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The long-term effects of phase advance shifts of photoperiod on cardiovascular parameters as measured by radiotelemetry in rats

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Abstract

Cardiovascular parameters, such as blood pressure and heart rate, exhibit both circadian and ultradian rhythms which are important for the adequate functioning of the system. For a better understanding of possible negative effects of chronodisruption on the cardiovascular system we studied circadian and ultradian rhythms of blood pressure and heart rate in rats exposed to repeated 8 h phase advance shifts of photoperiod. The experiment lasted 12 weeks, with three shifts per week. Spectral power as a function of frequency for both circadian and harmonic ultradian rhythms was expressed as the circadian–ultradian power ratio. The circadian rhythms of blood pressure, heart rate and locomotor activity were recorded during the control light:dark (LD) regimen with higher values during the D in comparison with the L. Phase advance shifts resulted in a diminished circadian–ultradian power ratio for blood pressure, heart rate and locomotor activity indicating suppressed circadian control of these traits greater in heart rate than blood pressure. In conclusion, rats kept under irregular LD conditions have suppressed circadian control of heart rate, blood pressure and locomotor activity and rely more on an acute response to the LD regime. Their ability to anticipate regular loads can be weakened and in this way chronodisruption can contribute to the pathogenesis of cardiovascular diseases.

Keywords: radiotelemetry, circadian rhythm, ultradian rhythm, blood pressure, heart rate

1. Introduction

Biological clocks have developed in organisms exposed to regular changes of environment, mainly a light:dark (LD) cycle. These clocks generate circadian rhythms that are endogenous with a period close to 24 h and help organisms anticipate regular changes of environmental conditions. In contrast to circadian rhythms, ultradian rhythms are biological oscillations with a period shorter than 20 h. Ultradian and circadian rhythms form a temporal organization of organisms and have a generally accepted role in the control of the cardiovascular system (Durgan and Young 2010). As such, the cardiovascular system exhibits distinct circadian and ultradian rhythms in its parameters, amongst which blood pressure (BP) and heart rate (HR) have been most studied (Yates and Benton 1991).

Circadian rhythms are governed by the master clock localized in the suprachiasmatic nuclei of the hypothalamus. Deletion of the suprachiasmatic nuclei results in a loss of the circadian pattern of BP, HR and locomotor activity (Witte *et al* 1998). Further evidence for the link between suprachiasmatic nuclei and BP circadian rhythmicity comes from recent studies with transgenic mice that lack the functional expression of a vasoactive intestinal polypeptide receptor gene (*Vipr*2-/-). These studies show significant residual rhythms of BP in control mice that were not found in a *Vipr*2-/- mutant strain (Sheward *et al* 2010). Moreover, spontaneously hypertensive rats, that are used as a model of essential hypertension, have a shorter endogenous circadian period of wheel running (Peters *et al* 1994) and different responses to phase shifts of the LD cycle in comparison with normotensive rats (Avidor *et al* 1989). Also, the transplantation of the rostral hypothalamus containing the suprachiasmatic nuclei from spontaneously hypertensive rats to normotensive rats resulted in the increase of BP (Eilam *et al* 1991). Finally, in transgenic rats with additional copies of the renin gene, circadian rhythms of BP are out of phase with the physical activity indicating that locomotor activity itself cannot explain the daily variations in BP (Lemmer *et al* 1993). Therefore, when taken as a whole, the current research does indicate a role of the suprachiasmatic nuclei in control of BP rhythm.

BP is controlled via baro-, chemo- and osmo-receptors together with hormones which exhibit ultradian rhythmicity. For example, 8 h oscillations have been recorded for endothelin-1 levels (Herold *et al* 1998) along with 60–150 min oscillations for insulin (Lefcourt *et al* 1999), approximately 60 min pulses of glucocorticoids (Conway-Campbell *et al* 2012) and 50–100 min for epinephrine and 12 h oscillations for norepinephrine (Schoefl *et al* 1997). The direct interactions between circadian and ultradian rhythms in BP control are not well understood. However, some understanding may come from the fact that spontaneously hypertensive rats have been found to have significantly more ultradian than circadian power in comparison with normotensive rats. It is therefore assumed that the circadian rhythm may modulate the power in the ultradian band and this modulation is more pronounced in normotensive rats amongst which ultradian activity is higher during the active phase of the day, than in spontaneously hypertensive rats (Holstein-Rathlou *et al* 1995). The circadian but not ultradian rhythmicity of BP is controlled by vascular autonomic activity (Oosting *et al* 1997) and the increased BP variability in the ultradian frequency range cannot just be a consequence of the increased BP *per se* (Holstein-Rathlou *et al* 1995).

HR is another important cardiovascular trait controlled mainly via the autonomous nervous system that exhibits a strong circadian and ultradian pattern. Experimental studies with suprachiasmatic nucleus lesioned normotensive rats provide clear evidence that the suprachiasmatic nucleus is one of the key intrinsic factors contributing to the control of circadian fluctuations in HR (Warren *et al* 1994). Cardiac function is characterized by irregular time intervals between consecutive heart beats (Acharya *et al* 2006). The sinoatrial node acts

as the primary pulse generator for heart beats. Other sympathetic and parasympathetic neurons and local circuits of the intrinsic cardiac nervous system, as well as the artrioventricular node, temperature changes and endocrine influences are also capable of modulating autonomous heart beat stimulation properties (Hu *et al* 2008). In terms of ultradian rhythms of HR both plasma catecholamines and intrinsic myocardial activity are potential sources of control (Koch *et al* 1999). Furthermore, correlations across a range of time scale invariant periods (from minutes to 24 h) suggest that the mechanisms related to suprachiasmatic nuclei and peripheral cardiac regulations are coupled (Hu *et al* 2008).

Alterations in the cardiac scale invariance are associated with cardiovascular diseases and predict reduced survival rates (Bigger *et al* 1996, Makikallio *et al* 2004). As such, shift work that results in the disruption of circadian organization can be involved in lifestyle disease development or progression (Boggild and Knutsson 1999). However, epidemiological studies have not provided unequivocal results till now mainly due to methodological limitations in many of these studies (Wang *et al* 2011). Therefore, more focused experimental studies are needed to understand the mechanisms that induce chronodisruption and its possible negative effects on the cardiovascular system.

The purpose of our experiment was to investigate changes in cardiovascular parameters after repeated LD shifts under controlled laboratory conditions in rats. We evaluated circadian and ultradian rhythms of BP and HR under synchronized and unsteady LD conditions to reveal if repeated phase advance shifts (PAS) of the LD cycle were able to change absolute levels of BP and HR. Moreover, we aimed to characterize the relationships between ultradian and circadian rhythms under regular and irregular lighting cycles.

2. Materials and methods

2.1. Animals

Normotensive mature male Wistar rats ($n = 8$; 356 ± 8 g) were kept under controlled temperature, 21 ± 1 °C, conditions under a regular 12L:12D cycle, with lights on from 06:00. Light intensity was 150 lux as measured with an automatic datalogger (KIMO KH100, Chevrier Instruments Inc., Canada). The rats were housed singly with food and water *ad libitum*. The experiment was approved by the Ethical Committee for the Care and Use of Laboratory Animals at the Comenius University in Bratislava, Slovak Republic, and the State Veterinary Authority.

2.2. Measurement of cardiovascular parameters and the experimental design

The cardiovascular parameters were measured with a radiotelemetry device (Data Science International, St Paul, Minnesota, USA) that allows continuous measurement of BP, HR and locomotor activity in freely moving animals. The implementation procedure for the device is as previously validated at our department (Molcan *et al* 2009) and is as follows. Before the surgery the rats were anesthetized by a ketamine hydrochloride (75 mg kg^{-1}) and xylazine hydrochloride (10 mg kg^{-1}) mixture. The pressure radiotelemetric transmitter TA11PA-C40 (DSI, USA) was surgically implanted into the abdominal aorta just above its bifurcation (Brockway *et al* 1991). The catheter was then stabilized to the aorta with tissue glue (3M Vetbond; DSI, USA) and a cellulose patch (Cellulose Patch Kit—Small Animals; DSI, USA). The transmitter battery was then secured to the muscular wall.

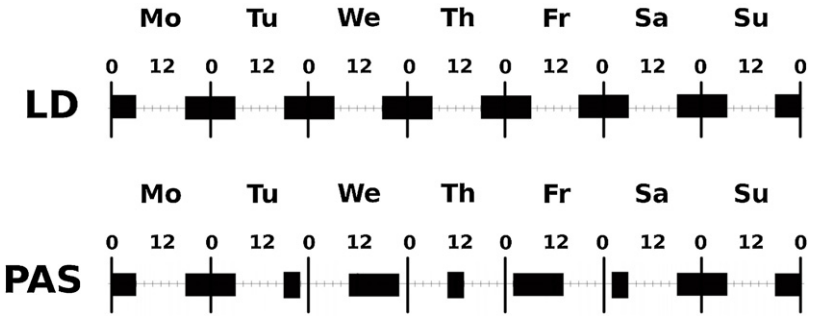

Figure 1. The experimental design consisted of 1 week of 12 h light (L) and 12 h dark (D) and then 12 weeks of PAS. Longer horizontal black bars represent the dark phase (4 or 12 h) of the day.

2.3. Experimental protocol

The animals were included into the experiment 2 weeks after the surgical procedure. Data were acquired by scheduled sampling interval of 10 s with segment duration of 30 s for BP, HR and locomotor activity. At first, the rats were kept for 1 week under control LD conditions. Afterwards, they were exposed for 12 weeks to 8 h PAS three times per week. Radiotelemetric sensors were ON during weeks 1, 5, 10 and 11 of the experiment when the PAS were applied (figure 1).

2.4. Time series analysis and statistical evaluation

We evaluated HR, mean BP (mean arterial pressure (MAP)) and locomotor activity from the acquired data. The paired *t*-test and repeated measures ANOVA with the Fisher LSD *post-hoc* test were used for the evaluation of differences between groups. Values are presented as mean $\pm$ the standard error of the mean (s.e.m.). Circadian and ultradian rhythm analysis of the individual measured data was performed with a Lomb–Scargle periodogram using Chronos-Fit software (Zuther *et al* 2009). The circadian to ultradian power rhythm ratio (CUPR) was calculated from the original filtered data as a ratio of circadian (24 h) and the average of ultradian (12, 8, 6, 4.8 and 4 h) periods. Since the Shapiro–Wilk normality test of power spectra rejected the null hypothesis for a normal data distribution, the non-parametric Friedman test followed by the Wilcoxon test for multiple comparisons was used. Due to catheter closing in two rats during the experiment, six animals were used for evaluation of long-term differences among weeks while the evaluation of LD differences during the control lighting regimen was performed with eight rats.

3. Results

Rats exposed to control LD conditions exhibited distinct circadian rhythms in HR, with higher values during the active (D) in comparison with the passive (L) phase of the day (L: 315 $\pm$ 6 beats min^{-1}; D: 355 $\pm$ 8 beats min^{-1}; $t = 11.658$; $n = 8$; $p < 0.001$). Similarly, both MAP (L: 96 $\pm$ 2 mm Hg; D: 100 $\pm$ 2 mm Hg; $t = 5.852$; $n = 8$; $p < 0.01$) and locomotor activity (L: 0.9 $\pm$ 0.1 counts min^{-1}; D: 3 $\pm$ 0.4 counts min^{-1}; $t = 6.094$; $n = 8$; $p < 0.001$) reached higher levels during the dark phase than during the light phase. Significant dominance of circadian rhythm power over harmonic ultradian rhythm power was calculated for the entrained rhythms

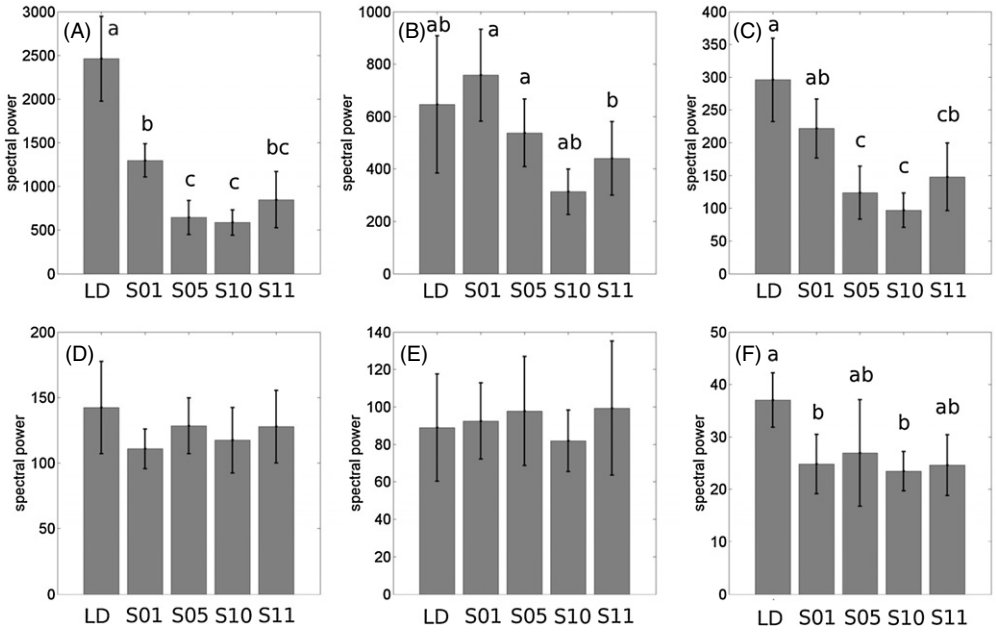

Figure 2. The rats exposed to 12 weeks of PAS revealed a decreasing profile of 24 h (circadian) periods for HR (A), MAP (B) and locomotor activity (C) while average harmonic ultradian (12, 8, 6, 4.8 and 4 h) periods for HR (D), MAP (E) and locomotor activity (F) did not alter. *Y* axis—spectral power calculated by a Lomb–Scargle periodogram. Columns with different superscript letters are statistically different. Error bars indicate s.e.m.

Table 1. Average daily values of HR, MAP and locomotor activity (LA) ± s.e.m. of rats ($n = 6$) exposed at first to control 12 h light and 12 h dark conditions and then 8 h PAS of light (weeks 01, 05, 10 and 11—S01, S05, S10 and S11, respectively). L and D differences are expressed as D–L values. Statistical significance (** $p < 0.01$; *** $p < 0.001$) is expressed in comparison to the LD week.

	HR (beats min^{-1})		MAP (mm Hg)		LA (counts min^{-1})	
	Mean	D − L	Mean	D − L	Mean	D − L
LD	337 ± 8	37 ± 4	99.2 ± 1.1	2.7 ± 1.0	1.8 ± 0.4	1.8 ± 0.4
S01	345 ± 5***	20 ± 2***	100.3 ± 0.9	1.7 ± 0.3	2.0 ± 0.3	1.1 ± 0.3
S05	333 ± 6	21 ± 2***	99.8 ± 0.7	1.9 ± 0.5	1.8 ± 0.2	0.6 ± 0.2**
S10	303 ± 7***	19 ± 2***	96.3 ± 0.7***	1.2 ± 0.5	1.9 ± 0.2	0.4 ± 0.2***
S11	307 ± 8***	23 ± 4**	98.6 ± 0.7	1.8 ± 0.5	1.8 ± 0.2	0.7 ± 0.2**

of HR ($t = 6.704$; $n = 8$; $p < 0.001$), MAP ($t = 3.573$; $n = 7$; $p < 0.05$) and locomotor activity ($t = 5.951$; $n = 8$; $p < 0.001$) under the LD 12:12 regimen (figure 2).

The repeated exposure of rats to PAS decreased mean HR ($F_{(4,40)} = 81.796$; $p < 0.001$) as well as resulted in differences between L and D values (table 1). During the first week of PAS we found negative D − L values after three shift days while on week 10 or 11 a positive D − L ratio was calculated for all measured parameters (figure 3). 11 weeks of PAS exposure failed to affect MAP values as compared to the BP measured in rats kept under control LD conditions (LD: 99.2 ± 1.1 mm Hg versus PAS week 11: 98.6 ± 0.7 mm Hg).

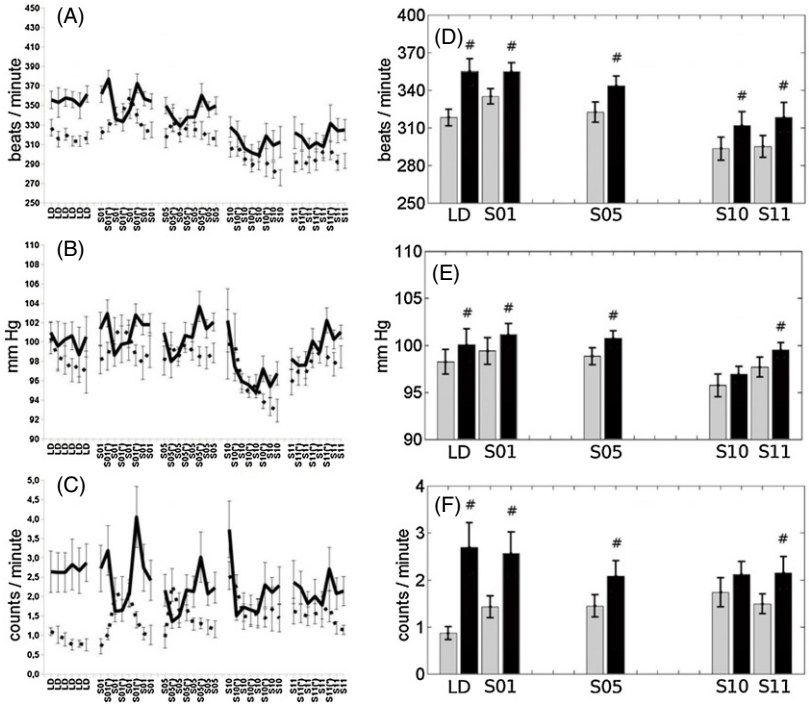

Figure 3. The daily (A), (B), (C) and weekly (D), (E), (F) pattern of HR (A), (D), mean arterial BP (B), (E) and locomotor activity (C), (F) in rats ($n = 6$) exposed for 1 week to control 12L:12D conditions and for 12 weeks (S01, S05, S10, S11) to PAS three times per week. The dark solid lines (A), (B), (C) and dark bars (D), (E), (F) represent the dark phase mean values and the dotted lines (A), (B), (C) and gray bars (D), (E), (F) represent the light phase mean values. Columns with superscripts are statistically different. Error bars indicate s.e.m.

The spectral power of circadian rhythms in HR decreased markedly during the first 5 weeks of PAS exposure (figure 2(A)) in comparison with the initial LD values ($p < 0.05$). The decrease of spectral power of circadian rhythms for locomotor activity ($p < 0.01$; figure 2(C)) paralleled the pattern in HR. The decline in MAP was less pronounced and diminished values ($p < 0.05$) were recorded for week 10 in comparison with the first week (figure 2(B)). The circadian to ultradian spectral power ratio for HR decreased to a half after the first week and to a quarter of initial power values during week 11 of PAS exposure (figure 4). This decline of CUPR reflects diminished circadian variability in spectral power while ultradian spectral power was not changed (figures 2(D), (E), (F)). CUPR for MAP ($p = 0.11$) and locomotor activity ($p < 0.05$) exhibited a similar declining pattern as for HR ($p < 0.01$) after PAS exposure but the decrease was less pronounced. The Wilcoxon multiple comparison test of CUPR for MAP revealed a significant ($p < 0.05$) decrease in comparison to LD values only in week 5 of PAS exposure. Finally, CUPR for locomotor activity decreased significantly ($p < 0.05$) for weeks 5 and 10 in comparison with the first PAS week values (figure 4).

4. Discussion

Rats exposed to regular 12L:12D conditions exhibited the expected differences in HR, MAP and locomotor activity between the active (D) and passive (L) phases of the daily cycle, with higher values occurring during the D in comparison to the L phase. This finding is in accordance

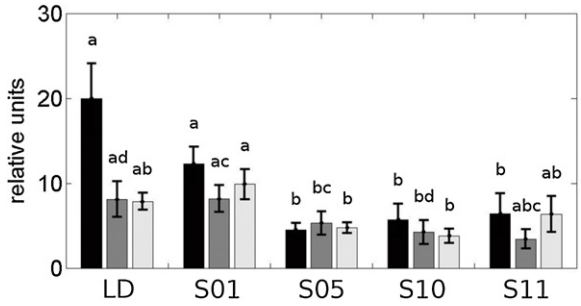

Figure 4. The circadian to ultradian power ratio changed with time for HR (black), less for mean arterial BP (gray) and locomotor activity (white). The data are expressed as mean ± s.e.m.; LD—control LD week; S01, S05, S10 and S11—weeks 1, 5, 10 and 11 of PAS, respectively; *Y* axis—ratio of circadian (24 h) to ultradian harmonic (12, 8, 6, 4.8 and 4 h) period power. Columns with different superscript letters are statistically different. Error bars indicate s.e.m.

with previously published data (Witte *et al* 1998). The experimental design involving repeated 8 h PAS three times per week, which lasted for 12 weeks, resulted in a decrease of HR but no significant changes of MAP and locomotor activity values. Similar decreases in HR have also been previously observed in rats exposed to photoperiod manipulation by advancing the dark phase by 4 h or by advancing and delaying the dark phase by 2 h (Zhang *et al* 2000). The decrease of HR may result either from increased parasympathetic tone activity or decreased sympathetic tone activity induced by the photoperiod changes. Different patterns of HR and locomotor activity over the 12 week period clearly show that the locomotor activity profile cannot explain the observed alterations in hemodynamic variables.

The expected circadian rhythms of measured variables were observed in rats exposed to control lighting cycles. Specifically, the highest circadian power was shown for HR, which was more than 20 times higher in comparison with the power of harmonic ultradian rhythms. Approximately eight times higher power of circadian over ultradian period has been shown for MAP and locomotor activity. These results are in line with data obtained in rats exposed to a normal LD cycle (Witte and Lemmer 1995).

The circadian power of HR, MAP and locomotor activity was diminished after PAS exposure. The circadian pattern was well detectable for HR, MAP and locomotor activity during the first week of PAS. During the next weeks of PAS exposure (weeks 5, 10 and 11), CUPR decreased. Daily changes of MAP represent an output of several control centres and, at least in humans, ultradian rhythms oscillate independently from 24 h rhythm parameters (Kawamura *et al* 2003, Hadtstein *et al* 2004). Therefore, the generation and regulation of ultradian rhythms must be able to be influenced independently of the circadian rhythm control centre (Perez-Lloret *et al* 2004). For example, suprachiasmatic nucleus lesions of rats kept under 12L:12D resulted in only an incomplete abolishing of day–night variations (Witte *et al* 1998) and rats after ablation of suprachiasmatic nuclei were still able to discriminate between a morning and an afternoon feeding session (Mistlberger *et al* 1996).

A complex interaction model (neuronal, endocrine, excretion) is involved in the control of circadian and ultradian rhythms in BP. However, the ultradian changes in the functions of the autonomic nervous system have been assumed to be responsible for the ultradian oscillations of BP (Benton and Yates 1989). Since higher BP or non-dipping status leads to target-organ damage (Syrseloudis *et al* 2011), good control of BP is important in order to keep BP in a distinct range over a day. Therefore, stable and multilevel regulations are necessary for BP control while a rapid and relatively simple control system is needed for HR control.

HR is controlled mainly via sinoatrial node pacemaker cells and autonomous nervous system branches (Mighiu and Heximer 2012) which are modulated directly by the suprachiasmatic nuclei (Buijs *et al* 2003, Scheer *et al* 2003). The circadian pattern of HR has been shown to be completely abolished in rats with suprachiasmatic nuclei ablation (Warren *et al* 1994, Sheward *et al* 2010). Moreover, the suprachiasmatic nucleus itself contains interacting nodes that together with the intrinsic cardiac nodes are responsible for scale invariance of HR fluctuations (Hu *et al* 2008).

In our experiment, rats entrained to LD exhibited a pronounced 24 h pattern, more so for HR than for MAP. Since the number of factors and the resulting interactions involved in the generation of circadian and ultradian rhythms of BP are higher than those for HR, (1) exposure to LD conditions resulted in smaller CUPR for MAP than for HR and (2) long-term PAS exposure induced a smaller decrease in CUPR for MAP as compared with CUPR for HR. However, our experimental design did not allow us to differentiate whether the rhythmicity in cardiovascular parameters was due to periodic masking effects or truly reflected the activity of the endogenous pacemaker.

We assume that the irregular LD conditions disturbed circadian outputs from the suprachiasmatic nuclei which influenced the circadian rhythmicity of HR, MAP and locomotor activity. Our results demonstrate that circadian rhythms in HR are more sensitive to disturbances caused by PAS than BP. Since both ultradian and circadian rhythms can help the cardiovascular system to adapt to changing environmental conditions, disturbed daily variability of cardiovascular parameters could be involved in an inadequate response to stress conditions. Under unpredictable conditions the abilities of organisms to predict environmental changes can decrease and the loss of predictability may result in higher stress responses to unexpected negative aspects of the environment. This has implications for those individuals who are exposed to shift work, especially in unpredictable high stress environments such as hospitals or industrial settings.

5. Conclusions

In conclusion, in mature male Wistar rats exposed to the long-term PAS, BP did not change and HR values decreased over a 12 week experimental period. In addition, a prominent circadian variability of HR, MAP and locomotor activity was shown under LD cycles. Furthermore, long-time exposure to PAS resulted in a decrease of circadian rhythm dominance more for HR than BP and no alterations of ultradian rhythms. As such, disrupted circadian control of the cardiovascular system may disturb the anticipation of regular loads and contribute to the pathogenesis of cardiovascular diseases.

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