World Heart Journal 2010;2:279-306.

EXTENDED CONSENSUS ON NEED AND MEANS TO DETECT VASCULAR VARIABILITY DISORDERS (VVDS) AND VASCULAR VARIABILITY SYNDROMES (VVSS)

Franz Halberg[1], Germaine Cornélissen[1], Kuniaki Otsuka[2], Jarmila Siegelova[3], Bohumil Fišer[3], Jiří Dušek[3], Pavel Homolka[3], Salvador Sánchez de la Peña[4], R.B. Singh[5] and the BIOCOS Project

[1]Halberg Chronobiology Center, University of Minnesota, Minneapolis, Minnesota, US
[2]Tokyo Women's Medical University, Daini Hospital, Tokyo, Japan
[3]Masaryk University, Brno, Czech Republic
[4]Chronomics Research Center, ENMH-IPN, Mexico City, Mexico
[5]Halberg Hospital and Research Institute, Centre of Nutrition and Heart Research, Moradabad, India

ABSTRACT

Given that conventional health care practice is concerned mainly with high blood pressure (BP), and given the fact that other variability disorders -- circadian overswing, excessive pulse pressure, odd circadian BP timing and deficient heart rate (HR) variability (in their own right or in combination with MESOR-hypertension) -- are not diagnosed but contribute to cardiovascular disease risk, we wanted to find out 1. how many patients escape current diagnosis (and treatment), and 2. what are the risks such patients incur. A first available database consists of 297 patients (121 normotensives and 176 treated hypertensives). Each condition was considered separately, except that in the case of an excessive pulse pressure, all had also a high BP.

In each case, the number of patients who have one, two, three or all four conditions (vascular variability disorders, VVDs) was counted. Their risk was assessed as the percentage incidence of morbid events (cerebral ischemic event, coronary artery disease, nephropathy, retinopathy) that occurred during the 6 years following the BP monitoring (used to diagnose the VVDs). Subjects had no history of morbidity at the time of monitoring.

MESOR-Hypertension (MH). Of 176 patients, only 103 had uncomplicated MESOR-hypertension, 55 had one other complicating VVD, 15 had 2 (additional) VVDs and 3 had all 4 VVDs. This means that 41.5% of the hypertensives were only partly diagnosed. The undetected risk of these patients is greatly increased, from about 10% for uncomplicated MH to 100% for the 3 patients with all 4 VVDs.

Excessive Pulse Pressure (EPP). Since all these patients also happened to have MH, it is not surprising that the increase in risk as a function of the number of VVDs present is similar to that found for patients with MH alone.

Circadian Hyper-Amplitude-Tension (CHAT) and Deficient HR Variability (DHRV). These two conditions in their own right, without any complication by other VVDs, are found in 7 (CHAT) and 5 (DHRV) patients, representing 2.4% and 1.7% of the total population. These numbers are small in this study, yet if the percentages reflect what happens in the general population, this may actually represent MANY people who completely escape medical attention in the current system. Again, it is seen that when these conditions coexist with other VVDs, the incidence of morbid events is proportionately increased. There is actually a small exception to this general trend in the case of CHAT: the risk of CHAT alone is actually slightly higher than the risk of CHAT with one additional VVD (usually it is MH, and the two conditions may alternate, notably under treatment). This result is in keeping with the earlier result that CHAT is associated with a larger relative risk than MH in this population.

In a second database, a population of 1,177 untreated, presumably normotensive subjects, MH was diagnosed in a total of 289 subjects, representing 24.6%. Among these subjects, 137 (47.4% of those diagnosed with MH) have at least one additional VVD that is not part of the current screening but increases the vascular disease risk beyond that associated with MH alone. VVDs other than MH occur in the absence of MH in very few patients with EPP and in more patients with CHAT and in yet more with *BP ecphasia (*an odd timing of the circadian rhythms in BP but not in that of HR) and in 87 patients with DHRV, that is for a total of 182 subjects, representing 15.5% of the study population.

In view of the foregoing, the current guidelines for diagnosing abnormal, notably high BP in a substantial segment of the population have to be revised, according to a consensus meeting held at St. Anna

Hospital, Masaryk University, Brno, Czech Republic, on October 6, 2008 (in the setting where instrumentation for beat-to-beat measurements of BP was developed) [1-3]. Specifications are needed for the minimal number of measurements, for how long and how often they should be taken, including their temporal placement. Methods are also needed for the assessment of dynamics, in keeping with a document originally prepared for this meeting by Dr. Germaine Cornélissen, Professor of Integrative Biology and Physiology at the University of Minnesota, revised in Brno by those undersigned. The terms "normotension" and "hypertension" can be replaced by the terms "MESOR-normotension" (MN) and "MESOR-hypertension" (MH), respectively, whenever the conditions for a chronobiologically-interpreted 24-hour/7-day BP and HR monitoring (C-ABPM) are met. The term MH indicates only one of several VVDs that can combine to form sets of 2, 3, and n-component vascular variability syndromes (VVSs). For current health care practice, the foregoing diagnoses do not include changes in day-night ratios (DNRs). DNRs and their alterations are routinely computed for research. Thus far for predicting outcomes, DNRs were all inferior to the parametric and nonparametric assessment of VVDs, including some that carry a risk higher than MH itself. In diagnosing MESOR-pre-hypertension, correctly identified with a chronobiologic approach, the DNR misled: the DNR was normal in patients with minimal change retinopathy, and abnormal in the normal controls without any retinal involvement. Pre-diabetes was diagnosed chronobiologically, while the DNR failed to detect it. Any chronobiologically-assessed consequences of MESOR-hypotension (MO) have yet to be assessed in terms of outcomes and remain beyond the scope of this consensus.

VVDs and VVSs derived from C-ABPM gauge an increased vascular disease risk, including conditions unnoticed in current practice, some of which may be treated. When the conditions for C-ABPM 24/7 are met, the term "Diagnosing hypertension" can be replaced by the wider scope of the terms "Diagnosis of VVDs and of VVSs".

Keywords: BIOCOS, MESOR, MESOR-Normotension, MESOR-Hypertension, Excessive Pulse Pressure, CHAT, Deficient Heart Rate Variability, Blood Pressure Ecphasia, outcome.

INTRODUCTION

Complementing other indices of risk studied, e.g., after a myocardial infarction [4, 5], the search for VVDs and VVSs, albeit aimed in particular at

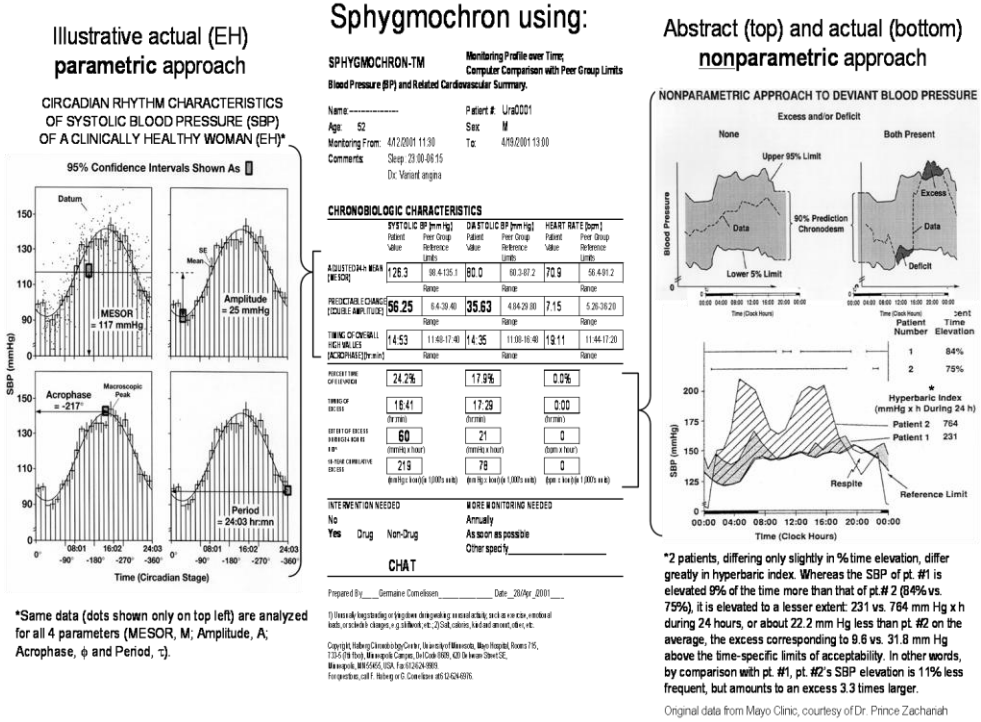
healthy subjects [3, 6-12] to detect earliest alterations, concerns a very large number of patients diagnosed conventionally as "hypertensive" [13-25] (about 72 million in the USA) [26]. The following diagnoses can be based upon a summary called a "sphygmochron", provided with accompanying materials [27-30], Figure 1.

1) MESOR-Normotension (MN), when a) all characteristics of a model fitted parametrically are within the limits of 90% prediction intervals (PI) [31] and b) all endpoints obtained non-parametrically by stacking the data are acceptable (do not exceed thresholds) computed from data of peers matched by gender and age, and preferably, when possible, ethnicity and geography.
2) MESOR-Hypertension (MH), a chronobiologically validated elevated BP, Figure 2. This term is used only if the diagnosis is based on the MESOR, obtained by the least squares fit of cosine curves with anticipated (24- and 12-hour) periods, for comparison with ranges (90% PIs) of acceptable MESORs characterizing data from clinically healthy peers matched by gender and age. The minimal time series length is a 24-hour/7-day record of data collected automatically at half-ourly or shorter intervals (or manually for 7 days at 4-hour intervals), analyzed both daily and for the week as a whole. It serves to rule out MH, if negative when analyzed parametrically for the weeklong record as a whole, but data collection is continued when abnormality is found. MH is a condition where the BP-M is above the upper 95% prediction limit of BP-Ms from clinically healthy peers matched by gender and age. BP elevation is noted when the hyperbaric index (extent of excess during 24 hours) exceeds the threshold of 50 mmHg x hour during 24 hours. MH can be the sole VVD or it can coexist and/or alternate with other VVDs to constitute a VVS, Figures 3 and 4.
3) CHAT (Circadian Hyper-Amplitude-Tension), or circadian BP overswing (excessive BP swing) is a condition characterized by a double amplitude of BP (BP-2A) derived from a 24/7 record exceeding the upper 95% prediction limit of BP-2As from clinically healthy peers matched by gender and age, Figure 2. CHAT can occur alone in MN and with a usual timing of the circadian BP rhythm, or it can coexist and/or alternate with other VVDs, such as complicating MH, Figure 2. C-ABPM is recommended to all patients with treated MH to ascertain that the elimination or

reduction of MH is not a trade for the greater risk of CHAT, Figure 5, Section IIC.

A measure of the extent of predictable change in this model, approximating the within-day BP change, the 24-hour BP-2A can be grossly underestimated by the DNR that does not account for alterations in the circadian acrophase and/or waveform. The DNR neither accounts for change with age in circadian BP characteristics, notably in terms of a post-prandial BP dip, nor does it have reference values for differences between genders and is limited to a few aspects of within-day change, ignoring the many rhythms with frequencies other than circadian, Figures 6 and 7.

4) BP ecphasia is a condition characterized by an odd timing of the circadian acrophase (ϕ) of BP but not of the ϕ of HR (BP ecphasia with HR euphasia). ϕ is a measure of the timing of overall high values recurring each day, measured as the lag from a given reference time (e.g., local midnight) of the peak in the 24-hour cosine curve of the model approximating the data. BP ecphasia is differentiated from the consequences of shift-work that can be associated with an altered timing of both BP and HR, Figure 2. It is defined by the BP-ϕ derived from a 24/7 record lying outside the 90% PI of BP-ϕs from clinically healthy subjects matched by gender and age.
5) Excessive pulse pressure (EPP) is defined by a difference between the systolic (S) and diastolic (D) BP-Ms in a 24/7 record above 60 mmHg (until gender- and age-matched reference standards become available), Figure 2.
6) Deficient HR variability (DHRV) is defined as a standard deviation (SD) of HR from a 24/7 record below 7.5 beats/minute (until gender- and age-matched reference standards become available), Figure 2.



© Halberg.

Figure 1. Illustrative parametric (left) and non-parametric (right) approach bracket a sphygmochron (middle) from a MESOR-normotensive man with CHAT, a first tentative diagnosis requiring additional monitoring. After data covering preferably at least 7 days

of blood pressure (BP) and heart rate (HR) are downloaded from the e-mail into a computer for analysis, the following results are provided (since the 1990s and currently cost free from corne001@umn.edu) for the patient as well as for the care provider: 1. A list of actual measurements and the times at which they were obtained. 2. A plot of data as a function of time, shown together with the time-specified prediction intervals (PIs) of acceptability for systolic (S) and diastolic (D) BP and HR characteristics. 3. A data summary, and a report of any BP and/or HR excess in consecutive 3-hour intervals. This part of the report may be accompanied by a "rhythmometric summary", which is just a more technical form from which the information is derived to prepare the: 4. "Sphygmochron". A sample "sphygmochron" (center) illustrates how results are being reported. First, above, the participant's name is kept confidential; a codename is used instead. Gender and age are listed, along with the date and time at which monitoring started, and for how long data were collected. The numerical report consists of two parts labeled "Characteristics" (parametric results) and "Indices of Deviation" (non-parametric results). In each case, results are shown for SBP (when the heart contracts) on the left, DBP (when the heart relaxes) in the middle, and HR on the right. Under "parametric results", a mathematical model of a smooth curve is fitted to the data to assess their circadian variation, which is primarily characterized by four numbers shown in the left-hand section of the graph, one of which, the period, covers with its uncertainty the precise 24 hours, so that the other 3 numbers are given from the fit of a 24-hour cosine curve. One characteristic, called the "MESOR", is the average value around which values fluctuate. It is very similar to the mean value, but yields more reliable results when the data are not collected at precisely regular intervals, and has a smaller error when the data are equally spaced. Another characteristic, called the "double amplitude", is a measure of the predictable change occurring within a day, from the overall low values found usually during sleep to the high values during the daily active span. The third characteristic, called the "acrophase", is a measure of the time when overall high values are likely to recur each day. For each of the three characteristics ("parameters"), the participant's value is compared to a range of acceptable values, derived from data provided by clinically healthy people of the same gender and age group as the participant. For instance, in the example shown here in Sphygmochron, the average SBP, the DBP and all other parameters are within the range of acceptable values except for the double amplitudes of SBP and DBP. Under "non-parametric results", the participant's data are compared by computer with time-specified reference values, also derived from chronobiological archives on clinically healthy subjects matched by gender and age. For this analysis, all data are stacked over an ideal-ized 24-hour day. Whenever a given person's profile exceeds the limits of acceptability of peers, the data are marked as being excessive or deficient. The "percentage time of elevation" reports the relative incidence of excessive values during a 24-hour day. It is common to have occasional high values, but in the example herein there is reason for concern. The next item, the time of excess, becomes useful when drug treatment should be timed prior to the peak in excess. Excessive values may either be barely above the limit or in turn can be very much higher than the limit. It is therefore important to express the extent of deviation by the "area under the curve", that is the area between the values when they exceed the limit and this limit itself. Empirically, it has been shown that excess up to about 50 (mmHg x

hour during 24 hours) may still be acceptable and accountable for by daily worries and/or physical activities. In the case summarized, the HBI is 60, in bold, and if confirmed in the next 7/24 profile, a reason for treatment. On the top right, an abstract illustration of excess and deficit is accompanied below by two cases that are similar in terms of percent time elevation. They are very different in terms of hyperbaric index. In patient #2, although the percent time elevation is 9% smaller than that in patient #1, the hyperbaric index is several times larger. The "timing of excess" can be used as a guide to time the administration of non-drug or, if need be, of drug treatment once there is BP excess above 50 (mmHg x h during 24 hours) and/or an elevation in MESOR, taking into account the chronopharmacokinetics of the drug prescribed. When, e.g., a tentative diagnosis of MESOR-normotension with CHAT is made, with insight into information provided on the questionnaire given to the participant with the monitor, as a first step, additional analyses may be carried out. Additional monitoring is recommended to check on any abnormality detected during the first monitoring, and if confirmed, the need for intervention is reported to the person monitored so that it can be reported to the health care provider. In one case summarized elsewhere, the follow-up 7-day monitoring showed that CHAT persisted for both SBP and DBP, while the MESORs were again acceptable. Thus, the diagnosis of CHAT with MESOR-normotension was confirmed. Consultation with a health care provider was strongly and urgently recommended. In two cases of CHAT without an elevation of the BP MESOR, when such recommendations were ignored, catastrophic disease and high cost occurred, a myocardial infarction in a man [29, 30] or eclampsia in a pregnant woman with pressures of 115/67 mm Hg (SBP/DBP), leading to the delivery of a very premature boy hospitalized for 26 months at a cost of $1 million U.S. [28].

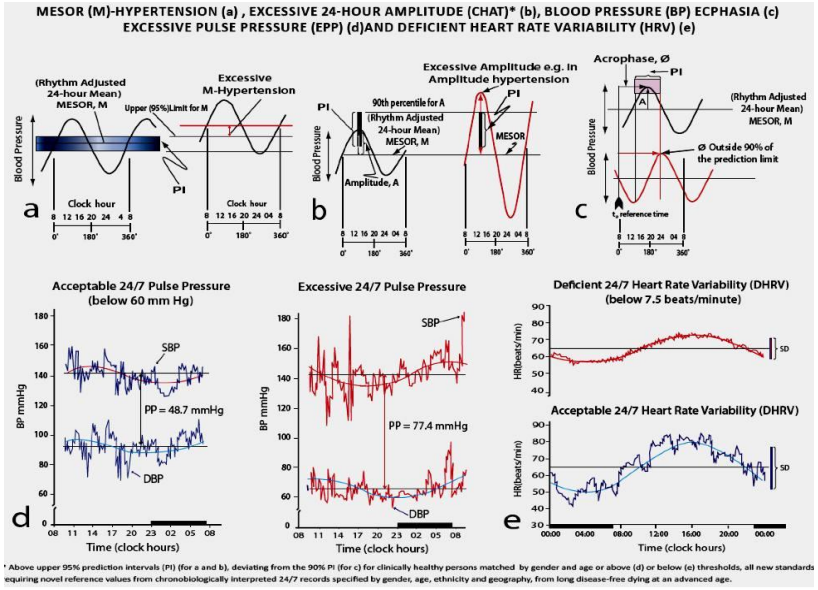


Figure 2. Abstract definitions and illustrations of vascular variability disorders: a. MESOR-hypertension (MH), can be systolic (S-MH), diastolic (D-MH) or both (SD-MH), or mean arterial (MA-MH), demonstrated parametrically. b. Circadian Hyper-Amplitude-Tension (CHAT), which can also be systolic (S-CHAT), diastolic (D-CHAT), both (SD-CHAT) or mean arterial (MA-CHAT). c. SBP, DBP or SDBP ecphasia (odd timing of the circadian rhythm of BP but not of that in HR). d. Excessive pulse pressure (EPP), when the difference in the MESORs of SBP and DBP for adults exceeds 60 mmHg, a threshold that remains to be replaced by reference values from clinically healthy peers (eventually with disease-free long-life outcomes), specified further by gender, age, ethnicity and geography. e. A deficient HR variability (DHRV), defined as a standard deviation of HR less than 7.5 beats/minute, a threshold that remains to be replaced by reference values from clinically healthy peers (eventually with disease free long-life outcomes) specified further by gender, age, ethnicity and geography.

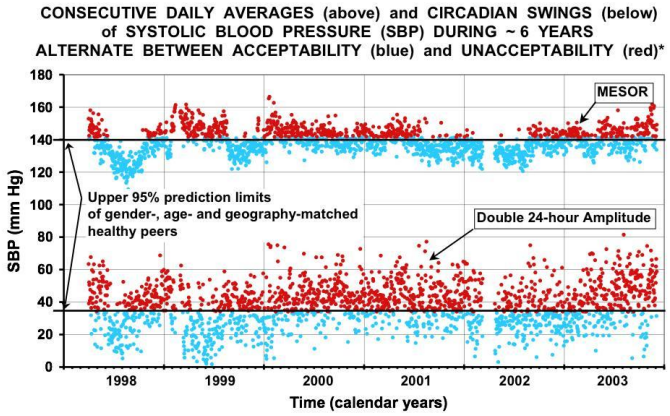


Figure 3. Results from a chronobiologically-interpreted longitudinal record of SBP from an elderly man (GSK) treated for a prior decade for "hypertension" diagnosed as MESOR-hypertension, MH, complicated by presumably iatrogenic CHAT. Data collected around-the-clock at 30-minute intervals, with very few short gaps, are analyzed by the least squares fit of 24-hour cosine curves. The daily MESOR estimates are shown on top, as dark or light dots respectively, depending on whether the SBP-MESOR was above or below the SBP-MESOR threshold (horizontal line) derived as the upper 95% prediction limit for clinically healthy men of the same age group. Similarly, the SBP-2A estimates obtained on a daily basis are shown on the bottom as dark or light dots depending on whether CHAT was diagnosed or not on that particular day, respectively. The upper limit of acceptability for the 24-hour SBP-double amplitude (2A), shown as a horizontal line, was also derived as the upper 95% prediction limit for the 24-hour SBP-2As of clinically healthy men of the same age group. Both the SBP-MESOR and the SBP-2A vary greatly from one day to another, resulting in differing diagnoses from day to day: MH is present part of the time but not all of the time. It is sometimes complicated by CHAT, but not invariably so, and CHAT can occasionally be present in the absence of MH. These results illustrate the need for continuous surveillance, so that treatment can be adjusted as needed (as indeed it was). Of interest is the last part of 2001, when MN prevailed most of the time, but CHAT occurred frequently. This may be an undesired tradeoff since CHAT carries a risk of cerebral ischemic accidents and nephropathy higher than MH, even among MN patients. The record shows a span of days when both vascular variability disorders were eliminated, with CHAT recurring first thereafter, yet with some MH as well. In such cases, several weeks of acceptable values do not assure that a treatment is validated in the long term.

Several prospective and also much larger retrospective outcome studies have shown that VVDs such as CHAT carry a vascular disease risk that can be higher than the risk of MH, even among normotensive subjects [32]. For example, the risk of vascular morbidity (cerebral ischemic event, coronary artery disease, nephropathy and retinopathy) associated with CHAT alone (in MESOR-normotensive subjects) is twice as large as that associated with uncomplicated MH. The VVDs listed above are mostly independent and additive. When two or more coexist to constitute a VVS, the risk is usually larger than that of any one of the VVDs present alone. The risk of vascular morbidity in patients with three VVDs is much higher than the risk of patients with any one VVD alone, Figure 4.

VVDs and/or VVSs detect earliest risk elevations, when these may be more readily reversed as pre-hypertension [6-10], pre-diabetes [11, 12], and possibly with a focus on pulse pressure and obesity [13], a pre-metabolic syndrome, Figure 8. Hospitals with modern technology, equipped with hardware and software for automatic continuous self-surveillance could make a change in health care by cost-effectively detecting the earliest changes when they precede severe vascular disease.

A manned website, Figure 9, for pre-habilitation, rather than only for rehabilitation, can provide self-helpers with analyses of their data collected with devices for ABPM and data transfer, as is now done on a small scale by e-mail within the scope of the BIOCOS project (corne001@umn.edu).

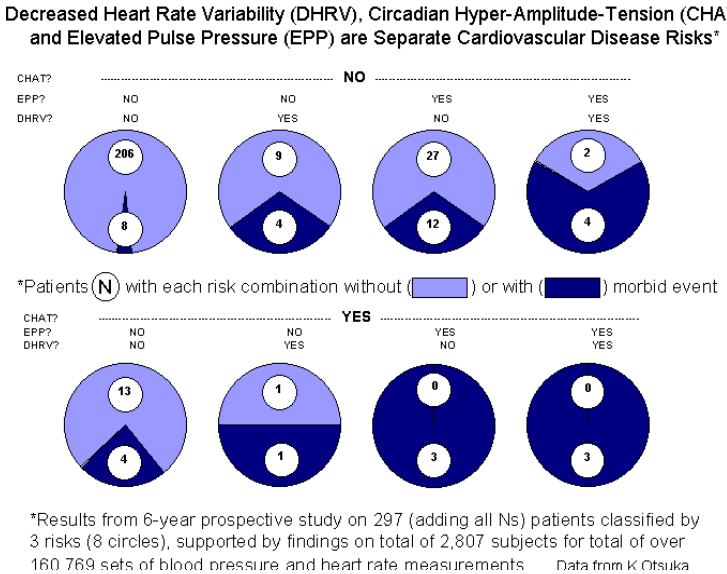
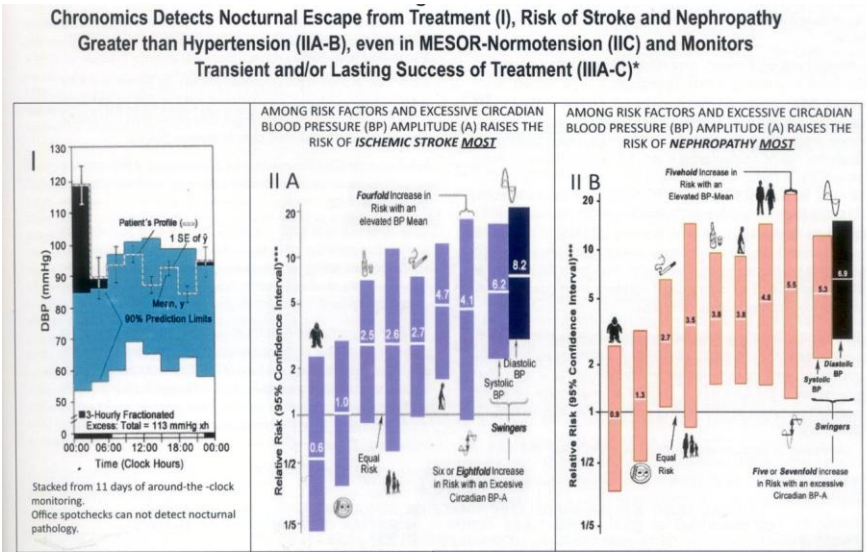


Figure 4. Decreased heart rate variability (DHRV), circadian hyper-amplitude-tension (CHAT) and elevated pulse pressure (EPP) are separate cardiovascular disease risks. CHAT is one of several conditions related to the variability in blood pressure (BP) and/or heart rate (HR) that is associated with an increase in vascular disease risk. The circadian (or preferably circaseptan profile) with too large a pulse pressure (the difference between systolic BP and diastolic BP, i.e., between the heart's contraction or relaxation, or the extent of change in pressure during a cardiac cycle) and a decreased HR variability (gauged by the standard deviation of HR) in relation to a threshold, preferably eventually all in gender- and age-matched peers are two other risk conditions (as is an abnormal circadian timing of BP but not of HR, not shown). Vascular disease risk is elevated in the presence of any one of these risk factors, and is elevated further when more than a single risk factor is present, suggesting that these abnormalities in variability of BP and HR are mostly independent and additive. Abnormalities in the variability of BP and HR, impossible to find in a conventional office visit (the latter aiming at the fiction of a "true" BP), can raise cardiovascular disease risk (gauged by the occurrence of a morbid event like a stroke in the next six years) from 4% to 100%. By comparison to subjects with acceptable BP and HR variability, the relative cardiovascular disease risk associated with DHRV, EPP and/or CHAT is greatly and statistically significantly increased. These risks, silent to the person involved and to the conventional care provider, notably the risk of CHAT, can usually be reduced if not reversed by chronobiologic self-help, also with a non-pharmacologic approach in the absence of MESOR-hypertension [32]. © Halberg.



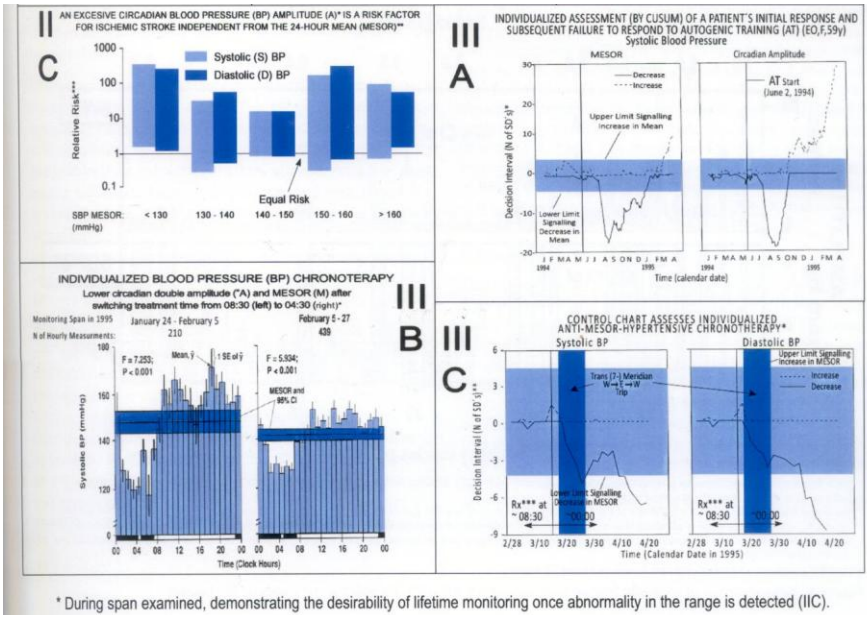
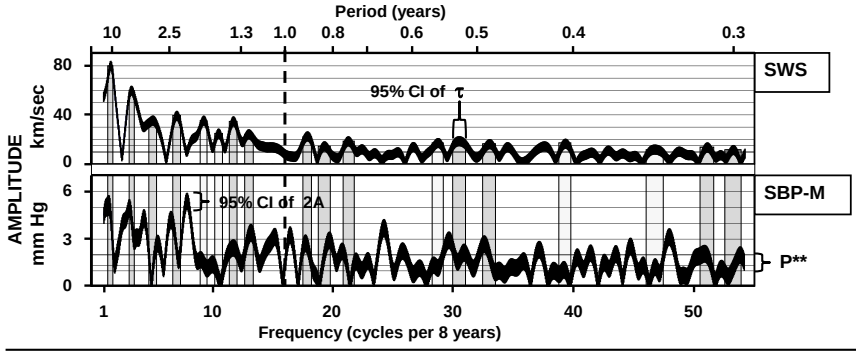


Figure 5. Illustrative results supporting the need for continued surveillance and for a chronomic analysis of blood pressure (BP) series. I: Nocturnal hypertension: data stacked from 11 days of around-the-clock monitoring. Office spotchecks during regular hours cannot detect nocturnal abnormality. II A: Among risk factors, an excessive circadian BP amplitude (A) raises the risk of ischemic stroke most. II B: Among risk factors, an excessive circadian BP-A raises the risk of nephropathy most. II C: An excessive circadian BP-A is a risk factor for ischemic stroke independent from the 24-hour mean (MESOR). III A: Individualized assessment (by CUSUM) [16] of a patient's initial response and subsequent failure to respond to autogenic training (AT) (EO, F, 59y). III B: Individualized BP chronotherapy. Lower circadian BP-2A and MESOR (M) after switching treatment time from 08:30 (left) to 04:30 (right). III C -- Control chart assesses individualized anti MESOR-hypertensive chronotherapy. Chronomics detects nocturnal escape from hypotensive treatment taken in the morning (I above) and conditions such as CHAT, associated with a risk of stroke and nephropathy greater than hypertension (IIA, B), even in MESOR-normotension (IIC), and monitors transient and/or lasting success of treatment (IIIA-C). Merits are:

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

- Detection of abnormal circadian pattern of BP (CHAT, "overswinging") associated with a risk of cerebral ischemia and nephropathy larger than other risks (including "hypertension") assessed concomitantly (IIA, B);
- Finding that CHAT carries a very high risk even among MESOR-normotensives who do not need antihypertensive medication (IIC);
- Availability of statistical procedures such as a self-starting cumulative sum (CUSUM) applicable to the individual patient to determine whether an intervention such as autogenic training is effective and if so for how long it remains effective (IIIA, IIIC);
- N-of-1 designs for the optimization of treatment timing: the same dose of the same medication can further lower the same subject's blood pressure MESOR and circadian amplitude when the timing of daily administration is changed (IIIB and C), as ascertained by as-one-goes (sequential) testing and parameter tests, procedures applicable to the given individual. © Halberg.

DECADAL, MULTI- & EXTRA-ANNUAL CONGRUENCE OR SIMILARITY GAUGED BY OVERLAPPING OR OVERLYING VS CONTIGUOUS CIs[¶] OF PERIOD, τ, IN SPECTRA OF SOLAR WIND SPEED (SWS) AND SYSTOLIC BLOOD PRESSURE (SBP) MESOR (M) *



*** SWS: daily data from ftp://nssdcftp.gsfc.nasa.gov/spacecraft_data/omni, N=5272. BP data: daily averages from Dec 1989 to Jul 2006 monitored ~ every 30 min (with gaps) by FH, a man of 70 y at start of records. N = 2684.**
**** Horizontal lines indicate ordering significance at the 0.001 and 0.05 levels only as a first approximation; until more robust methods become available, that are not dependent upon the assumptions of independence, normality and homogeneity of variance, a transdisciplinary congruence of periods and a "remove – replace" approach remain the criteria of importance. Congruence between components with amplitudes differing from zero with an ordering P betweein 0.001 and 0.05 are questionable.**
[¶] CI = 95% confidence interval of τ (of each component fitted separately).

© Halberg.

Figure 6. Bioresonance of multiple frequencies of human BP with the solar wind's speed. © Halberg.

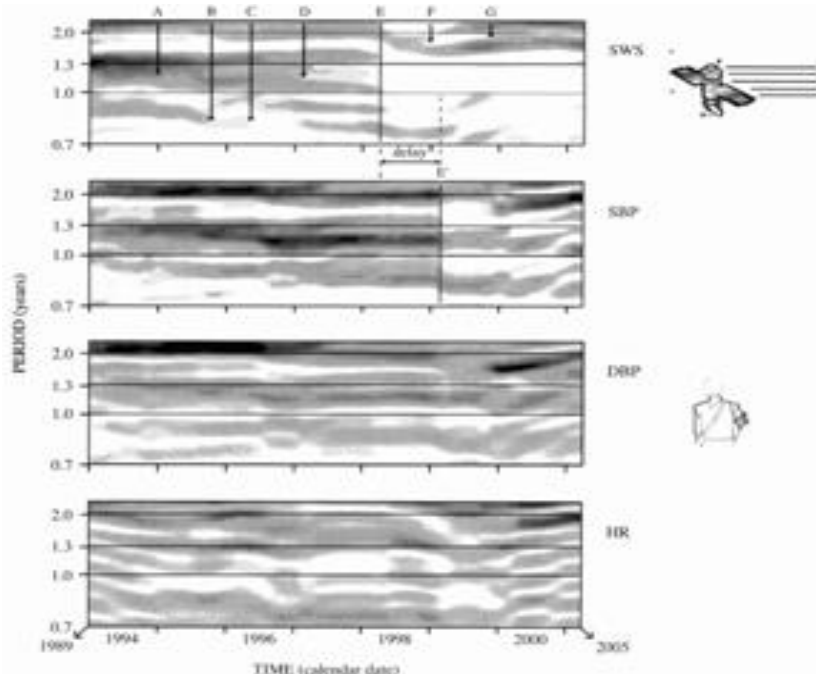
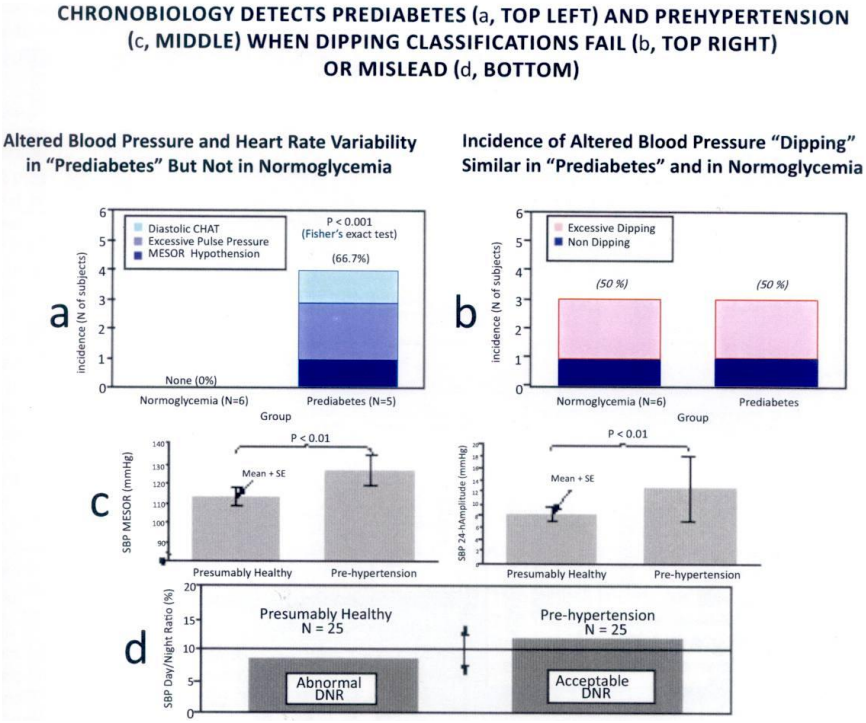


Figure 7. Time courses of the frequency structures of the speed of the solar wind (SWS) (top) and of an elderly man's (FH) systolic (S) and diastolic (D) blood pressure (BP) and heart rate (HR) (rows 2-4, respectively), examined by gliding spectral windows. Human SBP selectively resonates with SWS (top row). No obvious resonance, only minor coincident change in DBP or HR is seen (bottom 2 sections). Nonstationary intermittent frequencies such as those in SWS, dubbed Aeolian (derived, as an analogy to the solar wind, from Aeolus, Greek god of winds) resolved in gliding spectra of SWS and SBP change in frequency (smoothly [A] or abruptly [B, C, D], bifurcating [D, F] and rejoining [G]; they also change in amplitude (B) (up to disappearing [C, E] and reappearing).

During a nearly 16-year span, there are no consistent components with a period averaging precisely 1 year in the three physiologic variables, probably an effect of advancing age. While post hoc ergo propter hoc reasoning can never be ruled out, an abrupt change in SWS is followed in SBP by the disappearance of some components, suggesting that as a first demonstration, some of FH's cis- and transyear components were driven by the SW [since they dampened with a lag of about a transyear following the disappearance (subtraction) of the same components from the SWS spectrum]. The persistence of other spectral features in turn suggests endogenicity, i.e., an evolutionary acquisition of solar transyear oscillations that may reflect solar dynamics for the past billions of years. BP and HR data are from a man 70 years of age at start of automatic around the-clock monitoring, mostly at 30-min intervals,

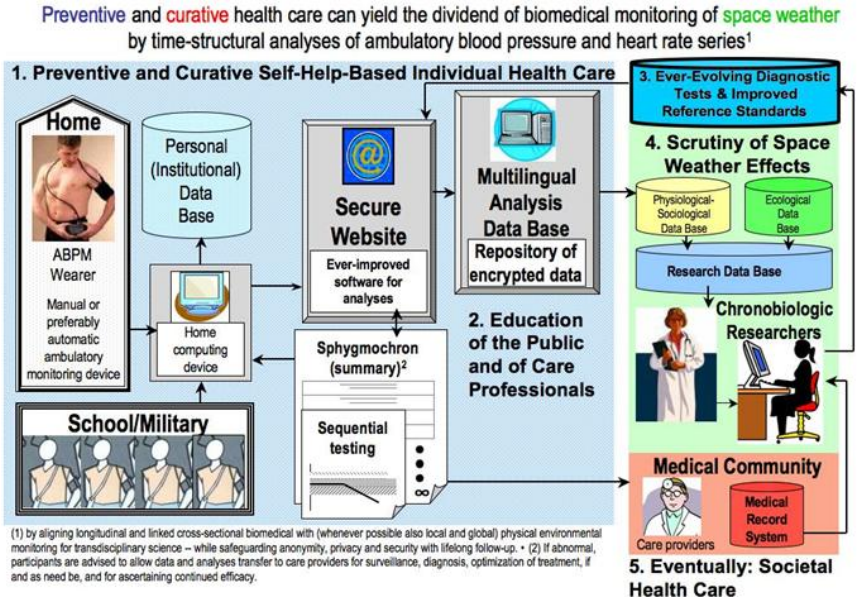
with interruptions for nearly 16 years (N=2,418 daily averages, total N ≈ 55,000). Gliding spectra computed with interval = 8 years, resolution low in time but high in frequency, increment = 1 month, trial periods from 2.5 to 0.4 year(s), with harmonic increment = 0.05. Darker shading corresponds to larger amplitude. When several of these broad bands disappear in the SWS, at E, parts of the bands in SBP also disappear, with a lag (delay) at E', while other parts persist. These components are presumably built into organisms over billions of years, as persistence without corresponding components in SWS shows, but can be driven in part by the solar wind, as their disappearance after loss of corresponding components in SWS suggests.



© Halberg.

Figure 8. (top) With the relatively small sample sizes of 6 patients with a moderately elevated fasting glucose and a slightly abnormal glucose tolerance versus 6 healthy controls, all undergoing 7-day/24-hour ambulatory BP and HR monitoring, analyses indicate that a chronobiological approach works when a classification in terms of "dipping" based on the day-night ratio (DNR) fails. Indeed, no abnormality was detected in the light of time-specified reference standards qualified by gender and age among the 6 controls, but 4 of the 6 pre-diabetic patients showed one or more VVDs ($P<0.001$). By contrast, in both groups, there were two patients with a DNR > 20%

("excessive dipping") and one patient with a DNR < 10% ("non-dipping"). It was thus impossible to discriminate the patients with pre-diabetes from the healthy controls in terms of "dipping", when a chronobiological interpretation worked [12]. (middle and bottom). Circadian parameters and day-night ratios (DNRs) of systolic blood pressure (SBP) are compared between groups of presumably healthy MESOR-normotensive subjects and pre-hypertensive subjects with incipient signs of minimal change hypertensive retinopathy. Minimal retinal alterations, presumably reflecting an increased vascular disease risk, are associated with a higher MESOR and a larger circadian amplitude of SBP (P<0.01). A classification in terms of dipping, based on the DNR of SBP, however, is misleading, as the pre-hypertensive patients as a group are "dippers" with a DNR between 10% and 20%, but the MESOR-normotensive controls as a group are non-dippers, with a DNR of SBP below 10% [7].



Modified from Figure 1 (Phoenix Architecture) in Adams C Privacy requirements for low-cost chronomedical systems. Int Conf on the Frontiers of Biomedical Science: Chronobiology, Chengdu, China, September 24-26, 2006, p 64-69, originally with Larry A. Beaty (www.sphygmochron.org) of the Phoenix Project (www.phoenix.to-ieee.org/).

Figure 9. Currently, a project on The BIOsphere and the COSmos (at corne001@umn.edu) provides analyses multilingually, in English, French and German (and as soon as possible in Arabic and Spanish) to all comers worldwide, in exchange for the data. These analyses serve multiple purposes transdisciplinarily: for the person monitored, the analyses diagnose any VVD and guide treatment via consultation by a care provider for lifelong self-help in continuously monitored

sphygmochrons, data summaries in the light of gender, age and other temporal norms. The data in turn also serve for eventually improving reference standards (after lifetime records from disease-free subjects become available) and to look for novel harbingers in records from individuals with adverse events. Furthermore, the data can be used with illustrations to educate the public and care professionals. Finally, analyses of the data flow can monitor solar activity with signatures in blood pressure and heart rate and in archived hard events. The Phoenix Project of volunteering members of the Twin Cities chapter of the Institute of Electrical and Electronics Engineers (http://www.phoenix.tc-ieee.org) is planning on developing an inexpensive, cuffless automatic monitor of BP and on implementing the concept of a website (www.sphygmochron.org) for a service providing automatic analyses in exchange for the data that in turn are to be used for refining methods and for monitoring psychophysiological effects of space weather. © Halberg.

BENEFIT

The self-helper in health care gets the needed information on his or her health status cost-free, without requiring support from caregivers, unless the analyses suggest the need for a consultation. We here illustrate what can be gained by chronobiologically-implemented ambulatory BP and HR self-monitoring, carried out automatically, as a start around the clock at half-hourly or shorter intervals for 7 days (C-ABPM 24/7; or at about 3- to 4-hour intervals manually, the ambulatory automatic instrument being much preferred).

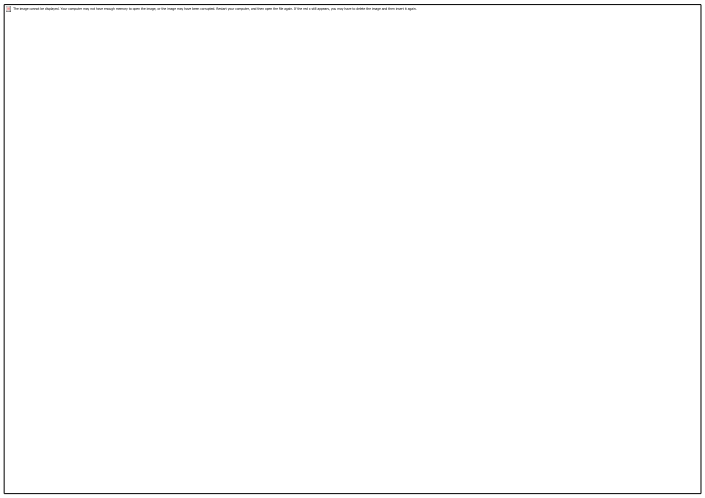
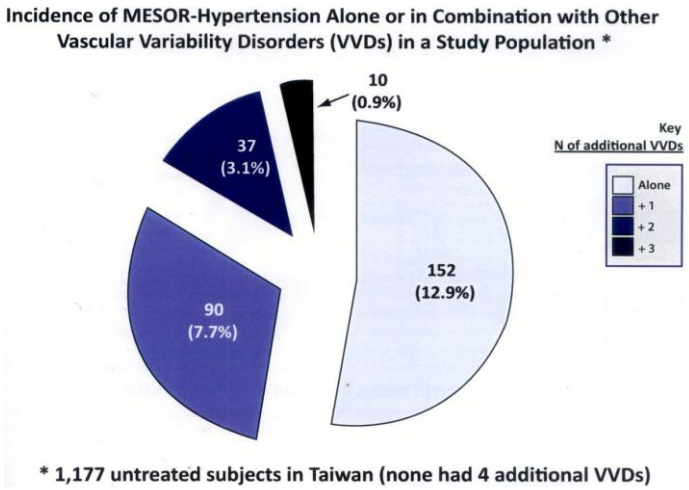


Figure 10. Percentages of VVDs and VVSs missed in current practice. The incidence of VVDs in this graph is assessed in a clinic population of 297 patients. BP and HR

of each subject were monitored around the clock for 2 days at 15-minute intervals at the start of study. Each record was analyzed chronobiologically and results interpreted in the light of time-specified reference limits qualified by gender and age. On this basis, MH (diagnosed in 176 patients), EPP, CHAT, and DHRV were identified and their incidence related to outcomes (cerebral ischemic attack, coronary artery disease, nephropathy, and/or retinopathy). Outcomes, absent at the start of study in these non-diabetic patients, were checked every 6 months for 6 years, to estimate the relative risk associated with each VVD alone or in combination with 1, 2, or 3 additional VVDs, shown in columns complementing each circular display of incidences of variability disorders. Earlier work showed that CHAT was associated with a risk of cerebral ischemic event and of nephropathy higher than MH (Figure 5), and that the risks of CHAT, EPP, and DHRV were mostly independent and additive. It thus seemed important to determine the incidence of each VVD, present alone or in combination with one or more additional VVDs. Results from this investigation are summarized in this graph. Results related to MH are shown in the upper left section of the graph. The 176 patients with MH are broken down into 103 (34.7% of the whole study population of 297 patients) with uncomplicated MH, 55 (18.5%) with MH complicated by one additional VVD (EPP, CHAT, or DHRV), 15 (5.1%) and 3 (1.0%) with MH complicated by two or three additional VVDs. In the latter group, all 3 patients had a morbid outcome within 6 years of the BP monitoring. Ambulatory BP monitoring over only 48 hours, used for diagnosis, is much better than a diagnosis based on casual clinic measurements, yet its results apply only to groups. With this qualification, of the 176 patients with MH, 73 (42.2%) have additional VVDs that further increase their vascular disease risk, and that are not considered in the treatment plan of these patients since current practice does not assess these VVDs. This proportion may be smaller in a 7-day record (available for CHAT). Results related to EPP (upper right), CHAT (bottom left), and DHRV (bottom right) illustrate that these conditions can be present in the absence of MH in as many as 12 (4.0%) of the 297 subjects. Since they do not have MH, it is unlikely that these subjects would be treated from a conventional viewpoint, even though their vascular disease risk can be as high as or even higher than MH. Evidence exists to suggest that treatment of these conditions may translate into a reduction in morbidity and/or mortality from vascular disease [60]. Another lesson from these results is that around-the-clock monitoring of BP and HR interpreted chronobiologically is needed, even in the absence of MH, to detect vascular disease risk associated with VVDs such as CHAT and DHRV, that cannot be assessed on the basis of casual clinic measurements, so that non-pharmacologic and/or pharmacologic intervention can be instituted in a timely fashion before the occurrence of adverse outcomes. Once implemented across the board rather than in selected patient populations, vascular disease could be curbed to a much larger extent at relatively low cost if the monitoring is offered directly to the public and care providers become involved only after detection of a VVD. A website has to be built to interest many people and to provide cost-free analyses in exchange for the data, as is now provided worldwide by the BIOCOS project on a small scale (corne001@umn.edu). © Halberg.

Merits are compared with the status quo, limiting the use of ABPM to special cases, for one or a few days only, without any chronobiologic

interpretation. Under such current practice, the proportion of cases that remain unrecognized and hence untreated corresponds to the darker shaded segments in the upper left corner of Figure 10 and in Figure 11a, corresponding to MH complicated by one, two or three additional VVDs.



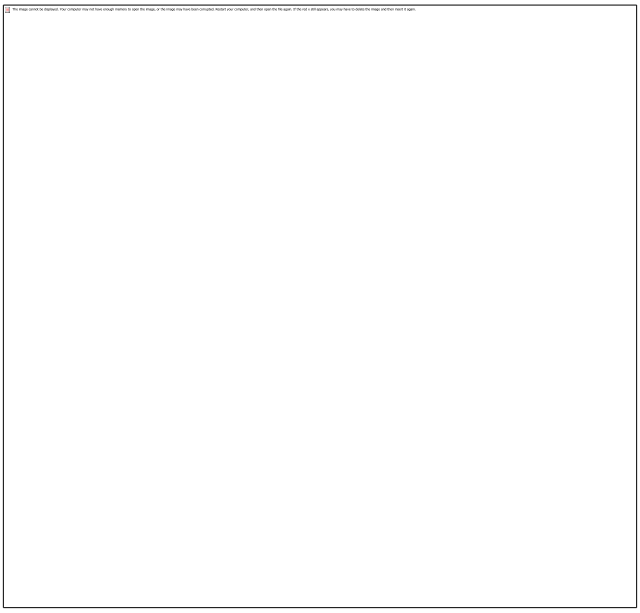
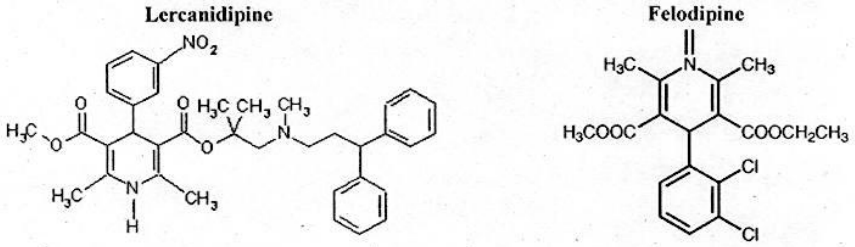


Figure 11. Single VVDs (lightest shading) are complicated to a differing extent by one or more added VVDs (darker shading). A. MH is diagnosed in a total of

289 subjects, representing 24.6% of the 1,177 untreated, presumably normotensive subjects included in the study. Among these 289 subjects, as many as 137 (47.4% of those diagnosed with MH) have at least one additional VVD that is not part of the current screening but increases the vascular disease risk beyond that associated with MH alone, as shown in Figure 10. B. Graphs illustrating that VVDs other than MH occur in the absence of MH in very few patients with EPP and in more patients with CHAT and in yet more with ecphasia and in 87 patients with DHRV, that is for a total of 182 subjects, representing *15.5%* of the study population. In this study, BP and HR data available hourly for only 24 hours were complemented by an assessment of the left ventricular mass index as a surrogate outcome measure. In addition to MH, EPP, CHAT, and DHRV summarized from another earlier study (Figure 10), ecphasia was assessed. The great limitation of a record covering only 24 hours is not overcome by the relatively large study population of 1,177 subjects not treated with antihypertensive agents, yet results in keeping with those obtained in a clinic population of 297 patients suggest that MH is to be recognized as a VVD and that its risk can be very greatly increased when other VVDs combine into VVSs that escape current diagnostics (see Figure 10). © Halberg.

Toward multiply-individualized chronotherapy*: Different calcium channel blockers can have different effects on blood pressure (BP) and heart rate (HR) deviations associated with elevated vascular disease risk



	For a specific requirement, we ask of each drug:	
NO	1. Does it reduce the circadian BP amplitude?	**YES**
YES	2. Does it increase the circadian HR variability (HRV)?	NO
YES	3. Does it reduce pulse pressure (PP)?	**YES**
YES	4. Does it reduce the BP MESOR?	**YES**

Figure 12. Seemingly differential effects of lercanidipine and felodipine on the variabilities of BP and HR illustrate the need for individualizing, perhaps even in the case of drugs with superficially similar pharmacodynamics, the kind of treatment in the light of desired effects. These desiderata range from the lowering of an excessive circadian amplitude of SBP and/or DBP to reducing too high a SBP- or DBP-MESOR and/or too large a pulse pressure, to raising deficient HR variability. The

chronodiagnosis is made on the basis of around-the-clock monitoring of BP and HR, 24/7, with results interpreted in the light of time-specified reference values of gender- and age-matched clinically healthy peers. With the qualifications that monitoring was limited to 24 hours and treatment timing was not specified in the study summarized herein, results suggested that both drugs lowered the BP-MESOR as well as the pulse pressure, but an increase in HR variability was only observed with lercanidipine and not with felodipine in studies by Brian Tomlinson. Lercanidipine may thus be the preferred choice between these two drugs for patients whose MESOR-hypertension is complicated by a deficient HR variability [49]. © Halberg.

It also corresponds to the lightest shading of the other parts of Figures 10 and 11b, representing VVDs other than MH not complicated by any other VVD (including MH).

BACKGROUND

The 7th Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) describes a SBP <120 mmHg and DBP<80 mmHg as normal. A SBP of 120-139 mmHg and DBP of 80-89 mmHg has been termed as pre-hypertension, while a SBP > 140 mmHg and/or a DBP > 90 mmHg is hypertension [33]. These guidelines are based on the (office) spot measurements of BP, which are suspect in the diagnosis of normotension, pre-hypertension or hypertension. A "control" group can have many false negative diagnoses. Vice versa, a group of mild hypertensives may have false positives. There is evidence from 24/7 records of half-hourly data that "spotcheck-hypertensives" (so misdiagnosed based only on a single 24-hour profile) can be MESOR-normotensive based on a 7-day/24-hour record and thus have some acceptable 7-day MESORs and vice versa. This observation may contribute to questionable results such as 48% cures by a placebo when the false positives at entry into a clinical trial and the false negatives at its end are not assessed [27, 34].

Current practice no longer needs to rely on one or a few measurements of BP taken in the physician's office under standardized conditions with a mercury sphygmomanometer, interpreted against fixed limits applying to all adults 18 years or older [17, 33]. Thirty home measurements without indication of their temporal placement are required by the Austrian guidelines [18] to be interpreted in the light of a time-unspecified limit, as in the international guidelines [33]. A fixed limit for a rhythmically changing variable can make the diagnosis dependent on the time of day when the measurement is made, an abstract fact [20], documented in clinical practice

as checked at the U.S. National Institutes of Health [21]. Such limitations notwithstanding, treatment of an elevated BP has been related to a decline in the incidence of cardiovascular morbidity and mortality [22], yet there are a number of people who receive treatment they do not need while others, who need treatment, do not get it, Figure 10 [35]. With rising health care costs, any robust reduction in cardiovascular disease will be extremely helpful for those concerned about the cost of health care for preventing incapacitation and suffering.

Several improvements are directly within reach. It is widely accepted that BP is not constant but varies predictably, among others according to the individual's circadian rhythm usually of large amplitude [19]. Measuring BP around-the-clock is now readily feasible with ambulatory monitors without too much disturbance of sleep and the daily routine. Measurements from these monitors have also been shown to be superior to clinic measurements in terms of diagnosis and prognosis [24]. BP is also known to change as a function of age and to differ between men and women [25] and among individuals of the same gender, age and ethnicity [16]. Not yet generally known is that in decades-long series, a number of newly discovered cyclicities have been mapped, that all contribute to variability that has to be resolved. Their periods coexist with those of the environmental day and year or replace the calendar year, differing from a precise year. Some of the periods reflect different aspects of solar activity, including beat periods of non-radial solar rotations at different solar latitudes [36-48].

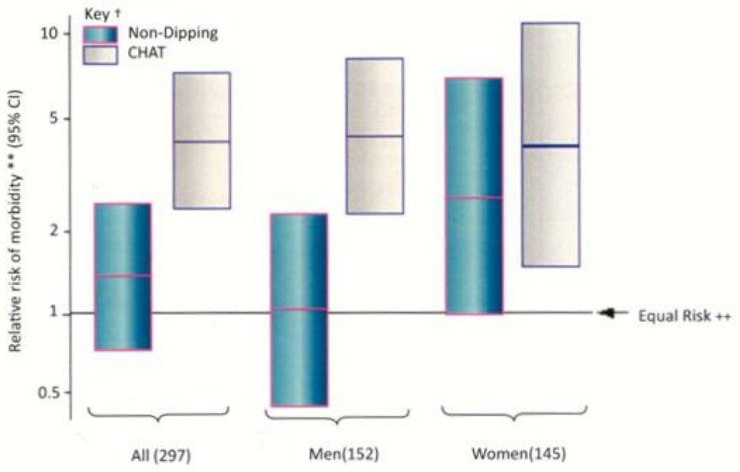
Accordingly, at variance with guidelines [33], an international project on the BIOsphere and the COSmos (BIOCOS) [29, 36, 37, 49] has derived time-specified reference values qualified by gender and age to interpret data from ambulatory monitors, collected around-the-clock, preferably for at least 7 days and in some cases for decades [44, 48]. A double-barreled approach has also been developed that consists of a parametric and non-parametric assessment of the data [29, 49].

The current chronobiologic approach relies as a first step on the estimation of circadian rhythm characteristics (parameters), obtained by the least squares fit of a two-component model consisting of cosine curves with periods of 24 and 12 hours, Figure 1. The inclusion in the model of a second harmonic with a period of 12 hours accounts for the non-sinusoidal waveform of the circadian rhythm in BP (and HR). With 24/7 monitoring, half-weekly and weekly components can be included in the model, yet one has only 1 or 2 cycles available for assessment, which is the equivalent of taking the pulse for one or two cycles (or seconds). As longer series become

available over years and decades, they serve for the detection of infradian alterations that may also signal pre-hypertension [48].

At this time, parametrically, about 3.5- and 7-day as well as circadian rhythm characteristics can be routinely estimated by the fitting of several cosines, their number depending on the length and density of the record. The parameters are an improved mean, the MESOR (M) and at each period fitted, the double amplitude (2A), and the acrophase (ϕ). For each of the infradian endpoints, improved reference standards (90% PIs) will have to be computed from data of clinically healthy peers of each gender and several age groups, e.g., for about half-weekly and weekly as well as circadian (A, ϕ) pairs and for the PP and the HR-SD. In a complementary non-parametric approach, data from a 24/7 record are stacked over an idealized 24-hour day and are compared with the time-specified 90% PIs of healthy peers matched by gender and age. The stacking can be done over periods different from 24 hours, if pertinent, but awaits the derivation of appropriate reference limits for non-24-hour components. Deviations from parametric and/or non-parametric limits guide the diagnosis of VVDs and VVSs, interpreted in the light of actual and/or proxy outcomes [32, 49-55].

Just as it is possible to treat MH, CHAT can also be treated in the absence as well as in the presence of MH non-pharmacologically or with anti-hypertensive drugs [27, 35, 49, 52, 53, 56-60]. Sometimes, in the case of iatrogenic CHAT, all it takes is to change the timing of administration of the same dose of the same treatment [35]. Treating CHAT may reduce cardiovascular morbidity and mortality by about 50% [60].



Data from 6 year prospective study by K. Otsuka [50].
**Coronary artery disease, cerebral ischemic event, nephropathy and/or retinopathy.
Diagnosis based on diastolic blood pressure (DBP), non-dipping; DNR < 10%, where DNR = day/night ratio = 100x(average daytime [10:00-20:00] DBP-average night time [00:00-6:00]DBP/average 24-hour DBP); CHAT: circadian amplitude (A) of DBP > 90^{th} percentile of clinically healthy peers of same gender and ethnicity and similar age.
**Incidence of morbidity events equal in tested and referenc populations (e.g. among dippers and non dippers).

Figure 13. The relative risk (RR) of morbidity occurring within 6 years of monitoring of 297 patients in Tokyo, Japan, associated with diastolic CHAT is statistically significant for men and women, as well as overall, as evidenced by the 95% confidence intervals of RR values not overlapping one (equal risk). By contrast, the relative risk associated with ‘non-dipping' (DNR < 10%) is only marginally elevated, and only so for women and not for men [32]. © Halberg.

Clinical studies have relied on groups or populations for diagnosis [61-63] or treatment, seeking the optimal timing of administration of a given drug. All subjects in a given group usually receive the same medication at the same circadian stage, irrespective of symptoms. In view of the different risks associated with the VVDs that all have to be optimized on an individualized basis, it becomes critical to monitor both for a chronodiagnosis and for finding the best timings of each treatment, varied for each patient systematically along the 24-hour scale, so as to validate that all VVDs are eliminated, or at least reduced as far as possible. Such linking of chronotherapy to the chronodiagnosis has been referred to as "chronotheranostics" [49]. The best time to administer a given anti-hypertensive agent may differ, e.g., among individuals [49] and/or among drugs used [56, 57], depending on whether the patient has CHAT or a small circadian BP-2A. The decision to treat a patient with MH with felodipine or lercanidipine differs depending on whether the patient has an acceptable or a deficient HR variability since only one of the two drugs, lercanidipine, seems to be able to increase HRV [49]. By contrast, in a case with MH and CHAT, felodipine should be tried first since it reduces the BP-M and the BP-2A, Figure 12. These chance findings require confirmation.

Comparison with DNR

Attempts have been made to simplify the assessment of a circadian rhythm by the computation of day-time and night-time means and of day-night ratios (DNRs). Many studies have linked some cardiovascular pathologies to the DNR [e.g., 64-68]. Whenever the merits of the DNR have been compared with those of the circadian rhythm characteristics on the same data with outcomes, the chronobiologic characteristics were shown to be superior: in a 6-year prospective study of 297 patients in Japan [35, 49, 50], Figure 13; in a smaller 7-year prospective study of dental patients in Minnesota [55], Figure 14; in a study of 25 controls and 25 patients with minimal change retinopathy [7; cf. 6]; and in a study of 1,177 patients, using the left ventricular mass index as surrogate outcome measure, Figures 11a and 11b [15].

The latter has served group assessment in studies based on populations, but does not allow inferences for the individual, for whom the goal of chronobiology is as dense as practical, and eventually a lifelong monitoring. This continued around-the-clock surveillance suggests already that infradian spectral alterations such as the replacement of a calendar year component by cycles longer than a year by about 4 months (far-transyears) may also be a harbinger to be considered for preventive treatment, decades before the onset of MESOR-hypertension [48]. The role of other infradian components in the spectra of HR or BP and of hormonal variables and in those of environmental variables near and far as yet is a topic for research.

The comparisons already completed were, without exception thus far, in favor of a chronobiologic approach. The latter allows the differentiation between undue changes in phase-only vs. amplitude-only which are assessed separately by the parametric approach while they are confounded in the DNR. Moreover, chronobiology uses added independent requirements for assessment, such as a much longer time series (of at least 7 days, rather than 24 hours), and reference standards, some of which can already be qualified by gender and age, which as yet is not done for the DNR. Apart from a more thorough since less incomplete database for a circadian assessment, the chronobiologic approach requiring a week-long record allows further the exploration of about half-weekly, near-weekly and weekly cycles that cannot be assessed by a (highly variable) 24-hour monitoring-based DNR.

A comparison of the relative merits of DNRs and circadian parameters derived from a chronobiologic approach should be continued on the large data sets with outcomes already collected via research grants from public

sources by different investigations that included ABPM at the start. The refusal in the past of advocates of the DNR to carry out that comparison or allow BIOCOS to do so may be based on the misconception that the major source of changes in BP relates to the cycle of sleep, wakefulness and activity which favors an analysis based on the waking-sleeping difference (dipping), and that the dipping classification system makes no assumption of an intrinsic circadian rhythm. A partly genetically-anchored circadian variation in BP was documented in the clinic by a free-run of SBP from sleep-wakefulness and activity [69]. Beyond circadians, there is a broad spectrum of infradian rhythms that, their relatively small amplitude notwithstanding, may be of clinical [38-42] as well as basic interest, since they are signatures of beat periods of solar rotation in phenomena such as sudden cardiac death [44] as well as suicide [46] and hormones that influence BP.

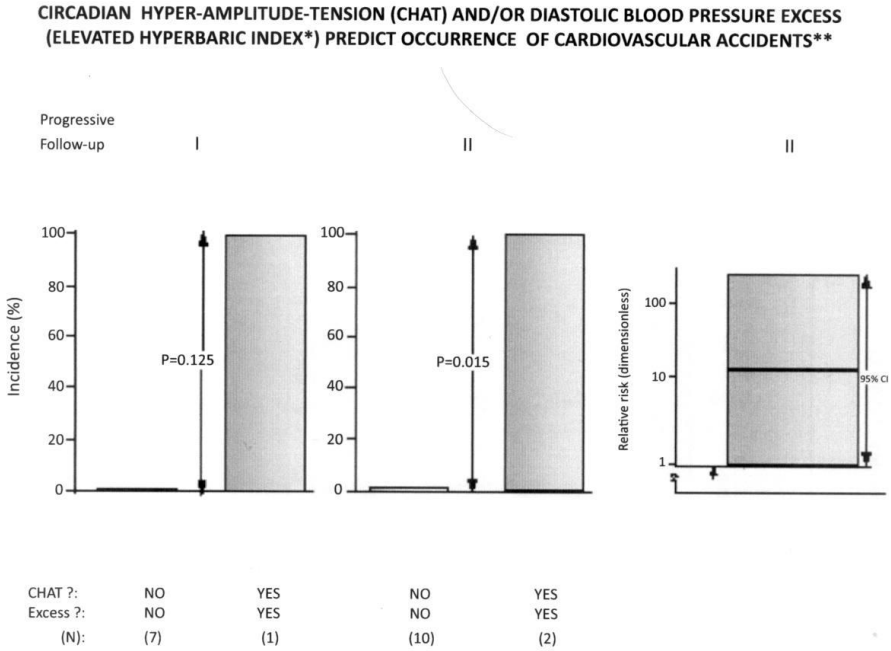


Figure 14. BP and HR data were automatically collected around the clock, at 15-minute intervals, on three occasions a few weeks apart, from 24 patients, each profile bracketing a dental appointment, and lasting 4, 2, and 3 days, respectively. Whereas the patients were presumably normotensive, a chronobiological interpretation of the records found abnormalities, including an elevated BP, in 11 of the 23 patients who completed the study (48%). In 3 patients (13%), VVDs were consistently present in

all three profiles. Since deviations may be detected in one profile but not invariably in all records a few weeks apart, BP monitoring over a minimal span of 1 week is recommended at the outset. Such a recommendation is supported by outcomes 7 years later. A comparison of the incidence of adverse outcomes in patients with BP abnormality in all three sessions vs. that in patients with abnormality in two, one or none of the sessions, was first carried out after 8 patients could be reached (left). No adverse outcome was reported by the 7 patients who did not have MH or CHAT, whereas the single patient who had MH complicated by CHAT suffered a vascular accident. After 4 more patients could be reached (middle), no adverse outcome was seen for the 10 patients who did not have MH or CHAT, whereas the two patients who had MH complicated by CHAT, both suffered a vascular accident. The difference in outcome is statistically significant by Fisher exact test ($P<0.05$) between patients identified 7 years earlier with or without MH and CHAT. Accordingly, the relative risk associated with MH complicated by CHAT is statistically significantly higher than one (equal risk) (right), the small sample size notwithstanding. The prognostic value of a consistently (in three of three sessions) deviant chronobiological assessment is illustrated by the relative risk obtained as the ratio of incidences between the two groups being compared. © Halberg.

A chronobiological approach detects pre-hypertension and pre-diabetes. In the latter case, discrimination by means of the DNR fails [12]. In a study of patients with minimal change retinopathy and healthy controls by Cugini et al. [6], differences were found in terms of circadian rhythm characteristics but not in terms of the DNR. The latter misled [7; cf. 6].

Exploring circadian parameters as part of the dynamics of HR and BP can extend the range of rhythms from seconds and days [70] to infradians [71] and can explore the possibility of infradian signaling of pre-hypertension [48]. Whether infradian rhythm alterations have prognostic value will have to be investigated with automatic, ambulatorily usable instrumentation that is unobtrusive and affordable. Data already collected on test pilots for decades document the possibility of the implementation of self-surveillance, with currently only slightly obtrusive instrumentation.

AFFORDABILITY

Automatic ambulatorily usable monitors are available through a project on The BIOsphere and the COSmos, briefly BIOCOS (corne001@umn.edu), in exchange for the data, with a great cost reduction. Cost is further reduced by the planned use of these tools on a friends-and-family basis. In systematic continuous use for at least 50 profiles/year (good for 5 years), the collection of a 7-day profile now costs less than US $3, allowing for the acquisition of

an automatic monitor for each set of a family and friends, if not yet for an economical automatic monitor for each individual. Monitors become affordable as the demand for them increases. The implementation of the latter aim is planned by the Phoenix Study Group, composed of volunteering members of the Twin Cities chapter of the Institute of Electrical and Electronics Engineers (http://www.phoenix.tc-ieee.org), along with a website (http://www.sphygmochron.org/) for free analyses in exchange for the data to be used for research, Figure 9.

BROADER IMPLICATION

The example eventually set by benefit from VVD and VVS detection and treatment may be followed by a change from a health care based on spotcheck evidence (obtained in office visits or in one- or a few-day profiles without inferential statistical tests applied to the individual's data) to cost-effective inferential statistical personalized self-surveillance. Notably after the diagnosis of a VVD or VVS is made, treatment is prescribed by a care provider, and self-surveillance is again automatically implemented with sequential and parameter tests [72, 73] applied to time series of the given person. Beyond BP and HR, the dynamics of each variable have to be mapped, rather than assuming, as does homeostatic physiology, that there is the fata morgana of a "true" BP or a "true" HR or, more generally, that a de facto variable can be approximated as an imaginary constant by invoking control theory and homeostasis. The assessments of decades-long records of patients with MH have already demonstrated to medical practice that once the diagnosis of MH is made, there is no alternative to continuous monitoring of the treatment's efficacy or failure, Figure 3 [74]. Self-surveillance was done by opinion leaders from the time of diagnosis of their VVDs for a lifetime by manual measurements [75, 76]. This is now feasible automatically as well as ambulatorily, during sleep and one's waking routine. Individualized test procedures are available to detect abnormality [72, 73] in order to something about it. By monitoring, a relaxation or other treatment may be seen to lower the BP-M. But the desired lowering effect shown by control chart (Figure 5, Section IIIA), assessing changes in BP-M that can be tracked to a given intervention, must not be accompanied by an increase in BP-2A that can lead to CHAT [49, 52, 53].

SUMMARY

This consensus proposes the use in clinical practice of C-ABPM 24/7 to rule out a VVD (or VVS). If in turn a VVD is detected (and as long as it is not absent for a full week), the monitoring is continued so that the caregiver and receiver do not fly blind [77]. Currently, hundreds of millions of people are diagnosed (some rightly, others wrongly) to have "high BP". Only relatively few of them are recognized as false positives (white-coat effect) or false negatives (masked hypertension) under the misconception that there is a "true" BP. This current approach can be replaced by developing a system via a website for monitoring BP and HR on a large scale, as is already done on a smaller scale by BIOCOS worldwide, so that the diagnosis of a VVD or VVS can be made without undue cost by earliest public education in self-help. Finding out how best to treat is a major challenge. This focus on variability is not new: Ignaz Zadek recommended assessing variability as far back as 1880 in a doctoral thesis and then in 1881 [23]. In 1904, Theodore C. Janeway of Johns Hopkins University (Baltimore), the opinion leader of his time, wrote [78]: "...it is essential that a record of the pressure be made at frequent intervals at some time previous [presumably to an examination], to establish the normal level and the extent of the periodic variations. When this is done, it may be possible to demonstrate changes of small extent, which, lacking this standard, for comparison, would be considered within the limits of normal variation." Janeway was right: even if he could not foresee that BP can undergo not only partly endogenous circadian rhythms, but also cycles longer than a year, driven by counterparts in the solar wind, yet genetically coded like circadians, since they persist when the solar driving at the given frequency is no longer detected.

And in 1974 Bartter [21] suggested, writing about a patient whose BP was diagnosed differently by two physicians who saw him at different times of day: "By conventional standards, this patient is clearly normotensive every morning. Yet the blood pressure determined each day at 6 in the afternoon provides especially convincing evidence that this patient is a hypertensive. .... My plea today is that information contained in such curves [cosinor fits] becomes a routine minimal amount of information accepted for the description of a patient's blood pressure. The analysis of this information by cosinor should become a routine. It is essential that enough information be collected to allow objective characterization of a periodic phenomenon, to wit, an estimate of M [the time structure or chronome-adjusted mean, or MESOR], an estimate of [the amplitude] A itself, and finally an estimate of

acrophase, ϕ [a measure of timing]. In this way, a patient can be compared with himself at another time, or under another treatment, and the patient can be compared with a normal or with another patient."

CONCLUSION

Today we have the wherewithal to implement Zadek's, Janeway's, Bartter's and others' [10] extensively documented suggestions. We monitor garages around the clock to prevent crime. We monitor small rodents by telemetry to develop drugs. Let us use available technology to consider those who have to be reliably diagnosed, who need the drugs, and establish the approach to the diagnosis and treatment of each patient in an individualized inferential statistical way by now-available [72, 73, 79] and yet to be further extended software.

Based on chronobiologically-interpreted C-ABPM 24/7, five VVDs can be diagnosed (MH, CHAT, BP ecphasia, EPP and/or DHRV). Eventually, alterations of cycles in the ultradian and infradian domains may be found to be useful and should be added to a screen with repeated passes over the continuously accumulating data, first mapping and thereafter interpreting infradians with longer and longer periods.

In case of a VVD, to make the diagnosis reliable 24-hour/7-day C-ABPM should be repeated for at least 7 added days, this approach may rule out transient VVDs. Alternatively, as long as a VVD persists, C-ABPM should be made continuous, depending on outcomes of C-ABPM 24/7. The effect of treatment should be controlled by C-ABPM with as-one-goes sequential tests [72] and, when the CUSUM in a control chart emerges from the decision interval, and parameter tests [73] indicate a change, treatment is accordingly introduced or modified.

EPILOGUE

Earlier consensus meetings were held in Brussels on March 17-18, 1995 [35], by the New SIRMCE Federation (the International Society for Research on Civilization Diseases and the Environment), followed by consensus meetings in Moscow on Oct. 10-12, 2005 (III International Conference, Civilization diseases in the spirit of V.I. Vernadsky, People's Friendship

University of Russia) [80], in Baku, Azerbaijan, on September 24-27, 2007 (International Interdisciplinary Workshop, Natural Cataclysms and Global Problems of the Modern Civilization) [14], and in Sudak, Crimea, Ukraine, on October 1-6, 2007 (VII International Crimean Conference "Cosmos and biosphere") [81]. At all these consensus meetings, a 24-hour/7-day profile interpreted by a parametric and non-parametric approach was recommended to likely rule out abnormality once generally affordable automatic instrumentation for continuing observation becomes available on a large scale.

This consensus also strongly recommends that reference values be collected continuously from test pilots such as astronaut and cosmonaut candidates and their families. Thus, human BP and HR reference values from conception to old age (preferably to be monitored prospectively for successive generations) may become available. There is a need for institutes to accomplish the research on data collected preferably automatically by a website which provides the individual with analyses in exchange for using the information for both health care and research, including improved reference values and refined earliest indicators of disease on the one hand. On the other hand, the time series on BP and HR and those from archives of population morbidity and mortality, including crime, war and terrorism, may serve to prevent these societal cataclysms.

Among telluric, atmospheric and solar oscillations and their associations in physiology, psychology, sociology, epidemiology, criminology and warfare, criteria of the cycles involved, qualified by CIs (95% confidence intervals) of their characteristics become measures amenable to a subtraction and addition approach occurring naturally, implemented by the sun and the broader cosmos. Just as we currently have heat and air conditioning and meet other extremes of the unduly seen, felt, tasted or smelled environs, we need to understand the unseen and not consciously noticed, yet no less important non-photic environmental risks [82, 83].

We live in the atmosphere of the sun. We learned of effects of magnetic storms and found geographic and temporal differences in association with the incidence patterns of various diseases. We find signatures of solar activity in everyday physiology. We need to learn more of the consequences of unseen non-photic effects that can override the seasons and can replace them in the incidence patterns of sudden cardiac death, of suicide and apparently also of terrorism, influencing public opinion as well. The tasks on hand are those of transdisciplinary science that ranges broadly from politics to philanthropy. This science will pay for itself in BP and HR monitoring that can fend off

hard events like stroke for millions of people now treated for hypertension or in a pre-hypertensive state who actually have risks as VVSs greater than hypertension, which are currently unrecognized, yet could be treated if detected.

To meet the challenge of noninvasive cardiology, BIOCOS aims at the construction of a universal, multilingual website for both series in health care and research in science without disciplinary barriers. All interested are welcome to participate.

BIOCOS MEMBERS

Bulgaria

Shopov, Yavor, Department of Physics, Sofia University, Sofia, yyshopov@phys.uni-sofia.bg

Tankova, Tzvetalina, Diabetic Clinic, Medical University, Sofia, tankova@iname.com

Canada

Olson, Karin, University of Alberta, Edmonton, Alberta, Karin.Olson@ualberta.ca

Stinson, Shirley, University of Alberta, Edmonton, Alberta, shirley.stinson@ualberta.ca

China

Wan, Chaomin, Department of Pediatrics, West China Second Hospital, Sichuan University, Chengdu, wcm0220@sina.com

Wang Zhengrong, School of Basic Medicine and Forensic Medicine, Sichuan University, Chengdu. wangzhengrong@126.com

Wu Jinyi, China-West Yak Industry Group, Chengdu, wujinyi@hotmail.com

Zhao Ziyan, Shandong Academy of Medical Sciences, Jinan, ziyanzhao@yahoo.com

Czech Republic

Dusek, Jiri, Masaryk University, Brno. Dusek@nco.nzo.cz
Fiser, Bohumil, Masaryk University, Brno. bfiser@med.muni.cz
Homolka, Pavel, Masaryk University, Brno. homolka@fnusa.cz
Prikryl, Pavel, Gerontology Institute, Mostiste. pavel.prikryl@email.cz
Siegelova, Jarmila, Masaryk University, Brno. jarmila.siegelova@fnusa.cz
Strestik, Jaroslav, Geophysical Institute, Czech Academy of Sciences, Prague. JSTR@IG.CAS.CZ

France

Amory-Mazaudier, Christine, Centre d'Étude des Environnements Terrestre et Planétaires, CETP, Saint-Maur-des-Fossées. Christine.Amory@cetp.ipsl.fr

Georgia (Republic of)

Gigolashvili, Marina, Georgian National Astrophysical Observatory, Tbilisi. marinagig@yahoo.com
Janashia, Ketevan, Ministry of Labor, Health and Social Affairs of Georgia, Tbilisi.
Tvildiani, Levan, Department of Internal Medicine, Tbilisi State Medical University, Tbilisi. ltvildiani@access.sanet.ge

Germany

Berger, Sigrid, Max-Planck-Institut für Zellbiologie, Ladenburg. sberger@spup.de
Hecht, Karl, Humboldt University, Berlin c/o ankedahmen@gmx.de
Ulmer, Waldemar. consultant, Gelnhausen Waldemar.Ulmer@gmx.net

Hong Kong

Deng, Hanbing (Debbie), Chinese University of Hong Kong, Prince of Wales Hospital and Shatin. debbiedeng@cuhk.edu.hk
Tomlinson, Brian, Chinese University of Hong Kong, Prince of Wales Hospital and Shatin. btomlinson@cuhk.edu.hk

Hungary

Jozsa, Rita, Faculty of Health Sciences, University Pecs rita.jozsa@aok.pte.hu
Olah, Andras, Faculty of Health Sciences, University Pécs. andras.olah@etk.pte.hu

India

Singh, R.B., Halberg Hospital and Research Centre, Moradabad drkk@dataone.in
Singh, R.K., King George's Medical College, Lucknow singhrk23a@hotmail.com

Italy

Carandente, Franca, University of Milan. franca.carandente@unimi.it
Galvagno, Andrea, Pioneer Researches, Ancona. galvagno@worldnet.it
Laffi, Giacomo, Department of Internal Medicine, University of Florence g.laffi@dfc.unifi.it
Maggioni, Cristina, Department of Obstetrics, University of Milan cristina.maggioni@unimi.it
Montalbini, Maurizio, Pioneer Researches, Ancona († 19 Sept 2009)
Perfetto, Federico, Department of Medicine, University of Florence. perfetto@unifi.it
Salti, Roberto, Meyer Pediatric Hospital, University of Florence saltir@unifi.it
Tarquini, Roberto, Department of Medicine, University of Florence rtarquini@unifi.it

Japan

Burioka, Naoto, Tottori University, Yonago burioka@grape.med.tottori-u.ac.jp
Kawasaki, Terukazu, Kyushu University, Kasuga kawasaki@ip.kyusan-u.ac.jp
Kumagai, Yuji, Jichi Medical School, Tochigi kuma-guy@za2.so-net.ne.jp
Mitsutake, Gen, Tokyo Women's Medical University, Tokyo gmitsutake@hotmail.com
Otsuka, Keiko, Department of Medicine, Tokyo Women's Medical University, Tokyo.
mother-k@ba2.so-net.ne.jp
Otsuka, Kuniaki, Department of Medicine, Tokyo Women's Medical University, Tokyo otsukagm@dnh.twmu.ac.jp
Uezono, Keiko, Institute of Health Sciences, Kyushu University, Fukuoka uezono@ihs.kyushu-u.ac.jp
Watanabe, Yoshihiko, Waseda University, Saitama yoshi-w@jd5.so-net.ne.jp

Mexico

Sánchez-de la Peña, Salvador, Chronomic Research Center, Instituto Politécnico Nacional.ENMH. Mexico City. ssalvadoral@yahoo.com
Sánchez-Castro, Salvador, Halberg Chronomics Center A.C., Tijuana, Baja California, Mexico. www.cronomica.com

Norway

Weydahl, Andi, Finnmark College, Alta andi@saturn.hifm.no

Peru

Chirinos, Julio, Santa Maria Catholic University, Arequipa jchirinos@prevencionperu.org

Russia

Blank, Mikhail, N.N. Petrov Oncology Research Institute, Ministry of Health, St. Petersburg, mablank@mail.ru

Breus, Tamara K., Space Research Institute, Moscow, breus36@mail.ru
Chibisov, Sergey M., Russian People's Friendship University, Moscow chibisov@med.rudn.ru, kalcna@mail.ru
Gubin, Denis, Tyumenskii Gosudarstvennyi Meditsinskii Institut, Tyumen dgubin@mail.ru
Masalov, Anatoly, Lebedev Physical Institute, Moscow masalov@sci.lebedev.ru
Katinas, George S., St. Petersburg, gkatinas@mail.ru
Syutkina, Elena V., Institute of Pediatrics, Academy of Medical Sciences, Moscow, c/o masalov@sci.lebedev.ru
Zaslavskaya, Rina M., Hospital #60, Moscow tatpav44@yandex.ru, vilkov@online.ru

Slovakia

Mikulecky, Miroslav Sr., Comenius University, Bratislava biometrik@pobox.sk
Zeman, Michal, Comenius University, Bratislava. mzeman@fns.uniba.sk, ubgzmzem@savba.sk

Spain

Revilla, Miguel, Department of Mathematics and Computer Science, University of Valladolid. revilla@mac.cie.uva.es

Taiwan

Chen, Chen-Huan, National Yang-Ming University, Taipei Veterans General Hospital, Taipei. chench@vghtpe.gov.tw

United Kingdom

Simpson, Hugh, Department of Surgery, University of Glasgow, Scotland gcl306@clinmed.gla.ac.uk, SimpsonHWSimpson@AOL.com

Wilson, Douglas, ADAS, Cardiff, Wales. d.wilson470@ntlworld.com, d.w.wilson@durham.ac.uk

USA

Bakken, Earl, North Hawaii Community Hospital, Kamuela, Hawaii bakken@bakkenhale.com

Borer, Katarina, University of Michigan, Ann Arbor, Michigan katarina@umich.edu

Cornélissen, Germaine, University of Minnesota, Minneapolis, Minnesota (coordinator) corne001@tc.umn.edu

Engebretson, Mark, Augsburg College, Minneapolis, Minnesota engebret@augsburg.edu

Greenway, Frank, Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, Louisiana. greenwfl@mhs.pbrc.edu

Gupta, Alok, Pennington Biomedical Research Center, Louisiana State University,Baton Rouge, Louisiana. guptaak@pbrc.edu

Halberg, Franz, University of Minnesota, Minneapolis (coordinator). halbe001@umn.edu

Hillman, Dewayne, University of Minnesota, Minneapolis. hill0093@tc.umn.edu

Holley, Dan, San José State University, San José, California dcholley2004@yahoo.com

Pan, Weihong, Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, Louisiana. Weihong.Pan@pbrc.edu

Refinetti, Roberto, Circadian Rhythm Laboratory, University of South Carolina, Walterboro, SC. lab@circadian.org

Schwartzkopff, Othild, University of Minnesota, Minneapolis. schwa115@umn.edu

Sothern, Robert B., University of Minnesota, Minneapolis. sothe001@umn.edu

SUPPORT

"National Institutes of Health (GM-13981) (FH) and University of Minnesota Supercomputing Institute (FH, GC)".

REFERENCES

[1] Penaz J. Indirect continuous recording of blood pressure in man. *Physiologia Bohemoslovaca* 1970; 19 (4): 341.

[2] Penaz J, Honzikova N, Fiser B. Spectral analysis of resting variability of some circulatory parameters in man. *Physiologia Bohemoslovaca* 1978; 27 (4): 349-357.

[3] Fiser B, Honzikova N, Penaz J. Power spectra of spontaneous variations of indirectly recorded blood pressure, heart rate and acral blood flow. *Automedica* 1978; 2: 143-147.

[4] Honzikova N, Semrad B, Fiser B, Labrova R. Baroreflex sensitivity determined by spectral method and HRV and two-years mortality in patients after myocardial infarction. *Physiol. Res.* 2000; 49: 643- 650.

[5] Bailey JJ, Hodges M, Church TR. Decision to implant cardioverter-defibrillator after myocardial infarction: the role of ejection fraction v. other risk factor markers. *Medical Decision Making* 2007; 27: 151-160.

[6] Cugini P, Cruciani F, Turri M, Regine F, Gherardi F, Petrangeli CM, Gabrieli CB. 'Minimal-change hypertensive retinopathy and arterial pre-hypertension', illustrated via ambulatory blood-pressure monitoring in putatively normotensive subjects. International *Ophthalmology* 1998; 22(3): 145-149.

[7] Cornélissen G, Cugini P, Siegelova J, Fiser B, Halberg F. Cugini's minimal change hypertensive retinopathy, resolved chronobiologically while dipping fails, supports the concept of pre-hypertension In: Halberg F, Kenner T, Fiser B, Siegelova J (Eds.) *Proceedings, Noninvasive Methods in Cardiology 2007*, Brno, Czech Republic, November 11-14, 2007. Brno: Department of Functional Diagnostics and Rehabilitation, Faculty of Medicine, Masaryk University (ISBN 978 80 7018 463 4); 2007. p. 55-61.

[8] Kumagai Y, Shiga T, Sunaga K, Cornélissen G, Ebihara A, Halberg F. Usefulness of circadian amplitude of blood pressure in predicting hypertensive cardiac involvement. *Chronobiologia* 1992; 19: 43-58.

[9] Halberg J, Halberg E, Hayes DK, Smith RD, Halberg F, Delea CS, Danielson RS, Bartter FC. Schedule shifts, life quality and quantity modeled by murine blood pressure elevation and arthropod lifespan. *Int. J. Chronobiol*. 1980; 7: 17-64.

[10] Carandente F, Halberg F (Eds.) Chronobiology of blood pressure in 1985. *Chronobiologia 1*984; 11 (3): 189-341.

[11] Sánchez de la Peña S, Gonzalez C, Cornélissen G, Halberg F. Blood pressure (BP), heart rate (HR) and non-insulin-dependent diabetes mellitus (NIDDM) chronobiology. *Int. J. Cardiol*. 2004; 97 (Suppl 2): S14.

[12] Gupta AK, Greenway FL, Cornélissen G, Pan W, Halberg F. Pre-diabetes is associated with abnormal circadian blood pressure variability. *J. Human Hypertension* 2008; 22: 627-633. doi:10:1038/jhh.2008.32.

[13] Cornélissen G, Siegelova J, Abramson J, Sundaram B, Mandel J, Holley D, Halberg F. Body mass index (BMI), pulse pressure (PP) and pre-metabolic syndrome. In: Halberg F, Kenner T, Fiser B, Siegelova J (Eds.) *Proceedings, Noninvasive Methods in Cardiology*, Brno, Czech Republic, October 4-7, 2008. p. 116-123.

[14] Halberg F. Challenges from "60 years of translational chronobiology". In: Kofler W (Ed.) Proceedings, International Interdisciplinary Workshop, Natural Cataclysm and Global Problems of the Modern Civilization, Baku, Azerbaijan, September 24-27, 2007. Transactions of the International Academy of Science HandE. Baku/Innsbruck: ICSD/IAS; 2007. p. 165-178.

[15] Cornélissen G, Halberg F, Otsuka K, Singh RB,Chen CH. Chronobiology predicts actual and proxy outcomes when dipping fails. Hypertension 2007; 49: 237-239. doi:10.1161/01.HYP.0000250392 .51418.64.

[16] Halberg F, Cornélissen G, Otsuka K, Sánchez de la Peña S, Schwartzkopff O, Watanabe Y, Pati AK, Wall DG, Delmore P, Borer K, Beaty LA, Nolley ES, Adams C, Siegelova J, Homolka P, Dusek J, Fiser B, Prikryl P. Why and how to implement 7-day/247-day/24-hour blood pressure monitoring? *Int. J. Geronto-Geriatrics* 2005; 8 (8): 1-31.

[17] Hagen P (Ed.) Mayo Clinic Guide to Self-Care: Answers for Every day Health Problems. Rochester, MN/Jacksonville,FL/Scottsdale, AZ: Mayo Clinic; 2003. p. 180-181.

[18] Magometschnigg D. Definition und Klassifikation der Hypertonie. *J. Hyperton* 2004; 8(1): 12-13.

[19] Richardson DW, Honour AJ, Fenton GW, Stott FH, Pickering GW. Variation in arterial pressure throughout the day and night. *Clin. Sci*. 1964; 26: 445-460.

[20] Cornélissen G, Halberg F. Impeachment of casual blood pressure measurements and the fixed limits for their interpretation and

chronobiologic recommendations. *Ann. NY Acad. Sci*. 1996; 783: 24-46.

[21] Bartter FC. Periodicity and medicine. In: Scheving LE, Halberg F, Pauly JE (Eds.) Chronobiology. Tokyo: Igaku Shoin Ltd.; 1974. p. 6-13.

[22] Lenfant C. Reflections on hypertension control rates: a message from the director of the National Heart, Lung, and Blood Institute [Editorial]. *Arch. Intern. Med*. 2002; 162: 131-132.

[23] Zadek I. Die Messung des Blutdrucks am Menschen mittelst des Basch'chen Apparates. *Z. klin Med*. 1881; 2: 509-551.

[24] Verdecchia P, Clement D, Fagard R, Palatini P, Parati G. Blood pressure monitoring. Task Force III: Target-organ damage, morbidity and mortality. *Blood Pressure Monitoring* 1999; 4: 303-317.

[25] Lakatta EG. Mechanisms of hypertension in the elderly. *J. Am. Geriatrics Society* 1989; 37: 780-790.

[26] Rosenfeld I. Take control of your blood pressure. Parade, July 8, 2007, p. 16. http://www.parade.com/articles/editons/2007/edition_07-08-2007/High_Blood_Pressure

[27] Halberg F, Cornélissen G, Halberg E, Halberg J, Delmore P, Shinoda M, Bakken E. Chronobiology of human blood pressure. Medtronic Continuing Medical Education Seminars, 4th ed. Minneapolis: Medtronic Inc.; 1988. 242 pp.

[28] Halberg F, Cornélissen G, Carandente F. Chronobiology leads toward preventive health care for all: cost reduction with quality improvement. A challenge to education and technology via chronobiology. *Chronobiologia* 1991; 18: 187-193.

[29] Cornélissen G, Otsuka K, Halberg F. Blood pressure and heart rate chronome mapping: a complement to the human genome initiative. In: Otsuka K, Cornélissen G, Halberg F (Eds.) *Chronocardiology and Chronomedicine: Humans in Time and Cosmos*. Tokyo: Life Science Publishing; 1993. p. 16-48.

[30] Cornélissen G, Halberg F, Gubin D, Carandente F, Halberg J, Zaslavskaya R, Syutkin V, Kumagai Y, Watanabe Y, Otsuka K. Carpe diem mensuratem: Fulminant CHAT, its recognition a chronobiologic path to preventing a myocardial infarction? Abstract, 4 Convegno Nazionale, Società Italiana di Cronobiollogia, Gubbio (Perugia), Italy, June 1-2, 1996. p. 35-36.

[31] Nelson W, Cornélissen G, Hinkley D, Bingham C, Halberg F. Construction of rhythm-specified reference intervals and regions with

emphasis on "hybrid" data, illustrated for plasma cortisol. *Chronobiologia* 1983; 10: 179-193.

[32] Cornélissen G, Halberg F, Otsuka K, Singh RB. Separate cardiovascular disease risks: Circadian Hyper-Amplitude-Tension (CHAT) and an excessive pulse pressure. *World Heart J.* 2008; 1(3): 223-232.

[33] World Health Organization, International Society of Hypertension Writing Group. 2003 World Health Organization(WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J. Hypertension* 2003; 21: 1983-1992.

[34] Wilcox RG, Mitchell JRA, Hampton JR. Treatment of high blood pressure: should clinical practice be based on results of clinical trials? *Br. Med. J.* 1986; 293: 433-437.

[35] Halberg F, Cornélissen G, International Womb-to-Tomb Chronome Initiative Group: Resolution from a meeting of the Intenational Society for Research on Civilization Diseases and the Environment (New SIRMCE Confederation), Brussels, Belgium, March 17-18, 1995: Fairy tale or reality? Medtronic Chronobiology Seminar #8, April 1995, 12 pp. text, 18 figures. http://www.msi.umn.edu/~halberg/

[36] Halberg F, Cornélissen G, Otsuka K, Watanabe Y, Katinas GS, Burioka N, Delyukov A, Gorgo Y, Zhao ZY, Weydahl A, Sothern RB, Siegelova J, Fiser B, Dusek J, Syutkina EV, Perfetto F, Tarquini R, Singh RB, Rhees B, Lofstrom D, Lofstrom P, Johnson PWC, Schwartzkopff O, International BIOCOS Study Group. Cross-spectrally coherent ~10.5-and 21-year biological and physical cycles, magnetic storms and myocardial infarctions. *Neuroendocrinol. Lett.* 2000; 21: 233-258.

[37] Halberg F, Cornélissen G, Regal P, Otsuka K, Wang ZR, Katinas GS, Siegelova J, Homolka P, Prikryl P, Chibisov SM, Holley DC, Wendt RW, Bingham C, Palm SL, Sonkowsky RP, Sothern RB, Pales E, Mikulecky M, Tarquini R, Perfetto F, Salti R, Maggioni Jozsa R, Konradov AA, Kharlitskaya EV, Revilla M, Wan CM, Herold M, Syutkina EV, Masalov AV, Faraone P, Singh RB, Singh RK, Kumar A, Singh R, Sundaram S, Sarabandi T, Pantaleoni GC, Watanabe Y, Kumagai Y, Gubin D, Uezono K, Olah A, Borer K, Kanabrocki EA, Bathina S, Haus E, Hillman D, Schwartzkopff O, Bakken EE, Zeman M. Chronoastrobiology: proposal, nine conferences, heliogeomagnetics, transyears, nearweeks, near-decades, phylogenetic and

ontogenetic memories. *Biomed and Pharmacother* 2004; 5 (Suppl 1): S150-S187.

[38] Otsuka K. (Ed.) Proceedings, 1st International Symposium Work-shop on Circadian Rhythms and Clinical Chronotherapy, 11 Nov2000, Tokyo, Japan. *Biomed and Pharmacother* 2001; 55 (Suppl 1): 7s-190s.

[39] Otsuka K. (Ed.) Proceedings, 2nd International Symposium Workshop on Circadian Rhythms and Clinical Chronotherapy, 17 Nov 2001, Tokyo, Japan. *Biomed and Pharmacother* 2002; 56 (Suppl 2): 231s-382s.

[40] Otsuka K (Ed.) Proceedings, 3rd International Symposium Workshop on Circadian Rhythms and Clinical Chronotherapy, 9 Nov 2002, Tokyo, Japan. *Biomed and Pharmacother* 2003; 57 (Suppl 1): 1s-198s.

[41] Otsuka K (Ed.) Proceedings, 4th International Symposium Workshop on Circadian Rhythms and Clinical Chronotherapy, 8 Nov 2003, Tokyo, Japan. *Biomed and Pharmacother* 2004; 58 (Suppl 1): S1-S188.

[42] Otsuka K (Ed.) Proceedings, 5th International Symposium Workshop on Circadian Rhythms and Clinical Chronotherapy, 6 Nov 2004, Tokyo, Japan. *Biomed and Pharmacother* 2005; 59 (Suppl 1): S1-S261.

[43] Cornélissen G, Masalov A, Halberg F, Richardson JD, Katinas GS, Sothern RB, Watanabe Y, Syutkina EV, Wendt HW, Bakken EE, Romanov Y. Multiple resonances among time structures, chronomes, around and in us. Is an about 1.3-year periodicity in solar wind built into the human cardiovascular chronome? *Human Physiology* 2004; 30 (2): 86-92.

[44] Halberg F, Cornélissen G, Katinas G, Tvildiani L, Gigolashvili M, Janashia K, Toba T, Revilla M, Regal P, Sothern RB, Wendt HW, Wang ZR, Zeman M, Jozsa R, Singh RB, Mitsutake G, Chibisov SM, Lee J, Holley D, Holte JE, Sonkowsky RP, Schwartzkopff O, Delmore P, Otsuka K, Bakken EE, Czaplicki J, International BIOCOS Group. Chronobiology's progress: season's appreciations 2004-19 2005. Time-, frequency-, phase-,variable-, individual-, age- and site-specific chronomics. *J. Applied Biomedicine* 2006; 4: 1-38. http://www.zsf.jcu.cz/vyzkum/jab/4_1/halberg.pdf

[45] Katinas GS, Halberg F, Cornélissen G, Sánchez de la Peña S, Czaplicki J, Siegelova J, BIOCOS project. C-ABPM reveals solar cis-halfyear and transyear signatures in human diastolic blood pressure. In: Halberg F, Kenner T, Fiser B, Siegelova J (Eds.) *Proceedings, Noninvasive Methods in Cardiology*, Brno, Czech Republic, October 4-7, 2008. p. 144-146.

[46] Halberg F, Cornélissen G, Berk M, Dodd S, Henry M, Wetterberg L, Nolley E, Beaty L, Siegelova J, Fiser B, Wolff C, BIOCOS project. Solar signatures in Australian suicide incidence: gender differences in prominence of photic vs. nonphotic spectral components. In: Halberg F, Kenner T, Fiser B, Siegelova J. (Eds.) *Proceedings, Noninvasive Methods in Cardiology,* Brno, Czech Republic, October 4-7, 2008, p.44-62.

[47] Cornélissen G, Tarquini R, Perfetto F, Otsuka K, Gigolashvili M, Halberg F. About 5-month cycle in human circulating melatonin: signature of weather in extraterrestrial space? Poster presentation Fourth UN/ESA/NASA/JAXA Workshop on the International Heliophysical Year 2007 and Basic Space Science: "First Results from the International Heliophysical Year 2007", Sozopol, Bulgaria, June 2-6, 2008.

[48] Watanabe Y, Cornélissen G, Halberg F, Hillman D, Czaplicki J, Sothern RB, Otsuka K, Siegelova J, BIOCOS project. Transyears, no calendar-year in blood pressure decades before MESOR-hypertension: normal or abnormal? In: Halberg F, Kenner T, Fiser B, Siegelova J (Eds.) *Proceedings, Noninvasive Methods in Cardiology,* Brno, Czech Republic, October 4-7, 2008. p. 184-188.

[49] Cornélissen G, Halberg F, Bakken EE, Singh RB, Otsuka K, Tomlinson B, Delcourt A, Toussaint G, Bathina S, Schwartzkopff O, Wang ZR, Tarquini R, Perfetto F, Pantaleoni GC, Jozsa R, Delmore PA, Nolley E. 100 or 30 years after Janeway or Bartter, Healthwatch helps avoid "flying blind". *Biomed and Pharmacother* 2004; 58 (Suppl 1): S69-S86.

[50] Otsuka K, Cornélissen G, Halberg F. Predictive value of blood pressure dipping and swinging with regard to vascular disease risk. *Clinical Drug Investigation* 1996; 11: 20-31.

[51] Cornélissen G, Otsuka K, Chen C-H, Kumagai Y, Watanabe Y, Halberg F, Siegelova J, Dusek J. Nonlinear relation of the circadian blood pressure amplitude to cardiovascular disease risk. *Scripta medica* (Brno) 2000; 73: 85-94.

[52] Halberg F, Cornélissen G, Wall D, Otsuka K, Halberg J, Katinas G, Watanabe Y, Halhuber M, Müller-Bohn T, Delmore P, Siegelova J, Homolka P, Fiser B, Dusek J, Sanchez de la Peña S, Maggioni C, Delyukov A, Gorgo Y, Gubin D, Carandente F, Schaffer E, Rhodus N, Borer K, Sonkowsky RP, Schwartzkopff O. Engineering and governmental challenge: 7-day/24-hour chronobiologic blood pressure and

heart rate screening: *Part I. Biomedical Instrumentation and Technology* 2002; 36: 89-122.

[53] Halberg F, Cornélissen G, Wall D, Otsuka K, Halberg J, Katinas G, Watanabe Y, Halhuber M, Müller-Bohn T, Delmore P, Siegelova J, Homolka P, Fiser B, Dusek J, Sanchez de la Peña S, Maggioni C, Delyukov A, Gorgo Y, Gubin D, Carandente F, Schaffer E, Rhodus N, Borer K, Sonkowsky RP, Schwartzkopff O. Engineering and governmental challenge: 7-day/24-hour chronobiologic blood pressure and heart rate screening: *Part II. Biomedical Instrumentation and Technology* 2002; 36: 183-197.

[54] Müller-Bohn T, Cornélissen G, Halhuber M, Schwartzkopff O, Halberg F. CHAT und Schlaganfall. *Deutsche Apotheker Zeitung* 2002; 142: 366-370 (January 24).

[55] Schaffer E, Cornélissen G, Rhodus N, Halhuber M, Watanabe Y, Halberg F. Blood pressure outcomes of dental patients screened chronobiologically: a seven-year follow-up. *JADA* 2001; 132: 891-899.

[56] Watanabe Y, Cornélissen G, Watanabe M, Watanabe F, Otsuka K, Ohkawa S-i, Kikuchi T, Halberg F. Effects of autogenic training and antihypertensive agents on circadian and circaseptan variation of blood pressure. *Clin. Exp. Hypertens* 2003; 25: 405-412.

[57] Tamura K, Kohno I, Saito Yuzo, Wakasugi K, Achiwa S, Imanishi Y, Cugini P, Halberg F. Antihypertensive individualized therapeutic strategy. *Difesa Sociale* 1991; 6: 109-124.

[58] Watanabe Y, Cornélissen G, Halberg F, Beaty L, Siegelova J, Otsuka K, Bakken EE. Harm vs. benefit from losartan with hydrochlorothiazide at different circadian times in MESOR hyper-tension or CHAT. In: Halberg F, Kenner T, Fiser B, Siegelova J (Eds.) *Proceedings, Noninvasive Methods in Cardiology*, Brno, Czech Republic, October 4-7, 2008. p. 149-167.

[59] Halberg F, Cornélissen G, Katinas G, Tvildiani L, Gigolashvili M, Janashia K, Toba T, Revilla M, Regal P, Sothern RB, Wendt HW, Wang ZR, Zeman M, Jozsa R, Singh RB, Mitsutake G, Chibisov SM, Lee J, Holley D, Holte JE, Sonkowsky RP, Schwartzkopff O, Delmore P, Otsuka K, Bakken EE, Czaplicki J, International BIOCOS Group. Chronobiology's progress: Part II, chronomics for an immediately applicable biomedicine. *J. Applied Biomedicine* 2006; 4:73-86. http://www.zsf.jcu.cz/vyzkum/jab/4_2/halberg2.pdf

[60] Shinagawa M, Kubo Y, Otsuka K, Ohkawa S, Cornélissen G, Halberg F. Impact of circadian amplitude and chronotherapy: relevance to

prevention and treatment of stroke. *Biomed and Pharmacother* 2001; 55 (Suppl 1): 125s-132s.

[61] Lemmer B. The importance of circadian rhythms on drug response in hypertension and coronary heart disease -- from mice and man. *Pharmacol. Therapeut* 2006; 111: 629-651.

[62] Lemmer B, Middeke M, Schaaf B, Eckes L. Prescribing practices and morning blood pressure control: results of a large-scale, primary-care study conducted in Germany. *J. Human Hypertension* 2008; 22:295-297.

[63] Middeke M, Lemmer B, Schaaf B, Eckes L. Prevalence of hypertension-attributed symptoms in routine clinical practice: a general practitioners-based study. *J. Human Hypertension* 2008; 22: 252-258.

[64] O'Brien E. Ambulatory blood pressure measurement: a trove of hidden gems? *Hypertension* 2006; 48: 364-365.

[65] Stolarz K, Staessen JA, O'Brien ET. Night-time blood pressure: dipping into the future? *J. Hypertens* 2002; 20: 2131-2133 (review).

[66] Jerrard-Dunne P, Mahmud A, Feely J. Circadian blood pressure variation: relationship between dipper status and measures of arterial stiffness. *J. Hypertens* 2007; 25: 1233-1239.

[67] Giles TD. Circadian rhythm of blood pressure and the relation to cardiovascular events. *J. Hypertens Suppl.* 2006; 24: S11-S16 (review).

[68] Zweiker R, Eber B, Schumacher M, Toplak H, Klein W. "Non-dipping" related to cardiovascular events in essential hypertensive patients. *Acta Medica Austriaca* 1994; 21: 86-89.

[69] Halberg F, Good RA, Levine H. Some aspects of the cardiovascular and renal circadian system. *Circulation* 1966; 34, 715-717.

[70] Hoyer D, Clairambault J. Rhythms from seconds to days: Physiological importance and therapeutic implications. *IEEE Eng. Med. Biol. Mag.* 2007; 26 (6): 12-13.

[71] Watanabe Y, Cornélissen G, Katinas G, Schwartzkopff O, Halberg F. Case report: a drug for damping circannual and transannual amplitudes of blood pressure and heart rate. Abstract, 2nd International Symposium, *Problems of Rhythms in Natural Sciencies*, Moscow, March 1-3, 2004. Moscow: Russian People's Friendship University; 2004. p. 18-20.

[72] Cornélissen G, Halberg F, Hawkins D, Otsuka K, Henke W. Individual assessment of antihypertensive response by self-starting cumulative sums. *J. Medical Engineering and Technology* 1997; 21: 111-120.

[73] 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.

[74] Katinas GS, Cornélissen G, Otsuka K, Haus E, Bakken EE, Halberg F. Why continued surveillance? Intermittent blood pressure and heart rate abnormality under treatment. *Biomed and Pharmacother* 2005; 59 (Suppl 1): S141-S151.

[75] Bartter FC, Delea CS, Baker W, Halberg F, Lee JK. Chronobiology in the diagnosis and treatment of mesor-hypertension. *Chronobiologia*, 1976; 3: 199-213.

[76] Levine H, Cornélissen G, Halberg F, Bingham C. Self-measurement, automatic rhythmometry, transmeridian flights and aging. In: Scheving LE, Halberg F (Eds.) *Chronobiology: Principles and Applications to Shifts in Schedules*. Alphen aan den Rijn, The Netherlands: Sijthoff and Noordhoff; 1980. p. 371-392.

[77] Fossel M. Editor's Note (to Halberg F, Cornélissen G, Halberg J, Fink H, Chen C-H, Otsuka K, Watanabe Y, Kumagai Y, Syutkina EV, Kawasaki T, Uezono K, Zhao ZY, Schwartzkopff O. Circadian Hyper-Amplitude-Tension, CHAT: a disease risk syndrome of anti-aging medicine. *J. Anti-Aging Med*. 1998; 1: 239-259). *J. Anti-Aging Med* 1998; 1: 239.

[78] Janeway TC. *The clinical study of blood pressure*. New York: D. Appleton and Co.; 1904. 300 pp.

[79] Refinetti R, Cornélissen G, Halberg F. Procedures for numerical analysis of circadian rhythms. *Biological Rhythm Research* 2007; 38 (4): 275-325. http://dx.doi.org/10.1080/09291010600903692

[80] Chibisov SM (summarized by). Resolution concerning chronobiology and chronomics. III International Conference, Civilization diseases in the spirit of V.I. Vernadsky, People's Friendship University of Russia, Moscow, Oct. 10-12, 2005, p. 23-25.

[81] Halberg F, Cornélissen G, Hillman D, Sothern RB, Nolley ES, Beaty LA, Schwartzkopff O, Otsuka K, Chibisov SM, Valenzi V, Pantaleoni G, Singh RB. Bakken's prehabilitation in the service of a budding chronoastrobiology. Invited lecture, VII International Crimean Conference "Cosmos and biosphere", Sudak, Crimea, Ukraine, October 1-6, 2007. p. 10-13.

[82] Halberg F, Cornélissen G, Sothern RB, Katinas GS, Schwartzkopff O, Otsuka K. Cycles tipping the scale beween.death and survival. (="life"). *Progress of Theoretical Physics* 2008; Suppl 173: 153-181.

[83] Halberg F, Bakken EE, Katinas GS, Cornélissen G, Zaslavskaya RM, Blank MA, Syutkina EV, Breus TK, Watanabe Y, Masalov A, Chibisov SM. Chronoastrobiology: Vernadsky's future science? Benefits from spectra of circadians and promise of a new trans-disciplinary spectrum of near matching cycles in and around us. Opening keynote, *Proceedings, III International Conference, Civilization diseases in the spirit of V.I. Vernadsky*, People's Friendship University of Russia, Moscow, Oct. 10-12, 2005, p. 4-22.