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Circadian and circaseptan (about-weekly) aspects of immigrant Indians' blood pressure and heart rate in California, USA

B. Sundaram^a, D.C. Holley^a, G. Cornélissen^b, D. Naik^a, R. Hanumansetty^a, R.B. Singh^c, K. Otsuka^d, and F. Halberg^{b,*}

^a Department of Biological Sciences, San Jose State University, San Jose, CA, USA

^b Halberg Chronobiology Center, University of Minnesota MMC 8609, 420 Delaware Street SE, Minneapolis, MN 55455, USA

^c Medical Hospital and Research Center, Center of Nutrition and Heart Research, Moradabad, India

^d Daini Hospital, Tokyo Women's Medical University, Tokyo, Japan

Abstract

Time structurally (chronomically) interpreted half-hourly monitoring of blood pressure (BP) and heart rate (HR) for at least 7 days and preferably for 17 days is recommended, separately for a diagnosis of BP disorders and when necessary again for the same or longer spans for treatment, whenever a positive diagnosis of a disorder is made. In this study, 30 clinically healthy subjects underwent 7-day monitoring and provided a series of findings, including the detection of Circadian Hyper-Amplitude-Tension (CHAT), that is blood pressure overswinging, which carries a high risk of hard cardiovascular events. The results specifically bear upon south-east Asian-Indian immigrants. They show that cardiovascular disease risk increases with age, with a positive family history of hypertension and/or other cardiovascular diseases and even with the duration of stay in the USA. A relation to body mass index is also shown. Such monitoring for prehabilitation may eventually reduce the need for rehabilitation.

Keywords

Cardiovascular disease risk; CHAT; Immigrant Indians; Prehabilitation; Sphygmochron

1. Background and significance

High BP is a serious public health problem in developing as well as developed countries. It is estimated that 65,000,000 (32.3%) people in the USA have high BP. The health care costs due to high BP are estimated to be \$59.7 billion and the overall death rate from high BP in 2000 was 17.1% of all deaths [1].

The sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High BP, convened by the National Heart, Lung, and Blood Institute, states that "Repeated blood pressure measurements will determine whether initial elevations persist and require prompt attention or have returned to normal and need only periodic surveillance" [2–4]. The Scottish Intercollegiate Guidelines Network (SIGN), an affiliate of the Royal College

*Corresponding authors. Tel.: +1 612 624 6976; fax: +1 612 624 9989. E-mail addresses: halbe001@umn.edu (F. Halberg) or corne001@umn.edu (G. Cornélissen).

Website: <http://www.msi.umn.edu/~halberg>.

of Physicians of Edinburgh, recommends at least three repeated BP measurements over a span varying from days to months before diagnosing high BP [5]. The detection and confirmation of high BP by looking at single or occasional measurements is unwise, however, even if it is officially sanctioned [2–5], because of a high chance of false positive and false negative diagnoses [6]. National and international meetings have addressed the clinical importance of the outcomes of ambulatory monitoring studies, and have emphasized the need for their incorporation into clinical diagnostic and prognostic guidelines. SIGN states that ambulatory BP monitoring has proved useful in certain circumstances, like borderline hypertension, suspected “white-coat” hypertension, i.e. in patients defined as those whose BP is consistently elevated in a hospital or physician’s office but normal at other times (a clock-hour-dependent “diagnosis”; 6), and apparent refractory hypertension.

The British Hypertension Society recommends the use of the ambulatory BP monitoring when clinic BP shows unusual variability and when symptoms suggest the possibility of hypertension [7]. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure [2] mentions that, among persons with hypertension, there is “an extensive and very consistent body of evidence” indicating that ambulatory BP correlates more closely than clinic BP with target organ damage such as left ventricular hypertrophy [8,9]. JNC-7 (The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure) suggests that “ABPM is warranted for evaluation of (white-coat) hypertension in the absence of target organ injury and is helpful to assess patients with apparent drug resistance, hypotensive symptoms with anti hypertensive medications, episodic hypertension, and autonomic dysfunction” [3]. The 2000 Canadian recommendations for the management of hypertension suggests that ABPM should be considered when an office induced increase in BP is suspected and, for (1) untreated patients with mild to moderate clinical BP elevations and without target organ damage, (2) treated patients with apparent resistance to drug therapy; symptoms suggestive of hypotension; or fluctuating office BP readings [4]. In patients in whom elevated clinic pressure is the only abnormality, ambulatory monitoring may identify a group at relatively low risk of morbidity [9–11]. Reportedly, ambulatory BP monitoring is “most clinically helpful and most commonly used” in patients with suspected “white-coat hypertension” and in patients with apparent drug resistance, hypotensive symptoms with anti hypertensive medications, episodic hypertension, and autonomic dysfunction [12].

While the foregoing line of clinical thought is in sharp contrast with an international resolution [6] that advocates around-the-clock 7-day monitoring as a start, which we have followed, we chose immigrant Indians (Asian Indians) living in California, USA as our study population because migration has been shown to influence BP [13–19]. The numbers of these immigrants have been increasing over the past 10 years, as many come for jobs in California’s high-technology industry. A study of Ethiopian immigrants in Israel found high BP, which was thought to be due to effects of urbanization [18]. Another study claiming to have evaluated the effects of “Americanization” (the adoption of American life-style and culture) in Filipino-American immigrant nurses found high diastolic (D) BP, low dips in BP during sleep and high norepinephrine, considered as the presence of physiological measures of a load (“stress”) [19]. Though the exact reasons behind an immigration-induced elevation of BP are still unclear, environmental factors like diet, climate, and exposure to chemical and biologic agents, and indirect psychosocial factors might play a role. Immigrant Indians who were born and raised in their traditional setting are now living in an entirely new environment, experiencing different cultures, lifestyle, work style and food habits. Because migration is such a widespread phenomenon, studies of the effects of accompanying life change on the health and well-being of the migrant have special significance in areas like California that support large migrant communities, but a desirable monitoring of people before and after migration was not possible for us.

We note that in other parts of the world, (Singapore, Trinidad, South Africa and Fiji), Asian Indians have a three-fold higher prevalence of cardiovascular disease (primarily coronary artery disease) than the corresponding native population [20–27]. A report on South Asian–Americans’ health by the South Asian Public Health Association (<http://www.sapha.net>) states that in the USA, heart disease has a higher prevalence in Asian Indians than in other Asians and non-Hispanic whites, and that one of the top chronic illnesses concerns high BP [28]. Our research seeks to explore the circadian variations of BP and HR in immigrant Indians in the light of reference values from Caucasians, clearly a compromise with practicability.

2. Subjects and methods

Following advertisement for immigrant Indian subjects through fliers posted at San Jose State University, religious places where Indians gather in large numbers, Silicon Valley companies where immigrant Indians work in large numbers, and Indian grocery stores, 19 men and 11 women volunteered to participate in this study. The study was approved by the Institutional Review Board at San Jose State University. Before data collection, each subject was briefed on the use of the equipment and signed an informed consent form. All subjects also filled out a BP family history and risk questionnaire, asking routine questions about the subject’s dietary habits and his/her family and personal medical history.

The subjects wore the TM-2421 ambulatory BP monitor from A&D (Tokyo, Japan) for 7 consecutive days, mostly 24 h/day. The monitor took automatic BP and HR measurements once per 30 min during the day (06:00 to 22:00) and once per hour during the night (22:00 to 06:00). Schaffer et al. [29] and Watanabe et al. [30] showed the importance of 7-day monitoring to secure reliable estimates of circadian rhythms. The BP and HR data were stored in the monitors’ memory and downloaded to a personal computer at the end of the 7 days. The procedures followed by the subjects have been used by a wide range of individuals in several other research studies [29–39].

The data were analyzed by **sphygmochron** [38,39], which provides both a parametric and a non-parametric assessment of the data. Based on a 2-component model consisting of cosine curves with periods of 24 and 12 h, the parametric endpoints considered herein are: the **MESOR**, a rhythm-adjusted mean value; the **double circadian amplitude**, a measure of the extent of predictable change within a day; and the **circadian acrophase**, a measure of the timing of overall high values recurring each day. Estimates of these parameters for each subject were compared with 90% prediction limits for clinically healthy Caucasian peers matched by gender and age. The non-parametric endpoints are obtained by comparing each subject’s profile with time-specified reference limits (chronodesms) derived from clinically healthy Caucasian peers matched by gender and age [38,39].

The MESOR and circadian double amplitude of systolic (S) and diastolic (D) BP and HR were correlated with a cardiovascular disease risk score developed by one of us (GC), based on family history [32], body mass index (BMI, body weight in kg/height in m²), age and duration of stay in the USA.

3. Results

Based on Caucasian reference limits, out of 30 subjects, two women and one man were found to have systolic (S) CHAT (circadian **hyper-amplitude-tension**); two men to have diastolic CHAT, and two women to have systolic MESOR-hypertension. The excessive variation in SBP of a 27-year-old woman with systolic CHAT is illustrated in Fig. 1. Interviews of subjects with CHAT revealed the presence of worries and other loads. The 27-year-old woman, whose data are shown in Fig. 1, reported a weight loss of 22 pounds over the past 24 months, whereas

the 31-year-old man with D-CHAT reported a drop in his physical activity resulting in a weight gain of about 3 pounds over the past 2 years.

Regression analyses indicate that the MESOR of DBP tends to correlate positively with the duration of stay in the USA ($r = 0.390$, $P = 0.032$), Fig. 2, which could mean that a longer duration of stay could increase cardiovascular risk. It also correlates positively with age ($r = 0.617$, $P = 0.002$), Fig. 3. The double circadian amplitude of HR correlates negatively with the family history risk score ($r = -0.403$, $P = 0.020$), Fig. 4, and this may mean that a decreased HR variability is seen in families with increased cardiovascular risk. The double amplitude of SBP increases with an increase in family history risk score ($r = 0.462$, $P = 0.010$), Fig. 5, and decreases with an increase in BMI ($r = -0.440$, $P = 0.010$), Fig. 6. The double amplitude of DBP also correlates negatively with BMI ($r = -0.355$, $P = 0.053$), Fig. 7, and this inverse relationship of BMI with both SBP-2A and DBP-2A goes along with the observation that obesity is slightly protective against a cerebral ischemic event made in one of our outcome studies in Japan [44]. Also, the MESOR of SBP increases with age ($r = 0.355$, $P = 0.054$).

4. Discussion

In this study, circadian BP and HR data were collected from 30 subjects and interpreted chronomically. The results show that:

- Five subjects were diagnosed with CHAT and two subjects were found to have systolic MESOR-hypertension.
- The double circadian amplitude of SBP was higher in the presence of a positive (vs. negative) family history of cardiovascular disease and/or high BP ($P = 0.01$), a statistically highly significant observation also made in earlier studies on other populations [31–41].
- The MESOR of DBP correlated significantly with age ($P = 0.002$), and the MESOR of SBP also correlated with age, although with only borderline statistical significance ($P = 0.054$). These results are consistent with studies which observed that older hypertensive subjects have more SBP and DBP fluctuations and age correlated with BP variability [42]; even in normotensive healthy subjects, age correlated with the mean and circadian amplitude of BP [43].
- The double amplitude of SBP decreased with increasing BMI ($P = 0.01$), as did the double amplitude of DBP, albeit with borderline statistical significance ($P = 0.053$). This inverse relationship was observed in one of our observational studies in which a higher body mass was found to be slightly protective against ischemic events [44]. BMI was found to have an inverse relationship with the nocturnal fall of BP in hypertensive men in the Northwick Park Hospital database study [45].
- The MESOR of DBP was found to be increased in subjects who had stayed in USA for a longer span as compared to the other study participants ($P = 0.032$). This is consistent with at least one study, which concluded that long-term immigrants are more likely than more recent immigrants to report hypertension [15]. The duration of stay varied between 9 and 92 months with an average of 46.5 months. But, the MESOR of DBP increased also with age. The average age of our subjects is 28 years and it varied from 23 to 33 years. Since we found a positive correlation of the MESOR of DBP with both the duration of stay and age, both age and duration of stay, alone or in combination, may increase the cardiovascular risk of immigrants. This is particularly important in the case of younger immigrants, who constitute the majority of our study population, who, if they choose to stay for a longer duration, may increase their cardiovascular risk because of altered circadian parameters of BP.

- The double circadian amplitude of HR decreased with an increasing family history risk score ($P = 0.02$). In earlier studies [31–41], a decreased HR variability was associated with an increased cardiovascular risk. The data from this study show that subjects at a higher cardiovascular disease risk, based on family history, exhibited a decreased HR variability. This is important since decreased HR variability adds more to a subject's cardiovascular risk load, when present along with a more positive family history.

Two of the five subjects with CHAT reported considerable subjective loads (“stress”) related to work, school and family. The average family history score of our study population was 0.776 with a standard deviation of 0.711. The family history score was 2.5 for one woman with systolic CHAT (which is more than two standard deviations above the mean), 1.25 for another woman with systolic CHAT (which is almost one standard deviation above the mean) and 0.5 for one of the men with diastolic CHAT. This is noteworthy if we take into account the statistically significant relationship between the double amplitude of SBP and the family history score observed herein and in earlier studies [33–35,38].

Ambulatory Blood Pressure Monitoring (ABPM) allows us to measure the variability of BP and HR throughout the day and night, which is used to categorize patients in terms of the day-night ratio into (1) dippers (>10%), (2) non-dippers (0–10%), (3) reverse-dippers (<0%) and (4) extreme-dippers (>20%). Previous research reported that non-dipping is directly associated with cognitive impairment/vascular dementia [46], influences cardiovascular risk by altering hemostasis/endothelial function [47,48], is independently associated with the Left Ventricular Mass Index (LVMI), even after adjustment for mean BP and angiographic CAD [49,50], and has a J-shaped relationship with stroke incidence/silent cerebral infarcts [51].

Researchers suggest that BP variability in general and non-dipping in particular has a consistently reproducible pattern [49,52–55]. Though this type of categorization potentially serves to increase the validity of risk stratification and mortality/morbidity prediction, we have demonstrated that chronobiologically derived parametric endpoints such as CHAT represent a greater and clinically more important risk factor than non-dipping [34,56]. Fig. 8 shows that CHAT is a better predictor of morbidity than “non-dipping”. A research study in Spain [54] confirmed the usefulness of ABPM in predicting the incidence of gestational hypertension and preeclampsia as early as the first trimester [32,39,56]. Also, anti-hypertensive treatment may be less effective when based on clinic BP rather than on ABPM [55].

Chronobiologic analyses combined with ABPM allows us to obtain refined diagnoses, namely MESOR-hypertension when the chronome-adjusted mean value (MESOR) of BP is above the upper limit of acceptability, excessive pulse pressure (EPP) when the difference in MESOR between the systolic and diastolic BP is too large, CHAT when the circadian BP amplitude is excessive, DHRV (decreased HR variability) when the standard deviation (SD) of HR is below the acceptable range, and/or ecphasia when the overall high values recurring each day occur at an odd time. This approach further serves as a guide to optimize the efficacy of any needed treatment by timing its administration (chronotherapy) and normalizing abnormal patterns in BP and HR.

5. Future research

Chronobiologically analyzed BP and HR plays an important role in BP diagnosis and therapy. The first author of this study has started a research study in which chronobiologically analyzed ABPM data would be collected before and after initiation of 1. anti-hypertensive medicines in newly diagnosed hypertensives and 2. a change of medicines in uncontrolled hypertensives. We hope to learn whether this would show that chronobiologically analyzed ABPM values are very useful and practically applicable in our patient setting, to better manage the hypertensive

patients by adjusting the dose and timing of the medicines. This approach is a critical step toward prevention (prehabilitation) rather than treatment initiated only after the occurrence of disease (rehabilitation) and must be carried into the clinic (*see* Appendix).

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Appendix

A proposal by one of us (S.S.), approved by his Institutional Review Board (IRB), follows as a potentially useful document for use by others. He proposed to measure the extent and timing of variations in human BP and HR of individual subjects over a span of up to 17 initial monitoring days, while analyzing any record of 24 h or preferably of much greater length. Human subjects are to wear the fully automatic ambulatory BP monitors around-the-clock for up to 17 days (or longer when interim (weekly or other) analyses indicate the need for so doing). We will thus collect multiple BP and HR values recorded at nearly regular intervals for analysis with time structure-resolving statistical methods using the vascular profile SPHYGMOCHRON [1] and a set of other electronic computer programs.

One major question that will be addressed revolves around the usefulness of chronobiologic surveillance of ambulatory B P values in the management of newly diagnosed (MESOR-) hypertensive patients vs. the spotcheck diagnosis in the clinic. Second, on patients who are on one or more anti-hypertensive medicines, we wish to compare their needs before vs. after the chronobiologic approach.

Chronobiology, the study of biological variability and of its underlying mechanisms, and chronomics, the mapping of time structures called chronomes, accumulate reference standards that represent the rules of variability. Deviations from these standards allow the early detection of an elevated vascular disease risk. They do so when the 24-h mean or the day and night means or non-dipping or over-dipping or reversed-dipping are non-contributory [1]. The detection of chronomic alterations was possible and still is with disciplined manual measurements but it is greatly facilitated by chronomic (ally interpreted) **home ambulatory blood pressure monitoring** (ABPM), i.e. CHABPM. ABPM without chronomics is under-evaluated. In summary, with ABPM evaluated chronomically we do not ‘fly blind’ [2], which we do when relying only on ‘spotchecks’ or again only on a 24-h ABPM without a chronobiologic evaluation of changes that occur in the normal range and are not assessed by alterations of nocturnal dipping [1]. The considerations for a chronodiagnosis apply to a chronomically-guided treatment which is checked again by CHABPM and optimized not only by finding for the given individual a satisfactory kind of drug and the right dose, but also the right timing. We wish to combine a chronodiagnosis with chronotherapy, i.e. achieve chronotheranostics [3].

Specific aim #1

Management of hypertension is routinely done based on office BP measurements. We wish to apply CHABPM in any volunteering newly diagnosed hypertensive patient, when a decision needs to be taken regarding any start of anti hypertensive treatment, or if a known hypertensive patient’s BP is above a “clinically acceptable” value or if any changes and/or additions to the existing anti hypertensive regimen are considered. By instituting a 1- to 17-day ambulatory BP monitoring and chronobiologic analysis, additional information will be obtained about the particular patient’s need, whether for treatment institution or for any changes in the medications, eventually targeted in time for highest efficacy with minimal side effects. This could avoid a potential misdiagnosis on such patients and assist physicians in providing more effective BP treatment.

Specific aim #2

Patients in whom anti-hypertensive treatment is started or the existing anti-hypertensive regimen is changed due to uncontrolled high BPs, ABPM for 1–17 days after the new regimen is started will provide a chronobiologically analyzed summary for comparison with similar data collected before the change in regimen. This will help to determine the therapeutic efficacy of the new regimen, if any, and make any necessary changes, based on the chronobiologic summary of the ambulatory BP values.

Research design and methods

The goals of the proposed research work will be accomplished by non-invasive, physiological monitoring, carried out around-the-clock, for 1–17 days as a start. ABPM will be used to measure and store the accumulating BP and HR values until transfer to a computer.

Chronobiologic analysis of the ambulatory BP values will help us to:

- Expand the existing evidence for the usefulness of chronobiology and its application in the clinical management of hypertension by comparing the clinical diagnosis with chronomic home ABPM (CHABPM).
- Examine the usefulness of chronobiologic monitoring of anti-hypertensive therapeutic efficacy by CHABPM.

We will monitor both male and female subjects 18 years of age or older. This study is strengthened by the fact that it will be part of a worldwide study known as BIOCOS, meaning “The BIOSphere and the COSmos”, coordinated by Dr. Germaine Cornélissen, the co-founder and director of the Halberg Chronobiology Center at the University of Minnesota, there and at other international sites. The Halberg Chronobiology Center has accumulated extensive time-specified data of BP, HR and several hormones over half a century. The archives here contain longitudinal series of self-measurements for up to 38 years and of automatic ones for up to 20 years. Dr. Cornélissen will provide her expertise in rhythmometric analyses of our data.

Experimental strategy

We plan to recruit male and female subjects at or above 18 years of age fulfilling the following inclusion criteria:

- Patients with documented diagnosis of “hypertension” who are being treated with one or more anti-hypertensive medications with BP above the target values WITHOUT any of the following:
 - Documented non-compliance in taking medicines.
 - Pregnancy.
- Newly diagnosed hypertensive patients EXCLUDING pregnant patients.
- Patients referred by their Primary care physician for ABPM.

Failure to obtain informed consent will be an exclusion criterion. We will talk to every physician in our center personally, explain this study, and give him or her a copy of the study design, which will enable him or her to identify patients within the inclusion criteria. We will also post fliers inside the family medical center building informing the patients about this study, which will give them an opportunity to discuss this study with their primary care physician. All participants will personally benefit from this study by receiving a copy of their own circadian rhythm patterns, which can be used in establishing their own individualized reference values and in diagnosing any elevation or other abnormal variations of BP and HR.

The subjects will wear the monitor for 1–17 days, around-the-clock. A majority of the published research studies on BP variations used a 24-h ambulatory BP monitoring span to collect data. We are doing it for up to 17 days because this will give us more BP recordings than a 24-h span and will allow us to analyze the data not only for circadian (about-a-day) rhythm but also for circaseptan (about-weekly) and circasemiseptan (about-half-weekly) endpoints along with a more reliable assessment of circadian end-points. Also, this will help us to see if the 24-h and other BP rhythms are altered and represent an elevated cardiovascular disease risk. We plan to cover 24 h of each day because every one has his or her own circadian patterns which may be altered at times other than a doctor's-office hours.

Abnormal BP may be found at night rather than during the day or vice versa. By monitoring for 24 h, we can measure these changes throughout the entire day for each person. The 30-min interval was chosen because of its convenience for many subjects. For the researcher, automatic readings at no more than 30-min intervals will give an adequate number of values, and have most hours represented if some readings are rejected because of artifacts. Also, BP variability obtained every 30 min by ABPM was an independent predictor for cardiovascular mortality in the general population. Each automatic reading takes no more than 3 min. If the time intervals were any shorter the subject would become annoyed by the frequent measurements and this might affect the compliance of the subject and the quality of the data collected.

The data will be analyzed by the Halberg Chronobiology Center at the University of Minnesota for rhythmometric analysis using the SPHYGMOCHRON program. This program provides estimate of the circadian characteristics of systolic and diastolic BP (and HR). Both parametric and non-parametric endpoints are calculated for each subject's data. The parametric endpoints include ultradian, circadian and weekly rhythm characteristics: e.g. the Midline-Estimating Statistic Of Rhythm (MESOR), i.e. a rhythm-adjusted mean value; the double amplitude, a measure of extent of predictable change within a cycle, and the acrophase, a measure of timing of overall high values recurring in each cycle. The non-parametric endpoints include the percentage time an individual's profile lies above the upper reference limits or below the lower reference limits during the 24 h. Other non-parametric endpoints are the hyper- and hypobaric indices, measures of the extent of excess or deficit, defined as the area delineated by the reference limit and the subject's profile when it lies outside the reference range. A SPHYGMOCHRON lists the circadian rhythm parameters estimated on the basis of a two-component model, consisting of cosine curves with periods of 24 and 12 h interpreted in the light of 90% prediction limits derived from the data on clinically healthy Caucasian peers matched by gender and age. Rhythmometric analysis by the MESOR also offers a more accurate and more precise estimate of the overall mean value provided than does the arithmetic average. Accuracy usually gains when the data are non-equidistant. When the data are equidistant, the estimate of the MESOR usually has a smaller standard error (<http://www.msi.umn.edu/~halberg/introd/biom.html>). Based on the above-mentioned analysis, we will be able to

- determine the degree of correlation of office BP with the ambulatory BP;
- accurately estimate the effectiveness of treatment regimen in controlling BP around-the-clock;
- change the timing of medication depending on the individual patient's time structures including circadian and whenever pertinent other rhythms. Thus, we anticipate a greater lowering of BP than conventional BP treatment and the reduction, if not elimination, of any disorders of BP variability.

References

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Fig. 1.

Illustrative time plot of systolic blood pressure from a case of circadian hyper-amplitude-tension (CHAT). Note that the fitted two-component model $[124.2 + 20.0 \cos(360 t/24 - 237) + 10.9 \cos(360 t/12 - 328)]$ exceeds the upper 95% prediction limits of acceptability for the circadian amplitude, shown as horizontal dashed lines around the MESOR, which at 124 mmHg is within acceptable limits for Caucasians of corresponding gender and age. The fitted curve reaches values that are slightly too high during the day and much too low during the night. In such cases of MESOR-normotension and CHAT, the risk of hard events may be associated with the transient hypotension. © Halberg.

Fig. 2.
Regression analysis of the MESOR (M) of diastolic blood pressure (DBP) with the duration of stay (DOS). © Halberg.

Fig. 3.
Regression analysis of the MESOR (M) of diastolic blood pressure (DBP) with age. © Halberg.

Fig. 4. Regression analysis of the double amplitude (2A) of heart rate (HR) with the risk score assessing the family history of developing cardiovascular disease. © Halberg.

Fig. 5. Regression analysis of the double amplitude (2A) of systolic blood pressure (SBP) with the risk score assessing the family history of developing cardiovascular disease. © Halberg.

Fig. 6. Regression analysis of the double amplitude (2A) of systolic blood pressure (SBP) with body mass index (BMI). © Halberg.

Fig. 7.
Regression analysis of the double amplitude (2A) of diastolic blood pressure (DBP) with body mass index (BMI). © Halberg.

Fig. 8.

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 seen by the non-overlap of one (equal risk) by the 95 % confidence intervals of the RR values. By contrast, the relative risk associated with “non-dipping” (day–night ratio less than 10%) is only marginally elevated, and only so for women and not for men. © Halberg.