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Effect of Examination on the Circadian Structure of ECG Parameters

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Abstract

Seasonal rhythms are an important tool for an organism to adapt to the environment. As part of the problem of adjustment to a load ("stress"), infradian (including seasonal) biorhythms deserve special attention, notably in a climate with a strong contrast between summer and winter. Evolutionary circannual rhythms contribute to the survival of individuals, species and populations of different animals in the face of seasonal changes in habitat. The changing of seasons imposes great demands on organisms, especially in the continental climate of Kazakhstan. This investigation examines any influence of seasons on the daily dynamics of some ECG parameters (notably endpoints of heart rate variability, HRV) in association with the load of an examination in this Central Asian region. All exams were conducted in the morning (at 09:00). Circadian rhythm characteristics of ECG endpoints were compared between days with vs. without an exam, when exams were taken either during winter or summer. In summer, on days with an examination, 24-hour means of SDNNidx and rMSSD (HRV parameters) were decreased, more so at night, when the parameters SDNNidx, rMSSD, pNN50, pNN100, and pNN200 undergo statistically significant changes. Changes of lesser extent were observed in winter. In both seasons, the load of an examination was associated with a shift in the circadian acrophase (phase of maximum of cosine curve approximating the data) that was more pronounced in winter than in summer. On days with an examination, the harmonic content increased, components with a frequency higher than 1 cycle per day (ultradians) accounting for a larger proportion of the overall variance.

Responses of blood pressure (BP) and heart rate (HR) to a load can vary greatly as a function of the circadian stage when the stimulus is applied. Recently, cycles other than circadian and circannual have also been reported, notably components with periods of about 5 and 16 months, detected in longitudinal BP and HR records as well as in mortality statistics from myocardial infarction and sudden cardiac death in different geographic locations. Whether the response to a load such as an examination is also characterized by such non-photic infradians (with a frequency lower than 1 cycle per day) deserves further investigation.

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Introduction

"Stress" (or rather load) is one of the most important health problems in modern society today, being at the same time an integral part of our lives. The ability of an individual to adapt to loads, gauged by success within society and by critical achievements in work, education and sports, depends strongly on their adaptive capacity at the right time. Effects of loads are largely circadian periodic [1]. Research on shift-work also showed the disparity of responses upon presentation of loads at different times of the day [2]. The importance of circannual rhythms ("seasonal variation") is evidenced from the large predictable changes in the incidence of major diseases, notably from cardiovascular causes [3, 4]. Changes in the circadian response to a load, however, have not been extensively studied as a function of when during the year it is administered. This investigation aims at assessing any circannual differences in the circadian rhythm characteristics of ECG endpoints as they are affected by the load of an examination.

Seasonal rhythms are an important tool for an organism to adapt to the environment. As part of the problem of adjustment to a load ("stress"), infradian (including seasonal) rhythms deserve special attention, notably in a climate with a strong contrast between winter and summer. Evolutionary biological rhythms contribute to the survival of individuals, species and populations of different animals in the face of seasonal and daily changes in habitat.

Subjects and Methods

Seven apparently healthy student volunteers aged 21-35 years residing in the city of Almaty (Kazakhstan) was investigated. Each subject contributed a 24-hour record of the electrocardiogram (ECG) using a 3-channel ECG (SHILLER MT-200 HOLTER-EKG V 2.10, Switzerland). This Holter system uses bipolar leads (one positive and one negative diversion) for each channel. Channel 1 corresponds approximately to the modified abstraction V5, channel 2 corresponds approximately to V2, and Channel 3 to V3. Subjects followed their normal lifestyle without limitations in their daily activity during the monitoring session, which was carried out before, during and after the examination, invariably taken from 09:00 to 12:00. Monitoring was carried out on a day without examination and on a day with examination. The same protocol was followed by the same students once during the summer and once during the winter. HRV endpoints were assessed during consecutive 5-minute intervals. They included the magnitude of RR (ms) and the time intervals restricted to normal QRS complexes (NN-intervals). In addition, hourly values of the maximal, minimal and average HR were analyzed.

Each data series was analyzed by cosinor [5-7]. A 24-hour cosine curve was fitted by least squares to the data of each student during each 24-hour recording session, yielding estimates of the MESOR (Midline-Estimating Statistic Of Rhythm, a rhythm-adjusted mean), double amplitude (a measure of the extent of predictable change within a day), and acrophase (a measure of the timing of overall high values recurring each day). Results from the seven subjects were further summarized by population-mean cosinor, separately for control days and for examination days in each season. Parameter tests [8] were carried out to determine whether there were any differences in the circadian rhythm characteristics between summer and winter, and/or between the control day and the day of examination.

Hourly average HR data were also analyzed by least-squares spectra in the frequency range of 1-10 cycles per day in order to determine whether the 24-hour rhythm was invariably the best-fitting component or whether the examination disturbed the circadian rhythm to such an extent that a harmonic term became more prominent than the 24-hour component.

Because the examination lasted only a fraction of the 24-hour span, an effect on circadian rhythm characteristics may not be large enough to be detected, even though an effect better localized around the time of the examination may be present. For this reason, the hourly HR values of each subject on the day of examination were expressed as a percentage of the HR value at the corresponding clock-hour on the control day, separately for each season. Paired t-tests were applied at each clock-hour to determine whether, across all subjects, there were any differences localized in time, and if so, when did these effects take place.

Results

Most HRV endpoints remained stable. Only SDNNidx and rMSSD showed a statistically significant decrease during the summer session. In summer, SDNNidx (the average of standard deviations of N-to-N intervals for each 5-minute interval), reflecting the integrated effects of sympathetic and parasympathetic divisions of the autonomic nervous system (ANS), averages 70.9 ± 4.5 ms and decreases during the examination to 59.9 ± 4.2 ms. In winter, during the examination, SDNNidx is barely changed and is even slightly (numerically) increased.

Similar results are found for rMSSD (the root mean square successive difference of N-to-N intervals), an indicator of the activity of parasympathetic autonomic regulation. In the summer, it is reduced during the day of examination (daytime: $P = 0.028$; nighttime: $P = 0.018$), but in the winter, there are no statistically significant changes. A comparison of HRV endpoints shows a statistically significant change associated with the examination in 5 of the 11 HRV indices (SDNNidx, rMSSD, pNN50, pNN100, pNN200).

The average value of all intervals between successive normal QRS complexes (NN) is reduced during the day of examination, but the difference is not statistically significant. In the summer, NN drops from 714 ± 17 to 669 ± 37 ms during the day of examination, and in the winter from 691 ± 29 to 679 ± 29 ms.

SDNN, which reflects the overall tone of the ANS, does not change statistically significantly. SDANN also does not change statistically significantly between the control day and the examination day.

Nightly values of pNN50 (the proportion of over 50 ms intervals divided by the total number of NNs) are higher than the daytime values ($P<0.05$ for both control day and summer session, but not statistically significantly for the winter session). During the summer session, nightly values were significantly reduced from 29.3 ± 3.9 to 17.6 ± 3.7 in association with the exam. In the summer, pNN100% was also statistically significantly reduced at night (from 5.9 ± 1.6 to 2.5 ± 0.6). These changes demonstrate an increased sympathetic coordination which suppresses the activity of an autonomous circuit in association with a load.

Thus, the load of an examination was associated with a statistically significant decrease in rMSSD and SDNNidx in summer, the changes being more pronounced at night, when important changes affect a larger number of parameters (SDNNidx, rMSSD, pNN50, pNN100, pNN200). Changes associated with the examination are more pronounced in summer than in winter. These results are in keeping with earlier findings in rats [9].

In winter, the number of completed QRS complexes is sharply increased on the exam day by comparison with the control day, starting about 2 hours before the test and lasting for the first two hours during the examination. By contrast, in summer, the increase observed on the exam day vs. the control day is of lesser extent, but starts earlier, about 3 to 4 hours before the test, and lasts longer.

Maximal HR values are also increased between 07:00 and 09:00 on the examination day by comparison to the control day in winter. Only a slight elevation is observed in summer, seen primarily around 05:00 and 06:00. Minimal HR values are increased on the exam day from 09:00 to 10:00 by comparison to the control day in winter. In summer, the elevation is much less, but it is present (at least numerically if not statistically significantly) during the entire 24-hour span.

Hourly averages of HR are characterized by a prominent circadian rhythm. In summer, the 24-hour component is statistically significant ($P<0.01$) for all 7 subjects during the control day. During the day of examination, the circadian rhythm is significant ($P<0.001$) in 6 of the 7 subjects, an 8-hour component ($P<0.001$) being the most prominent in the least-squares spectrum of the other subject. In winter, on the control day, the 24-hour component is invariably statistically significant ($P<0.01$) for all 7 subjects, but on the day of examination, the 24-hour component is detected with statistical significance in only 4 of the 6 subjects (P<0.001 for 3 subjects; P=0.02 for the other subject), being of borderline statistical significance (P=0.057 for another subject and not significant for the remaining subject. Moreover, the 24-hour rhythm was the most prominent component in the least-squares spectrum for only 3 of the 6 subjects.

On a population basis, the circadian rhythm is statistically significant on the control days in summer and in winter (P<0.001). On the day of examination, the circadian rhythm was statistically significant in summer (P=0.003), but only of borderline statistical significance in winter (P=0.070). Parameter tests did not find any difference in the MESOR or in the circadian amplitude and acrophase of HR between summer and winter, whether the comparison is made between control days or between days of examination.

No difference is found between the control day and the day of examination in summer either. By contrast, in winter, the 24-hour acrophase is advanced by about 2.5 hours on the day of examination by comparison to the control day (P=0.004), Figure 1. Pooling data between the two seasons, a comparison between the control day and the day of examination also finds the 24-hour acrophase to be advanced by about 2 hours in association with the load of an exam (P=0.003). A very small difference in MESOR (P=0.113) stems primarily from a higher HR MESOR during the day of examination vs. the control day during the summer (84.8 vs. 77.0 beats/min), the difference being much smaller in winter (83.6 vs. 81.0 beats/min).

Figure 2 illustrates differences in the circadian pattern of HR between winter and summer during control days. The hourly data during summer were used as reference, and the HR values at the corresponding clock-hours in winter expressed as a percentage of the summer data, separately for each subject. Relative values averaged across all 7 subjects are displayed in Figure 2 with their standard errors (SEs). Differences from 100% determined by paired t-test (not corrected for multiple testing) are found primarily during the night and at 09:00, the scheduled start time of the examination to be administered on a different day.

Figures 3 and 4 illustrate differences in the pattern of HR on the day of examination by comparison with the control day. Again, the hourly data on the day of examination are expressed as a percentage of the corresponding data on the control day, separately for each subject. Relative values averaged across all subjects are displayed with their SEs. Differences from 100% determined by paired t-test (not corrected for multiple testing) are found primarily during the 2-3 hours preceding the examination.

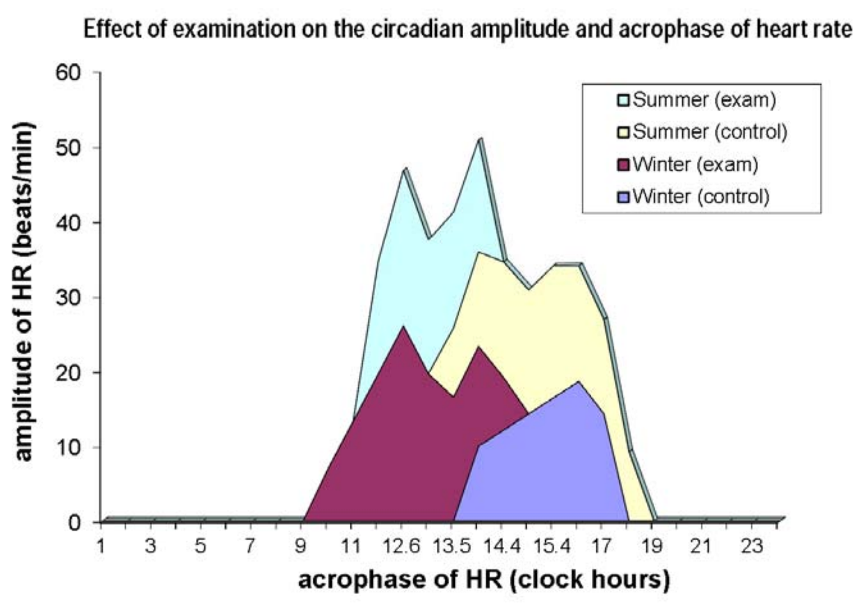

Figure 1. During the day of examination, the circadian acrophase is advanced by 2 to 3 hours. For this analysis, data collected during a day of examination were fitted with a 23-hour rather than a 24-hour cosine curve.

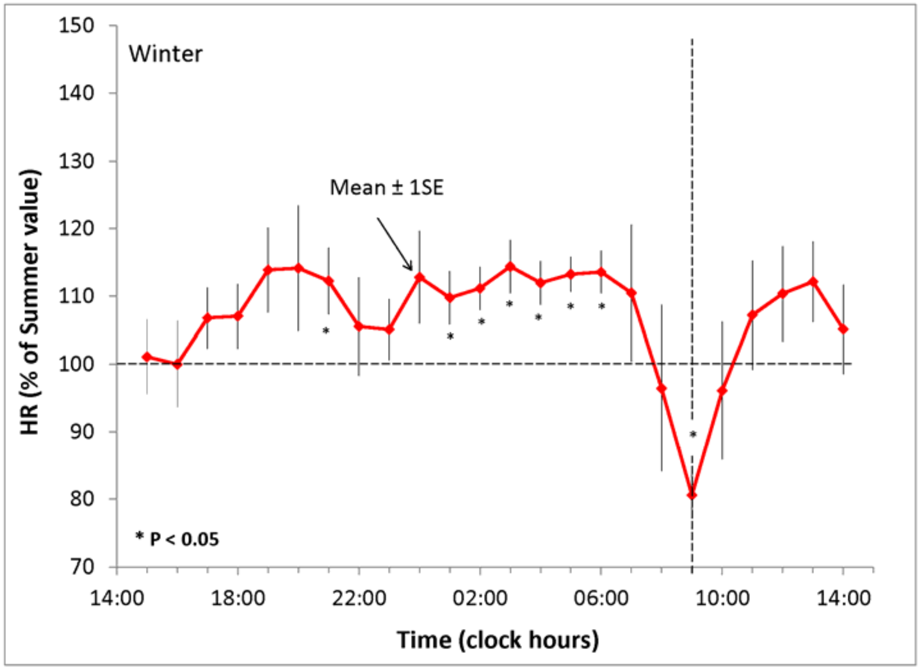

Figure 2. As compared to the circadian profile in summer, HR in winter is slightly higher during the night and lower around 09:00. Data from each subject at each clock hour are expressed as a percentage of the HR value at the corresponding clock hour during summer, and then averaged across all subjects to test for deviation from 100% by paired t test. Data collected during control days in both seasons.

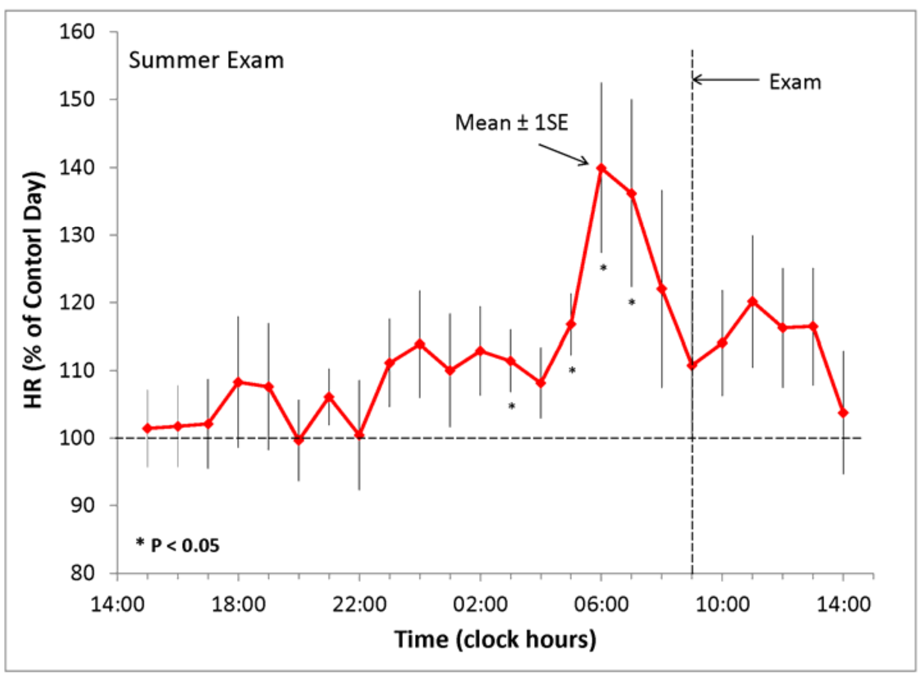

Figure 3. As compared to the circadian profile during the control day, HR on the examination day in summer is higher primarily 2 to 4 hours prior to the test. Data from each subject at each clock hour are expressed as a percentage of the HR value at the corresponding clock hour during the control day in summer, and then averaged across all subjects to test for deviation from 100% by paired t test.

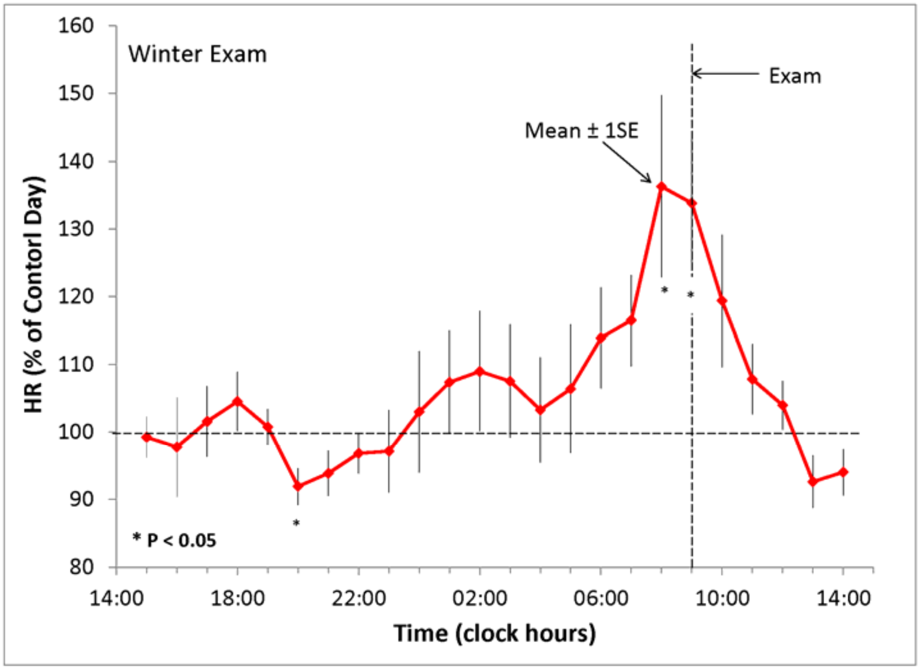

Figure 4. As compared to the circadian profile during the control day, HR on the examination day in winter is higher just before the test. Data from each subject at each clock hour are expressed as a percentage of the HR value at the corresponding clock hour during the control day in winter, and then averaged across all subjects to test for deviation from 100% by paired t test.

Discussion and Conclusion

Short-term responses of the hypothalamic-pituitary-adrenal (HPA) system are very effective in the presence of danger, but at the same time, long-lasting loads consume a marked amount of stored energy needed for winter survival [10], weakening the organism. Photoperiodic coordination of the HPA system can integrate positive and negative effects of stress hormones, as previously shown in studies of the influence of hypokinesia on catecholamines and corticosteroids in rats at different times of the year [11].

The lack of a difference in MESOR of the average HR between the day of examination and the control day indicates that the load was adequate and did not exceed the adaptive capacity of the organism. At the same time, changes in the circadian time structure evidenced by the shift in acrophase and the increased prominence of ultradian components indicate that the load of the examination was associated with a disturbance of the circadian system, in keeping with work by others [12, 13].

The effect of a load depends on the circadian stage when it is administered, notably in relation to the cardiovascular system [1, 14-16], sometimes accounting for differences in opposite direction. In this study, the examination always took place between 09:00 and 12:00. At that circadian stage, the load of an examination had different effects in summer and winter. Differences in 24-hour averages of different HRV endpoints were observed primarily in the summer. By contrast, a difference in the circadian acrophase of HR was most prominent in winter.

Whether these differences between summer and winter are related to seasonal differences reported in the concentration of corticosteroid hormones in peripheral blood and in the weight of adrenal glands and their reactivity to various stimuli [17] deserves further study.

In the experimental laboratory, stressful situations are associated with an increase in corticosterone, and the endocrine response to ACTH (if not to loads) also shows a circadian stage dependence [18-20]. A higher increase in corticosterone in response to ACTH occurs when the hormone is at its circadian minimum, and a lesser response occurs at the circadian maximum [18-20].

The critical circadian stage dependent response of the cardiovascular system to a load has been extensively documented by Franz Halberg. Herein, we show that the response to an examination taken in summer or winter also makes a difference. Recently, cycles other than circadian and circannual have also been reported, notably components with periods of about 5 and 16 months, detected in longitudinal BP and HR records as well as in mortality statistics from myocardial infarction and sudden cardiac death in different geographic locations [21-24]. Whether the response to a load such as an examination is also characterized by such non-photic infradians (with a frequency lower than 1 cycle per day) deserves further investigation.

In any event, as a minimum, further investigations should carefully record the date and time when a load is applied. Preferably, applying the same load at different rhythm stages rather than at a fixed time is likely to be more informative, notably when the response to periodontal surgery can be an increase in BP and HR when it is performed in the morning, or a decrease when the same procedure is done in the afternoon [15]. Other factors such as physical activity may be confounders with any examination effect, because exercise is asspciated with an increased heart rate variability [25].

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