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Chronobiologic Analyses of Weeklong around-the-Clock Records of Simultaneously Monitored Blood Pressure and Activity

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Abstract

Among the many different factors that influence blood pressure, activity was once thought to be the major determinant of the circadian variation in blood pressure. Whereas the endogenous nature of the circadian rhythm in blood pressure is no longer disputed, there is great interest in monitoring activity concomitantly with blood pressure. Herein, we reanalyze a dataset on weeklong ABPM records obtained concomitantly with actigraphy from 20 clinically healthy young adults. The purpose of this investigation is to review different approaches available for the characterization of the circadian variation in physiological variables such as blood pressure, heart rate, and activity. Topics covered include rhythm detection, the estimation of rhythm parameters, and the visualization of their waveform. Methods to examine how circadian rhythms of different variables may relate to each other are also discussed.

Introduction

Most, if not all, physiological variables undergo predictable circadian variations [1]. Circadian rhythms are genetically anchored [2, 3], including that of blood pressure, which was long thought to be no more than a direct response to activity [4].

The endogenous nature of the circadian rhythm in blood pressure is apparent from its persistence during continued bedrest [5, 6], from its ability to free-run [7, 8], and more recently from the discovery of clock genes in the periphery as well as in the suprachiasmatic nuclei [4].

Many factors affect blood pressure [9]. Among them, activity plays an important role and can be easily monitored. Interest in measuring activity concomitantly with blood pressure stems in part from the merit of defining more precisely the active and resting spans, which may differ greatly among individuals.

Herein, we re-analyze a dataset of weeklong ABPM and actigraphy records from clinically healthy young adults [10], with the aim to illustrate different approaches to characterize the circadian variation in variables such as blood pressure, heart rate, and locomotor activity.

Subjects and Methods

Study participants were 20 clinically healthy volunteers (14 women and 6 men), 20 to 54 years of age (mean ± SD: 26.5 ± 9.2). They were students and researchers, with mostly a sedentary work schedule, following mostly similar regular diurnal sleep-wake schedules. Four were overweight and one was obese. On the average, body mass index (BMI) ranged from 18.2 to 36.4 (mean ± SD: 22.7 ± 4.6).

Each study participant provided concomitant weeklong records of blood pressure and activity. Blood pressure and heart rate were automatically measured around the clock at 30-min intervals by ambulatory blood pressure monitoring (ABPM), using the TM-2421 device from A&D (Tokyo, Japan). Wrist activity was recorded every minute using the MicroMotion Logger from AMI (Ardsley, NY). We use the zero-crossing mode (ZCM) to assess activity. ZCM measures movement frequency, which is represented by the number of times the voltage fluctuations of the analog signals exceed a predetermined threshold value. In addition to ZCM, the device also measures wrist temperature, light exposure, and sleep (0 or 1, representing awake or asleep, respectively). Of the 20 participants, 15 completed the 7-day/24-hour monitoring. Records from the other 5 were shorter, covering approximately 6 days.

Blood pressure and heart rate measurements were taken at the hour and half-hour. Occasional missing values were linearly interpolated. Records that were slightly shorter than 6 or 7 full days were extrapolated in order for the records to cover an integer number of days. When gaps exceeded 90 minutes, interpolation was done by averaging data obtained at the same clock hour on other days. Data from the MicroMotion Logger were averaged over consecutive 30-minute intervals, and assigned to the midpoint, which matched the times of blood pressure and heart rate measurements.

A template was prepared in Excel where the 30-min pre-processed data from both devices were entered in a specified cell range. In the same Excel sheet, formulae were entered to approximately compute the autocorrelation function of each variable, as well as the cross-correlation function of pairs of variables. Simple Pearson product moment correlation coefficients were computed instead of the exact autocorrelation and cross-correlation formulae. While not exact, they provide a good first

approximation of these functions. Plots of each autocorrelation and cross-correlation function were prepared in separate Excel charts. This template was saved, so that it could be copied onto another file and data from a different study participant entered in the specified cell range to replace those of the template file. This way, the autocorrelation and cross-correlation functions are automatically computed and all corresponding graphs are generated without effort.

The pre-processed data were analyzed by least squares spectra [11, 12], using a fundamental period of 7 days and a frequency range from one cycle in 7 days to one cycle in 1.1 hour. Another sheet in the template Excel file accommodates the results from the least squares spectra in specified cell ranges for each variable. Noise levels are estimated, and plots are prepared of each spectrum in separate Excel charts. Results from least squares spectra from study participants were entered into the designated cell ranges of copies of the template Excel file to automatically obtain all plots. While it would have been preferable to use a fundamental period of 6 days instead of 7 days for those records that only covered 6 days, results related to the circadian variation are not affected by the choice of a 7-day fundamental component for all 20 records.

Population-mean cosinor spectra were computed by averaging results from the individual least squares spectra. Since spectral analyses of all variables showed prominent about 24-hour and 12-hour components, 2-component models were used to reconstruct the circadian patterns of each variable.

Stability (IS) and fragmentation (IV) are two indices that have been proposed to characterize the circadian variation in activity [13, 14]. IS is a signal-to-noise measure, calculated as the ratio between the variance of the average 24-hour pattern around the mean and the overall variance. IV estimates the intra-daily variability and gives an indication of the fragmentation of the rhythm (i.e., the frequency of transitions between rest and activity) and is calculated as the ratio of the mean squares of the difference between consecutive hours (first derivative) and the mean squares around the grand mean (overall variance). IS and IV are calculated based on hourly averages. IS and IV were computed from all study participants.

The Student's t test was used to compare the MESOR and circadian amplitude of each variable between men and women. Linear regression assessed relationships of the circadian parameters as a function of age and BMI. A P-value below 0.05 was considered to indicate statistical significance.

Results

Figure 1 illustrates the autocorrelation (ACF) and cross-correlation (CCF) functions of systolic blood pressure (SBP), ZCM, and wrist temperature (Temp). The presence of a circadian rhythm in each variable can be clearly seen by the naked eye. It can also be seen from the cross-correlation functions that systolic blood pressure and ZCM are in phase, but that wrist temperature is out of phase with both systolic blood pressure and ZCM.

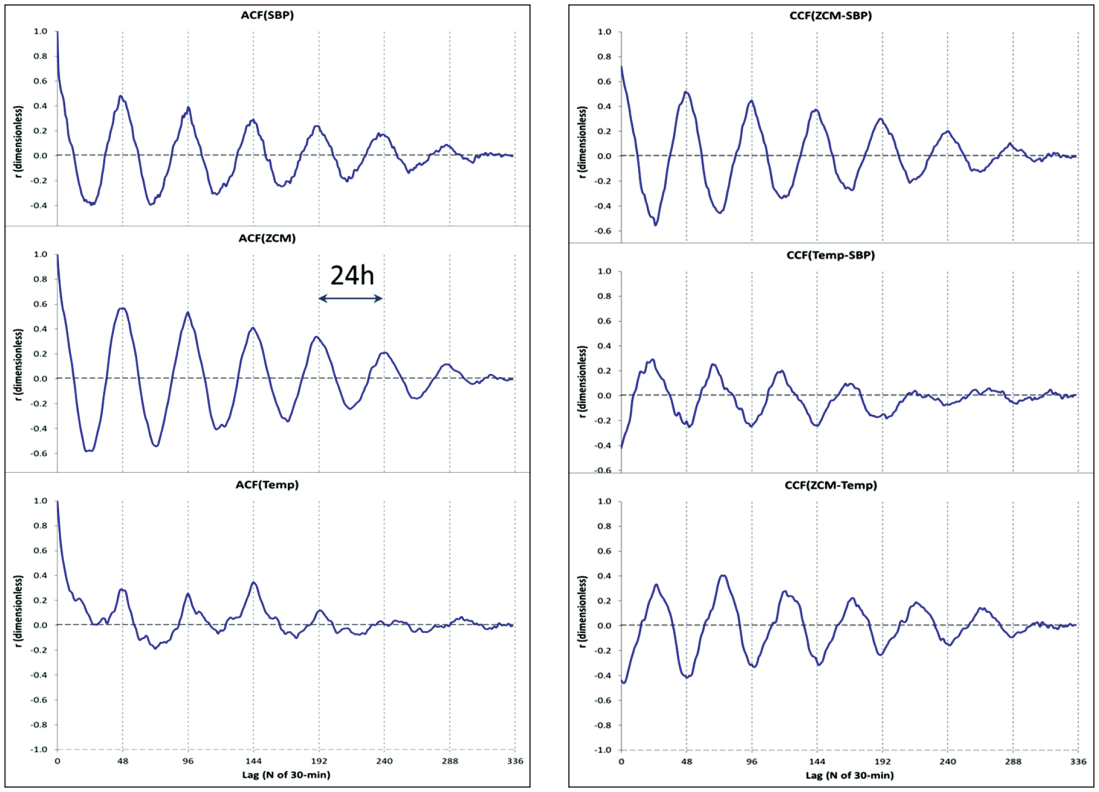

Figure 1. *Left: Autocorrelation functions of systolic blood pressure (top), activity (ZCM, middle), and wrist temperature (bottom) of one subject. Right: Cross-correlation functions of systolic blood pressure and ZCM (top), of systolic blood pressure and wrist temperature (middle), and of ZCM and wrist temperature (bottom). Note that the prominent circadian variation in these three variables is in phase between systolic blood pressure and ZCM, but that these variables are out of phase with respect to wrist temperature. © Halberg Chronobiology Center*

Figure 2 illustrates the least squares spectra of these three variables corresponding to the autocorrelation and cross-correlation functions shown in Figure 1. A large spectral peak at a frequency of one cycle per 24 hours emerges from the noise level in each case. Smaller peaks at harmonics of the circadian variation are also present. Population-mean cosinor spectra summarizing results from all 20 study participants clearly detect with statistical significance the presence of spectral components at frequencies of one and two cycles per 24 hours, Figure 3.

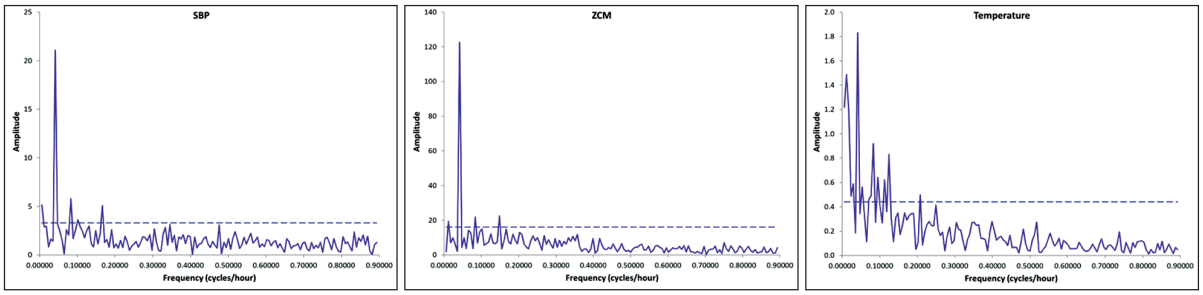

Figure 2. *Least squares spectra of systolic blood pressure (left), activity (ZCM, middle), and wrist temperature (right) of one study participant. The circadian variation is prominent, as seen by the large spectral peak at a frequency of 1 cycle per 24 hours. © Halberg Chronobiology Center*

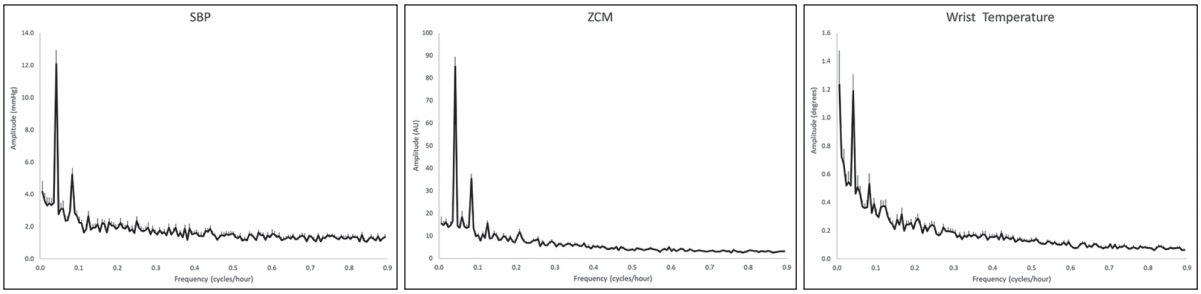

Figure 3. *Population-mean cosinor spectra of systolic blood pressure (left), activity (ZCM, middle), and wrist temperature (right), summarized across all 20 study participants. The 24-hour and 12-hour components are statistically significant. © Halberg Chronobiology Center*

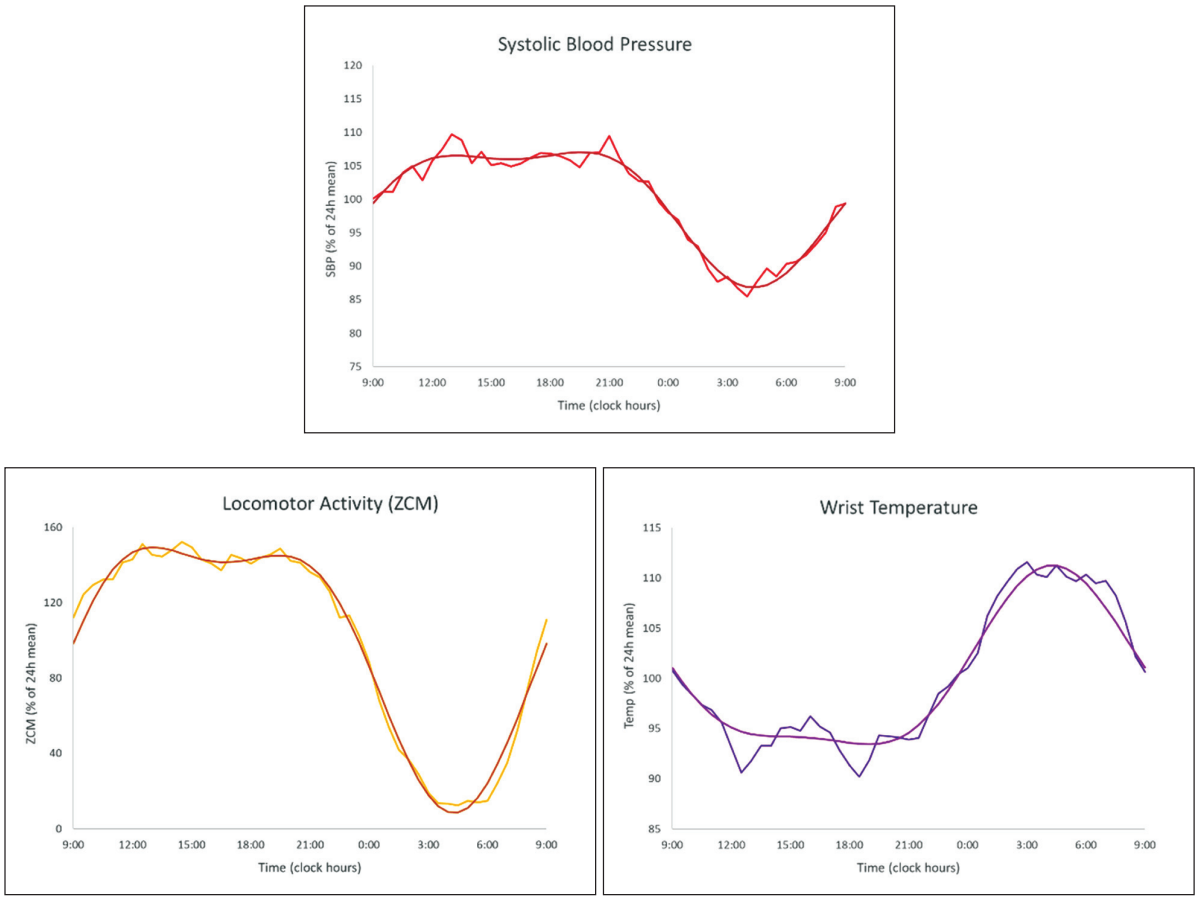

Figure 4. *Circadian waveform of systolic blood pressure (top), activity (ZCM, middle), and wrist temperature (bottom), reconstructed based on 2-component model, shown with the data expressed as a percentage of each record's arithmetic mean. © Halberg Chronobiology Center*

The circadian patterns of systolic blood pressure, activity, and wrist temperature are reconstructed in Figure 4 based on a 2-component model, consisting of cosine curves with periods of 24 and 12 hours, derived from results of the population-mean cosinor spectra.

Discussion

The stability and fragmentation indices averaged (± SD) 0.571 ± 0.152 and 0.475 ± 0.090, respectively, reflecting the relatively young population investigated herein. IS depends on the record length. It is higher in the 7-day (0.620) than in the 6-day (0.426) records ($t = 2.922$, $P=0.009$). It also correlates with activity (MESOR of ZCM) ($r=0.461$, $P=0.041$), and with the circadian amplitude of ZCM ($r=0.823$, $P<0.001$). It can be viewed as reflecting the percentage variance accounted for by the circadian variation in activity. Indeed, IS correlates strongly with the percentage rhythm of the circadian rhythm of ZCM, whether it is approximates by a single 24-hour component ($r=0.890$, $P<0.001$) or a 2-component model consisting of cosine curves with periods of 24 and 12 hours ($r=0.916$, $P<0.001$).

Anticipated gender differences are detected, despite the relative small sample size of this population. Women have a lower blood pressure than men (SBP: 112.8 vs. 129.4 mmHg, $t = 3.996$, $P<0.001$; DBP: 67.9 vs. 76.4 mmHg, $t = 3.533$, P-0.002). Women have also a smaller circadian amplitude of blood pressure as compared to men (SBP: 10.2 vs. 16.3 mmHg, $t = 4.760$, $P<0.001$; DBP: 7.9 vs. 11.3 mmHg, $t = 2.748$, $P=0.013$). Linear regression analyses as a function of age, BMI, and also accounting for gender find that the MESOR of heart rate is higher in women than in men ($t = 2.441$, $P=0.027$); that it decreases with advancing age ($t = 3.742$, $P=0.002$); and that it increases with BMI ($t = 2.559$, $P=0.021$). The model accounts for 57% of the total variance ($F = 7.076$, $P=0.003$). A similar model shows that the circadian amplitude of heart rate is larger in women than in men ($t = 2.654$, $P=0.017$) and that it decreases with advancing age ($t = 4.183$, $P<0.001$), accounting for 61% of the total variance ($F = 8.379$, $P=0.001$).

The acrophase of wrist temperature occurring during the night deserves some comment. Core temperature usually peaks in the afternoon, like activity, heart rate, and blood pressure. Differences in the circadian acrophase between distal skin temperature and body temperature are mainly related to counterbalanced physiologic processes of heat production and heat dissipation. Skin temperature measured on limbs corresponds mainly to distal vasodilation and heat transfer. Its circadian acrophase occurs approximately 90 to 120 minutes after the circadian acrophase of melatonin. Rectal, oral, and axillary temperatures are a closer approximation of core temperature and peak in the late afternoon or evening. They correspond to distal vasoconstriction and parallel heating of internal organs. For these reasons, the circadian acrophase is inverse to that of melatonin [13-15].

To summarize, the circadian rhythm of blood pressure, heart rate, activity and temperature accounts for a sizeable portion of the overall variance. These variables can easily be monitored around the clock. A number of different approaches are available to characterize the circadian variation in these variables and to explore how they are related to each other. Organizing the data in a systematic way in Excel facilitates the automatic analysis and graphic visualization of the results when a given procedure needs to be applied repeatedly to different sets of data that follow a specific protocol.

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