Chapter

Circadian Rhythms of the Autonomic Nervous System: Scientific Implication and Practical Implementation

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Abstract

Circadian rhythms are omnipresent in almost any biosignal. In this chapter, we join them with the need for practical tools for screening in preventive settings and point out heart rate variability (HRV), a measure of autonomic nervous system activity, as a chronobiologic, unspecific index of mental and physical health. We discuss methods to calculate the circadian variation of HRV measures, particularly the cosinor procedure. We present reference values for circadian variation parameters of HRV and data concerning reproducibility. Furthermore, we show data giving first evidence of HRV as a comprehensive health index by showing altered circadian variation patterns of HRV depending on mental (trait dysthymia) as well as physical (inflammatory markers) health. Finally, we present examples of disturbed chronobiology of HRV in clinical and preventive settings and its practical application in medical consultation.

Keywords: circadian variation, heart rate variability, prevention, health index, vagal activity, occupational medicine, autonomic nervous system

1. Introduction

1.1 The need for practical tools for screening in preventive settings

Circadian rhythms are omnipresent in nearly all biosignals particularly including heart rate (HR) and blood pressure [1]. Technological advances in wearables and ambulatory monitoring have made the continuous recording of real-time data highly accessible for health researchers and clinicians. Consider, 24–48 h recordings of blood pressure are frequently used in the clinical context to determine what grade of hypertension a patient has to ensure better options for treatment [2, 3]. In other areas, systematic and statistical analysis of circadian rhythms may offer adjuvant avenues such as in occupational medicine. Nonetheless, traditional approaches in this field included foremost prevention of injuries, e.g., from chemical or other environmental hazards. In the past years, the catalog of potential hazards was extended to mental health-related problems like stress and communicative problems. Moreover, the tasks in occupational medicine include now an active (occupational) health management

rather than just hazard avoidance. This is mirrored by federal demands. For example, the German Federal Institute for Occupational Safety and Health (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, BAuA) just recently extended the instrument for risk assessment at the workplace ("Gefährdungsbeurteilung") [4] now covering also psychological hazards such as work stress and thus moved the field further toward the area of occupational health management. Unfortunately, these risk assessments are often based on individuals' self-report only. This is not at least due to the fact that most objective biological methods are expensive, invasive, and/or complicated. For example, assessing a full cortisol profile (a prominent stress hormone) comprising eight saliva samples during the day is accompanied by low compliance because participants perceive the strict protocol (exact timings, no food, no coffee, no cigarettes in the first hour post-awakening) as impracticable and the reliability is being blunted by violating the measurement protocol [5]. In addition, most available biomarkers have a high disease specificity, since they originated from clinically focused applications. While in the clinical context a high disease specificity of a biomarker is a major diagnostic requirement, it precludes a broad application, for example, in the occupational prevention contexts (i.e., company-wide health screenings or health checks). For example, assessing a comprehensible health check with blood count, physical tests, and ophthalmologic and audiometric examination easily adds up to several hundred euros per examination, but the resources available for health screenings are limited. One solution is the enrollment of comprehensive health check to a limited group of persons—usually higher managers. Therefore, in the given scenario of limited resources, it appears desirable to identify biomarkers which are less disease-specific but more widely and reliably able to indicate that *something* is wrong even on a preclinical stage (high sensitivity) and, in this case, direct the individual to further examinations, e.g., at the company physician. In addition, in the context of prevention, this biomarker should be easy to measure at low costs and be practicable to assess in the routine of occupational health physicians [6–8].

1.2 Heart rate variability as a measure of autonomic nervous activity: a chronobiologic, unspecific index of mental and physical health

Several attempts to find a more general health index have been previously made. For example, the Allostatic Load Index (ALI) aims to measure the bodily "wear and tear" and to identify individuals before chronic health disturbances emerge [9–11]. It represents an assessment of the cumulative burden of psychosocial factors on health by exploring alterations in different biological systems but has some limitations [6–8, 11] including (A) invasive procedures, (B) cost-intensive examination, and (C) results which are relative to the investigated population and therefore not promptly available but only after the vast majority of the population has been investigated. Other screening tools encompass risk prediction of the development of (fatal) heart diseases (events) such as Framingham, PROCAM, SCORE-CVD, or SCORE-CHD risk scores but suffer from similar issues as the ALI score since they are based on a comparable set of biomarkers. One common aim of these screening tools is the detection of dysregulation, i.e., abnormal high or low values compared to a given clinical (usually age-adjusted) reference or population distribution (percentile). The vast majority of these biomarkers can be seen as an outcome of an underlying dysregulation—at least in part. The autonomic nervous system (ANS) plays a pivotal role in adaption and homeostasis, particularly the vagus nerve. This nerve is a primary, fast, and bidirectional route conveying physiological states to the brain (sensory fibers), as well as shaping and coordinating somatic responses to adapt to environmental challenges (motor fibers) [12–15]. The central-peripheral brain-heart integration can be indexed noninvasively and inexpensively by cardiac

autonomic activity using HR recordings, e.g., from chest belt HR monitors. From these HR recordings, beat-to-beat variability can be calculated (i.e., heart rate variability [HRV]), representing a valid and reliable measure of autonomic function [12, 15]. Thus, variability measures provide a window to the central autonomic nervous system (CAN). The working level of the CAN reflects the capacity of the body to adapt to environmental challenges [16] such as a problematic supervisor. It also corresponds to emotion regulation capacity [13]. Furthermore, decreased values of HRV predict premature mortality [17] and morbidity [12] such as higher inflammatory state [18–20], increased cardiovascular disease risk [21], and myocardial infarction risk [22] and have been implicated in fatigue [23], work stress [24], and pain regulation [25–28]. Latest research demonstrates associations with common mental disorders like depression [29]. Apart from diagnosed diseases, HRV shows associations with subjective measures like self-rated health [30]. Like many other biomarkers, ANS measures express a circadian variation pattern [31].

Taken together, measures of HRV seem to represent an integrative marker for mental and somatic health. Thus, these measures characterize an ideal psychosomatic marker. Promising first studies reveal short-term measures of HRV as an index of change pre- to post-therapeutic interventions [32]. However, while short-term measures (i.e., 5-minute resting baselines) are subject to situation-specific variations, long-term measures may overcome this disadvantage and additionally provide salient information from the recorded time series inherent in a 24 h signal (i.e., diurnal variation). Furthermore, the situation-related adaptability of an individual can be visualized by long-term measurements of HRV. The latter can easily be analyzed with spectral methods, shown as a comprehensive graph, and can easily be combined with diary information from a patient, making the impact of a particular situation obvious. For example, a difficult talk with a co-worker reduces the power spectrum and can be explained to the patient. Yet, the utility of long-term measures capturing the circadian variation of HRV has not been evaluated for this purpose. Still, to be further explored, circadian variation patterns of cardiac autonomic activity may present a promising candidate as an unspecific index of both overall physical and mental health.

In the following section (Section 2), we will outline how to calculate measures of circadian variation by two different methods. In Sections 3 and 4, we will present first evidence and examples of HRV as a comprehensive health index. Particularly Section 3 describes epidemiological and other research results of circadian variation patterns of cardiac autonomic activity (normal age decrements, implications in somatic and mental health disorders). In the final section (Section 4), we will present examples of disturbed chronobiology of HRV and its application in a clinical and an occupational setting as an index for health.

2. Measuring circadian variation of the ANS

While specific measures exist that represent an index of cardiac vagal activity (such as root mean square of successive differences [RMSSD], respiratory sinus arrhythmia [RSA], percentage of the NN intervals >50 ms [PNN50]), others measure index more general cardiac autonomic activity (i.e., mixed sympathetic and parasympathetic) such as the standard deviation of normal interbeat intervals (SDNN) or total power (TP). For an excellent and detailed overview of metric and norms, see, for example, [15].

Cardiac autonomic activity exhibits a pattern of diurnal variation. The circadian timing system regulates daily modulation of synchronized physiological activity in order to conserve energy expenditure and the use of internal resources, thereby

optimizing functioning at the ideal time of day (i.e., coordinate physiological functions and behavior) [1, 33]. The circadian timing system is organized hierarchically by the central pacemaker within the suprachiasmatic nucleus (SCN) [1, 2]. This master pacemaker orchestrates the rhythmicity of endogenous, or self-sustained, clocks within different central and peripheral tissues, which autoregulate through transcriptional and translational feedback loops. Genetic variations in circadian locomotor output cycles kaput (CLOCK) genes are implicated in unique phenotypes, including timing of sleep preference (evening type), metabolism, and mood regulation. More generally, endogenous molecular clocks enable organisms to anticipate environmental challenges. These endogenous pacemakers are also entrained by environmental context, including cyclical changes in season, tides, and daylight cues, which act as "zeitgebers" that anchor the internal clock [1, 34].

2.1 Analytical methods

Analytical methods for identifying and quantifying circadian rhythmicity among a time series of data (e.g., 24 h HR recording) include *spectral analysis* or *least squares procedures* [34, 35]. While the *spectral analysis*, in particular, allows an easy access through visual inspection of an individual 24 h ECG recording (see also Section 4), the *least squares procedure* allows for group aggregation and statistical comparisons/analysis due to mathematical quantification of rhythmicity, as demonstrated in Section 3. Therefore, in an individual consultation setting, a summarizing graph is of particular value, while the latter allows for scientific comparisons to detect alterations in circadian parameters, e.g., in persons reporting a high vs. low number of depressive symptoms (see Section 3).

2.1.1 Spectral analysis

Using available commercial software, the 24 h measurement is first subdivided into separate intervals (5 minutes have become standard), and within these intervals, the frequency spectrum and the height of the amplitude (= energy density) are color-coded (see left panel of **Figure 1**; the spectral graphs were calculated using the commercial software Cardiscope™ ANALYTICS Professional Edition Version 1.2.156, HASIBA Medical GmbH, Austria). The array of each spectrum results in a colored two-dimensional image of the color-coded energy density. These images

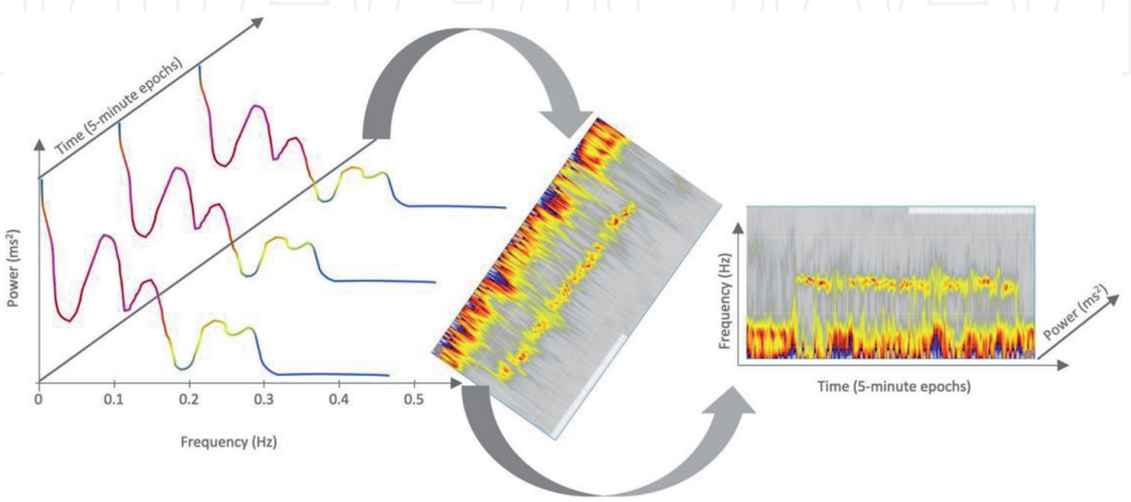

Figure 1.
Example of a color-coded power spectral segment (left panel) and its stacked representation of the 24 h time series (z-axis; right panel).

are stacked, introducing time as a third dimension, and of across frequency when viewed from a bird's eye perspective (see also **Figure 6**).

This individual graph, enhanced with diary information, can serve as a powerful tool in consultation (see Section 4).

2.1.2 Cosinor procedure

The cosinor procedure is suggested as the appropriate tool to detect circadian rhythmicity in cross-sectional studies with a single measurement [35]. In a first step, the 24 h recording is segmented into intervals, e.g., 5-minute intervals. In a 24 h recording, a total of 288 5-minute intervals are calculated. For each 5-minute interval, the HRV parameters need to be calculated.

Three individual-level cosine function parameters are estimated for each individual 24 h time series (now consisting of the 288 5-minute intervals) to quantify the circadian variation parameters of the selected HRV variables using the method of ordinary least squares regression (see Eq. (1)) [34]. Here, M is the midline-estimating statistic of rhythm (MESOR), a rhythm-adjusted mean, A is the amplitude (being the maximal distance between the oscillating signal and the MESOR), ϕ is the acrophase (defined as the clock time when A is reached), θ_i is the trigonometric angle, t_i is the sampling rate, P is the period (duration of one cycle, in this case, supposed to be 24 h), and e_i is the error term (**Figure 2**).

With the period P known, standard regression equations can be derived (see Eq. (2)) and analyzed using an ordinary least squares approach to minimize the residual sum of squared differences between observations and model estimation (see Eq. (3) and [34, 36, 37] for a comprehensive description).

$$Y_i = M + A\cos(\theta_i + \phi) + e_i \quad \text{where} \quad \theta_i = \left(\frac{2\pi t_i}{P}\right) \tag{1}$$

$$\begin{aligned} Y_i &= M + \beta x + \gamma z + e_i \\ with: \beta &= A\cos\phi;\ \gamma = -A\sin\phi\ ; \\ x &= \cos\left(\frac{2\pi t_i}{P}\right);\ z = \sin\left(\frac{2\pi t_i}{P}\right) \end{aligned} \tag{2}$$

$$RSS \sum_i \left[Y_i - \left(\hat{M} + \hat{\beta} x_i + \hat{\gamma} z_i\right)\right]^2 \tag{3}$$

Solving these equations provides the researcher with the three described variables per recording. In a second step, these can be easily used in further statistical analysis, as exemplified in the next section. Moreover, graphical between-group comparison including confidence intervals is possible (see examples in Section 3).

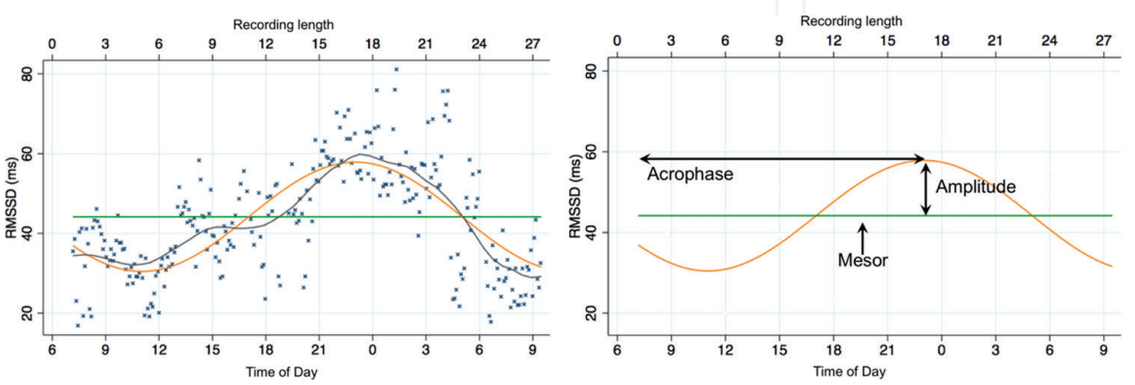

Figure 2.
Individual recording of 5-minute intervals of RMSSD (blue x on the left-hand panel) and the corresponding fitted cosine curve (orange) and LOWESS line (bluish-gray). The right-hand panel indicates the cosine measures that are calculated.

3. Examples of cosinor calculations detecting between-group differences of circadian HRV parameters

As with many other biomarkers, autonomic activity fluctuates in a pattern of diurnal variation with a frequency of an approximate solar day, with peak levels of vagal activity during nighttime in humans [21, 38, 39] and nonhuman primates [40]. Previous analyses by our group and other groups have demonstrated adverse or at least unfavorable intermediate health outcomes being associated with blunted circadian variation patterns, particularly with blunted or absent nighttime increase of vagal activity. This includes an elevated risk of cardiac events such as myocardial ischemia, myocardial infarction, malignant arrhythmias, and sudden cardiac death peaking in the early morning [41–44] as well as hyperglycemic states and elevated pro-inflammatory cytokines in a working population [21]. To use this information in daily work, a clinician needs reference values which are associated with clinical and preclinical conditions such as hyperglycemia. Only if these values exist, parameters can be used as a screening tool and help to identify individuals at risk in both clinical and nonclinical populations. In preventive settings, these parameters should be associated not only to somatic complaints but also to mental health conditions such as depressive symptoms. And finally, these parameters should index change, e.g., in a clinical population pre- to post-therapy or in occupational setting pre- to post-behavioral interventions.

Yet, reference values of circadian HRV parameter are scarce and of limited usefulness. For example, existing reference values of HRV (independent of diurnal variation) are based on varying recording length [45–49] with no reference to circadian variation, age, or sex. Studies reporting reference values based on 24 h recording length are analyzed with other time durations [50, 51] than the recommended 5-minute interval limiting comparability across studies or have a focus on young adults [52] or are based on rather small sample sizes (<200) [39, 52].

3.1 Reference values

We recently presented values for circadian variation of cardiac autonomic modulation in 931 rigorously healthy working adults (mean age 39 ± 10; 78% males) [31]. Consecutive 5-minute intervals of RMSSD were calculated from 24 h HR recordings that were collected at four distinct study sites of the Mannheim Industrial Cohort Study (MICS) in healthy working adults. "Healthy" was defined rigorously as indicating explicitly "no" to any of the following criteria (self-report): hypertension, dyslipidemia, hyperglycemia, respiratory diseases (e.g., asthma, COPD), angina pectoris, stroke, infarction, congenital heart defect (CHD), depression, burnout, other chronic diseases, cancer, and taking beta-blockers. First, three individual-level cosine function parameters were estimated to quantify the circadian variation as described in the previous section. Second, random-effect meta-analysis was used to estimate the impact of age group (18–24/25–34/35–44/55–65), shift work (Y/N), atypical employment (Y/N), the hierarchical position (division manager/project leader/employee/skilled worker/semiskilled worker), smoking, or being physically active on the three cosine parameters *MESOR*, *amplitude*, and ϕ. Results showed that older age and being female are associated with a significantly lower *amplitude*. Significant age decline in *MESOR* could be observed. Particularly, age-related decline in *MESOR* and *amplitude* was more pronounced in the younger age groups (see **Figure 3**). In addition, two age groups showed phase advances compared to the youngest age group. Interestingly, current smoking was associated with reduced *MESOR*, while physical activity was associated with increased *MESOR*. Working any kind of shift work is associated

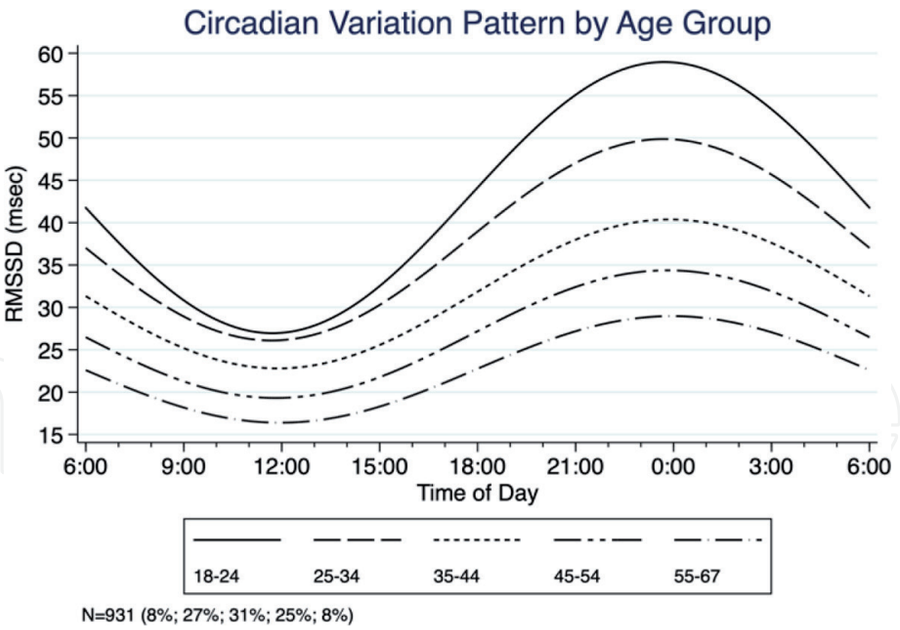

Figure 3.
Circadian variation pattern of RMSSD by age from N=931 rigorously healthy working adults of the MICS-cohort.

with higher oscillation in *amplitude*. Particularly, age declined in both the overall mean (= *MESOR*) and the oscillation (*amplitude*) indicating a decrease of nocturnal parasympathetic activity.

3.2 Test-retest reliability of circadian variation patterns

To the best of our knowledge, no study has yet investigated the short- or long-term reproducibility of circadian variation patterns of HRV parameters. We recently demonstrated short-term reliability in 74 men (age 41 ± 7) with repeated 24 h measures and a gap of 1 day between measures [53]. The vagal activity was indicated using estimates of HRV (RMSSD, pNN50, SDNN). Between-day associations were calculated using Pearson's correlation (PC). Short-term reliability was assessed using intra-class correlation (ICC) and Bland-Altman analysis (bias ± limits of agreement). The results demonstrate an excellent ICC (all > 0.82) and PC (all > 0.83) for the *MESOR*. *Amplitude* measures were good (ICC and PC > 0.71) for RMSSD and pNN50 but fair (ICC and PC < 0.60) for SDNN. Acrophase measures were fair (ICC and PC all < 0.60). Bland-Altman plots showed no systematic bias between measurement days for any measure. This study demonstrates high reliability for the rhythm-adjusted 24 h mean in primarily vagally mediated and mixed measures in men. As hypothesized, lower but still good reliability was demonstrated for the *amplitude* in vagally mediated HRV measures. This indicates a higher day-to-day variability of the vagally mediated HRV amplitude parameters and more trait-like *MESOR* parameters. However, future studies need to expand to female samples, collect potential (time lagged) determinates of the diurnal variation using ecological momentary assessments, and investigate the long-term test-retest reliability.

3.3 Depressive symptoms and circadian variation patterns

We also demonstrated previously a salient association between circadian variation patterns and depressive symptoms in 3030 predominantly healthy employees (mean age 41 ± 7; females 20.2%) [54]. Multivariate linear regression models revealed a negative association with *MESOR* and *amplitude* in men, but the

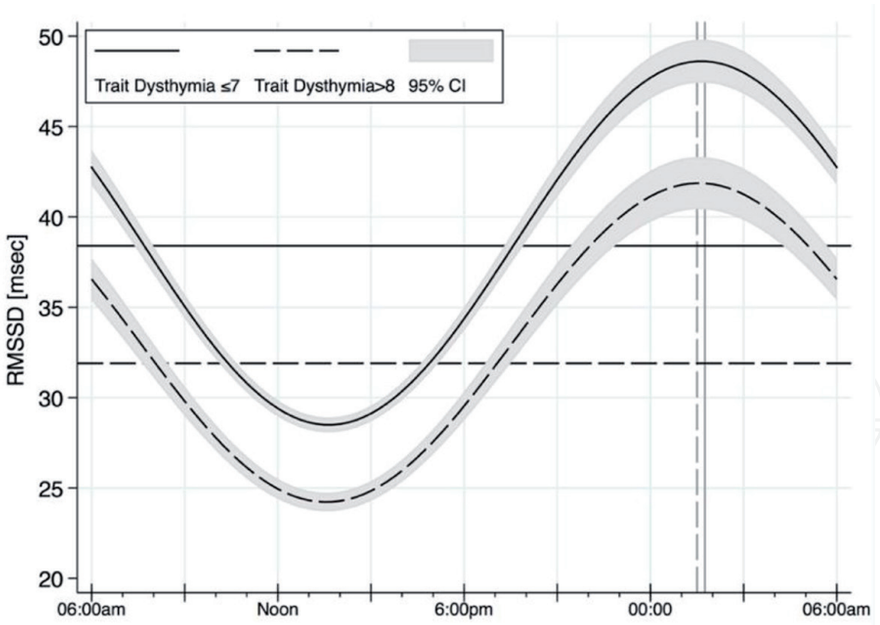

Figure 4.
Patterns of circadian rhythms of vagal activity vary by trait measures of dysthymia.

opposite in women. This pattern of findings indicates an important moderation effect of sex in the association of circadian variation patterns with RMSSD and depressive symptoms in a healthy (preclinical) population. These findings were partly replicated by investigating associations between affective trait measures with circadian variation patterns of RMSSD [55]. Here, trait measures of positive and negative affect in N = 81 male employees (mean age 41 ± 7) were significantly associated with *MESOR* in multivariate linear regression models. **Figure 4** exemplifies the results by showing the predicted diurnal variation of RMSSD by a median split of the negative affect scale and its corresponding *MESOR* line and θ around 1:30 a.m. It still needs to be explored if the decrement of circadian variation can be (partly) reversed if symptoms decrease. Two randomized controlled trials currently investigate the changes of circadian variation patterns of HRV pre- to post-therapy (DRKS00016616; NCT03080025).

3.4 Inflammatory markers and circadian variation patterns

The inflammatory reflex is a physiological mechanism through which the vagus nerve regulates immune function [56]. Here, efferent vagal activity inhibits the release of pro-inflammatory cytokines via the release of acetylcholine and has been termed the cholinergic anti-inflammatory pathway [57–59]. Moreover, the release of interleukin-6 (IL-6) and other cytokines triggers the hepatic synthesis of C-reactive protein (CRP) [60]. In addition, the vagus nerve is also known to relay information about the peripheral immune status to the brain via IL-1 receptors conveyed by paraganglia cells situated in parasympathetic ganglia [61]. Thus, both vagal efferent and afferent pathways seem to play an important role in immune regulation. We previously demonstrated that decreased vagally mediated HRV at baseline predicted increased low-grade systemic inflammation (a marker of CHD risk) after 4 years in healthy working adults [19]. The circadian variation pattern of RMSSD shows an association with systemic low-grade inflammation [62]. Data were collected at four distinct study sites of the Mannheim Industrial Cohort Study (MICS) in 3134 healthy working adults (mean age 42 ± 11; 80% males). Low-grade inflammation was measured by high-sensitive C-reactive protein (hsCRP).

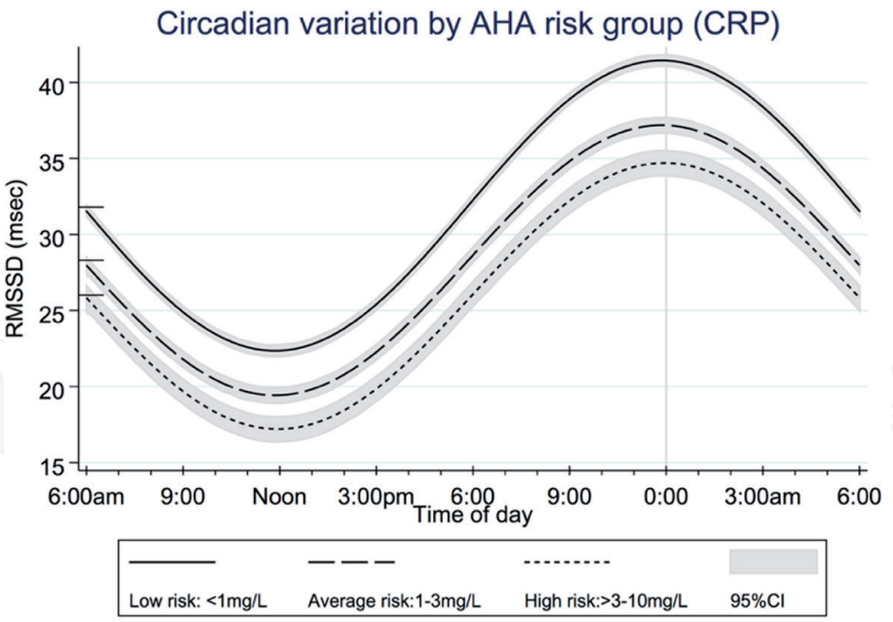

Figure 5.
Circadian variation in groups with different systemic inflammation levels as defined by the American Heart Association (AHA).

Participants with acute inflammation (hsCRP >10 mg/L) were excluded. CRP was categorized into the risk groups defined by the American Heart Association (AHA) as follows: low-risk group (<1 mg/L), medium-risk group (1–3 mg/L), and high-risk group (>3 mg/L). In the present study, lower *MESOR* and higher *amplitude* were associated with elevated levels of low-grade inflammation (see **Figure 5**).

4. Examples of 24 h HRV patterns in practical application

4.1 Clinical population

As described in the introduction, reduced HRV parameters have been shown in different risk states and diseases including depression [63]. At the same time, disturbances of circadian rhythms have been described in depression [64]. A 24 h measurement of HRV can help to detect the degree of disturbance that has already occurred. Furthermore, it supports recovery by identifying resources that can be enhanced and strengthened. Recovery from a chronobiologic point of view includes not only reduction in, e.g., depressive symptoms, but also restoration of chronobiologic rhythms. Repeated measurements can document the process of recovery and the effect of interventions.

Considering these points, a 24 h measurement of HRV could prove itself as a helpful psychophysiological tool in a psychotherapeutic setting. However, to the best of our knowledge, 24 h HRV was not yet implemented in this kind of setting. Therefore, we designed a study implementing 24 h HRV measurements into a psychosomatic consultation at the workplace (trial-ID German Clinical Trials Register DRKS00012473). The psychosomatic consultation at the workplace is a service of the Department of Psychosomatic Medicine and Psychotherapy at Ulm University Medical Center (Germany) and has been described in detail elsewhere [65]. In brief, it is open to employees who receive an early consultation by a doctor or a psychologist specialized in psychotherapy for all personnel reporting psychic (e.g., depressive symptoms, anxiety) and potentially psychosomatic complaints such as

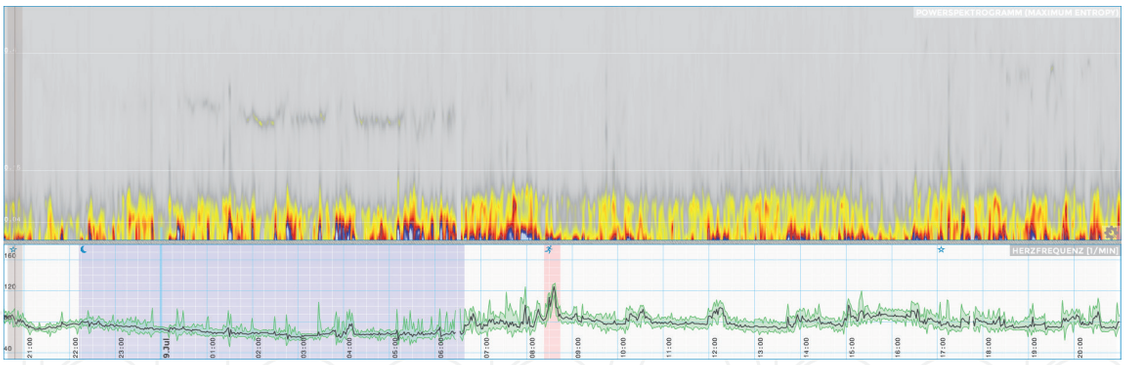

Figure 6.
24 h HRV measurement of a patient with major depression. Displayed are heart rate and spectral analyses.

back pain, sleep problems, and exhaustion. It comprises two parts—the diagnostic phase (max. three sessions) and the immediate short-term intervention of another max. 9 sessions (if indicated). The study took place at a large center for disabled care in Germany. HRV was measured after the first sessions and the results were discussed with the patients in the second or third session. All patients that continued the sessions received a second 24 h HRV measurement at the end of the intervention (marker of change). The study also covered disturbances of the hypothalamic pituitary adrenal (HPA) axis by collecting eight saliva samples for a cortisol day profile.

Recruitment was completed in May 2019, but repeated measurements are still ongoing, so final statistical analyses will be reported later. Preliminary findings suggest that about 50% of the patients were willing to participate in the study and that all patients that were offered a second measurement (i.e., all patients receiving a short-term intervention) completed the second measurement. The vast majority of patients indicated that they gained new insights in psychophysiological interactions and most of them (90%) would highly recommend the consultation (particularly the HRV measurement with feedback) to a close friend.

Here, we want to present a case with a major depressive episode. A 50-year-old man presented with depressed mood, diminished interest in all activities, fatigue, problems to concentrate at work, and sleeping disturbances with problems falling asleep, waking up in the middle of the night and in the morning, and lying awake for a longer time. He also complained about restlessness which had become better by starting medication with olanzapine 2.5 mg per day. Twenty-four hour HRV analyses revealed a pronounced overall reduction in variability as well as a reduced night-day variation (see **Figure 6**). At night, vagal indices normally increase. In this patient, RMSSD and HF power were low throughout the day and the night, confirming his subjective complaints of unrestful sleep (**Table 1**). His chronobiologic rhythms are obviously disrupted to a greater extent on the basis of an overall reduction in variability that does not allow much variation throughout the day. Searching for resources led to one single time point at about 5 o'clock in the afternoon where power spectral analyses show for a short time signals in the VLF, LF, and HF power band. The patient reported that at this time, he sat down in his garden and could enjoy the air and the birds singing for a while.

The symptoms aggravated in the following 2 weeks so that he was transferred to a hospital with psychiatric inpatient care.

4.2 Preventive setting

As discussed in the introduction, 24 h measurement of HRV may be a practical tool in preventive settings like occupational health. We implemented it in three large enterprises of the industrial, automotive, and metal sector into a regular

Parameter	Unit	Total	Daytime	Sleep
Duration	hh:mm	24:30	16:02	08:26
Mean HR	/min	75	80	67
SDNN	ms	99.5	72,6	76.9
rMSSD	ms	15.2	14,6	16.4
Total power-i	ms^2	1643	1461	1991
VLF-i	ms^2	1082	888	1454
LF-i	ms^2	407	417	387
HF-i	ms^2	70	66	79

Abbreviations: HR, heart rate; SDNN, standard deviation of normal interbeat intervals; RMSSD, root mean square of successive differences; VLF, very low frequency; LF, low frequency; HF, high frequency.
-i indicates that this value is calculated as a mean of the values of all 5-min timeframes.

Table 1.
HRV indices of a patient with major depression.

manager health checkup and as an offer for any manager and employee who presents at the occupational health physician (trial-ID German Clinical Trials Register DRKS00014653). First, we want to show a healthy example with intact chronobiology and after that an example out of the mentioned study with clear disturbances.

The first example shows the measurement results of a 36-year-old woman. The medical history contained no diagnoses, no medication, normal weight, and normal blood pressure. She was working part time, about 30 h/week, living with her husband and with three children. Alcohol consumption was moderate, and she engaged in sports activities of 3–4 h/week. She complaint feeling tired in the morning and sometimes during the day but reported falling asleep easily in the evening and sleeping well. Scores for irritation and depression showed low values, while the stress scale showed intermediate values, where she was reporting work piling up.

HRV analyses showed a pronounced and instant decrease of heart rate at night, with a distinct increase in RMSSD and HF. In spectral analyses, the nighttime is easily detected by a specific pattern inside the HF power band which represents respiratory sinus arrhythmia (RSA). In this healthy example, RSA is present almost throughout the whole night, with changing patterns in the LF power band as it is typical for sleep cycles. This is an example of well-functioning chronobiology. The daytime also shows variability with different patterns, e.g., at lunch break around 12 o'clock, during sports activity around 3 o'clock in the afternoon, and in the evening at home (see **Figure 7** and **Table 2**).

The second example shows the results of a measurement a 50-year-old male manager working full time about 40 h/week. He also had no diagnosed diseases and reported no medication. Weight and blood pressure were unobtrusive. He reported a moderate alcohol consumption and moderate sports activity of 1–2 h/week. His complaints were only some back pain from time to time. He reported almost half of the nights waking up in the middle of the night with problems continuing sleeping and marked his sleep as "fair." Irritation scale was low with only sometimes being irritated. No depressive or anxious symptoms were present.

In the spectral analyses (**Figure 8**), the typical RSA pattern at night is missing. Generally, the power seems to be "cut" with almost no spikes entering the HF power band. Though heart rate decreased at night, all HRV parameters, especially vagal values, were reduced at night, which is an inverted state. HR decreased only slowly and reached the lowest values after 4 o'clock and 5 h of sleep, respectively. Analyses of his daytime activity showed no breaks throughout the whole day and 1 h of a vigorous sports activity (ball game) from 20 to 21 o'clock with a mean HR of 130/min and a max

HR of 170/min (**Table 3**). Heart rate did not return to baseline for 2 h, which indicates overtraining. The first hours of sleep show reduced variability in all power bands, a pattern that stands for exhaustion. Allover, chronobiologic rhythms are markedly disturbed, though HRV indices are still higher than in the example with major depression.

The consultation revealed a highly ambitious personality who was used to well-functioning of his body all of the time and who a mostly postpones the needs of his body in order to solve a problem on the job or to win the game at sports. The graph helped to intriguingly demonstrate to the manager the impact of what he is doing to his body and motivated him to learn to perceive when he reaches his limits as well as to hold on to his limit and not try to overachieve.

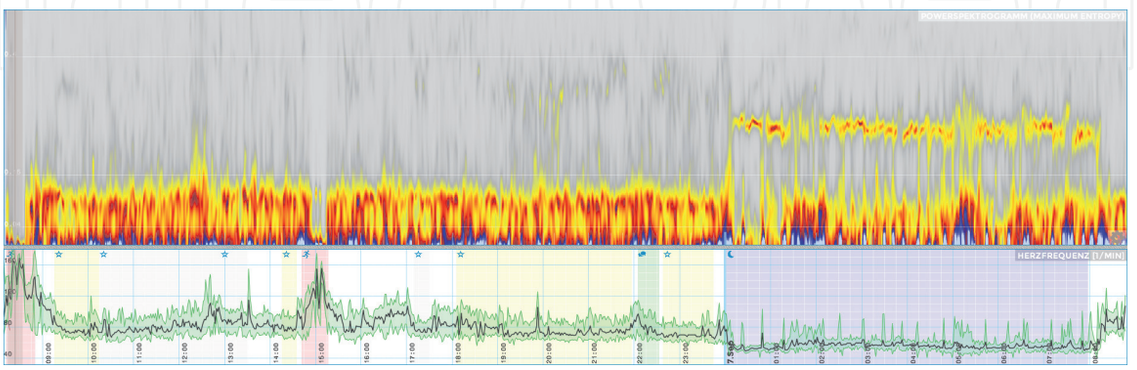

Figure 7.
24 h HRV measurement of a healthy, 36-year-old woman. Displayed are heart rate and spectral analyses.

Parameter	Unit	Total	Daytime	Sleep
Duration	hh:mm	24:41	16:44	07:57
Mean HR	/min	74	83	55
SDNN	ms	206.2	144.6	104.7
rMSSD	ms	34.8	30.3	46.0
Total power-i	ms^2	5305	4794	6364
VLF-i	ms^2	3105	2596	4160
LF-i	ms^2	1525	1650	1266
HF-i	ms^2	412	281	684

Abbreviations: HR, heart rate; SDNN, standard deviation of normal interbeat intervals; RMSSD, root mean square of successive differences; VLF, very low frequency; LF, low frequency; HF, high frequency.
-i indicates that this value is calculated as a mean of the values of all 5-min timeframes.

Table 2.
HRV indices of a healthy, 36-year-old woman.

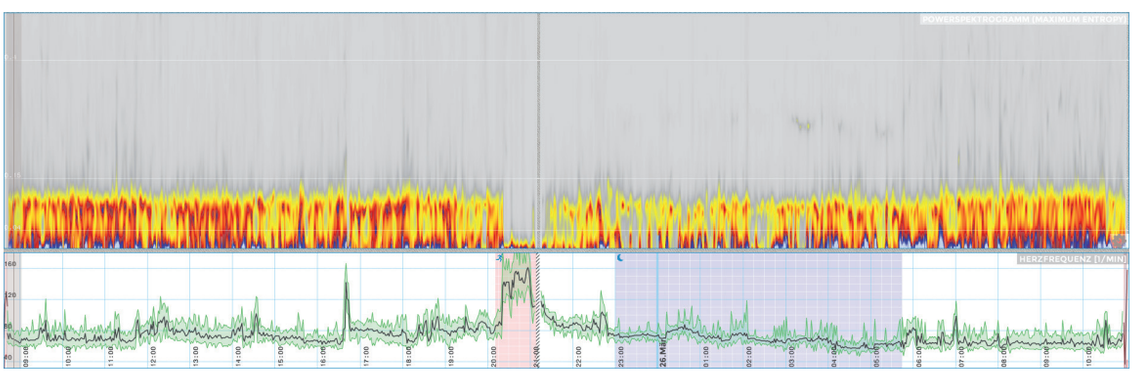

Figure 8.
24 h HRV measurement of a 50-year-old manager. Displayed are heart rate and spectral analyses.

Parameter	Unit	Total	Day	Sleep
Duration	hh:mm	26:27	19:44	6:43
Mean HR	/min	74	76	69
SDNN	ms	148.0	155.1	98.0
rMSSD	ms	21.4	22.7	16.5
Total power-i	ms^2	3630	3980	2657
VLF-i	ms^2	2086	2221	1714
LF-i	ms^2	1248	1410	800
HF-i	ms^2	82	95	46

Abbreviations: HR, heart rate; SDNN, standard deviation of normal interbeat intervals; RMSSD, root mean square of successive differences; VLF, very low frequency; LF, low frequency; HF, high frequency.
-i indicates that this value is calculated as a mean of the values of all 5-min timeframes.

Table 3.
HRV indices of a 50-year-old manager.

5. Conclusion

HRV as a chronobiologic, disease-unspecific biomarker holds the possibility to become a screening tool in preventive settings as well as a tool to monitor overall health status, e.g., pre- to post-therapy, and serve as an instrument to demonstrate to a patient the physiological reactions to his specific environmental cues. This could be beneficial to persons usually not so open to talk about feelings and thus pave the way into a conversation about psychosomatic interactions. Thus, its psychophysiological nature mirroring somatic as well as mental states implies HRV as a well-suited psychosomatic marker. Its usefulness in these settings should be further explored.

Acknowledgements

Parts of this work were conducted at the Leadership Personality Center in Ulm (Germany) with the support of the Karl Schlecht foundation.

MNJ positions were funded between 2016 and 2017 through the physician scientist program (Medical Faculty Heidelberg, Heidelberg University, Germany). The other studies were funded through internal funds of the Mannheim Institute of Public Health, Social and Preventive Medicine (Heidelberg University), the Institute for Medical Psychology (Center for Psychosocial Medicine, Heidelberg University), and the Clinic for Psychosomatic Medicine and Psychotherapy (University Medical Center Ulm).

JJM is awarded with a funding from the Canadian Institutes of Health Research and Fonds de Recherche du Québec-Santé that supports this work.

None of the funding entities had a role in data analysis, result report, or interpretation of this work.

Conflict of interest

EMB, MNJ and JJM declare to have no conflict of interest.

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