Biological Rhythm Research

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/nbrr20

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To cite this article: Lyazzat Gumarova, Zainab Farah, Alima Tyutenova, Zhanna Gumarova, Linda Sackett-Lundeen, Thomas Kazlausky & Germaine Cornelissen Guillaume (2022) Comparative analysis of circadian rhythms of hemodynamics and physical activity, Biological Rhythm Research, 53:9, 1321-1333, DOI: 10.1080/09291016.2021.1922827

To link to this article: https://doi.org/10.1080/09291016.2021.1922827

Published online: 05 May 2021.

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BIOLOGICAL RHYTHM RESEARCH
2022, VOL. 53, NO. 9, 1321–1333
https://doi.org/10.1080/09291016.2021.1922827

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Comparative analysis of circadian rhythms of hemodynamics and physical activity

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ABSTRACT

In determining the time structure (circadian rhythm) of blood pressure (BP), heart rate (HR), and physical activity (actigraphy indicators ZCM, HPIM) in everyday life and how they are related, 20 clinically healthy participants, 26.7 ± 2.3 years of age, were examined. Phase-weighted averages obtained by the population-mean cosinor detected statistically significant 24- and 12-h components ($P < 0.001$). The cross-correlation function between physical activity and BP shows a strong common circadian variation. The similarity of the circadian waveform of cardiovascular variables and activity, gauged by the ratio of the amplitudes of the 12-h and 24-h components, is statistically confirmed by their positive correlation. The best correspondence between fluctuations in hemodynamics and actigraphy data is shown for systolic BP and ZCM. Our results indicate the synchronicity of the circadian rhythms of BP, HR rate and physical activity, supporting the statement that the circadian rhythm of BP is not a sole direct response to the circadian rhythm of physical activity. At the same time, physical activity has a positive effect on the circadian system of the whole organism, through the central pacemaker, and thus indirectly affects the cardiovascular circadian rhythms.

ARTICLE HISTORY
Received 24 February 2021
Accepted 23 April 2021

KEYWORDS
Circadian; actigraphy; abpm; cardiovascular; physical activity

Introduction

The main function of the cardiovascular system is the transport of gases, nutrients, and wastes, and the need for this activity increases dramatically as physical activity increases. Aerobic exercise, done by healthy people is associated with high cardiac output and low resistance. The short-term response of arterial blood pressure (BP), mainly systolic (S) BP due to the large stroke volume, is an increase during dynamic exercise. Diastolic (D) BP may be slightly elevated or slightly reduced, because low peripheral resistance results in a rapid fall in arterial pressure during diastole (Mulroney and Myers 2009). Thus, in the short-term, physiology postulates the reaction of the cardiovascular system to physical activity, that is, it implies some lag in the response; in time, changes in the cardiovascular

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system follow changes in motor activity. Longer-term relationships between changes in hemodynamics and physical activity are not so obvious; there are different opinions in the relationship of their circadian rhythms.

Franz Halberg documented the partly endogenous nature of the circadian rhythm in BP (Halberg et al. 1966). Other studies of BP measured during continued bedrest also showed the persistence of the circadian rhythm in BP, albeit with a smaller amplitude (Reinberg et al. 1970; Stadick et al. 1987; Halberg et al. 1988).

Multiple actigraphy devices are now widely used, so that we can register physical activity automatically and compare the circadian rhythms of BP and HR with that of physical activity. Activity during the awake span has been correlated with the fall in BP during sleep (Shapiro and Goldstein 1998; Kario et al. 1999; Mansoor et al. 2000; Leary et al. 2000; Ancoli-Israel et al. 2003).

Herein, we investigate the relationship of BP and HR with activity and assess their synchronicity by monitoring BP, HR, and activity around the clock for a week in clinically healthy people.

Subjects and methods

Study participants

The participants of this study were clinically healthy volunteers (not patients), university students and researchers with mostly a sedentary work schedule, who followed mostly similar regular sleep-wake schedules. They were mainly young people; their age composition is: 85% (17 participants) were 20 to 30 years of age, and 15% (3 participants) were 41 to 54 years old; 14 were women and 6 were men (Table 1). The study was done after clearance from the local bioethical committee of the Al-Farabi Kazakh National University (IRB00010790, protocol No. IRB-A080) and consent was taken from all subjects.

Table 1. Demographic and activity (MESOR of ZCM and HPIM) data of 20 clinically healthy study participants, sorted by motion activity (MESOR of ZCM).

Participant ID	Gender	Age (y)	BMI	ZCM (mean ± SE)	HPIM (mean ± SE)
Sub5	M	24	20.34	78.39 ± 4.81	34,298.2 ± 2957.0
Sub7	F	24	20.03	104.17 ± 4.07	42,575.3 ± 3140.3
Sub4	M	30	24.62	109.95 ± 3.18	42,220.1 ± 2517.3
Sub13	F	22	19.23	110.81 ± 3.84	38,142.7 ± 2304.7
Sub10	F	20	22.04	112.19 ± 4.66	41,763.0 ± 2607.9
Sub19	F	22	19.23	113.88 ± 4.01	39,368.1 ± 2719.9
Sub6	F	23	20.03	115.05 ± 4.51	47,175.0 ± 3186.4
Sub15	F	54	27.32	115.66 ± 3.21	35,570.4 ± 1849.7
Sub2	F	21	29.14	117.52 ± 3.97	63,769.1 ± 3800.4
Sub18	F	24	18.97	118.00 ± 3.58	53,003.2 ± 3127.1
Sub9	F	24	18.97	118.08 ± 3.80	56,809.6 ± 3185.7
Sub16	M	21	23.04	120.41 ± 4.24	50,100.3 ± 3130.1
Sub3	F	21	21.09	125.18 ± 4.49	40,601.8 ± 2477.5
Sub14	M	26	36.42	127.77 ± 4.63	51,342.1 ± 2646.2
Sub11	M	21	23.04	132.82 ± 3.84	55,648.8 ± 3005.9
Sub20	F	22	20.00	134.91 ± 3.59	60,578.2 ± 3637.1
Sub8	F	41	18.22	135.40 ± 3.79	48,241.2 ± 2408.2
Sub12	M	45	25.93	138.23 ± 3.22	47,592.3 ± 1995.7
Sub17	F	21	27.55	140.42 ± 3.75	73,547.1 ± 3512.3
Sub1	F	24	19.47	154.66 ± 4.34	64,199.2 ± 3284.9

BMI in kg/m2; ZCM and HPIM: arbitrary units.

Concomitant around-the-clock monitoring of BP, HR and activity lasted for 6 to 7 days. Hemodynamic and activity data were collected around the clock from each of them. Records shorter than 6 days were excluded from analysis (6 participants), as was one case who worked shifts and two cases who were pregnant (total N = 9). The sample represents a fairly homogeneous group of clinically healthy people, despite some differences in terms of age, body mass index (BMI), medication and final medical diagnosis, which have to be considered as possible confounding effects on the findings. For this study, 20 weeklong continuous registrations of ABPM and physical activity were available for analysis.

This is a prospective study. From our experience, a sample size of about 20 individuals in a homogeneous population of clinically healthy subjects is sufficient to detect a difference in acrophase of about 1 h.

Methodology

BP and HR were measured every 30 min (at the h and half-h) by ABPM (TM-2430 from A&D, Tokyo, Japan). Physical activity was sampled every minute and recorded as ZCM (zero-crossing mode) and HPIM (High Proportional Integrative Measures), using wrist actigraphy (MicroMotion Logger, AMI, Ardsley, NY). The ZCM measures the wearer's movement frequency, the HPIM is the measurement of intensity in the activity pattern (Wuerzner et al. 2013). Activity data were averaged over consecutive 30-min intervals and assigned to the interval's midpoint to match the sampling times of BP and HR. An average activity measurement at the h thus includes 1-minute measurements taken in the interval spanning 15 min prior to the h to 14 minutes after the h.

Each participants' data series was analyzed by cosinor to assess the circadian rhythm in BP, HR, and activity. Least squares spectra were computed to determine which harmonic terms contributed statistically significantly to describe the circadian waveform. Results from the least squares spectra served to specify a multiple-component model, which was then fitted to each individual record. Rhythm characteristics include the MESOR (the rhythm-adjusted mean), the amplitude (measuring half of the predictable extent of change within a cycle), and the acrophase (the timing of overall high values recurring in each cycle, in reference to local midnight) for each component included in the model. Each variable was auto-correlated to qualitatively assess the circadian variation. Activity (ZCM and HPIM) was cross-correlated with SBP, DBP and HR to visualize the extent of their joint circadian variation and as a measure of any lag in the timing of their circadian rhythm. Results from the least squares spectra, auto- and cross-correlation functions were averaged across study participants (Cornelissen, 2014; Gierke and Cornelissen 2016). Parameter tests (Bingham et al. 1982) were used to compare the circadian characteristics of BP and activity. The inter-daily stability (IS), the 24-h value from the chi-square periodogram (Van Someren et al. 1996), and the intra-daily variability (IV) (Staessen et al. 1991) were correlated with the MESOR and circadian amplitude of BP and HR. IS was normalized for the number of data (Sokolove and Bushell 1978). This index gives an indication of the strength of coupling between the rest-activity rhythm and environmental synchronizers. The intra-daily variability (IV) gives an

indication of the fragmentation of the rhythm (i.e., the frequency of transitions between rest and activity).

Results

BP, HR, and activity fluctuations differ both among and within individuals, but all variables are characterized by a prominent circadian variation. Their waveform differs from a cosine curve, in part due to the fact that the sleep span lasts much less than 12 h, while the active span lasts much more than 12 h. The autocorrelation function (ACF) of motion activity records shows a clear circadian variation with a period of 24 h, as evidenced by maxima reached at multiples of 24 h. A stronger circadian variation is observed for ZCM than for HPIM, Figure 1A. The least squares spectra of ZCM and SBP (Figure 1B) show large spectral peaks at periods of 24 and 12 h, with a smaller contribution from the 8-h component. The least squares spectra of DBP, HR as well as HPIM also show the same peaks at periods of 24 and 12 h, with a smaller peak at a period of 8 h.

The study participant with the highest ZCM and HPIM MESORs has the highest ACF coefficient at a lag of 24 h for all variables (Figure 2A). The study participant who was least active has a slight circadian disruption: the highest ACF coefficient was reached at a lag of 45.5 h instead of 24 h, the maximum at 24 h being very small, Figure 2B. Differences in motor activity of these two study participants who have the same age (24 years) are apparently due to differences in their lifestyle at the time of monitoring (participant A is a bachelor's student, with a rigid class schedule and additional part-time work at a fixed time, whereas participant B is a doctoral student with a free schedule, working from home). We found a weak positive correlation between the MESOR and the ACF coefficient at a lag of 24 h ($r = 0.445$, $P < 0.05$ in ZCM; $r = 0.691$, $P < 0.001$ in HPIM). The cross-correlation function between physical activity and BP also shows a strong common circadian variation, Figure 2 (right).

Population-mean cosinor analysis confirmed the statistical significance of both the 24-h and the 12-h components. The 24-h and 12-h acrophases of BP coincided with those of physical activity (Table 2). Accordingly, there is a strong association between the circadian acrophases of BP in relation to ZCM and HPIM (r is in range of 0.807 to 0.852, $P < 0.0001$), and also between HR and ZCM ($r = 0.731$, $P < 0.001$) or HPIM ($r = 0.743$, $P < 0.001$).

The circadian waveform of SBP is similar to that of physical activity, as evidenced from the amplitude ratios of the 12-h to 24-h components (Table 3). In ambulatory weeklong records, the 12-h to 24-h amplitude ratio of SBP correlates with that of ZCM (r = 0,.614, $P < 0.005$) and that of HPIM ($r = 0.471$, $P < 0.05$). Comparison of the 12-h to 24-h amplitude ratios did not show significant correlations between any other variable combinations, with the exception of ZCM and HPIM ($r = 0.819$, $P < 0.001$) (Table 3).

The circadian amplitude of DBP is negatively related to the fragmentation index, IV, of motion activity ($r = -0.538$, $P = 0.017$), Figure 3. When excluding study participants older than 40 years, the correlation is slightly stronger ($r = -0.604$, $P = 0.01$). No statistically significant relationships were found between the circadian amplitude of SBP or DBP and the MESOR of activity (ZCM or HPIM). But the average circadian HR amplitude in weeklong records has a weak relationship with the circadian amplitude of HPIM; in the analysis of the12-h amplitude, such a correlation is statistically significant ($r = 0.49$, $P < 0.05$).

Based on the average spectral results, the circadian waveforms of SBP, DBP, and ZCM were reconstructed by modeling, as shown in Figure 4. The great similarity and synchronicity between BP and activity can readily be seen, both in terms of matching times of

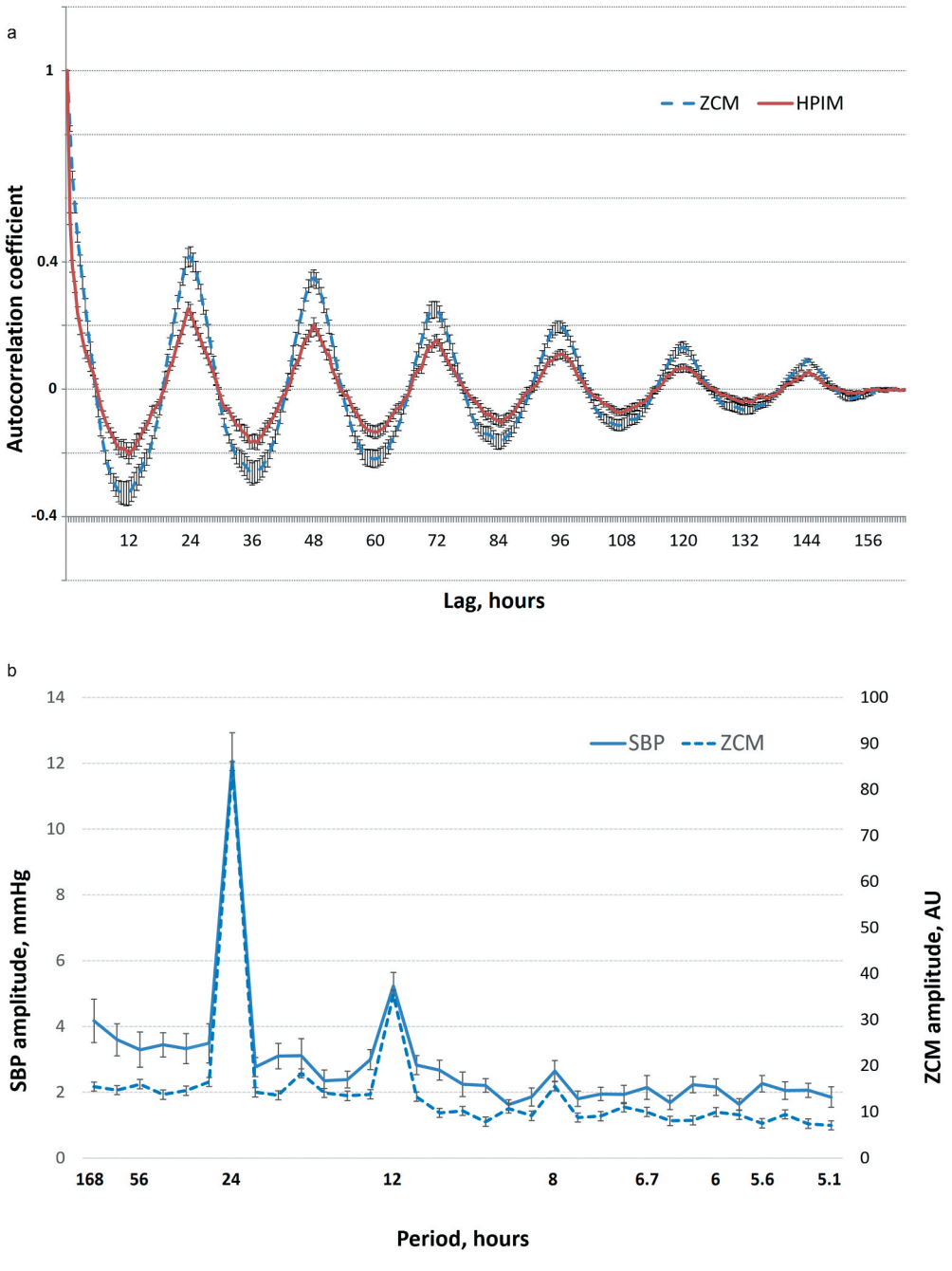

Figure 1. A. Autocorrelation function (ACF) of activity (ZCM and HPIM) – average from 20 study participants (mean ± SE). Peaks at lags of 24, 48, 72, 96, 120 and 144 h indicate the presence of a prominent circadian rhythm in these two variables. B. Least squares spectra of ZCM and HPIM exhibit a large peak at a period of 24 h ($P < 0.001$), confirming the presence of a circadian rhythm. Secondary peaks corresponding to periods of 12 and 8 h contribute to the non-sinusoidal waveform of the circadian variation in these variables.

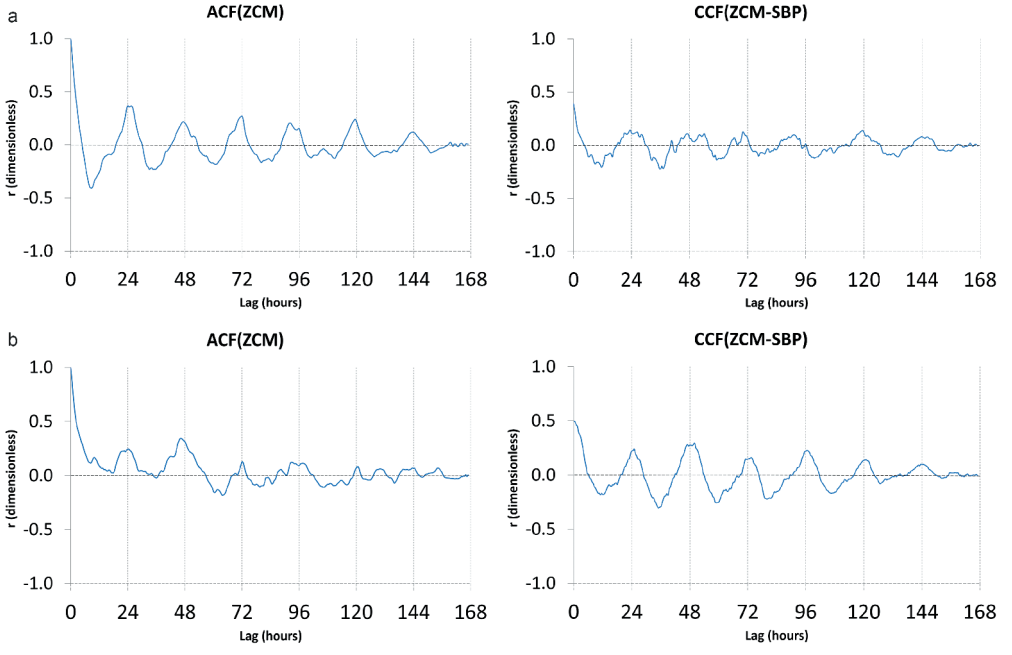

Figure 2. Illustrative examples of the autocorrelation function (ACF) of ZCM (left) and the cross-correlation function (CCF) between ZCM and SBP (right) for two study participants: the most active one (A, top) and the least active one (B, bottom). Whereas the ACF shows a stronger circadian variation in activity in the most active participant, the CCF between ZCM and SBP shows more similar changes between activity and SBP in the least active participant.

Table 2. Statistically significant 24-h and 12-h components in BP (mmHg), HR (beat/min), and activity (AU) found by population-mean cosinor in 20 clinically healthy study participants after weeklong continuous data collection. BP and HR collected at 30-minute intervals, physical activity (ZCM and HPIM) at 1-minute intervals, averaged over consecutive 30-minute intervals.

Variable	Period (h)	MESOR ± SE	Amplitude ±SE	Acrophase ±SE	P-value
ZCM	24	121.17 ± 3.61	85.09 ± 4.34	16 h 42 min ± 16 min	<0.001
HPIM	24	49,463.96 ± 2362.57	39,621.43 ± 2730.13	15 h 27 min ± 17 min	<0.001
SBP	24	117.78 ± 2.55	12.08 ± 0.86	16 h 12 min ± 19 min	<0.001
DBP	24	70.44 ± 1.40	8.92 ± 0.64	16 h 08 min ± 19 min	<0.001
HR	24	73.72 ± 1.71	11.33 ± 0.46	16 h 14 min ± 18 min	<0.001
ZCM	12		35.46 ± 2.19	18 h 39 min ± 1 h 21 min*	<0.001
HPIM	12		14,535 ± 1.39	14 h 59 min ± 1 h 44 min*	<0.005
SBP	12		5.23 ± 0.41	18 h 16 min ± 1 h 24 min*	<0.001
DBP	12		4.04 ± 0.37	18 h 56 min ± 1 h 09 min*	<0.005
HR	12		4.24 ± 0.45	18 h 39 min ± 1 h 20 min*	<0.001

ZCM: Zero-Crossing Mode; HPIM: High Proportional Integrative Measures; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate; MESOR: Midline Estimating Statistic Of Rhythm, a rhythm-adjusted mean; Acrophase referenced to local midnight. * the 12-hour component has two peaks a day; only the time of the first peak is shown, the second peak occurring 12 hours later

minima and maxima and in terms of the small post-prandial dip in early afternoon. Thus, in this group of participants, the circadian rhythms of cardiovascular variables and physical activity are very similar but the rise in BP does not follow an increase in activity,

Table 3. Correlation between 12-h to 24-h amplitude ratios of hemodynamic variables and activity.

r/P	ZCM	HPIM	SBP	DBP	HR
ZCM	1	0.00001	0.00401	0.06395	0.22924
HPIM	0.81871	1	0.03587	0.24684	0.17329
SBP	0.61360	0.47144	1	0.39934	0.30816
DBP	0.42182	0.27153	0.19939	1	0.82354
HR	0.28149	0.31697	0.23997	0.05326	1

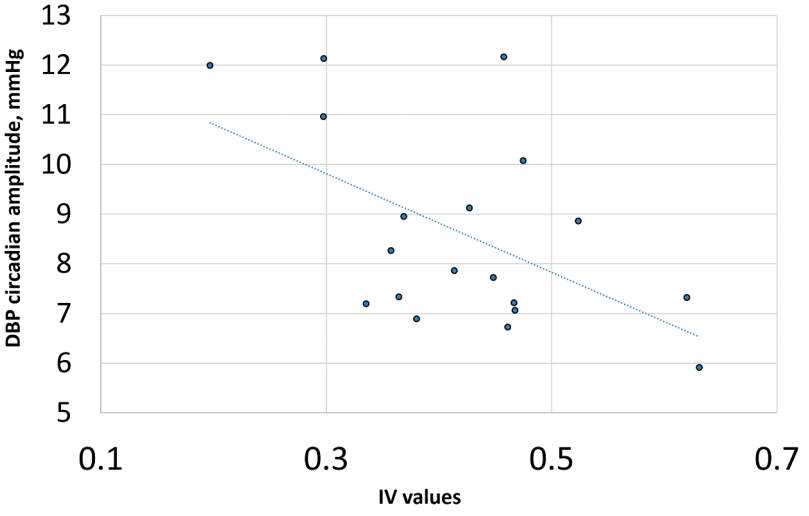

Figure 3. Motion activity's intra-daily variability (IV) is negatively related to the circadian amplitude of DBP ($r = -0.538$, $P = 0.017$).

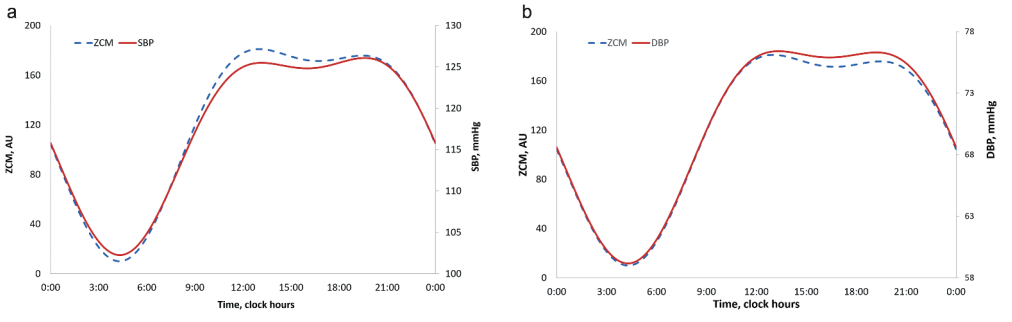

Figure 4. The reconstructed (by modeling) circadian waveforms of SBP (A) and DBP (B) show great similarity with the circadian waveform of ZCM.

supporting the proposition that the circadian rhythm of BP is not a mere response to changes in activity.

At the same time, we found the influence of circadian rhythms of these variables on each other, differing, however, from the usual short-term relationships, where an increase in BP and HR follows an increase in motor activity. Study participants who are more active,

i.e., who have a higher ZCM MESOR (Table 2) have a stronger circadian rhythm of BP, as evidenced by their ACF (Figure 2).

All of the above results were analyzed on weeklong continuous registrations. Since there is large day-to-day variability in circadian characteristics of BP and HR, and physical activity of the participants was not the same each day, the weeklong records were divided into separate days and each day analyzed separately. The difference between the 24-h acrophases of BP and physical activity (ZCM, HPIM) does not correlate with the level of physical activity, evaluated by the MESOR of ZCM or HPIM. In addition, no correlations were found between the MESORs of ZCM and HPIM and the MESORs of BP and HR, or between their amplitudes, estimated on a daily basis. Circadian acrophases of ZCM precede those of BP in half of the cases and follow in the other half of the cases. The circadian acrophases of HPIM precede those of BP in about 63% of the cases and follow in approximately 35% of the cases, occasionally coinciding in 2% of the cases. A weak correlation was found between the daily SBP vs. HPIM circadian acrophase differences and the BP MESOR in women($r = 0.31$, $P = 0.05$) but not in men.

The 24-h SBP mean (± SD) on workdays (Monday–Friday; N = 99) is 117.5 ± 12.5 mmHg, slightly higher than 114.89 ± 12.69 mmHg on weekends (Sunday–Saturday; N = 39). The 24-h DBP mean (± SD) is also slightly higher on workdays than on weekends (70.3 ± 6.9vs. 68.6 ± 7.3 mmHg) as is the 24-h HR mean (± SD) (73.7 ± 8.3vs. 71.9 ± 7.7 beat/min). A similar decrease of 2–2.5%on weekends is observed in actigraphy data, but differences are not statistically significant. Some participants have clearly lower values during the weekend, but others can have higher values instead, as seen for those who enjoy spending free time outdoors.

Discussion

On the average, BP, HR and physical activity were characterized by a prominent circadian variation, with a period close to 24 h.

The least squares spectra of SBP, DBP, HR, ZCM, and HPIM showed in addition to the main 24-h component also a 12-h and a smaller 8-h harmonic. These secondary spectral peaks at harmonics of 24 h indicate that the circadian rhythm in these variables is non-sinusoidal. The fact that these variables assume lower values during sleep than during the active span, sleep representing only about a third of the 24-h day, readily accounts for the non-sinusoidality of their circadian waveform. Whether specific physiological mechanisms also contribute to the statistical significance of the 12-h component would require further experimentation. Physiological mechanisms putatively involved include dopamine as a possible link between ultradian rhythms of rest–activity, foraging, behavior, activity, and the cardiovascular system; dopamine neurons in the midbrain and dopamine-sensitive neurons in the dorsal striatum are considered the ultradian oscillator (Steele and Mistlberger 2015).

Evidence that puberty has marked effects on the prevalence of ultradian rhythmicity of BP and HR (Hadtstein et al. 2004), that ultradian HR rhythmicity is dependent on autonomic tone (Oosting et al. 1997) contribute to the general understanding of the nature of the 8-h and 12-h rhythms of motor activity and the cardiovascular system.

The 24-h acrophases are very similar in all variables (Table 2), clustering around 16:00 (from 15:00 to19:00). Based on the average spectral results, the circadian waveforms of SBP, DBP and ZCM reconstructed by modeling (Figure 4) also demonstrate great similarity and synchronicity.

The similarity of the circadian waveform of cardiovascular variables with activity was also assessed by the ratio of the 12-h to 24-h amplitudes, which showed a positive correlation of SBP with ZCM ($r = 0.614$, $P < 0.005$) and HPIM ($r = 0.471$, $P < 0.05$). Thus, with a relatively calm and sedentary lifestyle, the circadian waveforms of physical activity and SBP are similar.

Correlation analysis of averaged weeklong individual series showed that the BP and HR MESORs do not affect the circadian acrophases of cardiovascular variables or physical activity. In order to take into account individual differences as well as differences in the regimes of different days of the week, data were reanalyzed on a day-to-day basis. Circadian acrophases of BP did not depend on those of physical activity. However, a very weak positive correlation was found between the difference in circadian acrophases of HPIM and SBP and the MESOR of SBP in women ($r = 0.31$, $P = 0.05$), but not in men. In women, the circadian acrophase of SBP followed that of physical activity in those women with a lower SBP MESOR, whereas it preceded it in those women with a higher SBP MESOR. Such gender differences may be influenced by the action of female sex and reproductive hormones on mechanisms of cardiovascular function relevant to the coordination of BP (Barnes and Charkoudian 2021).

The cross-correlation function between ZCM and BP also shows a strong common circadian variation, Figure 2. The 24-h and 12-h acrophases of BP coincided with those of physical activity (Table 2). Circadian rhythms in BP and physical activity thus have a strong relationship and are synchronized to each other. These results suggest that they are separate rhythms orchestrated by different pacemakers and/or oscillators. They show that circadian rhythms characterizing small movements (ZCM) may be not just the cause, but most likely are a response to changes in BP caused by other factors, for example, from the autonomic nervous system (ANS).

The conclusion that circadian rhythms of BP and HR are not derived from the rhythm in physical activity is consistent with data obtained by other researchers. Earlier work documented the persistence of a circadian rhythm in BP under conditions of bedrest (Reinberg et al. 1970; Halberg et al. 1988; Staessen et al. 1991; Celis and Staessen 2007). Shapiro and Goldstein (1998) found little or no relationship between activity and ambulatory BP and HR in 119 older healthy subjects (mean age 67 years, 68% were retired). During sleep, when there is little to no motor activity, BP was also shown to start increasing around mid-sleep, followed by a faster and larger increase upon awakening (Halberg et al. 1981).

The reconstructed circadian waveforms of SBP, DBP and ZCM show great similarity between these variables (Figure 4). The circadian waveforms of DBP and ZCM are completely matched during the night and morning, but during the day, DBP stays about the same irrespective of declining activity. The peak around 20:00 matches the timing of peaks in the circadian variation of endothelial cell products, such as nitric oxide and endothelin-1 concentrations, and endothelium-dependent and independent vasodilation in clinically healthy males (Elherik et al. 2002). Sympathovagal activity rhythm and renal system biorhythms also contribute to DBP circadian variability (Izzedine et al. 2006). According to the modeled circadian waveforms of SBP and ZCM, SBP raises faster relative to ZCM starting at 08:00, and reaches its maximum around 12:00–13:00. It shows additionally the influence of physical activity, which contributes more to SBP around this time, such as plasma norepinephrine and epinephrine and urinary catecholamine

concentrations (Linsell et al. 1985; Lakatua et al. 1986), emotional/mental stress, CNS, ANS and others (Gumarova et al. 2014; Smolensky et al. 2017).

The stronger circadian variation of ZCM versus HPIM, visualized by the ACF may stem from the sedentary lifestyle of the study participants, since ZCM reflects the number of movements, including very small ones that occur during mental work, but not the amplitude of movements, which increases with greater physical activity, as reflected by HPIM. The participant who had the highest MESOR of ZCM and HPIM also had the largest ACF coefficient at a lag of 24 h. The participant who had the lowest MESOR of ZCM and HPIM had a much lower ACF coefficient at a lag of 24 h and the second peak did not occur at 48 h, but at 45.5 h, suggesting some circadian disruption (Figure 2). The very different lifestyles of these two participants likely account for these differences. Free-style living at home may have been accompanied by weakened light-dark cycles and social routine, two important synchronizers of the circadian system. This interpretation is partially confirmed by data on the quality of sleep and cycles of sleep-wakefulness under quarantine conditions due to Covid-19 (Salehinejad et al. 2020).

Other researchers have also written about the effects of physical activity on the circadian system. In an animal model (mammals), a gain in synchronization has been shown by voluntary physical activity or exercise. Physical activity during the usual activity phase of the animal strengthens the function of the SCN (Michel and Meijer 2020).

A larger fragmentation of the activity rhythm (the intra-daily variability IV of ZCM) is associated with a smaller circadian amplitude of DBP (Figure 3). A large scatter in sleep-wake cycles and in the mode of activity during the week led to a decrease in the circadian amplitude of DBP. These results are an indicator of imbalance, reduced orderliness of work in the cardiovascular system and of an increase in stress. In results of the Rotterdam Study (persons aged 45–98 years), a more stable 24-h activity rhythm, evaluated by the stability and fragmentation indices, was associated with a lower mortality risk, and a more fragmented rhythm was associated with a higher mortality risk. Disturbed circadian activity rhythms reflect age-related alterations in the biological clock and could be an indicator of disease (Zuurbier et al. 2015).

Behavioral activity, which is itself under the direct coordination of the SCN, feeds back to the SCN, resulting in a positive feedback loop that potentially enhances the rhythm amplitude of the SCN. Exercise strengthens the circadian system (Hughes and Piggins 2012; Leise et al. 2013). For instance, scheduled exercise can boost the circadian rhythm of vasoactive intestinal peptide-deficient mice (Schroeder et al. 2012). Conversely, disruption of the circadian rhythm, such as the CLOCK mutation even only in the peripheral oscillator in a mouse model, alters physical activity. The overall activity of running on the wheel was significantly lower in cardiac-specific cardiomyocyte-specific CLOCK mutant mice compared to wild-type mice observed for 5 weeks (Ko et al. 2011). Our results, which included mainly young people, show that a fragmentation of motor activity is also associated with a deterioration of the balance of the circadian system of the cardiovascular system. A relatively healthy lifestyle, not only daily regime (fragmentation of motor activity), but also physical activity level (MESOR in ZCM) positively influences the quality of the circadian rhythm of BP (gauged by the autocorrelation coefficient at a lag of 24 h), Figure 2. Detection of an abnormal circadian BP pattern is associated with cardiovascular disease risk, "gauged by the occurrence of a morbid event like a stroke in the next six years" (Halberg et al. 2012). Thus, adherence to exercise regimens can contribute to the

prevention of CVD. Time ordered exercise, physical activity may thus contribute to cardiovascular diseases prevention.

Conclusions

Phase-weighted averages obtained by the population-mean cosinor detected statistically significant 24-h and 12-h components ($P < 0.001$). The cross-correlation function between activity (zero-crossing mode, ZCM) and BP shows a strong common circadian variation. On the average, in this sample of clinically healthy adults, the 24-h acrophases of all cardiovascular and actigraphy variables are similar in their timing, clustered around 16:00. The similarity of the circadian waveform of cardiovascular variables and activity is confirmed by the statistically significant correlation between the ratio of the 12-h and 24-h amplitudes of these variables. The best correspondence between fluctuations in hemodynamics and actigraphy data was shown for SBP and ZCM, a measure of actigraphy that reflects the number of movements, including micromotions. Our results indicate the synchronicity of the circadian rhythms of BP, HR and physical activity, as well as a certain degree of independence of the circadian rhythm in BP relative to activity. At the same time, physical activity has a positive effect on the circadian system of the whole organism, through the central pacemaker, thus indirectly affecting cardiovascular circadian rhythms.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the Ministry of Education and Science of the Republic of Kazakhstan [AP05133311].

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