

As-One-Goes Blood Pressure and Heart Rate Monitoring: A Chronobiology Approach with Applications in Clinical Practice and Basic Science

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Dedicated to the memory of Franz Halberg

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ABSTRACT

Assessing influences of space weather on human physiology often relies on correlations between the socio-biological variable and the environment. One major pitfall of such an approach is the disregard for periodicities characterizing both biology and nature, many of them shared between the two systems. Alternative, more robust analytical techniques of time series analysis, such as those used in chronobiology, are better suited to avoid spurious results. Blood pressure and heart rate are highly variable along several time scales, ranging from the fast oscillations of the brain and heart to the multi-decadal cycles associated with changes in solar activity. Since these variables can be easily monitored longitudinally, they lend themselves well to the study of helio-geomagnetic effects from a basic science viewpoint. At the same time, such physiological monitoring offers useful clinical applications.

Keywords

Blood pressure, Heart rate, Space weather, Variability.

Introduction

First by self-measurements and later by ambulatory monitoring, blood pressure (BP) and heart rate (HR) have been measured around the clock in health and disease, from womb to tomb [1]. Circadian rhythms were mapped in health to derive time-specified reference

values qualified by gender and age. Characterized by lower values during nighttime rest and higher values during the active daytime, the circadian waveform of BP is also changing with advancing age [2,3]. Based on these chronobiologic reference values, abnormal patterns of BP and HR variability were associated with increases in cardiovascular disease risk, beyond an elevated BP itself, as illustrated in a number of outcome studies [4]. Whole communities have been monitored around the clock for 7 days in Japan [5].

Results showed that adverse outcomes are better predicted when hypertension is diagnosed based on 7-day rather than on 24-hour ABPM. They also showed that adverse outcomes can be better predicted by screening for deviations from norms in all circadian rhythm parameters, known as “Vascular Variability Disorders” (VVDs) rather than for an elevated BP only [5].

Recent guidelines by the American College of Cardiology (ACC) and the American Heart Association (AHA) and those by the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) recommend out-of-office blood pressure (BP) measurement with ambulatory (ABPM; for 24 hours) and/or home (HBPM; morning and/or evening for a week) monitoring only if logistically and economically feasible [6-8]. For a reliable diagnosis and for a guide to treatment, BP and HR should be measured both around the clock to assess their circadian variation and longitudinally (for 7 days as a minimum) to account for the novelty effect [9] and day-to-day variability [9,10]. In health or disease, the 24-hour average BP varies by more than 5 mmHg from

one day to another (Figure 1). The average BP and the circadian amplitude are higher on the first day of monitoring, and it may take more than one day for the bias to become negligible (Figure 2).

The data also gain from being analyzed chronobiologically. Methods of analysis include spectral analysis [11], cosinor rhythmometry [12], CUSUM control charts [13], superposed epochs and a remove-and-replace approach [14]. Three ingredients are essential for clinical applications:

1. Time-specified reference values in clinical health need to account for gender (and ethnic) differences and for changes as a function of age in mean values and in circadian rhythm characteristics [2].
2. Deviations from norms in all circadian rhythm parameters need to be assessed (VVDs) [4]; specifically, abnormal amplitudes and phases have been associated with an increase in cardiovascular disease risk, even in the absence of an elevated BP [4].
3. Chronotherapy helps reduce adverse outcomes by optimizing the timing of treatment. Restoring a healthy circadian BP pattern can be more important than lowering BP to a larger extent [15].

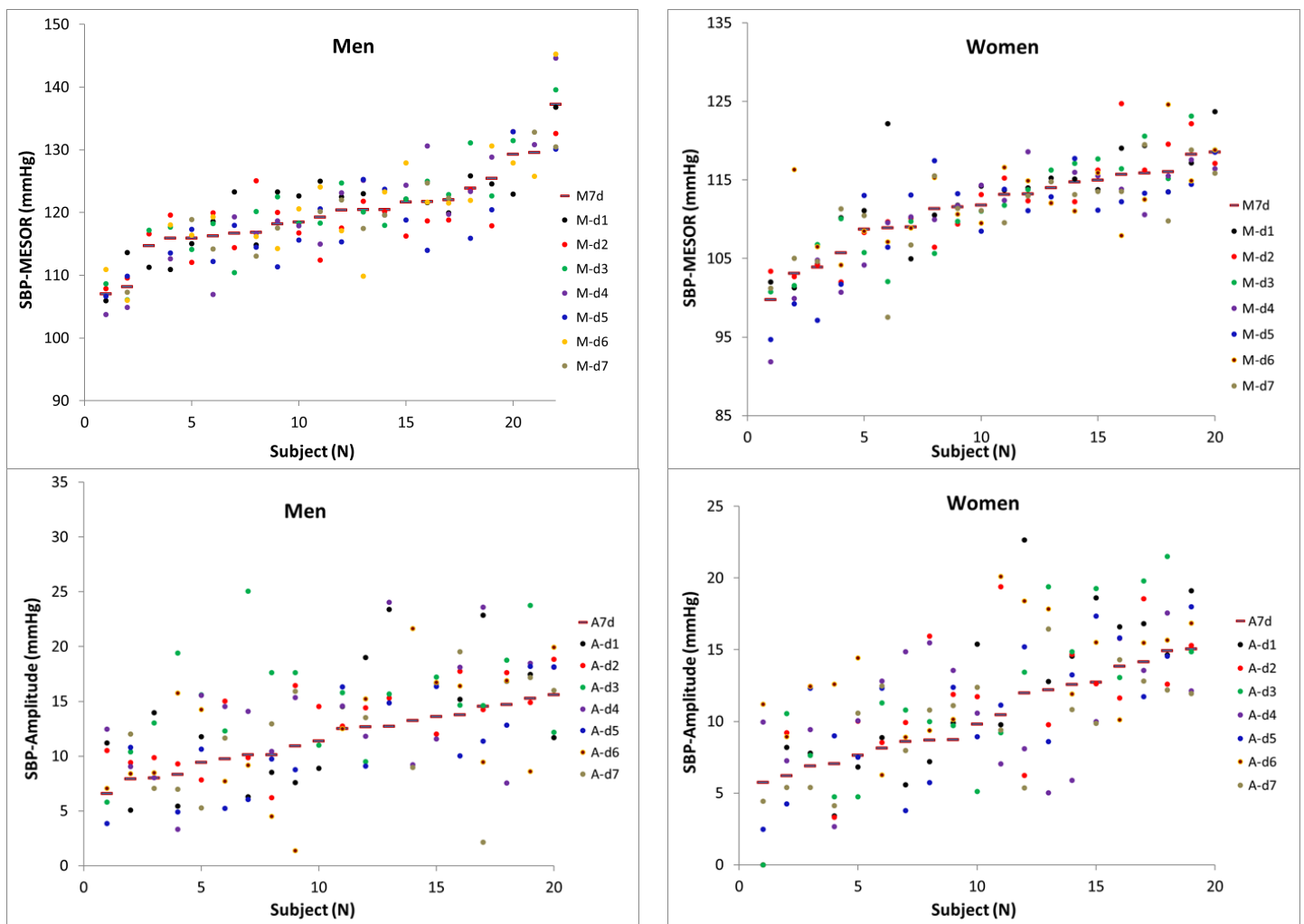


Figure 1: Day-to-day variability in the MESOR (top) and 24-hour amplitude (bottom) of SBP in men (left) and women (right). Bars are estimates based on 7-day records; dots are estimates based on separate 24-hour spans. Spreads of dots are an indication of the large day-to-day variability in circadian characteristics of SBP. © Halberg Chronobiology Center.

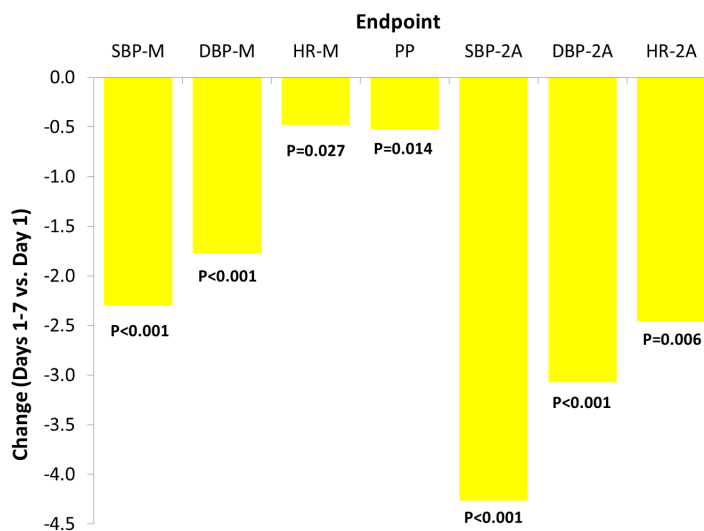


Figure 2: As compared to estimates on day 1 (used as reference; equated to 0), all circadian parameters are lower when they are estimated on the entire record. SBP: Systolic BP; DBP: Diastolic BP; PP: Pulse Pressure; -M: MESOR; -2A: double 24-hour amplitude (extent of predictable change within one cycle). SBP, DBP, PP in mmHg; HR in beats/min. © Halberg Chronobiology Center.

Many factors affect BP [16], including space weather [5]. Space weather refers to physical processes originating at the sun and ultimately affecting human activities on and around the earth. Flares of electromagnetic radiation (X-rays, ultraviolet, visible light, infra-red, radio waves) and energetic electrically charged particles propagating from the sun impact the plasma and magnetic environment near-Earth. Throughout evolution, the natural environment shaped life on earth. These interactions account for the co-periodisms shared between human physiopathology and the broad environment, from the fast brain waves, the heartbeat, respiration and sleep cycles, to the circadian, circaseptan (about-weekly), and circannual (about-yearly) rhythms, and the non-photic cycles with periods of about 0.42 year (cis-half-years), about 1.3 years (transyears), about 10.5, 21, 35, and 50 years, among others. Herein, we review some of our work providing supporting evidence for an influence of space weather on human BP and HR.

Circaseptans

Apart from the prominent circadian variation in BP and HR, about-weekly and half-weekly variations also characterize these variables on a population basis. Cross-spectral coherence with the planetary geomagnetic disturbance index Kp was also documented in a longitudinal record of human HR [17].

A report of the intermittent detection of an about-weekly variation in the rate of change in sunspot area [18] prompted our analysis of all longitudinal records of self-measurements of HR and BP obtained during spans matching those investigated in the study of solar activity. In the case of HR, but not BP, the about-weekly variation was amplified when circaseptans were detected in the sun and dampened when they could not be detected in the sun, Figure 3

[19]. Resonance of circaseptans in HR with solar circaseptans was also demonstrated with statistical significance on an individual basis for the longest self-measurement record ($P<0.001$) [19]. Moreover, the circaseptan component of HR was found to be modulated by an about 11-year cycle similar to the solar activity cycle, Figure 3 [19].

About-weekly and half-weekly components are particularly prominent in early extrauterine life [20]. In view of their free-running and of the fact that premature babies are monitored in isolation, largely shielded from external synchronizers, circaseptans go against a pure socio-ecological influence and are likely also partly endogenous. Analyses of around-the-clock records of BP and HR spanning at least one week from neonates and of the local geomagnetic disturbance index K during matching spans identified spectral peaks at a frequency close to one cycle in 7 days. They further documented a statistically significant correlation between the nonlinearly estimated periods of BP and HR with those of the geomagnetic index K [21].

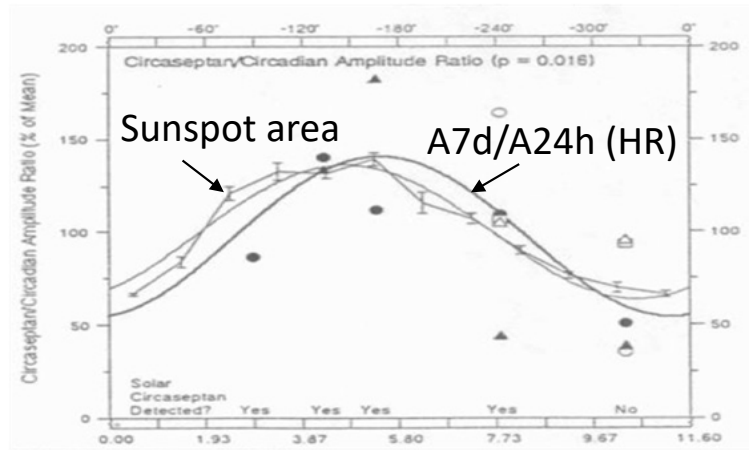
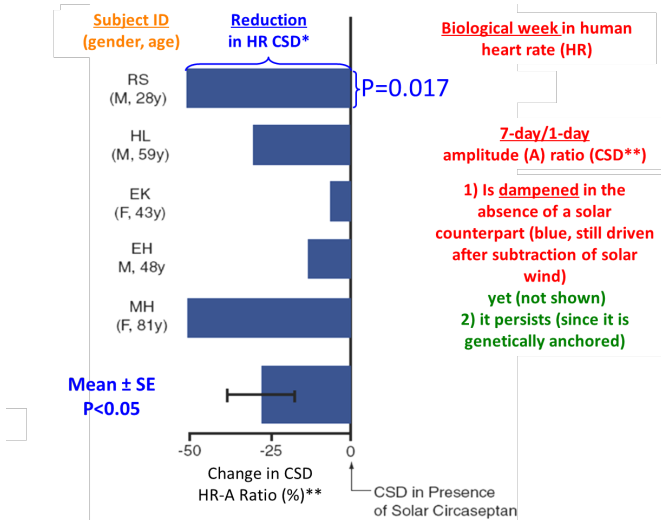
Cis-half-years

Physicists reported a periodicity of about 0.42 year in solar flares. They estimated the period to be approximately 154 days [22], ranging between about 150 to 160 days from different studies by different investigators. Our own analysis of the solar flare index for the span from 1968 to 2006 found a double peak around 0.42 year and an additional spectral line around 0.40 year. Like Wolf sunspot numbers, solar flares also undergo a prominent about 11-year cycle.

A unique longitudinal record of self-measurements of HR from a clinically healthy man lent itself well to investigate whether a cis-half-year could be detected, and, if so, whether its characteristics were equally modulated by the about 11-year cycle [23]. Since a circannual component was also present in the 40-year record, the analysis considered a 3-component model consisting of cosine curves with periods of 1.0, 0.5 and 0.41 year. This model was fitted to weekly mean values over a 4-year interval, progressively displaced in 2.5-month increments, throughout the 39-year record. While all three components can coexist for a while, they are nonstationary in their characteristics, and hence are not detected with statistical significance in all intervals. As shown in Figure 4, the cis-half-year is detected with statistical significance (filled rectangles) only part of the time, usually following a peak in solar flares and sunspot numbers. The cross-correlation function between the cis-half-year amplitude of HR versus the total solar flare index reaches a maximum of 0.79 at a 3.16-year lag [23]. Interestingly, the same three components with periods of 1.0, 0.5, and 0.41 year had been found with serially independent sampling in human circulating melatonin [24].

Circadecadals

When automatic BP monitors first became available for adults as well as for newborn babies, around-the-clock neonatal BP and HR monitoring took place internationally [25]. In Moscow, Russia,



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

Figure 3: An about 7-day spectral component in the heart rate (HR) of five individuals is less prominent when the rate of change in sunspot area loses its counterpart of corresponding length (left). The relative prominence of circaseptans versus circadian in human HR is modulated by an about 11-year cycle in phase with the solar activity cycle (right). © Halberg Chronobiology Center.

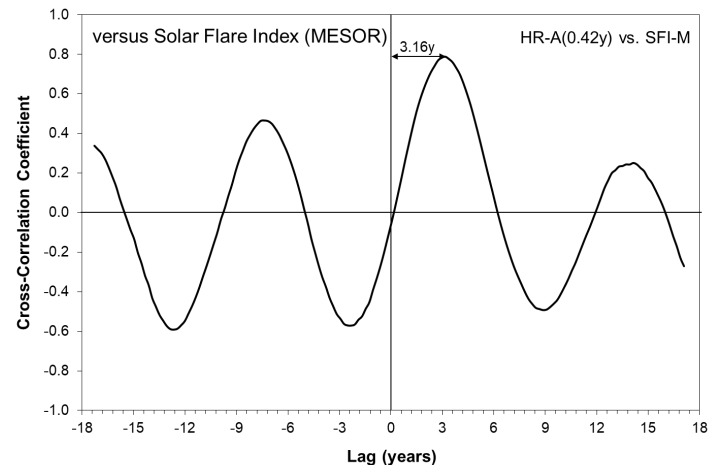
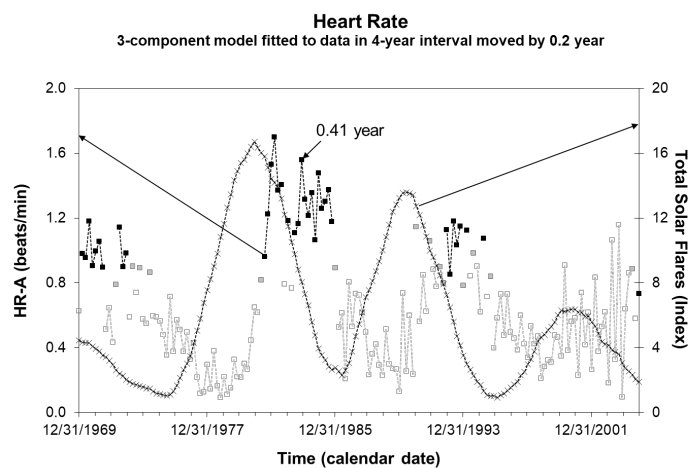


Figure 4: Cis-half-year amplitude (A) of heart rate (HR) of clinically healthy man shares about 11-year cycle with solar flares (left). Cross-correlation function (right) indicates that the cis-half-year HR-A lags behind the total flare index by about 3.16 years. Data are weekly averages of about 5 self-measurements of HR per day between 1968 and 2006, analyzed in 209-week interval moved by 11 weeks. HR-A of cis-half-year (0.41 year) assessed in 3-component model also including cosine curves with periods of 1.0 and 0.5 year. P-values from zero amplitude test of the cis-half-year of <0.05, 0.05 to 0.10, or >0.10 are shown as solidly filled, lightly filled, or open squares, respectively. Solar flare index plotted as 209-week moving averages, computed every 11 weeks. © Halberg Chronobiology Center.

681 records were obtained between 1988 and 2005, spanning almost two solar cycles. An about 11-year cycle was found to modulate both the MESOR (rhythm-adjusted mean value) and the 24-hour amplitude of neonatal BP and HR [14]. The circadecadal component of neonatal HR MESOR was more or less in phase with that of solar activity, gauged by Wolf sunspot numbers. By contrast, the circadecadal component modulating the circadian amplitude of HR, a measure of HR variability, was more or less in antiphase with that of solar activity, Figure 5 (top).

These results, obtained transversally on many different babies born at different times over two decades, are replicated in a

longitudinal record of a clinically healthy man. At the time of analysis, he had a 26-year ABPM record of around-the-clock data collected mostly at 30-minute intervals, with occasional short interruptions. Nonlinear analysis of detrended monthly means and standard deviations (SDs), using trial periods of 1.0 and 10.5 years corresponding to spectral peaks, detected both components with statistical significance. Period estimates and their 95% confidence intervals were 1.02 [95%CI: 1.00, 1.04] and 10.60 [95%CI: 9.21, 11.98] years for the monthly means, and 0.98 [95%CI: 0.96, 1.00] and 10.44 [95%CI: 8.85, 12.03] years for the monthly SDs of HR. In both cases, the about 11-year solar cycle length is included in the 95% CIs [26]. As illustrated in Figure 5 (bottom), the MESOR

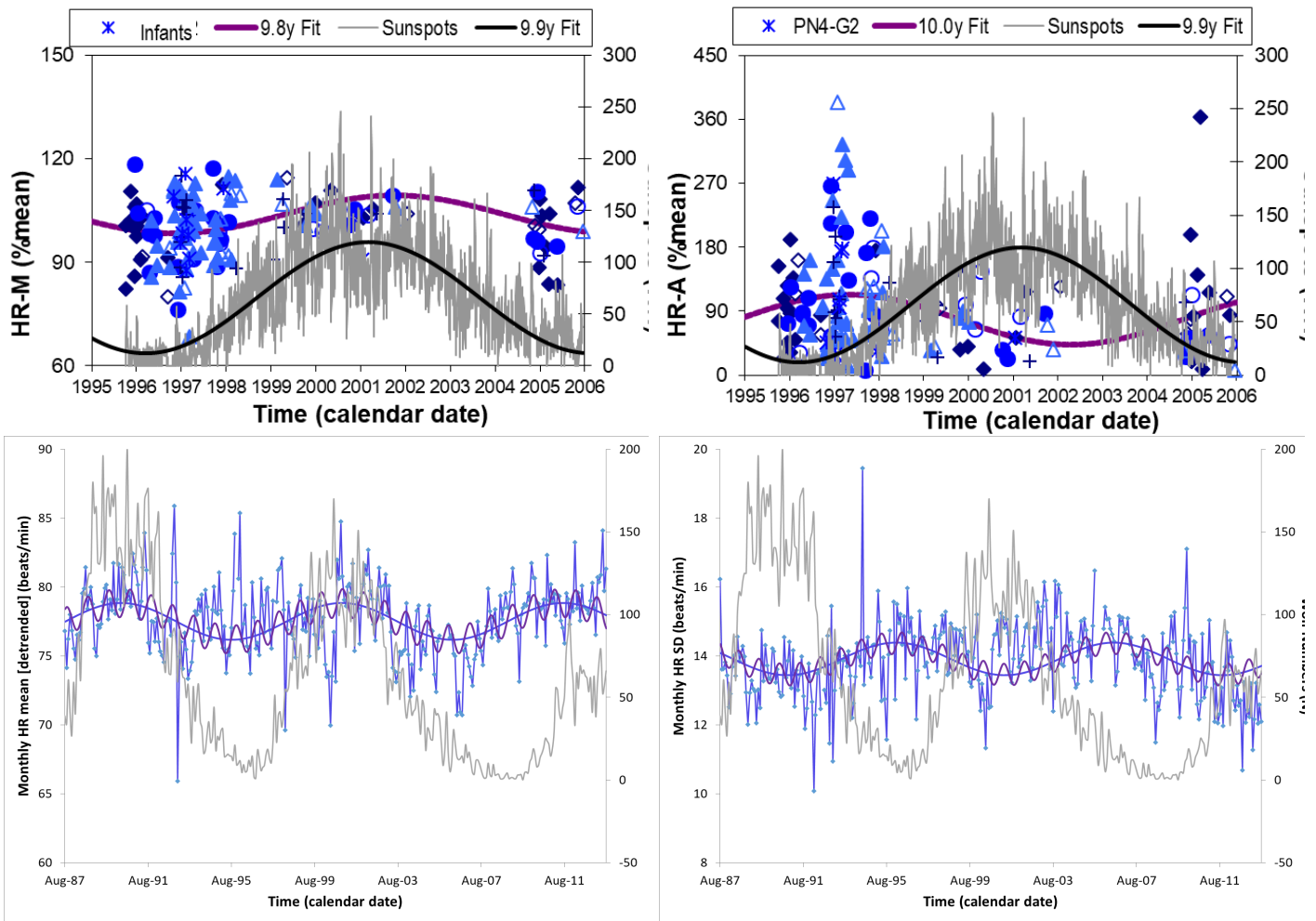


Figure 5: Circadecadal modulation of heart rate (HR, blue curves) of neonates (top; transverse approach) and in a clinically healthy man (bottom, longitudinal approach). HR MESOR (top left) or monthly mean (bottom left) varies more or less in phase with the about 11-year solar activity cycle, gauged by Wolf numbers (gray curves). HR variability, assessed by the circadian amplitude (top right) or the monthly standard deviation (bottom right) varies more or less in antiphase with the about 11-year solar activity cycle. © Halberg Chronobiology Center.

of HR is more or less in phase with solar activity, and the SD of HR is more or less in antiphase with solar activity.

A circadecadal modulation of BP and HR has now been documented in several other longitudinal records of both normotensive and hypertensive individuals [4,27,28]. Summarizing the periods of the cycles detected in these longitudinal records in a histogram reveals a sharp peak around 10 years, Figure 6 [29]. Decadal cycles are not trivial since they also characterize the incidence patterns of major vascular conditions such as myocardial infarctions [30].

Within the scope of a chronoecological health-watch in Ladakh, India, 3,418 of its residents, 1,428 men and 1,990 women, 13 to 92 years of age, were examined annually from 2001 to 2010, mostly during the 23rd solar activity cycle. The first visit in 2001 took place during a year of maximal solar activity; solar minimum occurred in 2008. Ladakh is a very arid region of east Kashmir, adjacent to Tibet, at an altitude of 2500–4600 m between the Karakoram and the Himalayan ranges. High-altitude environments are generally

harsh and fragile. They have little oxygen, low pressure, cold temperature, and strong ultraviolet radiation, and the weather in the mountains is very changeable. The BP of residents was measured during each visit. As illustrated in Figure 7, BP followed an about 11-year cycle similar to that of Wolf sunspot numbers: it was higher during years of high solar activity and lower during years of low solar activity [5].

Effect of space weather assessed by superposed epoch analysis

Shared periodicities do not imply causality. In order to determine whether circaseptans, cis-half-years, and circadecadals observed in human physiology are, at least in part, the result of non-photic solar influences, methods other than the characterization of periodicities are needed. Superposed epoch analysis [31] is such a method. In order to determine whether space weather affects human physiology, an index of stormy space weather, available as dense longitudinal measurements, is selected to identify the time of occurrence of key epochal events. In order to determine whether there is a physiological response to space weather, a window

In decades-long records from 7 subjects, about 10-year components are almost invariably detected

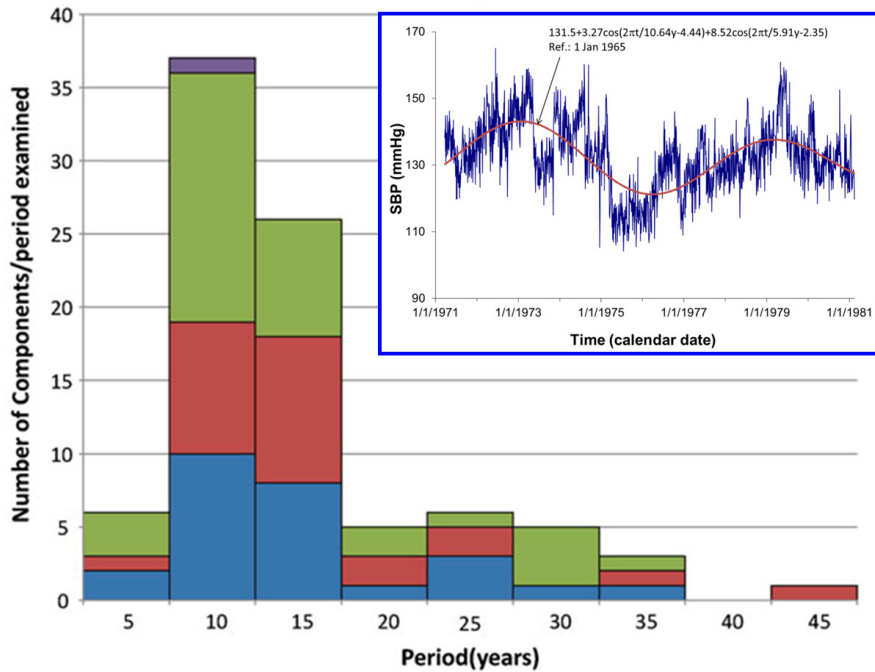


Figure 6: A circadecadal component is detected with statistical significance in the majority of longitudinal records of blood pressure and heart rate available to us for analysis. Key (records): blue: systolic blood pressure; red: diastolic blood pressure; green: heart rate; purple: urinary 17-ketosteroid excretion. Insert: example of one longitudinal record of systolic blood pressure and fitted circadecadal model. © Halberg Chronobiology Center.

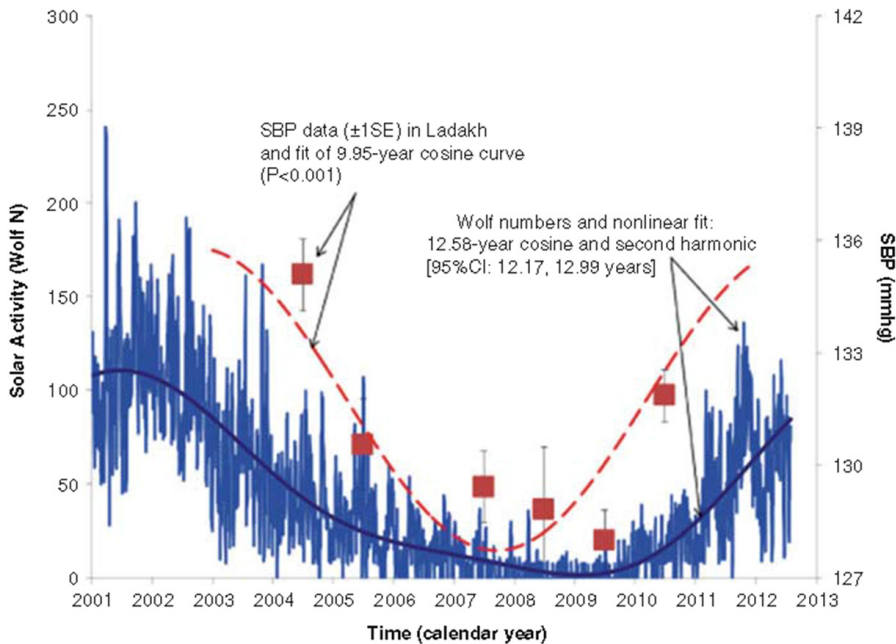


Figure 7: Solar cycle and chronoecological health-watch in Ladakh. Some similarities between systolic blood pressure (SBP) and sunspots. Daily values of Wolf numbers from January 1, 2001, to July 31, 2012, were analyzed by the linear-nonlinear extended cosinor. Using a trial period of 10 years, nonlinearly, the period estimate was about 17 years but converged to 12.58 (95 % CI: 12.17, 12.99) years when adding a second harmonic in the model, as shown here (blue curve). Using a similar model (10-year trial period, with added second harmonic) for the SBP data from Ladakh, the period estimate is about 9.95 years, but the 95 % CIs of the amplitude of both the fundamental and second harmonic cover zero, likely because the time series covers a shorter span of 7 years, shorter than a single solar activity cycle. The dashed red curve was obtained by using the parameters from the linear cosinor corresponding to a trial period of 9.95 years, with the qualification that linearly, the best fitting period is longer than 15 years, as was the case for Wolf numbers in the absence of a second harmonic term. © Halberg Chronobiology Center.

centered on the key epochal event is selected. Physiological data in these windows are then stacked over all events for analysis by signal averaging. Data may be pre-processed or normalized prior to signal averaging to reduce possible bias from outliers or other confounders.

For the analysis of a 16-year ABPM record from a clinically healthy man [32], the ground-based horizontal magnetic field SYM-H was selected to identify space storms. Typically, storms can be identified by a sudden worldwide increase in SYM-H by tens of nTs lasting several minutes to several hours (initial phase), followed by large negative perturbations of hundreds of nTs usually lasting on the order of tens of hours (main phase), slowly returning to pre-storm values over the next several days (recovery phase). The zero-crossing preceding the sharp drop in SYM-H below -100 nT served as key epochal event in this study, and the window of BP and HR data extended from 12 hours prior to each event to 13.75 hours thereafter. A statistically significant drop in HR during the main phase of space storms could thus be demonstrated [32].

An effect of space weather on HR and HR variability (HRV) was also documented in a study of 19 clinically healthy individuals (15 men and 4 women), 21 to 59 years of age, who recorded their ECG around the clock for 7 days in Alta, Norway, between 10 December 1998, and 2 November 2000 [33,34]. Space weather was assessed based on geomagnetic data at 1-min intervals from the Auroral Observatory of the University of Tromsø, in Tromsø, Norway. An increase in the 24-hour average of HR ($P = 0.020$) and a decrease in HRV ($P = 0.002$) were documented on days of high geomagnetic disturbance, as compared to quiet days, Figure 8 [34]. These results are in agreement with the finding in neonates and in a healthy man that the circadecadal variations of HR and HRV (gauged by the 24-hour amplitude or the monthly SD) are respectively in phase and out of phase with that of solar activity.

The decrease in HRV was 21.9% in the VLF range ($P < 0.001$) and 15.5% in the ULF range ($P = 0.009$). Being more pronounced at frequencies lower than 0.04 Hz suggests that the physiological mechanism involved may be other than the parasympathetic, usually identified with spectral power centered around one cycle

27 yrs., man

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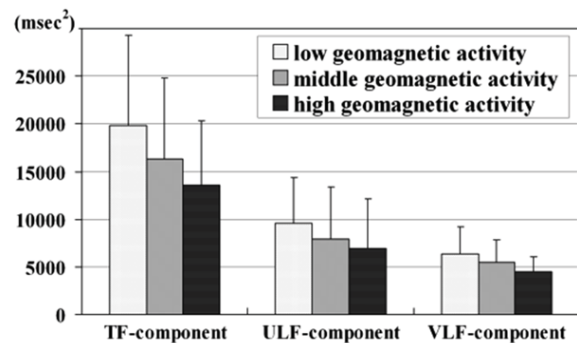
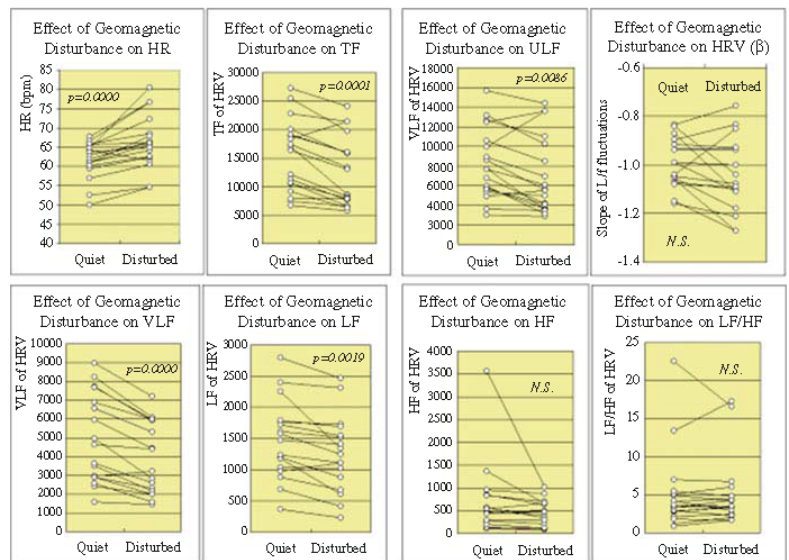
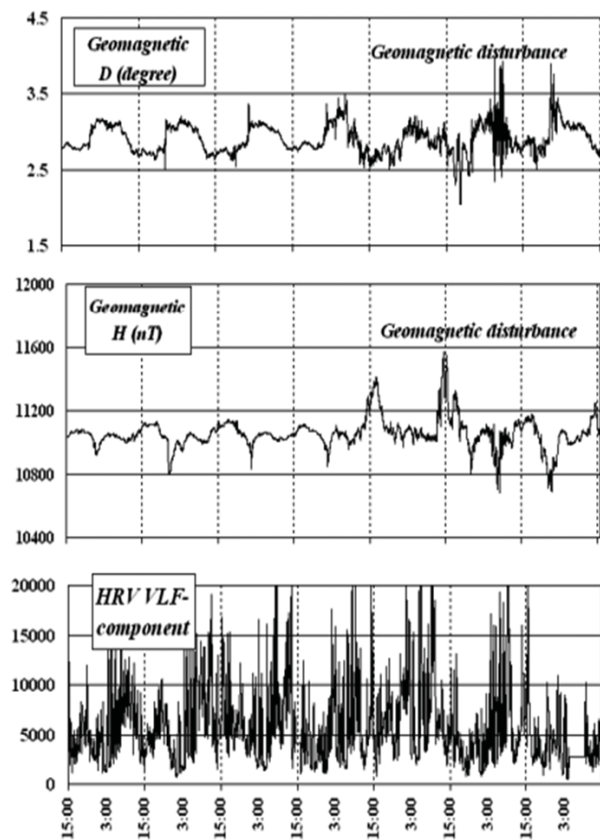


Figure 8: Example of geomagnetic record aligned with VLF component of one of the 7-day/24-hour ECG records (left). A comparison of heart rate (HR) and of different endpoints of HR variability (HRV) between geomagnetically disturbed days and quiet days shows that magnetic storms are associated with an increase in HR and a decrease in HRV, notably in the VLF spectral range (top right). A graded response to geomagnetic activity is suggested when measures of HRV in separate 24-hour spans were compared among days of low, middle and high geomagnetic activity (bottom right). © Halberg Chronobiology Center.

in 3.6 s. Another investigation of 7-day ECG records from five clinically healthy young men living above the Arctic Circle made it possible to compare measures of HRV in separate 24-hour spans among days of low, middle and high geomagnetic activity. A graded response was demonstrated, the extent of decrease in HRV depending on the degree of geomagnetic activity (Figure 8), suggesting the existence of human magnetoreceptors [34,35].

Discussion and Conclusion

Evidence presented herein primarily draws from the cardiovascular field. Results indicate that associations between space weather and human physiology occur at several frequencies, from the relatively high-frequency components characterizing HRV to the week, cis-half-year and circadecadals. These associations can involve more than a single spectral component. In particular, an about 11-year cycle modulates the circaseptan amplitude of HR [19], the cis-half-year amplitude of HR of a clinically healthy man [23], the MESOR and circadian amplitude of neonatal HR [14], and both the average and monthly SD of HR of a clinically healthy man [26]. This about 11-year variation prominently present in solar activity is also detected in most longitudinal records of BP and HR covering 10 years or longer [29].

Magnetic storms are more frequent when solar activity is high. They can affect electronic circuits of satellites, with tangible consequences in terms of the electric grid on earth and the global positioning system that planes rely on. It is perhaps not so surprising then that magnetic storms, and space weather more generally, also affect human health, the cardiovascular system in particular, since the heart is also the strongest electrical system of the human body.

The influence of space weather on physiology reviewed herein is likely to have repercussions on morbidity and mortality as well. For instance, the decrease in HRV observed in association with magnetic storms may account for the 5% increase in mortality from myocardial infarction during years of maximal solar activity as compared to years of minimal solar activity observed in Minnesota during the span of 1968 to 1996 [30,36]. An about 7% increase in the incidence of myocardial infarction on the day following a magnetic storm was also observed in Moscow during the span from 1979 to 1981 [37]. Already a century ago, a larger incidence of symptoms was reported on days when sunspots were present versus absent [38]. Symptoms included not only those related to the heart and vessels, but also those of various other diseases of the liver, kidney, and the nervous system. Solar influences on neural and mental disease have also been unveiled [39]. The rhythms of solar activity reportedly also influenced mass manifestations in human life, from epidemics to wars, riots and other phenomena [40].

The existence of so many co-periodisms, shared components between space weather and human physiology and pathology, speaks in favor of at least a resonance but perhaps also of a partly inherited broad time structure that living matter may have readily acquired from the open environment in which it evolved. The evidence presented herein can only provide a glimpse into a

new realm open for much further exploration. But we hope that by opening the door to this fascinating new field, as others have done before us, new knowledge will be gained that may become amenable to useful applications in medicine and the earth sciences.

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