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Light and diurnal cycle affect autonomic cardiac balance in human; possible role for the biological clock

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Abstract

The morning shift in cardiac sympatho-vagal balance seems involved in the increased risk of cardiovascular incidents at that time. To investigate the contribution of the biological clock in autonomic cardiac control, we investigated the presence of a diurnal rhythm independent of external factors, and of a circadian phase-dependent effect of moderate light in healthy volunteers. Recordings of heart rate (HR) and vagal and sympathetic cardiac tone were performed at different times over the day–night cycle during supine, awake, resting conditions, during exposure to different light intensities. The similarity between the diurnal rhythm in resting HR and that during previous constant routine conditions, demonstrated that our setup allowed accurate estimation of the endogenous circadian rhythm in HR. The present study suggests that, while a circadian rhythm in vagal cardiac tone is the main cause for the circadian rhythm in resting heart rate, the increase in sympathetic cardiac tone participates in the HR increase caused by early morning light.

Keywords: Autonomic; Circadian rhythm; Heart; Illumination; Light; De-masking; Suprachiasmatic nucleus

The risk of myocardial infarction, stroke, and sudden death shows a peak in the early morning, which seems partially of endogenous origin (Marler et al., 1989; Muller et al., 1989; Kranz et al., 1996). The morning shift in cardiac sympatho-vagal balance may be involved in this increased risk of cardiovascular incidents at that time (Furlan et al., 1990; Esler, 2000). Since the biological clock, located in the suprachiasmatic nucleus (SCN), generates the circadian rhythms in physiology and behaviour (Stephan and Zucker, 1972; Buijs and Kalsbeek, 2001), and shows a circadian phase-dependent response to light (Meijer et al., 1996), we investigated both the circadian rhythm and the circadian phase-dependent light-response of the cardiac sympatho-vagal balance.

In rodents, it has been demonstrated that the SCN sends multisynaptic projections to the heart via the autonomic nervous system and that the SCN is required for the circadian rhythm in resting heart rate (HR) and for the immediate effect of light on HR (Scheer et al., 2001). Also in humans, there is an endogenous circadian rhythm in resting HR (Kräuchi and Wirz-Justice, 1994; Kerkhof et al., 1998) and a time-of-day-dependent stimulation of resting HR by moderate light intensities (Scheer et al., 1999). This suggests that, also in humans, the heart is under control of the SCN. Heart rate is mainly determined by the autonomic nervous system (Bannister and Mathias, 1992). However, the relative importance of the sympathetic and parasympathetic nervous system, via which the biological clock brings about the endogenous circadian rhythm in resting HR, has received sparse attention, while their role in the phase-dependent HR response to light in humans is completely unknown. Therefore, we recorded in the present study, HR, vagal and sympathetic cardiac tone during strict resting conditions and in response to light exposure over 24 h. The HR data has been published before (Scheer et al., 1999).

For details on the experimental procedures, please see the work of Scheer et al. (1999). In short, all subjects were normotensive volunteers between 20 and 40 years of age

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with regular working weeks and without medication except for oral contraceptives. In *Experiment 1*, 11 males and 6 females participated, and in *Experiment 2*, 10 males participated. Each experimental day started after at least three regular working days, and each measurement session was performed after at least 2 h no food or caffeine, and 1 h minimized physical exercise. For at least 2 h before each measuring session in Experiment 1 and 24 h in Experiment 2, no alcohol was consumed. Before each measuring session, subjects walked calmly for 2 min, after which they assumed a supine position while at rest but awake throughout all recordings. During the first 20 min, subjects remained in complete darkness (sleeping mask covering their closed eyes; 0 lx), followed by 10-min light periods. Together, these procedures allow the recording of baseline cardiovascular state at least 10 min after lying down (Eriksen et al., 1990; Hofer and Battig, 1994; Piepoli et al., 1994; Toska and Walloe, 2002).

In Experiment 1, seven measurements were performed at 4-h intervals (Fig. 1). At ZT0, ZT4, ZT8, ZT12 and ZT24 (ZT stands for "Zeitgeber" Time, i.e. the regular time of awakening), the 20-min 0-lx periods were followed by exposure to indoor light (daylight supplemented with artificial light; illumination not determined) for 10 min (indoor-light period). ZT24 is the same circadian time as ZT0, only 24 h later.

The major difference between Experiments 1 and 2 was that in Experiment 2, the light intensities were controlled and equal for all five measurements. Experiment 2 consisted of five 40-min measuring periods over the day–night cycle (ZT0, ZT8, ZT15, ZT20 and ZT24. The 20-min 0-lx period was followed by 10 min of exposure to 100 lx (100-lx period), and then by 10 min to 800 lx (800-lx period). Light intensities were obtained by means of a portable light source, the Light visor (Medilx BV, Helvoirt, The Netherlands), in combination with a white diffuse-filter (800 lx), an

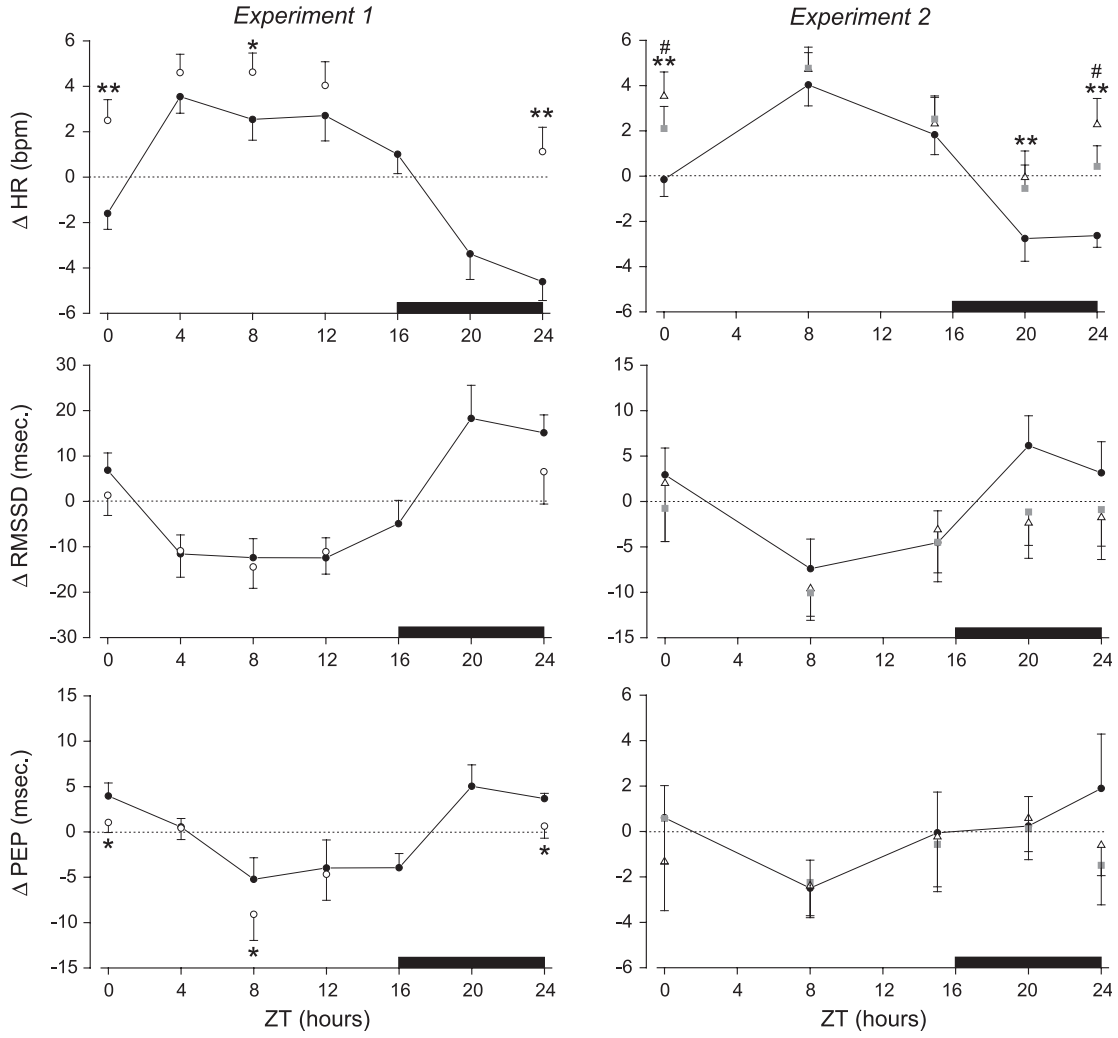

Fig. 1. Changes in resting HR ($n=17$ and $n=10$ for Experiment 1 and 2), RMSSD ($n=17$ and $n=10$) and PEP ($n=15$ and $n=8$) due to diurnal cycle and light. Symbols are the mean differences (Δ) relative to the daily mean as measured during 0 lx ± standard error. Solid circles, 0 lx; open circles, indoor-light; grey squares, 100 lx; open triangles, 800 lx; horizontal black bar, night period; significant difference compared to 0 lx: $^{*}P=<0.05$; $^{**}P<0.01$; significant difference compared to 100 lx: $^{\#}P<0.05$.

additional grey filter (100 lx), and a sleeping mask covering their closed eyes (0 lx).

HR, vagal tone and sympathetic tone were recorded by the VU-AMS (Free University, Amsterdam, The Netherlands) (Geus and Doornen, 1996; Willemsen et al., 1996), an ambulatory monitoring device that combines electrocardiography and thoracic impedance cardiography. Vagal tone was assessed by the root mean square of the successive differences of the inter-beat interval (RMSSD), which has previously been proven to be a valid index of vagal tone (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Sympathetic tone was assessed by the pre-ejection period (PEP), a reliable indicator of sympathetic tone (Cacioppo et al., 1994; Willemsen et al., 1996). HR, RMSSD and PEP were averaged over 30 s every 60 s for Experiment 1 and over 15 s every 30 s for Experiment 2. Because of high electrode resistance for two subjects in both experiments, PEP was determined for 15 of the 17 and 8 of the 10 subjects in Experiment 1 and 2, respectively. PEP values were determined with VU-AMS-software (AMSIMP). HR, RMSSD and PEP were determined over the last 10 min of the 0-lx periods and over the 10-min light periods. Periods from 1 min before to 1 min after each disturbance (sounds and movements as time-marked by the subject), or when increased HR coincided with increased motility (as measured by an accelerometer in the VU-AMS), were excluded from analysis. An increase in sympathetic cardiac outflow is indicated by a decrease of PEP, while an increase in parasympathetic activity is indicated by an increase of RMSSD.

The presence of a diurnal rhythm, i.e. the change in value over the day measured during the 0-lx periods, was evaluated with a one-way analysis of variance (ANOVA) for repeated measures (7 or 5; for Experiment 1 and 2, respectively). The light effect, i.e. the differences between the values in the light periods and those in the dark periods for each ZT, was analysed by using a two-way ANOVA, for both ZT-time (5) and illumination condition (2 or 3) as repeated measures. If significance was reached for the ANOVAs, Duncan's Post Hoc Test was used. To investigate the contribution of the sympathetic and parasympathetic cardiac tone in the daily rhythm in HR during the dark, the linear correlation between HR and RMSSD and between HR and PEP for all 0-lx periods was determined for all subjects together and for each subject individually. To eliminate absolute inter-individual differences, difference-scores (Δ) with the mean of all 0-lx periods defined as zero for each subject were used for these linear correlations.

In Experiment 1, the maximum–minimum difference in HR, between HR at midday (at ZT4, ZT8, and ZT12; average of 58.3 bpm) and that in the middle of the night (at ZT20) at 0 lx was 6.3 beats per min (bpm) (Fig. 1, Experiment 1). As published before, there were no significant differences between the HR at 0 lx in the early mornings 24 h apart, i.e. between ZT0 and ZT24. There was a highly significant diurnal rhythm in RMSSD during complete darkness ($F(6,96)=5.92$; $P=0.0002$; one-way ANOVA), while the rhythm in PEP was less strong but also significant ($F(6,78)=3.50$; $P=0.024$; one-way ANOVA). For the group average data in the dark, there was a significant linear correlation between ΔRMSSD and ΔHR, with changes in ΔRMSSD explaining 95% of the variation in HR over the day–night cycle ($R^2=0.95$; $\Delta HR=0.00-0.24*\Delta RMSSD$; $P<0.0005$; $n=7$). For the group average data in the dark, there was a significant linear correlation between ΔPEP and ΔHR, however, with ΔPEP explaining 62% of the variation in HR over the day–night cycle ($R^2=0.62$; $\Delta HR=0.04-0.59*\Delta PEP$; $P<0.05$; $n=7$). Although only seven measurements were performed for each individual, testing for a linear correlation of the 0-lx measurements for each individual revealed a significant correlation between HR and RMSSD for 11 of the 17 subjects, and between HR and PEP for only 3 of the 15 subjects. For RMSSD, there was no effect for light or interaction between diurnal time and light (two-way ANOVA) (Fig. 1, Experiment 1). For PEP, there was an effect of light ($F(1,13)=11.65$; $P<0.05$), but no interaction (Fig. 1, Experiment 1). The effect of light on PEP was significant for ZT0, ZT8 and ZT24 ($P<0.05$).

In Experiment 2, the difference between HR at the middle of the day (at ZT8; average of 58.4 bpm) and in the middle of the night (at ZT20) during 0 lx was 6.5 bpm (Fig. 1, Experiment 2). No significant differences in HR at 0 lx in the early mornings 24 h apart, i.e. between ZT0 and ZT24, were present. RMSSD showed a diurnal rhythm in the dark ($F(4,36)=2.58$; $P=0.05$; one-way ANOVA), but no effect of light (two-way ANOVA) (Fig. 1, Experiment 2). For the group average data in the dark, there was a significant linear correlation between ΔRMSSD and ΔHR, with changes in ΔRMSSD explaining 91% of the variation in HR over the day–night cycle ($R^2=0.91$; $\Delta HR=0.09-0.49*\Delta RMSSD$; $P<0.05$; $n=5$). There was no significant linear correlation between ΔPEP and ΔHR for the group average data in the dark. With only five measurements, testing for a linear correlation of the 0-lx measurement for each individual revealed a significant correlation between HR and RMSSD for only 2 of 10 subjects, and between HR and PEP for only 1 of 8 subjects. There were no significant effects of light or interaction between circadian time and light for RMSSD or PEP (Fig. 1, Experiment 2).

The results of the present study suggest that a daily rhythm in vagal cardiac tone is the main cause of the daily rhythm in resting HR, and a change in sympathetic cardiac tone participates in the increase in resting HR by early morning light exposure.

The present study provides several indications that the daily rhythm in basal HR is mainly due to the rhythm in vagal output to the heart, although we cannot rule out the involvement also of a diurnal variation in sympathetic output to the heart. In Experiment 1, there was a highly significant daily rhythm for RMSSD and a less strong

rhythm for PEP. In Experiment 2, RMSSD showed a daily rhythm, while there was no significant rhythm for PEP. Furthermore, the daily variations in RMSSD and HR were highly correlated for both experiments, while the daily variation in PEP showed a weaker correlation (Experiment 1), or no correlation (Experiment 2) with that in HR. With the present setup, we were able to exactly replicate, in the two separate experiments, the day–night difference in resting HR as demonstrated under three independent experiments conducted under constant routine conditions (Kräuchi and Wirz-Justice, 1994; Burgess et al., 1997; Kerkhof et al., 1998), the golden-standard for the measurement of the endogenous circadian rhythmicity. This demonstrates that the careful exclusion of masking factors, as applied in the present study, allows reliable estimation of the endogenous circadian rhythm in HR, even during every-day-life conditions. Therefore, the present results suggest that the actual endogenous circadian rhythm in HR, that prepares us for the activity of the day, is mainly caused by the circadian rhythm in parasympathetic cardiac outflow. Hereby, the present results confirm the results from the only previous constant routine experiment that investigated the endogenous circadian rhythm in parasympathetic and sympathetic cardiac activity (Burgess et al., 1997). In this study, Burgess et al. demonstrate an endogenous circadian rhythm in respiratory sinus arrhythmia, as index for parasympathetic cardiac outflow, without a rhythm in PEP. The importance of the parasympathetic versus the sympathetic nervous system in the circadian rhythm in HR is further illustrated by the maintenance of the circadian rhythm in HR in quadriplegic patients who have no sympathetic outflow to the heart (Krum et al., 1991) and in chronically chaired monkeys during blockade of the sympathetic nervous system (Talan and Engel, 1989).

Secondly, the present results suggest that the increase in HR due to light exposure in the early morning is, at least partially, caused by an increase in sympathetic cardiac activity. In Experiment 1, light repeatedly caused a significant increase in resting HR in the early morning (ZT0 and ZT24), together with a significant reduction in PEP, indicative of an increase in cardiac sympathetic outflow. The absence of an effect of light on PEP in Experiment 2 is probably due to the smaller group size in that experiment. There have been conflicting reports as to whether or not light increases sympathetic tone (Saito et al., 1996; Burgess et al., 2001). Saito et al. demonstrated an increase in muscle sympathetic nerve activity by light exposure in the morning, while Burgess et al. found no effect of evening light on autonomic cardiac regulation. The present study provides an explanation for these seemingly conflicting results by showing the phase-dependency of light to affect the sympathetic tone, with an effect of morning, but not evening light, in agreement with the phase-dependent effect of light on HR itself (Scheer et al., 1999). Future research in a larger population should characterize further the relative importance of sympathetic and parasympathetic cardiac outflow in the phase-dependent stimulation of HR by light. That the moderate light intensity used in the present study can influence the SCN and SCN-output is demonstrated by the immediate melatonin suppression in humans by nighttime light exposure of only 100 lx (Zeitzer et al., 2000). In experimental animals, the SCN has been demonstrated to be required for the phase-dependent effect of light on HR and to project to the heart via the autonomic nervous system (Scheer et al., 2001). We hypothesize that also in humans, light via SCN not only affects the pineal gland in the regulation of melatonin secretion, but also the heart, via the autonomic nervous system.

The present results indicate that, while the parasympathetic nervous system is more important for the endogenous circadian rhythm in HR, the sympathetic nervous system is more important for the increase in HR caused by light in the early morning. These results suggest that the SCN uses both the sympathetic and parasympathetic nervous system in cardiac regulation.

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