



## Original Article

## Dawn simulation light: a potential cardiac events protector

Antoine U. Viola <sup>a,1,\*</sup>, Virginie Gabel <sup>a,1</sup>, Sarah L. Chellappa <sup>b,1</sup>, Christina Schmidt <sup>a</sup>,  
Vanja Hommes <sup>c</sup>, Eleonora Tobaldini <sup>d</sup>, Nicola Montano <sup>d</sup>, Christian Cajochen <sup>a</sup>



<sup>a</sup> Centre for Chronobiology, Psychiatric Hospital of the University of Basel, Basel, Switzerland

<sup>b</sup> Cyclotron Research Centre, University of Liège, Liège, Belgium

<sup>c</sup> IT VitalLight I&D PC Drachten, Philips Consumer Lifestyle, Drachten, The Netherlands

<sup>d</sup> Department of Biomedical and Clinical Sciences, Division of Medicine and Pathophysiology, L. Sacco Hospital, University of Milan, Milan, Italy

## ARTICLE INFO

## Article history:

Received 28 October 2014

Received in revised form 27 November 2014

Accepted 5 December 2014

Available online 26 February 2015

## Keywords:

Light

Heart rate

Heart rate variability

Cardiac control

Circadian functions

## ABSTRACT

**Objective/Background:** Major cardiovascular events frequently increase in the morning due to abrupt changes in the sympatho-vagal cardiac control during the transition from sleep to wakefulness. These neural changes are translated into stepwise increases in cardiac functions, resulting in a potential cardiovascular stress. Here, we explored whether light can “optimize” heart rate and its neural control, by actively promoting a less steep transition from sleep to wakefulness, thus minimizing morning cardiovascular vulnerability. **Methods:** Seventeen healthy young men were awakened 2-hours before their habitual wake-time. In a counterbalanced within-subject design, we applied a control condition (darkness during sleep and dim light during wakefulness) or dawn-simulation-light (DSL) starting 30-minutes before and ending 30-minutes after scheduled wake-up time.

**Results:** Our data reveal a significantly gradient reduction in heart rate during the transition from sleep to wakefulness, when applying DSL as compared to a control condition. Likewise, cardiac sympatho-vagal control smoothly increased throughout the 30-min sleep episode preceding scheduled wake-up under DSL and remained stable for the first 30-min of wakefulness. Interestingly, these effects were mostly driven by changes in the parasympathetic cardiac control.

**Conclusions:** Our data demonstrate for the first time that a non-invasive strategy, as light exposure surrounding the wake-up process, can significantly reduce the deleterious sleep-to-wake evoked cardiac modulation in healthy young men awakened under conditions of increased sleep pressure. A translational approach of this light exposure, which closely resembles natural lighting conditions in the morning, may therefore act as a potential protector for cardiac vulnerability in the critical morning hours.

© 2014 Elsevier B.V. All rights reserved.

## 1. Introduction

Key cardiovascular events are increasingly more intense in the morning hours between 06:00 and 12:00 h [1–3], although they may also occur in the evening (between 18:01 h and midnight) [4], and are associated to higher blood pressure, heart rate (HR), platelet aggregation, vascular resistance and so forth [5]. In particular, sleep-wake transitions in the morning elicit high shifts toward sympathetic activation, in comparison to the remainder of the day, suggesting a key role in increasing cardiac vulnerability after awakening [6,7]. This “morning bias” in major cardiovascular regulatory mechanisms is a salient feature of ischemic diseases, such as brain vascular disease,

cerebral infarction, angina and myocardial infarction [5]. Physiological underpinnings for possible adverse cardiovascular events encompass abrupt changes in the autonomic nervous control of the cardiovascular system “around the clock” [8]. The circadian clock impacts on both endothelial and muscle cells [9], as indexed by the 24-h daily fluctuation in nearly 300 genes in the aorta *alone*, most of which directly involved in vascular function [10]. In mouse models deficient for specific “clock genes,” blood pressure and heart rate show abnormal timing and amplitude [11]. Conversely, clinical findings also suggest a small 1.28-fold greater incidence of acute MI in a wide window (6 am to noon) compared to other times of day [2], bimodal peaks in morning and evening hours [4], and stress-related contributors to adverse cardiovascular events [3]. Thus, it still remains a matter of debate whether circadian factors play a key role on the onset of long-term cardiovascular events. Nevertheless, a dysfunction of the circadian clock may be one possible risk factor for potential cardiovascular diseases, contributing to some extent to the morning increased rates of HR and heart rate variability (HRV). In this context, strategies allowing for the “optimization” of internal biological

\* Corresponding author. Centre for Chronobiology, Psychiatric Hospital of the University of Basel, Wilhelm Kleinstrasse 27, CH-4012 Basel, Switzerland. Tel.: +41613255318; fax: +41613255556.

E-mail address: [antoine.viola@upkbs.ch](mailto:antoine.viola@upkbs.ch) (A.U. Viola).

<sup>1</sup> Authors equally contributed for this work.

rhythms regulating cardiovascular events may provide a means to counteract possible adverse events. Quite surprisingly, no non-invasive strategies are known to date.

The present study investigated whether light can “optimize” heart rate and its neural control, by actively promoting a less steep transition from sleep to wakefulness, thus minimizing morning cardiovascular vulnerability. We hypothesized that a “naturalistic” dawn simulation light (DSL) surrounding the wake-up time would result in a smoother increase heart rate and heart rate variability during the transition from sleep to wakefulness, as compared to a control condition. Likewise, we hypothesized that cardiac sympatho-vagal control would smoothly increase during the transition from sleep to wakefulness, as light may minimize the deleterious sleep-to-wake evoked increases in cardiac modulation in the early hours of the morning.

## 2. Materials and methods

### 2.1. Participants

Eighteen healthy young men (age range, 20–33 years; mean,  $23.1 \pm 0.8$  years [SD]) participated in a laboratory study on impact of polychromatic light on cognitive performance and sleep–wake regulation [12]. All participants were nonsmokers, drugs and medication free (drug screening prior to the study onset), and devoid of medical, psychiatric, and sleep disorders. Clinical status of all participants was assessed by questionnaires, physical examination, and a polysomnographically recorded adaptation night. This night served as screening night for potential periodic limb movements and sleep apnea, as well as for optimal sleep quality (sleep efficiency >85%). During the baseline week preceding the study, participants were instructed to keep their individual bed- and wake-time within a self-selected range of  $\pm 30$  min and to sleep for 8 h, as assessed by a wrist activity monitor (Cambridge Neurotechnologies) and sleep logs. Adherence to this individually timed sleep–wake schedule was checked prior to the beginning of the study. Participants were requested to abstain from excessive caffeine and alcohol consumption. The study protocol, the screening questionnaires, and consent form were approved by the Ethical Committee of Basel, Switzerland and were in agreement of the Declaration of Helsinki. All study participants gave their written informed consent.

### 2.2. Protocol

The study was carried out during the winter season (January to March) in Basel, Switzerland, and comprised two segments in a balanced cross-over design, separated by at least 1-week intervening period. No order effects were observed due to this cross-over design. Participants remained in individual bedrooms with no information about time of day. All rooms were completely dark, without windows. The experiment lasted 48 h, including 2 days and two sleep restriction nights (6 h) following the habitual subject sleep time. The rationale for including a study protocol with two sleep restriction nights was due to two major reasons: (1) chronic sleep restriction (CSR) is increasingly usual in contemporary society, negatively impacting on numerous aspects of human physiology [13]. However, CSR impact on cardiac physiology is virtually unknown; (2) light dynamically promotes increased alertness and cognitive performance, and has been shown to ameliorate the deleterious effects of CSR on subjective alertness and performance [12]. However, it remains completely unknown if light can act as an adjuvant on minimizing potentially deleterious cardiovascular events, under increased sleep pressure. During the day, participants were exposed to dim light (<8 lux) during 2 h after wake-up and to 40 lux until they went to bed. Blood pressure measurements were performed after wake-up times on both days

of the study protocol, and no significant differences were observed between DSL and control conditions. The light treatment was administered after the sleep restriction night either with no additional light for the control condition or with a DSL. Polychromatic DSL light gradually increasing from 0 to 250 lux during 30 minutes before wake-up time; the light remained around 250 lux for 20 minutes after wake-up time, placed near the bed at eye level. DSL illuminance, photon density, and correlated color temperature, at 45 cm from the device, were: (1) 5 min after light onset: 1.2 lux,  $1.9E \pm 16/m^2$  s, 1090 K; (2) 15 min after light onset: 13 lux,  $1.4E \pm 17/m^2$  s, 1500 K; (3) 30 min after light onset: 250 lux,  $2.4E \pm 18/m^2$  s, 2750 K. The control “wake-up technique” (non-DSL condition) was with a technician’s voice.

### 2.3. Salivary cortisol

Saliva cortisol samples were scheduled during wakefulness every 30 min during the first 4 h after wake-up time and followed by hourly intervals thereof. Samples were frozen and kept at  $-20^\circ\text{C}$  until the cortisol assays were conducted. Cortisol was measured by ALPCO (ALPCO Diagnostics, Salem, NH, USA), using a direct salivary enzyme-linked immunosorbent assay (ELISA) for quantitative determination of cortisol. The sensitivity was 1.0 ng/mL and intra-assay coefficient of variances amounts to 10.3% for baseline values 6.6 ng/mL.

### 2.4. Electrocardiographic (ECG) recordings and analysis

A two-derivation ECG system was recorded throughout the laboratory study. R–R intervals, ie, time length between the R peaks of consecutive QRS complexes, were calculated, and all traces were visually checked for artifacts by an investigator. The R wave peak detection and R–R signal were analyzed by HeartScope software (AMPS, Inc, NY, USA). Occasional ectopic beats were identified and replaced with interpolated R–R interval data. All data acquisition and post-acquisition analyses were carried out in accordance with established standards, including those put forth by the Task Force on HRV Interpretation [14]. To avoid excluding large sections of the recording contaminated by movement artifacts during wakefulness, we used a sampling period of 2.5 min for HRV estimation [15], in accordance with the recommendations of the Task Force on HRV Interpretation [14]. Power densities in the low-frequency (LF) band (0.04–0.15 Hz) and in the high-frequency (HF) band (0.15–0.50 Hz) were calculated for each 2.5-min segment using autoregressive algorithms. Moreover, the LF-to-(LF + HF) ratio [LF/(LF + HF) ratio] was used as an index of sympatho-vagal balance. The indexes selected are those most commonly used in the analysis of HRV [16,17]. Furthermore, we also performed symbolic analyses to quantify different aspects of cardiac control related to the organization of different autonomic subsystems. Symbolic analysis is a non-linear method based on the conversion of the series into a sequence of symbols [17–19]. The full dynamic of the series (the min–max range) is spread over six bins, each of which is identified by a number (symbol) from 0 to 5. Original values inside each bin are substituted by the symbol defining the specific bin, thus obtaining a symbolic series. The symbolic series is converted into a series of patterns of three symbols. Four different families of patterns can be identified [17–19]: 0V (patterns with no variation, all symbols are equal), 1V (patterns with one variation, two consecutive symbols are equal and the remaining one is different), 2LV (patterns with two like variations, the second and the third symbol change with respect to the previous one and the changes have the same sign), and 2UV (patterns with two unlike variations, the second and the third symbol change with respect to the previous one and the changes have opposite sign) [19]. This method has been applied to evaluate cardiac autonomic control from HRV [18]. It has been demonstrated that 0V% is a marker of

sympathetic modulation of HR, while 2UV% is a marker of vagal modulation [17].

### 2.5. Statistical analysis

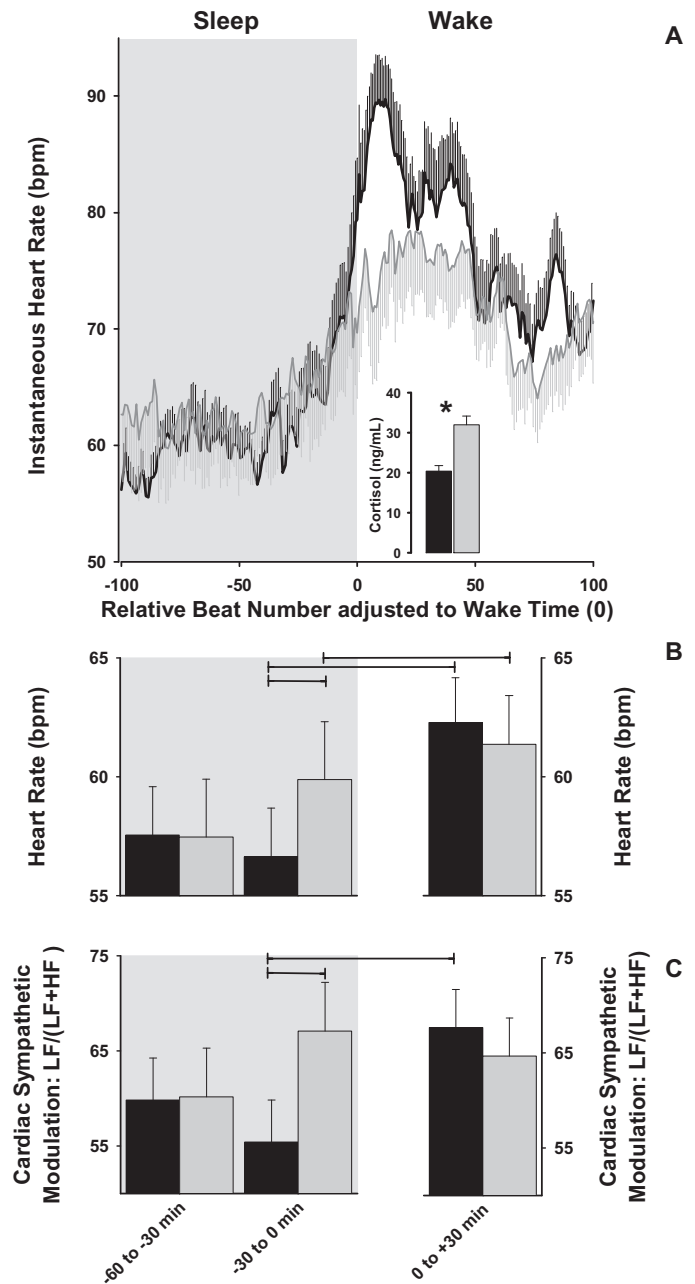
All statistical analyses were performed with SAS version 9.1. Mixed-model ANOVA for repeated measures (PROC MIXED) was used for the repeated measures analyses of within-factors 'light settings' (DSL and dim light) and 'time'. Contrasts were assessed with the LSMEANS statement. All *P* values were based on Kenward–Roger's corrected degrees of freedom (29).

## 3. Results and discussion

During the transition from sleep to wakefulness, salivary cortisol levels were significantly higher after 30 min of wakefulness under the "naturalistic" DSL source relative to the control condition (Fig. 1A). However, no significant time effects were observed between the two conditions thereof.

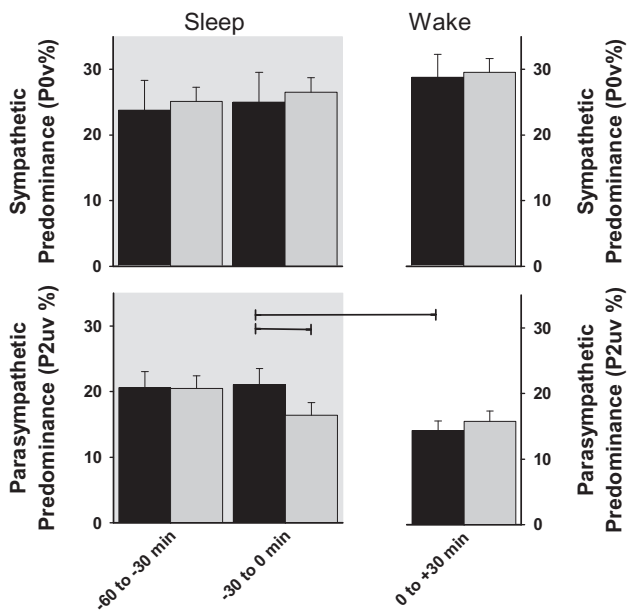
The time series of consecutive R–R intervals (heart rate; beats per minute) from sleep-to-wake transition, as indexed from continuous ECG recordings, exhibited with the control condition evoked a HR increases from  $63.6 \pm 2.5$  to  $89.7 \pm 3.7$  bpm. Conversely, the DSL condition resulted in HR increases from  $65.5 \pm 4.8$  to  $78.4 \pm 5.0$ , thus indicating a significant gradient reduction ( $p < 0.05$ ) (Fig. 1B). To better illustrate the dynamics of this less steep light effect on heart rate, data were collapsed in two time bins, ranging from "baseline period" (–60 to –30 min before wake-up time), centered on wake-up time (–30 to 0 min) and immediately after wake-up time (0–30 min after) (Fig. 1C). No differences were observed during the baseline period between light conditions (DSL and control condition: darkness). Thus, all participants were under a similar cardiac state prior to the experimental light setting. During the period centered on wake-up time, heart rate significantly increased when individuals were exposed to the DSL source, while it remained constant for the control condition (darkness) ( $p < 0.05$ ). Interestingly, in the period immediately after wake-up time, the increase in heart rate was significantly lower under DSL as compared to the control condition (Dim light <8 lux) ( $p < 0.05$ ). These less steep light changes in the dynamics of heart rate were mirrored by specific variations in cardiac sympatho-vagal modulation, as indexed by classical measures of heart rate variability, such as the ratio between power density of low-frequency (0.04–0.15 Hz) and high-frequency bands (0.15–0.50 Hz) (LF/(LF + HF)). Similar to instantaneous heart rate, cardiac sympatho-vagal modulation smoothly increased in the 30-min sleep episode preceding wake-up *only* when individuals were exposed to a "naturalistic" dawn simulation light, which remained stable during the subsequent 30 minutes of wakefulness after scheduled wake-time ( $p < 0.05$ ).

Heart rate variability comprises a powerful tool largely used in physiological and pathological conditions, as a window over cardiovascular control mechanisms [20,21]. To access different aspects of cardiac control related to the organization of different autonomic subsystems, we used a novel symbolic analysis method [17,22]. By means of this non-linear method, we indirectly measured the impact of light onto specific autonomic subsystems, as sympathetic and parasympathetic cardiac control. These are modulatory reacting systems that control heart rate with different latent periods and time courses, such that sympathetic effects on heart rate are much slower than parasympathetic effects [18]. We observe that DSL significantly impacts mostly on the parasympathetic cardiac activity (Fig. 2A and B). During the transition from sleep to wakefulness, sympathetic cardiac predominance is kept relatively stable between both experimental light settings (Fig. 2A). Conversely, parasympathetic cardiac activity is maintained



**Fig. 1.** Cardiac modulation surrounding the sleep–wake transition: Increase in instantaneous heart rate (A), heart rate (B) and cardiac sympathetic [LF/(LF + HF)] (C) variation during the transition from sleep to wakefulness under dim light (black) and dawn simulation light (gray). Data in Band C were averaged for 30 min bin, separately during sleep without light, gradual light increase and after wake time (0). Error bars represent SEs. Horizontal bar characterize the significant difference between conditions ( $p < 0.05$ ).

stable *only* when participants are exposed to DSL, while a drastic decrease is observed under dim light ( $p < 0.05$ ) (Fig. 2B). Therefore, dawn light exposure may minimize the sharp decrease in parasympathetic cardiac control, allowing for heart rate "stability", during the critical transition of sleep to wakefulness. Collectively, the data show that "naturalistic" light exposure centered during wake-up time potentially minimizes abrupt cardiovascular events, as indexed by less steep transitions in instantaneous heart rate, sympatho-vagal balance and in specific cardiac autonomic systems.



**Fig. 2.** Symbolic dynamics of HRV. Sympatho-vagal modulation during the transition from sleep to wakefulness under dim light (black) and dawn simulation light (gray). Data were averaged for 30 min bin, separately during sleep without light, gradual light increase and after wake time (0). Error bars represent SEs. Horizontal bar characterizes the significant difference between conditions ( $p < 0.05$ ).

Our data are the first demonstration that light exposure surrounding the wake-up process reduces rapid wake-to-sleep evoked increases in heart rate, as well as cardiac sympatho-vagal modulation. This less steep transition enveloping the wake-up process may play a protective role for cardiac events, which usually reach a peak in the early morning hours [1]. Indeed, our data show that dawn simulation light might protect the heart by an evolving preparation of cardiac physiology for the wake-up process, which is achieved by a subtle pre-stimulation of cardiac activity during sleep prior awakening. Importantly, these light-induced effects onto cardiac control did not depend on changes in the sleep-wake structure surrounding the wake-up time (see Supplementary Table S1). Thus, the naturalistic light condition reduces the temporal abruptness of key cardiac events, which are one of the major reasons for increased cardiac vulnerability in the morning [2].

Salivary cortisol levels were relatively higher following wake-up time, under DSL than the control condition, while no differences were observed in the time-courses after that. One likely explanation is that exposure to DSL condition, which gradually increases from 0 to 250 lux during 30 minutes before wake-up time, may have elicited a phase-advance in the circadian modulation of cortisol levels. Light exposure resets the phase of the internal biological clock, thus impacting on human physiology and behavior [23]. However, acute light effects on cortisol strongly depend on the intensity, duration, and circadian phase of light exposure [24]. As exposure to DSL was in the early hours of the morning that corresponds to the time-window for phase-advancing light effects, it may have phase-advanced the time-course of salivary cortisol. Physiologically, one may translate these results as an earlier “preparation” for wake-up time, which would go in line with our HR and HRV data. However, caution should be made as we did not collect cortisol samples prior to the participant’s wake-up time. While our study provides evidence for a significant impact of light as a tool to gradually prepare cardiac physiology during the sleep-to-wake time, limitations should be drawn. Our study was designed to probe how light impacts on HR and HRV under normal physiological conditions, as this is a topic that is still fairly unknown.

## A 4. Conclusions

Our current findings provide a proof-of-principle that light may act as an adjuvant in healthy young individuals. Future studies including normal and pathological aging, with the inclusion of biochemical analyses (ie, catecholamine release), may provide a more conclusive framework for the applicability of light as a countermeasure for acute cardiovascular events. Strategies that may counteract these potentially deleterious cardiovascular events are in dire need. In view of our results, light may provide a potentially non-invasive tool to minimize cardiovascular stressful events during the critical morning hours.

## B Conflict of interest

The authors declare no competing financial interests.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <http://dx.doi.org/10.1016/j.sleep.2014.12.018>.

## Acknowledgements

We thank Dr. Götz for medical screenings; Claudia Renz, Marie-France Dattler, and Giovanni Balestrieri for their help in data acquisition, Micheline Maire, Carolin Reichert and Amandine Valomon for her help in recruiting volunteers, and the volunteers for participating.

## Appendix: Supplementary material

Supplementary data to this article can be found online at <doi:10.1016/j.sleep.2014.12.016>.

## References

- [1] Paschos GK, FitzGerald GA. Circadian clocks and vascular function. *Circ Res* 2010;106:833–41.
- [2] Muller JE, Stone PH, Turi ZG, et al. Circadian variation in the frequency of onset of acute myocardial infarction. *N Engl J Med* 1985;313:1315–22.
- [3] Willich SN, Lowel H, Lewis M, et al. Association of wake time and the onset of myocardial infarction. Triggers and mechanisms of myocardial infarction (TRIMM) pilot study. TRIMM Study Group. *Circulation* 1991;84:VI62–7.
- [4] Hansen O, Johansson BW, Gullberg B. Circadian distribution of onset of acute myocardial infarction in subgroups from analysis of 10,791 patients treated in a single center. *Am J Cardiol* 1992;69:1003–8.
- [5] Sato M, Matsuo T, Atmore H, et al. Possible contribution of chronobiology to cardiovascular health. *Front Physiol* 2014;4:409. eCollection 2013.
- [6] Boudreau P, Yeh WH, Dumont GA, et al. A circadian rhythm in heart rate variability contributes to the increased cardiac sympathovagal response to awakening in the morning. *Chronobiol Int* 2012;29:757–68.
- [7] Furlan R, Guzzetti S, Crivellaro W, et al. Continuous 24-hour assessment of the neural regulation of systemic arterial pressure and RR variabilities in ambulant subjects. *Circulation* 1990;81:537–47.
- [8] Virag JA, Lust RM. Circadian influences on myocardial infarction. *Front Physiol* 2014;5.
- [9] Reilly DF, Westgate EJ, FitzGerald GA. Peripheral circadian clocks in the vasculature. *Arterioscler Thromb Vasc Biol* 2007;27:1694–705.
- [10] Rudic RD, McNamara P, Reilly D, et al. Bioinformatic analysis of circadian gene oscillation in mouse aorta. *Circulation* 2005;112:2716–24.
- [11] Richards J, Gumz ML. Mechanism of the circadian clock in physiology. *Am J Physiol Regul Integr Comp Physiol* 2013;304:10.
- [12] Gabel V, Maire M, Reichert CF, et al. Effects of artificial dawn and morning blue light on daytime cognitive performance, well-being, cortisol and melatonin levels. *Chronobiol Int* 2013;30:988–97.
- [13] Van Dongen HP, Maislin G, Mullington JM, et al. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* 2003;26:117–26.
- [14] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* 1996;93:1043–65.
- [15] Dumont M, Jurysta F, Lanquart JP, et al. Scale-free dynamics of the synchronization between sleep EEG power bands and the high frequency

- component of heart rate variability in normal men and patients with sleep apnea-hypopnea syndrome. *Clin Neurophysiol* 2007;118:2752–64.
- [16] Viola AU, James LM, Archer SN, et al. PER3 polymorphism and cardiac autonomic control: effects of sleep debt and circadian phase. *Am J Physiol Heart Circ Physiol* 2008;295:3.
- [17] Porta A, Tobaldini E, Guzzetti S, et al. Assessment of cardiac autonomic modulation during graded head-up tilt by symbolic analysis of heart rate variability. *Am J Physiol Heart Circ Physiol* 2007;293:16.
- [18] Guzzetti S, Borroni E, Garbelli PE, et al. Symbolic dynamics of heart rate variability: a probe to investigate cardiac autonomic modulation. *Circulation* 2005;112:465–70.
- [19] Porta A, Guzzetti S, Montano N, et al. Entropy, entropy rate, and pattern classification as tools to typify complexity in short heart period variability series. *IEEE Trans Biomed Eng* 2001;48:1282–91.
- [20] Montano N, Porta A, Cogliati C, et al. Heart rate variability explored in the frequency domain: a tool to investigate the link between heart and behavior. *Neurosci Biobehav Rev* 2009;33:71–80.
- [21] Porta A, Faes L, Mase M, et al. An integrated approach based on uniform quantization for the evaluation of complexity of short-term heart period variability: application to 24 h Holter recordings in healthy and heart failure humans. *Chaos* 2007;17:015117.
- [22] Tobaldini E, Porta A, Wei SG, et al. Symbolic analysis detects alterations of cardiac autonomic modulation in congestive heart failure rats. *Auton Neurosci* 2009;150:21–6.
- [23] Duffy JF, Wright KP Jr. Entrainment of the human circadian system by light. *J Biol Rhythms* 2005;20:326–38.
- [24] Jung CM, Khalsa SB, Scheer FA, et al. Acute effects of bright light exposure on cortisol levels. *J Biol Rhythms* 2010;25:208–16.