds to the difference between night and day blood pressure (5 mmHg of systolic and 4 mmHg of diastolic pressure) about 30 % higher incidence of cardiovascular events than at circadian double amplitude of 15 to 35 mmHg systolic and of 12 to 20 mmHg diastolic pressure but at double amplitude higher than 35 mmHg in systolic and 28 mmHg in diastolic pressure the incidence was double. This indicates the existence of overswinging or Circadian Hyper-Amplitude-Tension (CHAT) syndrome which is associated with a large increase in cardiovascular disease risk. The incidence of ultra-dipping is more frequent that the incidence of CHAT but existence of CHAT alone can lead to misdiagnosis of risk based on night-to-day blood pressure ratio.
In conclusion, despite the low night-to-day ratio of blood pressure predicted increased risk for cardiovascular events in large studies, the determination of this value is useless for management of arterial hypertension in individual patients.

Summary

The evaluation of night-to-day blood pressure variability during 7 days of ambulatory blood pressure measurement was the aim of the present study. Thirty subjects (18 males, 12 females), twenty one years to seventy three years old, were recruited for seven-day blood pressure monitoring. Colin Medical Instruments (Komaki, Japan) were used for ambulatory blood pressure monitoring (oscillation method, 30-minute interval between measurements). One-hour means of systolic and diastolic blood pressure were evaluated, when night-time was considered from midnight to 0600 h and day-time from 1000 to 2200 h, avoiding the transitional periods. Mean day-time and mean night-time systolic and diastolic pressures were evaluated every day.

Dipper status was evaluated every day. Dippers were defined as those individuals with a 10-20 % fall in nocturnal blood pressure. Non-dipping was defined as a less than 10 % nocturnal fall, and those with no fall in blood pressure were defined as reverse-dippers.

The day-to-day variability of night-to-day ratio is large. The dipping status classification in individual patients is not reliable.

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DAY AND NIGHT BLOOD PRESSURE VARIABILITY DURING SEVEN-DAY AMBULATORY BLOOD PRESSURE MONITORING

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The fact that raised nocturnal blood pressure predicted a higher rate of cardiovascular complications was established in several large-scale studies (1 – 6). Recently the investigators of the International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO) did 24-hour blood pressure monitoring in 7458 people from Denmark, Belgium, Japan, Sweden, Uruguay and China and calculated cohort, sex, age, body-mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, and antihypertensive drug treatment adjusted hazard ratios for day-time and night-time blood pressure (7). In fully adjusted models, the night-time blood pressure was additionally adjusted for day-time blood pressure. The subjects with mean age of 56.8 years were followed for approximately 10 years (median 9.6 years). Fully adjusted night-time blood pressure predicted total, cardiovascular and non-cardiovascular mortality.
Results of all those studies indicated the necessity of 24-hour ambulatory blood pressure recording in clinical practice. Because the diagnosis of hypertension is generally based on casual measurement of blood pressure in general practitioner office and these values of blood pressure are higher than values of ambulatory blood pressure monitoring, the table of blood pressure thresholds for definition of hypertension with different types of measurement is included in the Guidelines for Management of Hypertension (8). According to this table the threshold for systolic blood pressure is 140 mmHg in the office or clinic, 125 – 130 mmHg during 24 hours, 130 -135 mmHg during day and 120 mmHg during night. The corresponding values for diastolic blood pressure are 90 mmHg in the office and clinic, 80 mmHg during 24 hours, 85 mmHg during day and 75 mmHg during night. The values for home measurement are the same as for ambulatory monitoring during day.
The condition for reliability of diagnosis is low day-to-day variation of night-time and day-time pressure values.
The variation of night-time and day-time blood pressure during 7-day continuous ambulatory monitoring was the aim of the present study.

Methods

Thirty subjects (18 males, 12 females), twenty one years to seventy three years old, were recruited for seven-day blood pressure monitoring. Colin Medical Instruments (Komaki, Japan) were used for ambulatory blood pressure monitoring (oscillation method, 30-minute interval between measurements) (9). One-hour means of systolic and diastolic blood pressure were evaluated, when night-time was considered from midnight to 0600 h and day-time from 1000 to 2200 h, avoiding the transitional periods. Mean day-time and mean night-time systolic and diastolic pressures were evaluated every day (10).

Results

The patients were ordered according mean 7-day SBP (patient No 1: 107 mmHg, patient No 30: 131 mmHg; median value: 123 mmHg).

The variability of one-daytime SBP values during 7-day monitoring is seen in Fig. 1.

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

The night-time SBP values are seen in Fig. 2. Similarly, if 120 mmHg of night-time systolic pressure is the threshold, then 10 subjects (33 %) were indicated one day for treatment and the other day not. Corresponding value of threshold for diastolic day-time pressure is 85 mmHg, thus 22 patients (73 %) were one day indicated for treatment and the other day not (Fig. 3) and for night diastolic pressure of 70 mmHg 24 patients (80 %) were indicated one day for treatment and the other day not. Only one patient (3%) was indicated for treatment every day on the DBP night basis (Fig. 4).

Those data demonstrate large day-to-day SBP and DBP mean day-time and mean night-time variability.

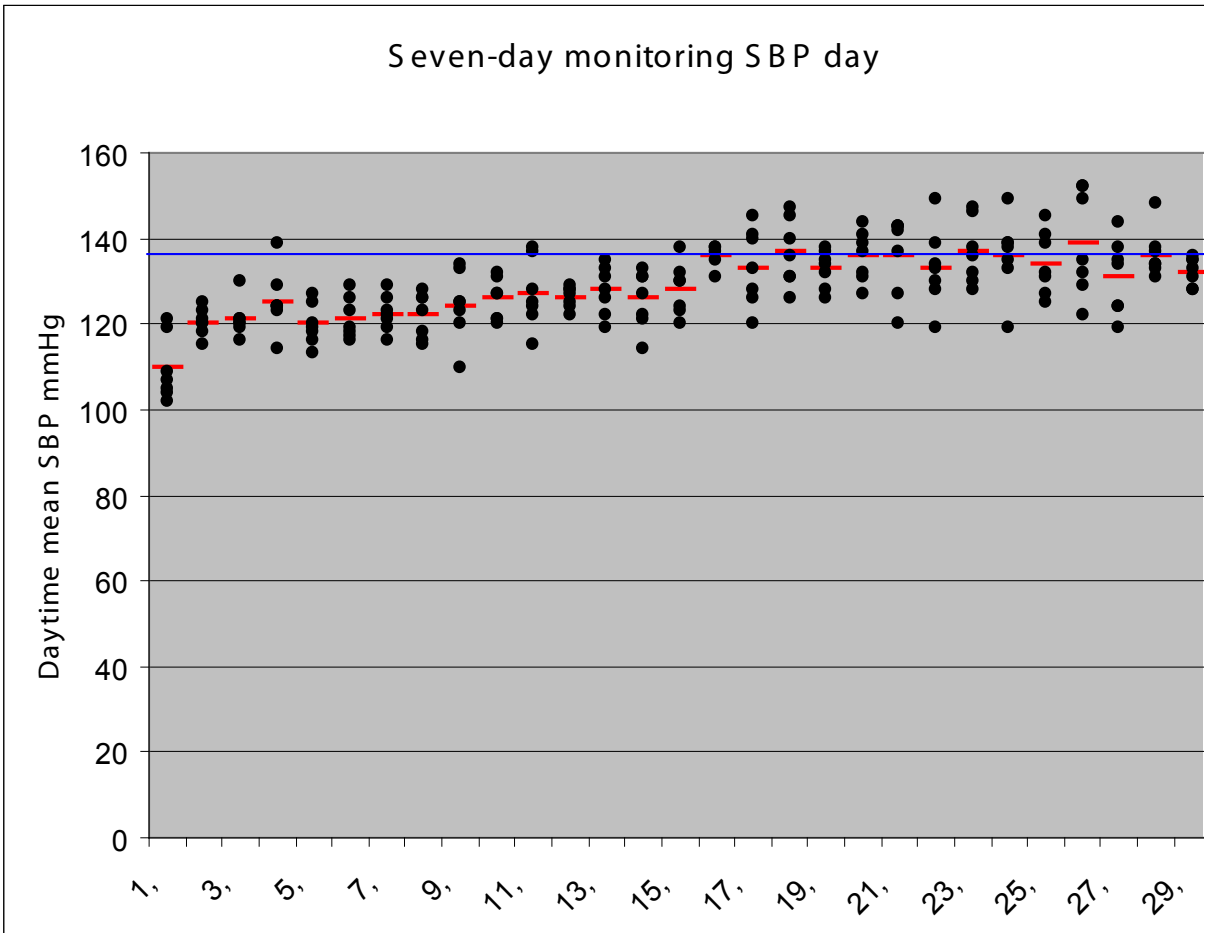

Fig. 1

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

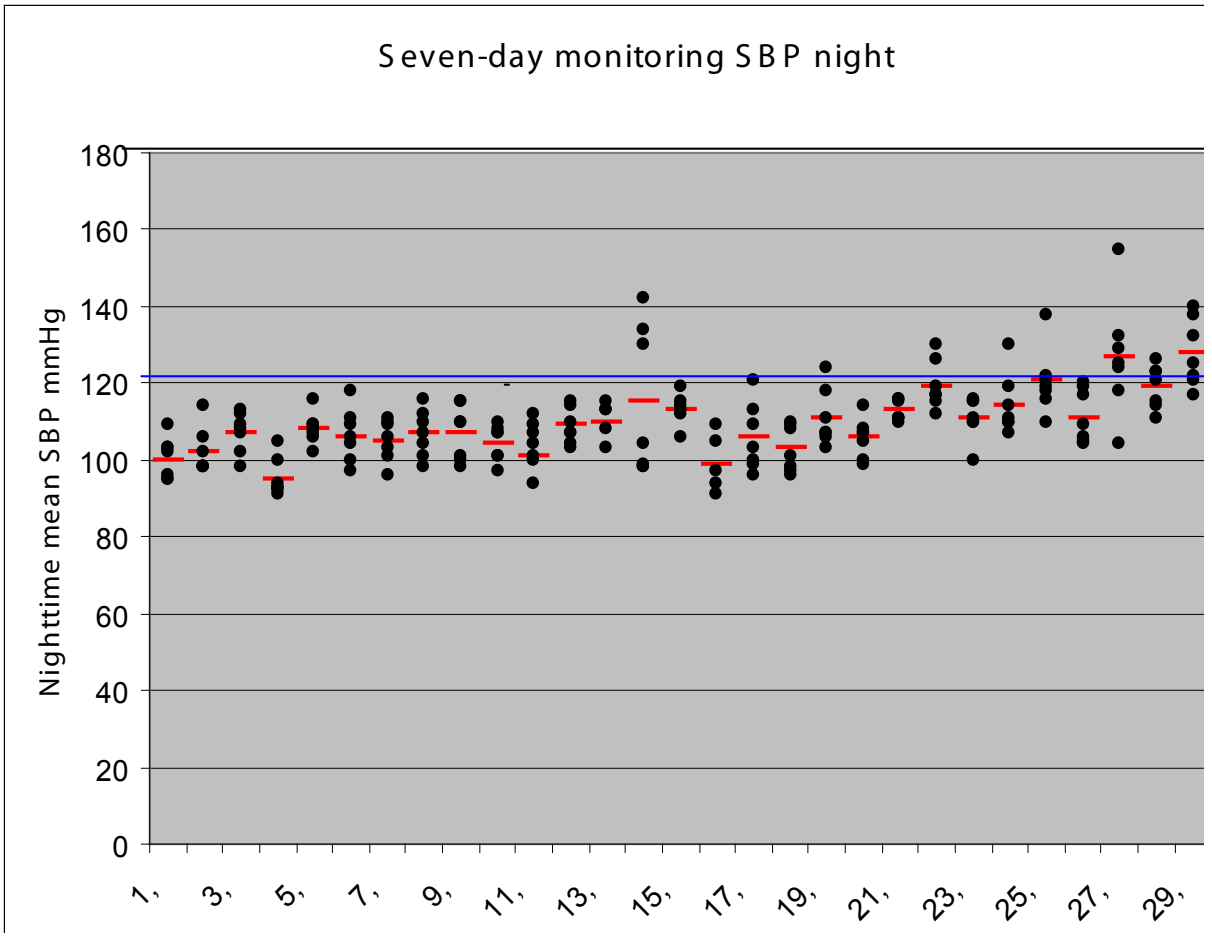

Fig. 2
The variability of one-nighttime SBP values during 7-day monitoring. The patients were ordered according mean 7-day SBP (patient No 1: 107 mmHg, patient No 30: 131 mmHg; median value: 123 mmHg). One-day mean values (point) and 7-day mean values (dash) are indicated.

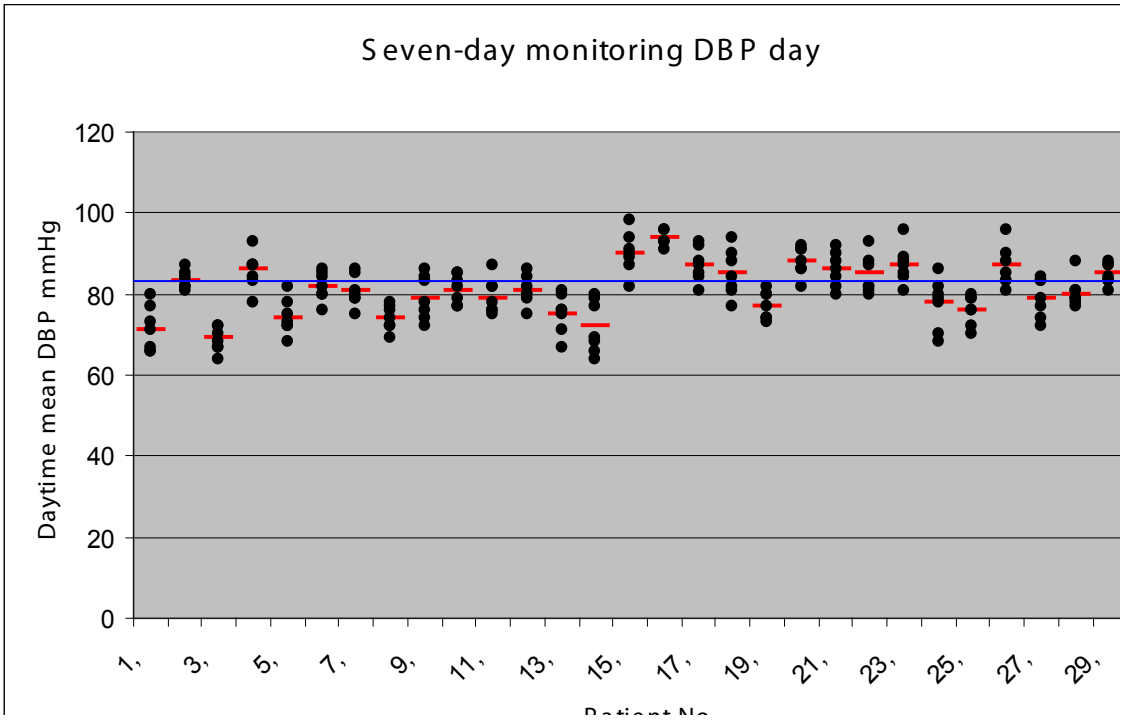

Fig. 3
The variability of one-daytime DBP values during 7-day monitoring. The patients were ordered according mean 7-day SBP (patient No 1: 107 mmHg, patient No 30: 131 mmHg; median value: 123 mmHg). One-day mean values (point) and 7-day mean values (dash) are indicated.

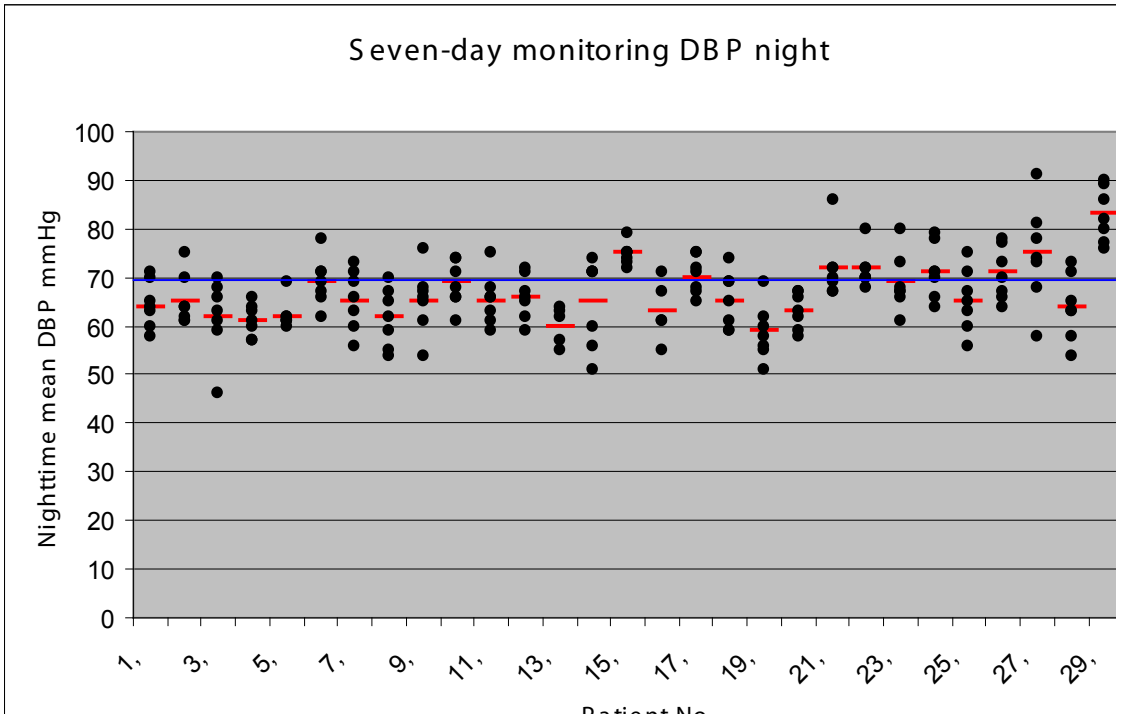

Fig. 4
The variability of one-nighttime DBP values during 7-day monitoring. The patients were ordered according mean 7-day SBP (patient No 1: 107 mmHg, patient No 30: 131 mmHg; median value: 123 mmHg). One-day mean values (point) and 7-day mean values (dash) are indicated.

Discussion

Hypertension is currently diagnosed mostly by means of a single or a few measurements during few consecutive examinations. This practice can be associated with over 40 % false diagnoses (11, 12), due in part to large variability in blood pressure as such and in response to external factors. Seven-day ambulatory blood pressure monitoring demonstrates large day-to-day variability of blood pressure. It is clear that 24-hour monitoring is better than a single or a few measurements, but for avoiding misdiagnosis is not sufficient. Our study indicates that longer monitoring, preferably for 7 days, is recommended.

Self-measurement of blood pressure at home can provide values that, when averaged over a period of a few days, are more reproducible and predict the presence and progression of organ damage as well as the risk of cardiovascular events better than office values. Home blood pressure measurement for suitable periods can be recommended before and during treatment also because this relatively cheap procedure may improve patient adherence to treatment (13).

In conclusion, the education for long-lasting self-monitoring is the best approach to management of hypertension.

Summary

The variation of night-time and day-time blood pressure during 7-day continuous ambulatory monitoring was the aim of the present study. Thirty subjects (18 males, 12 females), twenty one years to seventy three years old, were recruited for seven-day blood pressure monitoring. Colin Medical Instruments (Komaki, Japan) were used for ambulatory blood pressure monitoring (oscillation method, 30-minute interval between measurements). One-hour means of systolic and diastolic blood pressure were evaluated, when night-time was considered from midnight to 0600 h and day-time from 1000 to 2200 h, avoiding the transitional periods. Mean day-time and mean night-time systolic and diastolic pressures were evaluated every day. Seven-day ambulatory blood pressure monitoring demonstrates large day-to-day variability of blood pressure. In conclusion, the education for long-lasting self-monitoring is the best approach to management of hypertension.

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HOME BASED REHABILITATION PROGRAM USING TRANSCUTANEOUS ELECTRICAL MUSCLE STIMULATION IN PATIENTS WITH CHRONIC HEART FAILURE

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Abstract

Background. In chronic heart failure (CHF), persistent autonomic derangement and neurohumoral activation cause structural end-organ damage and decrease exercise capacity. Beneficial effects of exercise training in CHF have been documented at various functional and structural levels, including its positive influence on sympathetic overactivity and decrease of vasoconctrictive agents. Electromyostimulation (EMS) has been shown as alternative to aerobic exercise training in patients that cannot undertake conventional exercise; however the role of EMS on the reduction of vasoactive substances has still not been studied. **Patients and methods.** Eighteen patients with stable CHF (mean age 50.7 ± 9.6 years, NYHA class II-III, mean EF 28.7 ± 6.9 %) underwent 12 weeks of home based EMS of leg extensors using battery-powered stimulators (frequency 10Hz, mode "on-off"), 2x60min/day and 7 days/week. **Results.** EMS lasting 12 weeks increased significantly peak oxygen uptake, maximal workload and muscle power. EMS also reduced the plasmatic levels of endothelin assessed by ELISA assay (from 0.97 ± 0.6 pmol.l $^{-1}$ to 0.80 ± 0.2 pmol.l^{-1}), however without statistical significance. **Conclusion.** Twelve weeks of exercise home training using EMS has been shown to have direct beneficial effect on selected functional parameters in patients with CHF. Together with the clear tendency to the decrease of endothelin activity these results demonstrate the efficacy of EMS as valuable and safe home training program for patients with CHF

Key words

cardiovascular rehabilitation - heart failure - electrical muscle stimulation - exercise training - endothelin - muscle power

Background

Chronic heart failure (CHF) is characterized by limited physical capacity, related partly to the severe structural and biochemical changes in skeletal muscles. Classical exercise training has been definitely shown to improve exercise capacity, quality of life and improve the prognosis in congestive heart failure. However, not all patients with CHF are able to undergo the conventional cardiovascular rehabilitation program for many reasons. Recently, the electromyostimulation (EMS) has been proposed as possible alternative to endurance training in these patients. This new technique could improve the results of classical training in cardiac rehabilitation of severely deconditioned patients. According to previously published data EMS seems to be an ideal training method for patients who could not

perform standard forms of exercise, such as patients with muscular or neurologic disorders (1, 2). In conditions of chronic heart failure the blood perfusion is shifted towards the brain and myocardium at the expense of gastrointestinal, renal and other body compartments (3). Very intensive neurohumoral reaction then follows: rise of the activity of sympatoadrenergic system, renin-angiotensin-aldosterone cascade, variety of pro-inflammatory cytokines (interleukins, tumor necrosis factor alpha, etc.) and vasoconstrictive agents, such as vasopressin and endothelin. Because in the same time the secretion of antagonist vasodilatative substances falls down, the global peripheral resistance is raised; perfusion of skeletal muscles decreases (4) and its ability to vasodilation is reduced (5). According to previous reports it seems that endothelin is involved in the Plasmatic level of vasoconstrictor endothelin-1 contributes closely to exercise intolerance in patients with heart failure, perhaps by initiation and progression of impaired vasodilatory response during exercise (6). Exercise training has been shown to normalize autonomic derangements and neurohumoral overactivation in CHF patients (7), however the direct impact of physical exercise on the plasmatic activity of endothelin was poorly studied. In the one of rare existing reports Spinarova et al. (2001) found a positive influence of exercise bicycle training on plasma endothelin in patients with CHF (8). From this perspective, it is not surprising that the effects of EMS on endothelin plasmatic levels were not yet studied. Direct transcutaneous electrical muscle stimulation of large skeletal muscles has been shown to promote similar physiologic response as seen in classic cardiovascular exercise by increasing peak oxygen uptake, maximal load and muscle power. The handful of small studies that exist of home-based EMS training of leg muscles in heart failure show that EMS produces similar benefits to conventional exercise in improving exercise capacity, making EMS an alternative to aerobic exercise training in those that cannot undertake conventional exercise. Thus, it could be supposed that EMS could reduce the plasmatic activity of endothelin and its deleterious effects on the stability of muscle mass in chronic heart failure.

Patients and methods

Eighteen patients (4 women, 14 men) with congestive heart failure (mean age 50.7 ± 9.6 years, NYHA class II-III, mean EF 28.7 ± 6.9 %) underwent 12 weeks of home-based low-frequency electrical myostimulation (EMS) of leg extensors. Before the inclusion to the study all the subjects signed the Informed Patient's Consent. The study was approved by the local Ethical Committee, and conforms to the principles outlined in the Declaration of Helsinki and to GCP guidelines of European Community.

Inclusion criteria: stable CHF at least 3 months on basis of CAD or CMP, NYHA II-III, clinical stabilization at least 1 month, complex pharmacotherapy according to actual knowledge (excepting contraindications), dosing unchanged for at least 2 weeks, age 20 - 80 years, regardless of sex, EF below 40%, non-attendance in another study.

Exclusion criteria: angina pectoris, valvular disease determined by Doppler echocardiography, intermittent claudication, chronic obstructive pulmonary disease, uncompensated diabetes mellitus and disorders limiting physical performance other than heart failure.

Training protocols

Target muscles of the electromyostimulation were the extensors (quadriceps and triceps surae muscles) of both legs. Home based EMS training was done using dual-channel battery-powered (2 rechaergable 1.5V batteries) stimulator Rehab X2 (CEFAR®, Malmö, Sweden). The stimulator delivered a biphasic current of 10Hz frequency with preselected characteristics: "on-off" working mode (20s contraction, 20s relaxation), pulse width 200msec, and maximal stimulation intensity 60mA. Self-adhesive electrodes 80x130mm (PALS® Platinum, Axelgaard Manufacturing Co., Lystrup, Denmark) were placed on the thighs approx. 5cm under inguinal fold and 5cm over the upper patella border; in the

calves the electrodes were positioned approx. 2cm under the knee joint and just over the proximal end of Achilles tendon. Before the delivery of stimulators all the patients were instructed how to use the devices at home and how to place the electrodes. Patients were asked to perform the EMS procedure 2x60 min/day in supine position, and at the same day period (10-12:00 AM and 07:00-08:00 PM), 7 days a week for 12 consecutive weeks.

Muscle power testing

A dynamometric system PC-2 SDT (EXAMO® Brno, Czech Republic) with microprocessor for isometric dynamometry testing of leg extensors was used for the assessment of maximal muscle power at the onset and after the end of EMS training period. All measurements were performed in sitting position on the device; the chest was fixed by 2 straps, the pelvis and knees flexed at 90 angles. The ankle of tested leg was attached to the strength transducer (D.OS-SBEAM 1000N, EXAMO® Brno, Czech Republic) by a Velcro strip. Then, the patient carried out 3 consecutive maximal voluntary extensions (contraction time 3s - resting time 7s); the highest value was considered as the maximal power (F_{max}; N). The isokinetic muscle strength of knee extensors was assessed by the same dynamometric system, recording isokinetic strength as torque. Patients performed 3 consecutive knee extension movements with maximal effort and with an angular speed at 90 degrees.s^{-1} with both legs; the highest value obtained was regarded as the peak torque (PT_{max}; Nm).

At baseline and after 12 weeks of EMS training all the patients underwent standard spiroergometric test using respiratory gas analyzer (MedGraphics, USA) to assess the values of peak oxygen uptake (peak O_2 - VO_{2Speak} and O_2 at anaerobic threshold - VO_{2AT}), peak workload (W_{peak}) and peak heart rate (HR_{peak}).

Endothelin assay

Plasma endothelin measurement was done using an immunometric (i.e., sandwich) method ELISA (Biomedica Group, Wien Austria). This assay offers sensitive and specific analysis of endothelin in serum, plasma or cell culture media.

Statistics

All data are presented as mean ± SD. Statistical analysis was performed using paired Student t-test to compare within-group values before and after rehabilitation, and the Mann–Whitney *U* test to compare unpaired not normally distributed data. The P value <0.05 was considered as significant.

Results

Time duration of spiroergometric test

Time duration of the exercise during the control spiroergometric test has been extended after 12 weeks of EMS training 1 (from 432 ± 133s to 482 ± 176s), however without statistical significance.

Peak oxygen uptake - VO_{2peak} (ml.kg.min^{-1}). Twelve weeks of home EMS training increased significantly the value of peak O_2 uptake (from 16.2 ± 4.1 ml.kg.min^{-1} to 17.4 ± 4.3 ml.kg.min^{-1} ($P < 0.002$).

Oxygen uptake at anaerobic threshold - VO_{2AT} (ml.kg.min^{-1}). Also the value of VO_{2AT} increased significantly after 12 weeks of EMS - from 10.2 ± 2.3 ml.kg.min^{-1} to 11.1 ± 2.6 ml.kg.min^{-1} ($P < 0.04$).

Peak workload – W_{SL} (watts - W). After 12 weeks of EMS training the value of W_{peak} improved significantly from 89.8 ± 23.7 W to 98.5 ± 25.9 W ($P < 0.002$).

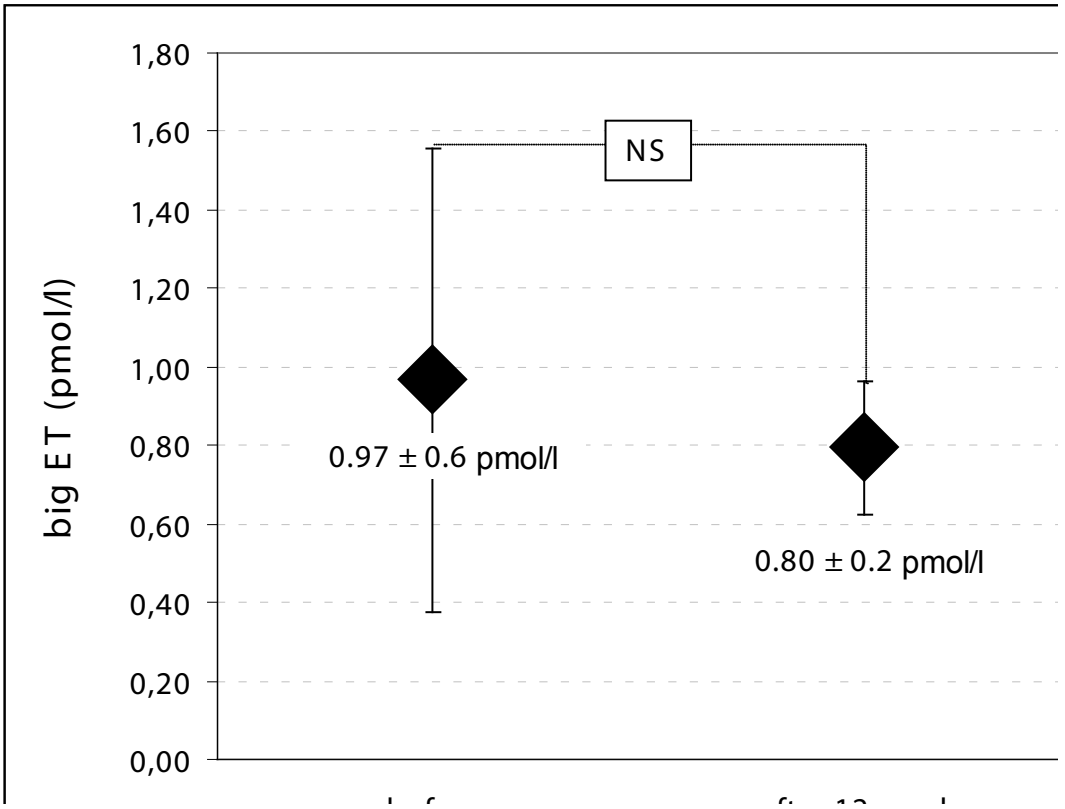
Peak heart rate – HR_{peak} (beats per minute – bpm). After 12 weeks of EMS HR_{peak} increased from 116.7 ± 19 bpm to 123.3 ± 22 bpm, however without statistical significance.

Assessment of muscle power. Measurements assessed by isometric dynamometry revealed a statistically significant increase of maximal muscle power (F_{max}) from the initial value of 311.8 ± 132 N to 344.1 ± 158 N at the end of the study ($P < 0.05$). It means that the maximal muscle power was improved cca

by 10% after 12 weeks of home based stimulation. Also the evaluation of the isokinetic peak torque (PT_{max}) showed a significant increase after 12 weeks of EMS from 138.9 ± 69 Nm to 156.7 ± 63 Nm ($P < 0.05$). PT_{max} after 12 weeks of stimulation was improved cca by 13%.

Endothelin assay. ELISA assay showed that 12 weeks of EMS training reduced the mean plasmatic levels of endothelin (from 0.97 ± 0.6 pmol.l $^{-1}$ to 0.80 ± 0.2 pmol.l^{-1}), however without statistical significance (see Fig.1).

Fig. 1
Results of the endothelin ELISA assay (expressed as mean ±SD).



Discussion.

Congestive heart failure is a widely known sequel of coronary artery disease, hypertension, dyslipidemia and other metabolic or endocrine disorders. Physical performance is strongly affected and the main factors contributing to the poor exercise tolerance include: impairment of myocardial function, disturbances in peripheral microcirculation, ventilatory disturbances such as pulmonary congestion or decreased perfusion, increased sympathetic activity, rise in the secretion of vasoconstrictor substances (catecholamines, renin-angiotensin-aldosterone, endothelin, etc.) and abnormal muscle function (atrophy, increase of anaerobic type II fibers, decreased regional blood flow, loss of oxidative mitochondrial capacity, etc.). In other words, all body systems, including skeletal muscle, are involved in the heart failure syndrome. Patients with chronic heart failure develop a skeletal muscle myopathy (9) that is associated with a worsened prognosis (10). The histology of skeletal muscle is abnormal, there is muscle fiber atrophy (11), and impaired blood flow in muscle (12), metaboreceptor dysfunction (13), abnormal muscle biochemistry, and skeletal muscle has reduced strength (14) and fatigues easily (15). Overall, impaired skeletal muscle function contributes to exercise intolerance and is related to the severity of heart failure (16). The endothelium plays a major role in the control of vascular tone.Endothelial-

dependent relaxation of skeletal muscle microcirculation in response to acetylcholine administration is altered in patients with heart failure (17). It likely that endothelial dysfunction of the peripheral circulation is involved in the inadequate rise in blood flow during exercise in patients with heart failure (18). Endothelin, which is often increased in severe heart failure, appears to be involved in the poor vasodilatory response to exercise, as are some prostaglandins (19). The endothelium plays a major role in the control of vascular tone. Nitric oxide (NO), which is continuously released by the endothelium, counterbalances the action of vasoconstrictive mediators such as nor adrenaline and angiotensin II and plays an important role in the vasodilatation of resistive vessels during exercise (20). The prognosis with conventional pharmacologic treatment is usually poor, but patients with stable form of CHF respond positively to exercise training programs. Reported benefits depend on the training program type and duration. The RHB training programs aim to increase the intensity of peak effort, to improve the ventilation and perfusion, to improve cardiac function, to strengthen the skeletal muscle and to increase the aerobic enzyme activity in the muscles. EMS-induced exercise was initially studied and shown to be effective in paraplegic patients to improve muscle tone and strength, particularly in those with spinal cord injury, and a modest increase in peak oxygen consumption (VO_2) was also seen with EMS in these studies (21, 22;). However, recent evidence suggests that EMS of the leg muscles can evoke cardiovascular responses such as those seen with conventional exercise in healthy volunteers (23) and heart failure patients (24). Although classic bicycle exercise training has been shown to improve the neuro-humoral status, which has been implicated in the process of heart failure progression and the genesis of sudden death, the similar effects of EMS have been poorly studied. Electrical stimulation of large groups of muscles with consequent repetitive muscle contraction is likely to stimulate muscle metabolism enough to produce a systemic metabolic and cardiovascular response that is significant. Our own study studied the effects of EMS home training in NYHA class II-III patients with left ventricular systolic dysfunction (EF<30%). Twelve weeks of EMS training produced significant increases in peak VO_2, VO_{2AT}, peak HR, time duration of exercise testing and muscle power (F_{max}) of leg extensors. These results are in full concordance with previously published reports. As was mentioned above, the reports focusing on the influence of EMS on the plasmatic activity of endothelin are not available. Although our study failed to show the significant effect of EMS on the plasmatic level of endothelin assessed by ELISA assay, there was a clear tendency to the decrease of endothelin activity and this result should be regarded as another evidence of the efficacy of EMS in patients with CHF. Karavidas et al. (2006) found that EMS training is acting as an exercise training program, improving markers of endothelial function and peripheral immune responses (25). This recent study certainly suggest that EMS training, like conventional exercise, may alter muscle histology, neurohumoral profile, immune markers, and endothelial function apart from benefiting exercise capacity and muscle performance. Despite a recent rise in interest of EMS in chronic heart failure, there are only a modest number of small trials on the subject that are either hospital based or home based. Several earlier small studies in much selected patients found improvement in metabolic measures of exercise capacity and muscle strength around the time of cardiac transplantation (26, 27, and 28). A more recent study comparing bicycle exercise with home-based EMS training of leg muscles for 8 weeks (n=15 in each group) in similar patients found a comparable and significant increase in peak VO_2, exercise duration, and 6-minute walk distance in both groups, prompting the authors to conclude that EMS training should be considered as a valuable alternative to classical exercise training in patients with CHF (29, 30).

Conclusion

Electrical muscle stimulation (EMS) of the leg muscles is an exciting new technique that has been shown in the past few years to be a potential therapeutic tool in chronic heart failure (CHF). EMS elicits contraction of large groups of muscles by electrical stimulation that produces exercise benefits

without any active movement from the participant. In the heart failure population with left ventricular systolic dysfunction, EMS training appears to produce the same benefits as conventional physical exercise training in increasing exercise capacity and it may also positively influence the endothelial function and reduce the activity of vasoconstrictor endothelin. EMS not only provides cardiovascular training benefits, but can also help with general rehabilitation by increasing leg muscle power and, thereby, mobility. EMS training may be a good alternative to conventional exercise training in chronic heart failure, especially in patients who cannot join the standard RHB hospital program due to severe reasons (home distance, poor social and economic situation, etc.). EMS may also have an important role in combination with conventional exercise. However, conventional exercise has a vast range of beneficial effects and EMS has not yet been investigated enough to be fully equated with conventional exercise in terms of all these effects. Further large-scale studies of EMS are needed to investigate the beneficial findings and to show exactly how EMS works.

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HEART RATE VARIABILITY IN MULTIPLE CEREBROSPINAL SCLEROSIS

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INTRODUCTION

Multiple sclerosis (MS) is a chronic system autoimmune 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 (Havrdová, 2002).
Dysfunctions of autonomic nervous system (ANS) are quite a frequent phenomenon in MS. They are characterized particularly by dysfunctions of urinary bladder, disorders of sexual and sudomotoric functions (Betts et al., 1994; Drory et al., 1995; Elie et al., 1995). Autonomic dysfunctions affecting the cardiovascular system regulation, however, are also documented more and more frequently (e.g. Senaratne et al., 1984; Nordenbo et al., 1989; Anema et al., 1991; Frontoni et al., 1993, 1996; Flachenecker et al., 1999; Acevedo et al., 2000; Gunal et al., 2002; etc.). Incidence of these dysfunctions varies as to frequency, importance of abnormities and autonomic reflex tests being used (Cartlige, 1972; Pentland, Ewing, 1987). Alterations of cardiovascular system parameters were demonstrated in MS patients both at rest and during physical load when ANS is responsible for compensation of hemodynamical cardiovascular response to physical stress. Autonomic dysfunctions can lead therefore to limitation of physical load capacity and can contribute to the fatigue of MS patients that has not yet been explained (Ziaber et al., 1997; Olindo et al., 2002; Konečný et al., 2007). It turns out that also subclinical manifestations of autonomic dysfunctions of cardiovascular regulation can become an unidentified risk factor with regard to farmacological and rehabilitation therapy of these patients. Cardiovascular autonomic dysfunctions show also trend towards accentuation of clinical manifestations in consideration of the characteristic progression of MS disease. Diagnostics of autonomic dysfunctions, presenting themselves particularly on subclinical level, can be therefore a key element of preventive and curative strategy in the complex care of patients with this disease.
Cardiovascular autonomic functions in MS are most frequently monitored by means of conventional reflex tests (Thomaides et al., 1993; Nasseri et al., 1998; Acevedo et al., 2000). These methods are limited mainly by difficult interpretation and differentiation of the sympathetic or parasympathetic component of cardiovascular regulation by autonomic nervous system. Heart rate variability (HRV) represents adaptation oscillation of heart rate values around its centre value. Distribution of these oscillations in specific frequency bands, from 0,02 Hz up to 0,50 Hz, expresses different mechanisms of acting on autonomic cardiovascular regulation. Spectral analysis of heart rate variability (SAHRV) offers a quick and non-invasive evaluation of the function of this regulation (Kautzner, Malik, 1998; Konečný et al., 2007; Pospíšil et al., 2004).

AIM

The aim of our study is examination of basic indicators of heart rate variability in the group of patients with multiple sclerosis, assessment of statistical dependence between HRV indicators and disability status (EDSS), duration and forms of MS disease and sphincter dysfunction in the monitored group.

METHODOLOGY

Criteria for inclusion into the study

Before the examined group was set up, specific entrance criteria for including the patients with MS into this study were stated. Into the study there were incorporated patients without established disease of autonomic nervous system on the central or peripheral level; patients without internal, metabolic and other disease which could influence validity of the results of autonomic testing; patients without permanent medication influencing HRV results; patients capable to be subjected to HRV examination (disability status according to EDSS ≤ 6); patients without manifestations of spastic symptoms which could influence HRV examination (Modified Ashwort scale of spasticity ≤ 2 points). The study was approved by the relevant ethical commission of St. Anna Teaching Hospital in Brno. All the patients being examined confirmed in writing their approval with participation in the study, so called „Informed approval of the patient".

Group of patients with MS

In the Department of Functional Diagnostics and Rehabilitation (KFDR) FN of St. Anna Teaching Hospital in Brno there were examined 48 patients altogether (39 women, 9 men; age 49,3±12,6 years; duration of the disease 15,3±13,0 years; EDSS 3,0±1,2) with positively verified MS disease according to McDonald criteria (McDonald et al., 2001). All patients were examined in clinically stabilized state of the disease (or in the stage of remission). In the group we have found 9 cases of quadruparesis, 10 cases of paraparesis of lower extremities, 3 cases of spastic paraparesis of lower extremities and 26 cases of hemiparesis. 48 % of patients had cerebelar disorders and 60 % of patients had symptoms of sensitive disorders. 6 patients were treated with cytostatics and immunosuppressants (azathioprin, glatimer acetate, beta-interferon), 16 patients were treated with corticoids (medrol, solu-medrol, prednison) and 23 patients had no MS specific pharmacotherapy (only vitamin therapy was used). No case with clinical manifestations of impairment of autonomic functions of cardiovascular regulation was registered. Only 7 patients (15 %) mentioned subjective feelings of orthostatic intolerance. As to other fields of autonomic dysfunctions, in 28 patients (58 %) manifestations of urinary bladder dysfunctions were verified (incontinency, nycturia, retention, imperative emiction). Anthropometrical characteristic and clinical characteristic of the disease activity in examined patients are in Table 1.

Control group

20 healthy controls altogether (14 women and 6 men; age 44,8±14,0 years) from the team of employees of KFDR of St. Anna Teaching Hospital in Brno were examined. For statistical evaluation, for the reasons of consistency of the presented results and of known influence of gender and age on HRV, control group of 12 women was followed up (age 48,3±11,8 years).

Methodology of examination and spectral analysis of heart rate valiability

Examination of heart rate variability and spectral analysis of heart rate variability were carried out under the standard conditions, i.e. elimination of physical stress of higher intensity for 24 hours before the examination; examination later than 4 hours after eating; limitation of smoking, drinking black coffee and alcohol at least 8 hours before the examination; examination between 9 o′clock and 12 o′clock; examination in a separate quiet room with minimal psychosocial stress (Placheta et al., 1999; Low, 1993). HRV examination was started after 10 minutes of relaxation in supine position during spontaneous breathing. HRV examination and spectral analysis of HRV were carried out by means of non-invasive short-time recording of ECG made by TASK FORCE MONITOR (CNSystems Medizintechnic GmbH, Graz, Austria) (TASK FORCE, 1996). The record was started during spontaneous breathing in supine position and then continued by the phase of metronome-controlled breathing, with the frequency of 20 breaths in a minute, i.e. 0,33 Hz. Breathing frequency was chosen on the basis of preceding results (Peňáz et al., 1978; Siegelová et al., 1999). By spectral

analysis of HRV examination in each case the record of at least 256 R-R intervals (minimally 5-minute record) was evaluated and the following indicators of heart rate variability were analyzed:

- spectral power of low-frequency band (LF, [ms^2]; 0,05 – 0,15 Hz)
- spectral power of high-frequency band (HF, [ms^2]; 0,15 – 0,50 Hz)
- total spectral power (TP, [ms^2])
- index of sympatho-vagal balance (LF/HF)
- length of cardiac interval (RRI, [ms])
- heart rate (HR, [beat · min^{-1}])

For the purpose of maintaining normality of the data and further statistical evaluation logarithmic transformation of native data of HRV by natural logarithm was made. Statistical analysis of the data (program STATISTICA for Windows – version 7.7) was made by means of t-test for independent specimens, Wilcoxon test, Spearman correlation, ANOVA test.

Table 1 Characteristic of the examined group of patients with MS

Monitored indicators	Whole group	Women	Men
Number of patients	48	39	9
Age [years]	49,1±12,6	48,2 ±12,3	53,7±12,6
Height [m]	1,6±0,1	1,7±0,1	1,7±0,1
Body weight [kg]	67,0±13,4	65,1±10,1	75,6±20,6
Body weight index (BMI)	24,7±4,6	23,7±3,8	26,5±7,0
Duration of MS disease [years]	15,4±12,5	16,1±13,8	11,7±7,7
Disability status (EDSS)	3,0±1,2	3,2±1,2	2,4±0,6
RR form of disease	23	20	3
SP form of disease	19	13	6
PP form of disease	6	6	0

Explanation: selected values are expressed as arithmetic mean ± SD.

RESULTS

Basic indicators of heart rate variability

By spectral analysis of HRV we obtained values of indicators describing heart rate variability during spontaneous breathing and during metronome-controlled breathing (0,33 Hz). By analysis of obtained HRV data we have not found significant impairment of the distribution of individual spectral bands in the examined group. In the group no substantial shift towards sympathicus or parasympathicus was noted. Modulation of autonomic response of metronome-controlled breathing with the frequency 0,33 Hz usually slightly accentuates spectral power of HF component. The same result is presented by the data of the monitored group in which no significant change of spectral power and distribution of spectral bands was noted. Overview of obtained results during spontaneous breathing is given in Table 2 and during metronome-controlled breathing in Table 3.

Table 2 Indicators of HRV of the group of patients with MS during spontaneous breathing

Monitored indicators	Whole group	Women	Men
Number of patients	48	39	9
Age [years]	49,3±12,6	48,2±12,3	53,7±12,6
HR [beat · min^{-1}]	73,9±10,5	68,9±12,4	82,6±8,9
RRI [ms]	870, 3±129,4	817,6±124,6	836,9±147,7
lnLF	5,26±0,84	5,29±0,84	5,09±0,82
lnHF	5,04±1,25	5,08±1,34	4,85±0,73
lnTP	6,14±0,91	6,19±0,95	5,90±0,70
lnLF/lnut	1,10±0,29	1,10±0,31	1,06±0,18

Explanation: RRI – length of R-R interval; lnLF – natural logarithm of spectral power in low-frequency band; lnHF – natural logarithm of spectral power in high-frequency band; lnTP – natural logarithm of total power; lnLF/lnHF – index of sympatho-vagal balance; selected values are expressed as arithmetic mean ± SD.

Table 3 Indicators of HRV of the group of patients with MS during metronome-controlled breathing with the frequency 0,33 Hz

Monitored indicators	Whole group	Women	Men
Number of patients	48	39	9
Age [years]	49,3±12,6	48,2±12,3	53,7±12,6
HR [beat · min^{-1}]	74,4±10,1	72,3±16,4	83,4±9,6
RRI [ms]	874,0±125,1	880,8±120,5	840,4±145,9
$lnLF_m$	4,83±0,99	4,85±1,0	4,73±0,97
$lnHF_m$	5,12±1,16	5,17±1,22	4,92±0,80
$lnTP_m$	5,92±0,92	5,97±0,96	5,68±0,67
$lnLF_m/lnHF_m$	0,97±0,20	0,90±0,21	0,97±0,19

Explanation: RRI – length of R-R interval; $lnLF_m$ – natural logarithm of spectral power in low-frequency band; $lnHF_m$ – natural logarithm of spectral power in high-frequency band; $lnTP_m$ – natural logarithm of total power; $lnLF_m/lnHF_m$ – index of sympatho-vagal balance; selected values are expressed as arithmetic mean ± SD.

Comparison of HRV indicators in the group of patients with MS and in the control group

For the reasons of consistency of the presented results and of known influence of gender, age and other variables on HRV indicators all 9 men were excluded from the original group. In the monitored group 12 examinations were found out the results of which could interfere with antihypertensive (n = 4) or antidepressive or antipsychotic medication (n = 8). These examinations were exluded from the final statistical evaluation. The final group for statistical processing consisted thus of 24 women with MS disease (EDSS 2,9±1,2; duration of the disease 15,6±15,9 years; RR form 13; SP form 6; PP form 5; 12 cases of sphincter dysfunction; 12 patients without sphincter dysfunction). To compare HRV indicators between individual patients, the results at metronome-controlled breathing with the frequency 0,33 Hz were statistically analyzed.

The control group was homogenized, after analysis of obtained data, to the group of 12 healthy women with valid results of SAHRV. The obtained values of HRV indicators of the group of women with MS disease were compared to the values of HRV indicators of the control group of healthy women.

No statistically significant ($p < 0,05$) differences in HRV indicators between the monitored group of women with MS disease (age 47,7±14,2 years; EDSS 2,9±1,2; duration of MS disease 15,6±15,9 let) and the control group (n = 12) were found by statistical analysis. The values obtained in the group of

women with MS disease can be regarded as values lying in the range of normal values. Comparison of the results of both groups and statistical significance are in Table 4.

Table 4 Comparison of HRV indicators of the group of MS patients and of the control group

Monitored i ndicators	MS	CO	p
Number of patients	24	12	-
Age [years]	47,7±14,2	48,3±11,8	NS
MR [beat · min^{-1}]	70,0±9,9	70,3±6,9	NS
RRI [ms]	874,1±123,9	835,0±76,0	NS
$lnLF_m$	4,76±1,03	5,33±1,03	NS
$lnHF_m$	5,06±1,21	4,87±1,22	NS
$lnTP_m$	5,88±0,95	6,28±1,02	NS
$lnLF_m/lnHF_m$	0,98±0,24	1,11±0,12	NS

Explanation: MS – group of patients with MS disease; CO – control group; p – statistical significance; RRI – length of R-R interval; $lnLF_m$ – natural logarithm of spectral power in low-frequency band; $lnHF_m$ – natural logarithm of spectral power in high-frequency band; $lnTP_m$ – natural logarithm of total power; $lnLF_m/lnHF_m$ – index of sympatho-vagal balance; NS – without statistical significance on the significance level 0,05; selected values are expressed as arithmetic mean ± SD.

Dependence of HRV indicators on disability status, on duration of MS disease and on the forms of MS disease

In the monitored group of 24 women with MS disease (age 47,7±14,2 years; EDSS 2,9±1,2; duration of MS disease 15,6±15,9 years) we further determined dependence of HRV indicators on disability status (EDSS), duration of MS disease and on the forms of MS disease. Statistical analysis (non-parametric Spearman correlation) did not establish statistically significant relation of monitored HRV indicators and EDSS score on the significance level $p < 0,05$n (lnLFm:r = -0,083; lnHFm:r = 0,142; lnTPm:r = 0,049; lnLFm/lnHFm: r = -0,154). No significant relation between HRV indicators and duration of MS disease was proved (lnLFm: r = -0,263; lnHFm:r = - 0,217; lnTPm:r = - 0,263; lnLFm/lnHFm:r = - 0,136). The analysis confirms, however, inverse relation of dependence of all HRV indicators on duration of the disease. It means that with increasing duration of MS disease the trend towards decrease of values of HRV indicators is apparent. Statistical analysis (ANOVA) studied dependence of HRV indicators of the patients with MS disease (age 47,7±14,2 years; EDSS 2,9±1,2; duration of MS disease 15,6±15,9 let) on the forms of MS disease: relapse-remittent (RR), secondary progressive (SP), primary progressive (PP). No statistically conclusive relation on the significance level between HRV indicators and forms of MS disease on the statistical significance level $p < 0,05$ was found (Wilks lambda = 0,783; F-ratio = 1,071; p = 0,393).

Dependence of HRV indicators on presence of sphincter dysfunctions

Statistical analysis (one-way ANOVA) also monitored whether there is any relation between HRV indicators of the tested group of 24 women with MS disease (age 47,7±14,2 years; EDSS 2,9±1,2; duration of MS disease 15,6±15,9 years) and presence or absence of sphincter dysfunctions in these patients. Statistically significant relation on the significance level $p < 0,05$ could not be verified (Wilks lambda = 0,658; F-ratio = 2,466; p = 0,799).

DISCUSSION

A number of authors dealt in the past with evaluation of autonomic regulation of cardiovascular functions in patients with MS (e.g. Senaratne et al., 1984; Sterman et al., 1985; Anema et al., 1991; Gutrecht et al., 1993; Ferini-Strambi et al., 1995; Caminero et al., 1995; Frontoni et al., 1996; Monge-Argilés et al., 1998; Nasseri et al., 1998; 1999; Flachenecker et al., 1999; Acevedo et al., 2000; Merkelbach et al., 2001; De Seze et al., 2001; Gunal et al., 2002; McDougall, McLeod, 2003; Sanya et al., 2005; Labuz-Roszak, Pierzchala, 2007, etc.). As to the studies of Czech and Slovak authors describing the function of autonomic regulation of cardiovascular system in MS disease, we can name particularly the studies of Bušek et al. (2004), Bušek et al. (2005) and Březinová et al. (2004). Partial results were published also by authors Konečný et al. (2005), Konečný et al. (2007, 2008) and Pospíšil et al. (2004), Pospíšil et al. (2005).

The most frequently used methods of examination of autonomic regulation of cardiovascular system included conventional reflex tests, so called Ewing battery of cardiovascular tests (Ewing et al., 1982). Utilization of spectral analysis of heart rate variability in patients with MS is described, besides the studies of the team of the author, only in several other studies: Ferini-Strambi et al. (1995), Frontoni et al. (1996), Monge-Argilés et al. (1998), Bušek et al. (2005), Bušek et al. (2004), Březinová et al. (2004). In these studies, however, there is no agreement on uniform methodology of measurement. Interpretation of results of individual authors can therefore lead to incongruous conclusions.

By analysis of obtained HRV data of the examined group of 48 patients with MS disease (not even in its parts, group of 39 women and 9 men) we have not found significant impairment of the distribution of individual spectral bands. In the monitored group (age 49,1±12,6 years; duration of the disease 15,4±12,5 let; EDSS 3,0±1,2) no significant autonomic shift towards sympathicus or parasympathicus was noted. Not even artificially induced modulation of autonomic response by means of metronome-controlled breathing (0,33 Hz), which, usually in supine position, accentuates spectral power of HF component, has shown any significant changes of spectral power and distribution of spectral bands. For this reason the monitored group was homogenized to 24 women with MS disease (age 47,7±14,2 years; EDSS 2,9±1,2; duration of the disease 6±15,9 let). The results of SAHRV were compared with the results of the control group during metronome-controlled breathing 0,33 Hz. We were not able to confirm statistically conclusive changes in individual HRV indicators in comparison with the control group. It can be therefore supposed that mechanisms of cardiovascular autonomic heart rate regulation are intact in the given group of MS patients. Similar results were achieved already in individual parts of the pilot study of authors Pospíšil et al. (2004, 2005) and Konečný et al. (2007).

In spite of that, in comparison of obtained HRV data with available reference values in some recent studies (see Tables 5 and 6) we can suppose that obtained results of native HTV data (LF 189,3±172,9 ms^2; HF 271,5±255,3 ms^2; TP 502,8±349,8 ms^2; LF/HF 1,2±1,1) show a relatively low heart rate variability, naturally at the sympathovagal balance being maintained. In a similar way also the native data of the control group manifest themselves (LF 349,4±363,1 ms^2; HF 316,3±487,9 ms^2; TP 940,7±1065,4 ms^2; LF/HF 1,4±1,0). For comparison we can name the study of the team of other Czech authors. Březinová et al. (2004) examined, by using short-time spectral HRV analysis, group of 36 patients with predominantly relapse-remitent MS form (11 men, 25 women; age 37,8 years; EDSS 3; duration of the disease 6,9 years) by methodology of the test lying-standing-lying position. In comparison with the control group statistically significant decrease concerning all HRV indicators was found out (LF 327,84±399,48 ms^2, HF 594,16±722,89 ms^2, TP 1137,92±1112,06 ms^2).

Table 5 Reference values of short-time HRV record for healthy population

Author	n	Age [years]	LF [m · s²]	HF [m · s²]	TP [m · s²]	LF/HF
Monitored group MS	24 (women)	47,7±14,2	189,3±172,9	271,5±255,3	502,8±349,8	1,2±1,1
Monitored group CO	12 (women)	48,3±11,8	349,4±363,1	316,3±487,9	940,7±1065,4	1,9±1,0
Task Force (1996)	-	-	1170±420	975±200	3500±1100	< 2,0
Virtanen et al. (2003)	56 (women)	44,4±5,2	721,8±105,1	541,2±93,9	2392,1±263,3	-
Virtanen et al. (2003)	49 (men)	44,1±5,2	1017,8±130,7	509,6±90,5	2977,4±364,1	-

Explanation: CO – control group, MS – group of patients with MS; HF – spectral power in high-frequency band; LF - spectral power in low-frequency band; TP – total power; LF/HF – ratio of low-frequency and high-frequency spectral power; n – number of patients in the group; - not given by the author.

Logarithmic calculated results of HRV of our group (because of maintaining normality of the data) do not prove such a clear decrease of individual HRV indicators, particularly for the reason of decrease of differences of standard deviations.

Table 6 Reference values of short-time HRV record for healthy population

Author	n	age[years]	lnLF	lnHF	lnTP	lnLF/HF
Monitored group MS	24 (women)	47,7±14,2	4,76±1,03	5,06±1,21	5,88±0,95	0,98±0,24
Monitored group CO	12 (women)	48,3±11,8	5,33±1,03	4,87±1,22	6,28±1,02	1,11±0,12
Virtanen et al. (2003)	56 (women)	44,4±5,2	6,13±0,13	5,63±0,16	7,49±0,10	-
Virtanen et al. (2003)	49 (men)	44,1±5,2	6,52±0,14	5,71±0,16	7,67±0,13	-
Kuo et al. (1999)	598 (women)	58,8±0,4	4,59±0,04	4,15±0,05	-	0,45±0,03
Kuo et al. (1999)	472 (men)	60,1±0,5	4,61±0,05	3,96±0,05	-	0,65±0,04
Kuo et al. (1999)	1070 (M+W)	59,4±0,3	4,6±0,03	4,06±0,04	-	0,54±0,03
Earnest et al. (2008)	87 (women)	57,5±5,8	5,21±0,9	5,20±0,9	6,28±0,9	1,6±2,0

Explanation: CO – control group, MS – group of patients with MS; lnHF - spectral power in high-frequency band; lnLF - spectral power in low-frequency band; lnTP – total power; lnLF/HF - ratio of low-frequency and high-frequency spectral power; n – number of patients in the group; - not given by the author.

On the basis of our results we can conclude that, in spite of a relatively lower level of total heart rate variability, we cannot definitely prove impairment of autonomic cardiovascular regulation in the monitored sample of patients with MS disease. The results, among others, point to interpretation differences in obtained data of heart rate variability when different authors are compared. It can be partially explained by a varied methodology od SAHRV examination.

Dependence of HRV indicators on disability status

Statistical methods did not prove a significant relation between HRV indicators and disability status (EDSS) in the monitored group (n = 24; age 47,7±14,2 years; EDSS 2,9±1,2; duration of MS disease 15,6±15,9 years). With regard to a relatively normal pattern of HRV indicators in the monitored group and relatively low disability status EDSS this finding is not surprising. Similar results are documented e.g. by the team of authors Gunal et al. (2002). We think that Kurtzke´s EDSS score is a rating scale describing mainly the motor and sensoric deficit. The scale cannot probably express specific impact of ANS dysfunctions on the above mentioned motor and sensoric functions. That is why EDSS wil not be probably a sufficiently sensitive scale reflecting projection of clinical or subclinical ANS impairment. In spite of that significant relations between increased clinical symptoms of ANS dysfunction, increased EDSS score for pyramidal functions and secondary progression (Sterman et

al., 1985; Anema et al., 1991; Flachenecker et al., 1999; Senaratne et al., 1984) were found out. Connection between increased score of motor subscale can be caused by proximity of pyramidal motor paths, autonomic centers and their interconnection in the brain stem and spinal cord. Some authors (Gunal et al, 2002; Nasseri et al., 1998; De Seze et al., 2001) think that, to be able to assess properly relation between results of autonomic tests and objective clinical picture, it would be suitable to complete clinical examination with magnetic resonance (MRI). In this respect e.g. the study of authors Nasseri et al. (1999) produced partial results. The study monitored autonomic functions in 20 patients with MS with active RR form of the disease for 2 years. Examination of autonomic functions assessed HRV indicators during deep breathing, standing and Valsalvov test. The tests being made showed indeed significant worsening of ANS functions during the period under consideration, but without correlation to EDSS and other clinical parameters, such as frequency of exacerbation, or number of lesions verified by magnetic resonance. In our study we were not able to include MR into the design of examination.

On the other hand, results presenting positive correlation of the results of ANS tests with disability status according to EDSS score are also available in literature. De Seze et al. (2001) documented, besides correlation of indicators of ANS function with EDSS score, also correlation with reduction of myelic substance, verified according to MRI. In the study of Labuz-Roszak and Pierzchala (2007), evaluating occurrence of autonomic dysfunctions in 24 Polish patients with MS (age 37,8±9,7 years; duration of the disease 6,1±5,5 years; 11 RR, 10 SP, 3 PP; EDSS 4,0±2,0), results of all autonomic tests correlated with EDSS score. The same results are given also by McDougall and McLeod (2003), Merkelbach et al. (2001), Acevedo et al. (2000), Caminero et al. (1995) and also Gutrecht et al. (1993).

Disparity of the results being presented can be probably caused by different methodology of testing autonomic functions. On the basis of obtained results we therefore think in conjunction with the above mentioned authors (Gunal et al., 2002; Nasseri et al., 1998) that in routine clinical monitoring and evaluating of patients by means of EDSS scale subclinical and clinical changes of ANS can be overlooked.

Dependence of HRV indicators on duration and forms of MS disease

The matter of relation of autonomic dysfunctions and duration or forms of MS disease produces also very controversial results. For example, the above mentioned study of Labuz-Roszak and Pierzchala (2007) did not find interdependence between results of autonomic tests and duration of MS disease (average duration of MS disease is 6,1±5,5 years), the results of all carried out autonomic tests, however, correlated with EDSS score. The team of authors De Seze et al. (2001) documented that presence of autonomic dysfunctions correlates positively with duration of MS disease and form of the disease, but also with EDSS score. Gunal et al. (2002) state that the patients with a longer duration of MS disease have a higher risk of occurrence of ANS dysfunctions than the patients with a higher EDSS score. Kodounis et al. (2005) state in analysis of the results that established impairment of parasympathetic part of ANS seems to be more noticeable in patients with a longer duration of the disease. Year-long longitudinal study of Bušek et al. (2005), monitoring influence of the disease activity on HRV indicators, did not confirm progressive deterioration of indicators of autonomic functions (duration of the disease 4,5±3,0 years).

In our monitored group we did not confirm dependence of HRV indicators on duration of MS disease and on the forms of MS disease. Average duration of the disease in the monitored group of women with MS disease was 15,6±15,9 years (range 0,5 – 24 years). We think that a relatively long average duration of MS disease, together with a relatively low disability status according to EDSS, need not represent quite a standard sample of MS population. On the other hand, statistical analysis confirmed inverse relation of dependence of all HRV indicators on duration of the disease. It means that there is trend to decrease of values of HRV indicators with increasing duration of MS disease. With regard

to the finding that the monitored sample of women population with MS disease does not show signs of alteration of HRV indicators, it is an interesting discovery. Further analysis would require examination made on larger sample of patients with a different distribution of the disease duration. We also think that for finding interrelationships between HRV indicators and forms of MS disease a bigger homogenous group of patients must be examined.

Dependence of HRV indicators on sphincter dysfunctions

In the monitored group of all patients with MS disease it was found out that 58 % of patients have symptoms of urinary bladder dysfunctions (incontinency, nycturia, retention, imperative miction). That is why we decided to evaluate whether there is statistically significant relation between HRV indicators and occurrence of sphincter dysfunction. Statistical analysis did not prove significant relation in the monitored group of 24 women with MS disease (age 47,7±14,2 years; EDSS 2,9±1,2). In spite of that there was found trend towards decrease of average values of HRV indicators in the patients with sphincter dysfunctions ($lnLF_m$ 4,9±0,7; $lnHF_m$ 5,1±1,2; ln TP_m 6,0±0,8; $lnLF_m/lnHF_m$ 0,9±0,7) in comparison with the patients without emiction problems ($lnLF_m$ 5,5±0,8; $lnHF_m$ 5,6±0,9; $lnTP_m$ 6,5±0,6; $lnLF_m/lnHF_m$ 0,9±0,8). This trend was not statistically significant (< 0,05). In the group there were 12 cases with sphincter dysfunctions (7 cases of incontinency, 4 cases of imperative emiction and 1 case of combined incontinency of both urine and defecation) and 12 cases without clinical symptoms of sphincter dysfunctions. Contrary to our finding there are results of a number of authors who state that emiction problems are significantly connected with disability status, duration and particularly with secondary progression of MS disease (Miller et al., 1965; Betts et al., 1994; Koldewijn et al., 1995; McDougall, McLeod, 2003). The team of Czech authors Bušek et al. (2004) found out in 50 patients with relapse-remittent form of MS (12 men, 38 women; age 33,5±8,6 years; EDSS 1,94±1,32; duration of the disease 5,63±6,3 years) that the patients with infratentorial lesions suffered 4,5 times more often from sphincter dysfunctions than the patients with supratentorial lesions, verified by magnetic resonance. Moreover, in the patients with sphincter dysfunctions they found the decrease of HF component both in standing and in lying positions. We were not able to confirm relation between sphincter dysfunctions and vulnerability of parasympathetic system described by Bušek. We noticed in our study the above mentioned trend towards the decrease, concerning, however, all HRV indicators.

CONCLUSION

Examination of basic indicators of heart rate variability (HRV) in the group of patients with MS disease (39 women, 9 men; age 49,1±12,6 years; duration of MS disease 15,4±12,5 years; EDSS 3,0±1,2) did not prove statistically significant impairment of distribution of individual spectral bands HRV. No significant shift towards sympathicus or parasympathicus was noted during spontaneous or metronome-controlled breathing (0,33 Hz) in the monitored group.

When the results of the group of 24 women with MS disease (age 47,7±14,2 years; duration of MS disease 15,6±15,9 years; EDSS 2,9±1,2) and of the control group were compared, no statistically significant differences in HRV indicators between both groups were found. Significant relation between HRV indicators and disability status (EDSS), duration of MS disease and forms of MS disease was not found in the group. Dependence of HRV indicators on the occurrence of sphincter dysfunctions was not proved. In spite of that there was found trend towards decrease of average values of HRV indicators in the patients with sphincter dysfunctions in comparison with the patients without emiction problems.

On the basis of our results we can conclude that, in spite of a relatively lower level of total heart rate variability in the group, we cannot definitely prove impairment of autonomic cardiovascular regulation in the monitored sample of patients with MS disease.

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SECOND PHASE OF CARDIOVASCULAR REHABILITATION IN PATIENTS WITH ISCHEMIC HEART DISEASE

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INTRODUCTION

Cardiovascular rehabilitation is a universally accepted part of complex therapy in patients with coronary artery diseases (8). It is perceived as a process helping the patients with cardiovascular diseases in maintaining optimum physical, mental, working and emotional condition. It increases physical fitness, improves quality of life (11, 19, 23) and reduces cardiovascular mortality (25, 26). Dynamic endurance aerobic activities (walking, biking, jogging, swimming, etc.) are the basis of cardiovascular rehabilitation program (2, 3, 4, 6, 16, 24, 27, 28). As a certain level of muscle strength that can be decreased in patients with ischemic heart disease (2, 18) is necessary for a number of working and recreational activities, usefulness of resistance training as an additional component of rehabilitation programs for cardiac patients was considered (2). As to cardiovascular safety of resistance training, it was proved that resistance exercises are a safe part of cardiovascular rehabilitation (1, 8, 10, 12, 20, 21, 29).

AIM OF THE STUDY

Our study was aimed at evaluation of the effect of 12-week controlled ambulatory rehabilitation on muscle strength and selected indicators of fitness and performance and verification of safety and effectiveness of combination of aerobic and resistance training in patients with chronic ischemic heart disease (ICHS).

SET OF PATIENTS

32 men with ICHS of average age 63 ± 10 years, with left ventricle ejection fraction 42 ± 8 %, were included into the study (Table 1). The disease was diagnosed at I cardioangiological dept. of St. Anna Teaching Hospital in Brno. The patients were examined coronarographically, treated by beta blockers, ACE inhibitors and statins. The established therapy was not changed during the course of cardiovascular rehabilitation. All patients being involved completed full 12-week controlled ambulatory rehabilitation program and finished it successfully. The study was approved by local ethical commission, all patients signed their informed approval.

Table 1. Basic characteristic of the set of patients

Number [n]	32
Age [years]	63 ± 10
Height [cm]	176 ± 7
Body weight [kg]	88 ± 6
EF [%]	42 ± 8

METHODOLOGY

Methods of examination

Spiroergometric examination up to symptom-limited maximum (Pulmonary Function System 1070, MedGraphics, USA) was made before the beginning, midway and after the finishing of the rehabilitation program. The examination was started by monitoring resting EKG in lying and sitting position (Schiller CS 100), followed by 3-min adaptation in sitting position on ergometer. The load was increased as standard every 2 minutes by 20 W up to symptom-limited maximum. Anaerobic threshold was determined from the course of changes of ventilation-respiratory parameters (22). The values of load, heart rate and RPE for the training corresponded to the anaerobic threshold level.

Before the beginning of resistance training (third week from the beginning of the program) we made isometric test („handgrip", DHG-SY3, Recens) for the determination of blood pressure response to static load. In the case of physiological response of blood pressure in this test the patients then passed the entrance test of one repetition maximum (1-RM). One repetition maximum test was made for three exercises of resistance training and was repeated also in the 6th and 12th week of rehabilitation program.

Rehabilitation program

The ambulatory controlled program lasted 12 weeks with the frequency of exercise units three times a week, 36 altogether. 60-min training unit consisted of several phases (Table 2).

Table 2. Composition of the training unit

1st- 2nd week only aerobic training	**3.- 12. week combined training**
10 min warm-up phase	10 min warm-up phase
40 min aerobic phase	25 min aerobic phase
10 min relaxation phase	15 min resistance training
	10 min relaxation phase

Warm-up phase was aimed at preparing the cardiovascular and motoric system for additional load. It consisted of dynamic endurance exercises (simple floor exercises with gymnastic apparatus) and of stretching of muscle groups tending to be shortened.

Aerobic phase on a bicycle ergometer (Ergoline REHA E900) was controlled by program ErgoSoft+ for Windows. Intensity of aerobic training was determined at the aerobic threshold level.

Resistance training was performed on multifunctional toning machines TK-HC COMPACT by means of four exercises (bench press, pull down, leg extension on the fitness apparatus and sitting-lying position). Intensity of resistance training was determined by the method 1-RM; training load way determined in per cents of maximum, namely 30 – 60 % 1-RM (every week increasing by 10 %). The patients did exercises in 3 – 5 series with 10 repetitions. Before starting the resistance training they were thoroughly informed about proper breathing and performing of exercises.

In relaxation phase modified Schultz autogenic training was used.

In the course of the whole training there were monitored heart rate, blood pressure and degree of subjective evaluation of severity of load according to Borg (RPE degree: rating of perceived exertion). During the aerobic phase and 1-RM test EKG was registered.

RESULTS

After the rehabilitation program statistically significant increase of symptom-limited oxygen consumption, symptom-limited physical performance (even in values converted to 1 kg of body weight) and statistically significant increase of muscle strength (bench press, pull down, leg extension) were found (Table 3).

Table 3. Parameters of aerobic capacity, performance and maximum strength power in the test 1-RM

	Before RHB	After RHB	p
VO_2SL [ml.min^{-1}]	1536 ± 245	1768 ± 421	<0,01
VO_2SL/kg [ml.min^{-1}.kg^{-1}]	17,4 ± 2,8	20,9 ± 4,7	<0,01
WSL [W]	95 ± 19	120 ± 33	<0,01
WSL/kg [W.kg^{-1}]	1,0 ± 0,21	1,3 ± 0,37	<0,01
Bench press [kg]	35 ± 9	42 ± 8	<0,01
Pull down [kg]	36 ± 8	44 ± 6	<0,01
Leg extension [kg]	33 ± 8	42 ± 8	<0,01

VO_2SL = symptom-limited oxygen consumption, WSL = symptom-limited performance, p = statistical significance

During the course of rehabilitation program with combined load the patients had no subjective problems, no signs of electrical, ischemic or hemodynamic instability appeared.
The results are presented as means ± standard deviation (SD). Statistical analysis was made by means of programs Microsoft Excel and Statistica, version 8. Distribution was tested by Lilliefors modification of Kolmogorov-Smirnov test of normality.
Even though some parameters had normal distribution, Wilcoxon test was used in all parameters.

DISCUSSION

Isometric load in patients with heart disease has not been previously considered to be suitable (23). Nowadays, however, resistance elements are a common part of everyday activities even in these patients. The fact that at the static load a more noticeable increase of blood pressure takes place than in the dynamic training, led to fears of possible side-effects, involving mainly provocation of ischemia, serious arrhytmias and adverse effect on remodelling of left ventricle after acute myocardial infarction. These adverse effects have not been mostly confirmed, on the contrary, numerous experience demonstrated a positive influence of this load. From the beginning of the nineties the training with resistance elements is therefore accepted in cardiological patients as a part of traditional rehabilitation programs. In this form of training there are less ischemic complications than in aerobic training (including exercise tests). It can be caused by a lower heart rate that, in combination with the increase of diastolic pressure, leads to improvement of myocardium perfusion. A dominant effect of resistance training that should be combined with aerobic load is the increase of muscle strength connected with the rise of attained performance and endurance in submaximal load and improvement of quality of life. Also the indications on a favourable effect of resistance training on glucose tolerance and insulin sensitivity appear (17, 23). Some results of our study may also have contributed to verification of a positive influence of this exercise on the health and functional condition of the patients with ICHS.
Spiroergometric examination made within the framework of rehabilitation program is very important because it provides functional values, of which particularly the amount of oxygen consumption has a decisive prognostic importance in patients with ICHS and with heart failure (5, 30). Weber and

colleagues (30) in the end of the eighties of the last century divided the patients with heart failure on the basis of their oxygen consumption at the height of symptom-limited maximum into several classes. The patients with maximum aerobic capacity lower than 10 $ml.kg^{-1}.min^{-1}$ are seriously ill with unfavourable prognosis, on the contrary, the patients with the value of oxygen consumption higher than 20 $ml.kg^{-1}.min^{-1}$ are considered to have a small or none functional impairment. Some research studies verified usefulness and mainly safety of resistance load in patients with left ventricle dysfunction (7, 9, 13, 14, 15). In the course of exercises no complications were observed in patients in these studies. Even in our set clinical manifestation of ischemia has not appeared in any patient. During continuous monitoring in the course of individual parts of the exercise unit serious rhythm disturbances have not been observed. The training with resistance elements was very well tolerated, the patients liked and required it.
Resistance training of a low to medium intensity in suitably chosen patients is safe and is an effective stimulus for the rise of muscle strength of big muscle groups; it does not lead as such, however, to the increase of symptom-limited oxygen consumption (15). After the completion of 12-week training with combined load we observed in our patients not only a substantial increase of muscle strength of trained muscle groups; due to the combination of resistance and aerobic training also aerobic capacity and exercise toleration increased substantially. Combination of resistance and aerobic training of the intensity at the aerobic threshold level is safe in practice and adequately physiologically effective under the conditions of a proper selection of patients and their careful current check.

CONCLUSIONS

Provided that safety limits are observed, combined training integrates positive effects of aerobic and resistance training, is not connected with a risk of serious health damage and seems to be optimal for the group of correctly chosen patients with ischemic heart disease.
The results of our study demonstrated that 12-week rehabilitation program in the form of combined training contributed to the statistically significant increase of capacity of transport system of oxygen, to the increase of physical performance, muscle strength of skeletal musculature, and probably also to the improvement of quality of life.
A favourable effect of cardiovascular training persists only under the condition that the patient proceeds with regular exercises of a similar type. If rehabilitation program is not followed by regular exercises, the values of aerobic capacity, physical performance and muscle strength return to the initial level.

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