

## **Sleep-wake differences in heart rate variability during a 105-day simulated mission to Mars**

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## Abstract

**Introduction:** In prolonged space flights the effect of long-term confinement on the autonomic regulation of the heart is difficult to separate from the effect of prolonged exposure to microgravity or other space-related stressors. Our objective was to investigate whether the sleep-wake variations in the autonomic control of the heart are specifically altered by long-term confinement during the 105-day pilot study of the earth-based Mars500 project. **Methods:** Twenty-four-hour EKG records were obtained before (pre), during (T1: 30, T2: 70 and T3: 100 days), and after (post) confinement in the six crew members that participated in the mission. Sleep and wake periods were determined by fitting a square wave to the data. Autonomic activity was evaluated through time and frequency domain indexes of heart rate variability (HRV) analysis in wake and sleep periods. **Results:** During confinement, wake HRV showed decreased mean heart rate and increased amplitude at all frequency levels, particularly in the very low (pre:  $13.3 \pm 0.2$ ; T1:  $13.9 \pm 0.3$ ; T2:  $13.9 \pm 0.2$ ; T3:  $13.9 \pm 0.2$ ; post:  $13.2 \pm 0.2$ ), and high (pre:  $7.6 \pm 0.4$ ; T1:  $8.3 \pm 0.5$ ; T2:  $8.2 \pm 0.4$ ; T3:  $8.1 \pm 0.4$ ; post:  $7.6 \pm 0.3$ ) frequency components (values expressed as mean  $\pm$  SE of wavelet power coefficients). Sleep HRV remained constant, while sleep-wake high frequency HRV differences diminished. **Discussion:** The observed autonomic changes during confinement reflect an increase in parasympathetic activity during wake periods. Several factors could account for this observation, including reduced daylight exposure related to the confinement situation.

## Key Words

Autonomic nervous system, confinement, Mars500, space physiology

## Introduction

Several environmental factors related to long-term space flight, like confinement, varying light exposure, noise or temperature changes, absence of earth-based Zeitgeber, are likely to play a role in sleep – wake cycle alterations (14). Some evidence has been found about the effect of confinement by itself on circadian rhythms. A 28-day isolation experiment revealed no major sleep disturbances besides an increase in self-rated tiredness (22). In contrast, during a 7-day confinement period, catecholamines and sleep motor activity exhibited significant increases (13). Moreover, adaptation to changed physical and social environments during isolation periods of 135 days was associated with specific changes in sleep architecture (25).

Although autonomic nervous system (ANS) activity may play a key role in performance during space missions (3), little is known about the specific impact of confinement on the circadian rhythm of ANS activity. This rhythm is characterized by a sympathetic predominance during the wake periods that allows an active engagement with the external environment with increased utilization of energy, and a parasympathetic predominance during the night related with a disengagement from external environment for recovery (18). A decrease in parasympathetic activity was reported in space (1) and ground (23) based bed-rest experiments with long periods of confinement. In an experiment conducted in order to characterize neurovegetative activity in a ground based unit that simulated the living conditions of a space station except microgravity, no major differences were disclosed before, during and after the isolation period of 60 days (16). Still, none of these studies evaluated the circadian rhythm of autonomic activity (1;16;23).

Hence, we sought to investigate the circadian profile of heart rate variability during a 105-day confinement period in the context of the Mars500 pilot study (Mars105). The aim of the Mars500 project is to gather data, knowledge and experience about the psychological and physiological effects of living in an earth-based enclosed environment during the 520 days as would be required for a real mission to Mars. This allows to separate the effect of long term confinement from the effect of long term exposure to microgravity. We hypothesize that sleep-wake variations of the autonomic control of the heart are altered by long term confinement.

## **Methods**

### Subjects

Six healthy non-smoking male subjects (mean  $\pm$  SD: age  $33 \pm 6$  years; height  $181 \pm 5$  cm; weight  $82 \pm 12$  kg; BMI  $25 \pm 3$  kg/m<sup>2</sup>) were selected to participate in a 105-day confinement pilot-study before the Mars500 project.

### Design

The Mars 500 project, organized by the European Space Agency (ESA) and the Institute for Biomedical Problems (IBMP) at Moscow, is designed to simulate a mission to Mars in duration, composition of the crew, activities, work load and communication facilities.

The protocol of the study reported herein was approved in advance by the Ethics Committee of the University Hospital Gasthuisberg of Leuven, Belgium and the ESA Medical Board, which complied with all guidelines stated in the Declaration of Helsinki. All participants gave informed consent to participate in the study.

Subjects were confined in the isolation facility at IBMP in Moscow from the 31<sup>st</sup> of March 2009 to the 14th of July 2009. The lay-out of the isolation facility comprises 4 hermetically sealed interconnected habitat modules with artificial lighting conditions (50 – 300 lux). The total volume of the habitat modules is 550 m<sup>3</sup>. Ambient temperature was maintained constant at 24 °C, with a relative humidity of 35-45%. Subjects were involved in different scientific protocols to assess the psychological and physiological effects of isolation and confinement. Their schedules were organized in order to maintain 8-hour periods of work, leisure and sleep. Crewmembers operated on night-shifts for one week each, in rotation.

Twenty-four hour Holter signals were obtained at five time points: in one day between 17 to 20 days before confinement (Pre); in one day between the 38th to the 40th day of confinement (T1); in one day between the 73th to the 76th day of confinement (T2); in one day between the 98th to the 100th day of confinement (T3); and in one day between 11 to 13 days after the end of confinement (Post). Data collection was performed

regardless of day or night shift of the subject.

## Procedure

Signal recording: Electrocardiogram signal was recorded using a digital Holter device. Ventricular depolarizations (R waves) were detected through the device software. The time elapsed between R waves (RR intervals) was then computed. Heart rate variability (HRV) indexes were computed in 1-hour segments. Premature and lost beats were identified by an automated filter and replaced by RR intervals resulting from linear interpolation (20).

Time domain: Quantitative time series analysis was performed on heart rate by evaluating measures of variation over time. Among these, RRm (mean duration of RR intervals in ms) quantifies the mean heart rate, SDNN (standard deviation of RR intervals in ms) represents a coarse quantification of overall variability, and RMSSD (square root of the mean squared differences of successive normal RR) measures short-term heart rate variations (20).

Frequency domain: These measurements provide an evaluation of the power of the contributing frequencies underlying HRV. Its high-frequency (HF) component (0.15-0.4 Hz) is related to respiratory sinus arrhythmia and mediated by parasympathetic activity, whereas the low-frequency (LF) component (0.04-0.15 Hz) is related to baroreflex control

and depends upon sympathetic and parasympathetic mechanisms. A very low frequency (VLF) component ( $<0.04$  Hz) of an uncertain origin is also found and has been attributed to thermoregulatory fluctuations in vasomotor tone as well as to humoral factors such as the renin-angiotensin system, with dependence on the presence of parasympathetic outflow (Figure 1) (20;21).

[Fig. 1 here]

To analyze the frequency components of HRV, the Discrete Wavelet Transform (DWT) was chosen rather than the traditional Fast Fourier Transform (FFT) because it is not affected by discontinuities or non-stationarities (2). Before applying the DWT, the linear trend and the mean value were subtracted from the signal. In addition, it was evenly sampled with a frequency of 2.4 Hz by means of a spline interpolation algorithm and zero padded to the next higher power of two (2). A six-level wavelet decomposition was employed to analyze the signal, using a Daubechies 4 wavelet function. Using this decomposition, wavelet levels A6 and D1-D6 represent the total power (TP, 0–0.6 Hz), wavelet levels A6 and D6 approximately correspond to the very low frequency band (VLF, 0-0.0375 Hz), wavelet levels D4-D5 to the low frequency band (LF, 0.0375-0.15 Hz), and wavelet levels D2-D3 to the high frequency band (HF, 0.15-0.6 Hz). In DWT, the square of the standard deviation of wavelet coefficients at each level is concordant with the spectral power of that level (2). Reported values are expressed as the natural logarithm of TP, HF, LF and VLF; normalized units of LF ( $LF/(TP-VLF) \times 100$ ) and HF ( $HF/(TP-VLF) \times 100$ ); and the ratio between LF and HF. The use of normalized units minimizes the effect of the changes in total power on the values of LF and HF, and emphasizes the balanced behavior

of the two branches of the autonomic nervous system (20).

Subject's reports of waking and sleeping times and actigraphy records were not available for the pilot study. In general, visual inspection of the individual records showed a typical fall of heart rate during the night, with abrupt transitions between periods. These observations suggest a square wave model (two alternating contiguous periods of low and high heart rate) of the 24-hour heart rate record. These variations are similar to those seen in 24-hour beat-to-beat blood pressure recordings, where square wave modeling accounted for a larger fraction of circadian variance than modeling based on visual inspection, cosinor method or fixed clock time (11).

Briefly, 20-minute consecutive averages of RR-intervals were calculated. Square waves were constructed using all the possible different combinations of the low- and high-heart rate periods length. Both the averaged signal and each square wave were standardized to a mean of zero and a standard deviation of 1.0. Cross correlation values of the standardized RR-interval signal with all possible different standardized square waves were determined. The best fitting square wave was identified by the highest cross correlation value. This square wave was used to segment the original RR-interval record in a high (wake) and a low (sleep) heart-rate period. The transience time from the high- to the low- heart rate period was identified as  $t_{\text{down}}$  while transience time from the low- to the high-heart rate period was identified as  $t_{\text{up}}$  (Figure 2) (11). The fit resulting from this model is optimal with respect to the square error. The square of the highest cross correlation value expresses the fraction of total variation (FTV) of the 24-hour blood pressure profile accounted by the model (11).

[Fig. 2 here]

In four of the thirty records a low heart rate period was identified by the model within the daytime (before 20:00). Visual inspection of these records revealed two different low-heart rate periods better described by a biphasic square wave model. Therefore, the original record was fragmented in a daytime record (before 20:00) and a nighttime record (after 20:00). The model was applied to these separate fragments in order to finally construct a biphasic square wave with two different low (sleep) heart rate periods.

Hourly HRV was averaged along wake and night-time sleep periods. HRV differences between night-sleep and wake averages were also calculated. Each hour was assigned to a wake or to a sleep period according to the transience times previously defined. At least 55 minutes of any hour should fall within a specific period to be assigned to it; otherwise it was marked as a transition hour and excluded from the wake or sleep period average. Daytime sleep periods were marked as naps and excluded from the wake period average.

Statistical analysis

Sleep-wake data and HRV indexes were expressed as mean  $\pm$  standard error. Normality was assessed by means of a Kolmogorov-Smirnov test. A natural logarithm transform was used where needed.

Initially, in order to assess the effect of confinement by itself, sleep-wake data, wake HRV and sleep HRV indexes were averaged along non-confinement days (T1 and T5) and confinement days (T2, T3, T4). Differences between both conditions were evaluated through a paired-samples T-test.

Then, differences between measurements days (T1, T2, T3, T4 and T5) were assessed by means of a repeated measures ANOVA test, followed by a Tukey HSD post-hoc test. A Mauchly's sphericity test was conducted in order to use a univariate approach for ANOVA analysis; when sphericity could not be assumed a multivariate approach was preferred.

## Results

The mean  $t_{\text{down}}$  and  $t_{\text{up}}$  time points varied non-significantly between midnight and 02:00 AM and between 06:00 AM and 09:00 AM, respectively. These time points determined sleep periods with a mean duration of six to eight hours. Only subject # 2 wore the Holter while he was awake on nightshift after 24:00, showing a short night-time sleep period three hours before midnight, and no day-time sleep period. The fraction of the

variance explained by the model varied non-significantly during isolation between 55% and 75% (not shown).

Confinement was associated with a diminished mean heart rate and an augmented global HRV during the day. While the increase in HRV was verified in all frequency components, the comparison between components revealed a relative decrease of LF. These changes seem to be more evident in the second month of isolation as revealed by the significant decrease in LF/HF in T2 (Table I).

[Table I here]

During sleep, RR interval duration showed an increase during confinement (pre:  $1088 \pm 62$  ms; T1:  $1169 \pm 55$  ms; T2:  $1211 \pm 60$  ms; T3:  $1176 \pm 72$  ms; post:  $1112 \pm 58$  ms;  $F(4, 20) = 3.45$ ;  $p < 0.05$ ; T2 different from pre and post). However, no significant differences were found along measurements days in sleep-HRV (not shown).

When comparing wake- and sleep-HRV, it was observed that confinement was associated with a reduction of HRV sleep-wake differences in SDNN, TP, VLF, LF, HF and LF/HF. In addition, for TP and VLF, the sign of the mean difference changed (Table II). The analysis of contrasts between measurement days showed a significant decrease in RMSSD, HF and LF/HF sleep-wake differences. Post-hoc pairwise comparisons between measurements days only revealed a significant reduction of HF-HRV sleep-wake difference, where  $T1 < \text{post}$ ,  $T2 < \text{pre}$  and  $T2 < \text{post}$  (Table II).

[Table II here]

## Discussion

The main result of the present study is that during confinement, wake HRV showed decreased mean heart rate and increased amplitude at all frequency levels, with a decrease in the normalized units of the low-frequency HRV component. Sleep HRV remained constant. In addition, confinement was associated with a decrease of VLF-HRV, LF-HRV, HF-HRV and LF/HF sleep-wake differences and with the appearance of negative VLF-HRV sleep-wake differences. These changes seem to be more pronounced for HF-HRV and in the middle of the confinement period. No significant differences were found in the length or phase of the sleep-wake periods.

Heart rate oscillations at all frequency levels (VLF, LF and HF) reflect parasympathetic influences (20;21), while LF fluctuations are also tightly coupled with synchronous oscillations of efferent sympathetic nervous activity (21). Thus, the increase in HRV at all frequency bands, with a relative decrease in the LF component along confinement, can be explained by an augmented parasympathetic activity with a loss of sympathetic predominance during wake periods. The increased vagal predominance during the day can also account for the vanishing of the sleep-wake differences of SDNN, LF and HF (usually positive) and LF/HF (usually negative), as well as for the appearance of negative sleep wake differences of TP and VLF (usually positive) (10).

These results are in line with observations reported in space analogue environments like Antarctica. In a 40-day stay in the Italian Antarctic Station of Terra Nova Bay, a relative significant decrease of LF was found, which was interpreted as a reduced sympathetic activity. This was associated with a significant reduction of the anterior pituitary and adrenal hormonal levels of the pituitary-adrenal hormonal axis. In addition, only daytime HRV values were different from baseline measurements, while nighttime measurements only differ within the isolation period (7).

Several factors may account for the observed results. Operational demands or social and recreational activities could cause sleep disturbances in spaceflights (5) that in turn may disrupt other circadian physiological rhythms (14). However, poor sleep quality is associated with daytime reductions in HF HRV and heartbeat intervals (12) that contrast with the present observations. Moreover, we failed to demonstrate significant differences in sleep periods length and phase.

Varying light exposure and reduced sensitivity to Zeitgeber strength during space missions were also associated with circadian rhythms disruptions. It is known that light is the dominant environmental input affecting rhythms (14). Sympathetic activity during the day increases with color light temperature (26) and light intensity (27). In this regard, the loss of sympathetic predominance reported herein may be associated with a prolonged exposure to the artificial environmental light of the isolation facility, of lower intensity and color temperature than natural light.

Changes in mood related to confinement stressors like loneliness, boredom or social stress should also be considered as factors that may explain the observed results. During a winter in Antarctica it was reported that tension, anxiety, depression, anger and confusion decline during the first half of the isolation period and increase close to the end of isolation (17). Psychophysiological data from this pilot study presented by other authors showed that, although mood tends to decrease until day 77 of isolation, differences within the 105 days of confinement were not significant (19). Also, apart from mean heart rate, no changes were seen in sleep HRV indexes, which are known to be sensitive markers to psychological stressors (9). Thus, the effect of mood changes in the observed results, if any, seems to be small.

Physical training is another factor that may be associated with changes in HRV. Confinement of almost any kind is associated with decreased physical load, even with implementation of special exercise programs. However, opposite to what is seen in the present study, HF HRV is reduced in sedentary subjects when compared to physically active ones (8).

The differences between confinement and non-confinement days could be magnified by a combined effect of increasing tension in anticipation of being locked up (T1) plus increased exposure to environmental and social demands after the confinement (T5). In this regard, the reduced environmental stimulation and regularly paced, quite predictable and well-structured activity schedules during the confinement could be interpreted as a less stressful and healthier situation (4). However, increased vagal tone by itself should not

necessarily be considered as an index of increased health, since it can also be seen in pathologic conditions such as panic disorder (15).

Although Holter measurements were performed almost exclusively on day-shifts, the effect of the night shifts in ANS activity should be taken into consideration. When comparing with day workers, shift work is associated with an increase in sympathetic activity either during wake periods (increase in heart rate and LF%, decrease in SDNN) or during sleep periods (decrease in SDNN) (24). Therefore, the increase of parasympathetic activity associated with long term confinement reported herein is unlikely to be due to the rotating shift work regime. The 520-day study will provide more data to analyze if the present results are modified by taking into account the day-time sleep periods associated with night-shifts.

The results from the present study may be important since performance is associated to autonomic arousal. Specifically, it has been reported that the increase in LF-HRV and HF-HRV (as seen during confinement) is related to decreased attentional processing evaluated through an attentional load test (d2 test) (6). Objective physiological measures could be used to characterize differences in operational efficiency, as well as abilities to adapt to extreme environments. In turn, fatigue-related performance decrements caused by sleep loss or sustained operations might be improved with training to regulate crew-member responses including autonomic and central nervous system parameters (3).

Several limitations should be considered. First, conclusions are restricted due to the small numbers of subjects, typical of this kind of research. Also, it remains to be seen how these results would translate to real space missions, where there is always the possibility of

not getting back to Earth, an important stressor by itself. In addition, the precise determination of sleep – wake periods requires other techniques such as the recording of actigraphic data, not accessible due to the limitations of experimental procedures within this pilot-study. Finally, the observed pattern of autonomic activity could be part of an infradian rhythm that could only be evidenced in longer confinement periods.

To conclude, data obtained during the 105-day isolation experiment revealed a loss of sympathetic predominance during wake periods. Several factors could account for this observation, including reduced daylight exposure related to the confinement situation. Further studies should address if decreased autonomic arousal may affect cognitive performance during long-term space missions.

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**Table I: Wake HRV**

	pre	T1	T2	T3	post	Conf. T (5)	Day F (4,20)
RRM (ms)	780 ± 37	908 ± 36	944 ± 46 <sup>§,¶</sup>	896 ± 54	797 ± 57	-2.42	4.73 <sup>†</sup>
SDNN (ms)	92 ± 10	128 ± 17 <sup>§,¶</sup>	120 ± 13 <sup>§,¶</sup>	121 ± 15 <sup>§,¶</sup>	90 ± 10	-3.78 <sup>*</sup>	7.68 <sup>†</sup>
RMSSD (ms)	31 ± 5	46 ± 9	46 ± 8	42 ± 9	31 ± 5	-2.39	4.55 <sup>†</sup>
ln TP (wpc)	13.4 ± 0.2	14.0 ± 0.3 <sup>§,¶</sup>	13.9 ± 0.2 <sup>§,¶</sup>	13.9 ± 0.2 <sup>§,¶</sup>	13.3 ± 0.2	-4.21 <sup>†</sup>	9.31 <sup>‡</sup>
ln VLF (wpc)	13.3 ± 0.2	13.9 ± 0.3 <sup>§,¶</sup>	13.9 ± 0.2 <sup>§,¶</sup>	13.9 ± 0.2 <sup>§,¶</sup>	13.2 ± 0.2	-4.18 <sup>†</sup>	9.18 <sup>‡</sup>
ln LF (wpc)	10.4 ± 0.2	10.9 ± 0.3 <sup>§,¶</sup>	10.7 ± 0.2	10.7 ± 0.3	10.3 ± 0.2	-3.79 <sup>*</sup>	5.51 <sup>†</sup>
ln HF (wpc)	7.6 ± 0.4	8.3 ± 0.5 <sup>§,¶</sup>	8.2 ± 0.4 <sup>§,¶</sup>	8.1 ± 0.4	7.6 ± 0.3	-4.09 <sup>†</sup>	8.52 <sup>‡</sup>
LF (nu)	93.5 ± 1.0	92.2 ± 1.3	92.0 ± 1.2 <sup>§</sup>	92.7 ± 1.1	93.3 ± 0.7	2.80 <sup>*</sup>	3.90 <sup>*</sup>
HF (nu)	6.5 ± 1.0	7.8 ± 1.3	8.0 ± 1.2 <sup>§</sup>	7.3 ± 1.1	6.7 ± 0.7	-2.80 <sup>*</sup>	3.90 <sup>*</sup>
LF/HF	17.1 ± 3.0	14.9 ± 3.0	13.9 ± 2.2 <sup>§,¶</sup>	15.4 ± 2.5	16.5 ± 2.6	3.00 <sup>*</sup>	5.03 <sup>†</sup>

Values are expressed as mean ± standard error. Conf.: contrast between confinement and non-confinement (paired-samples t-test); Day: contrast between measurement days (repeated measures ANOVA followed by Tukey HSD post-hoc test); RRM, mean of RR interval duration (ms); SDNN, standard deviation of RR intervals (ms); RMSSD, square root of the mean squared differences of successive normal RR (ms); TP, total area power; VLF, very low frequency power; LF, low frequency power; HF, high frequency power; wpc, wavelet power coefficients; nu, normalized units. \* p<0.05; † p < 0.01; ‡ p < 0.001; § different from pre; ¶ different from post.

**Table II: Sleep – wake HRV differences**

	pre	T1	T2	T3	post	Conf. T (5)	Day F (4,20)
RRM (ms)	308 ± 40	261 ± 30	267 ± 36	281 ± 25	315 ± 20	1.72	1.15
SDNN (ms)	16 ± 9	5 ± 7	-4 ± 9	-8 ± 6	23 ± 10	4.30 <sup>†</sup>	2.47
RMSSD (ms)	23 ± 7	11 ± 2	8 ± 5	13 ± 3	25 ± 6	2.38	2.96 <sup>*</sup>
ln TP (wpc)	0.1 ± 0.2	-0.1 ± 0.1	-0.3 ± 0.1	-0.3 ± 0.1	0.2 ± 0.2	3.76 <sup>*</sup>	2.34
ln VLF (wpc)	0.1 ± 0.2	-0.1 ± 0.1	-0.3 ± 0.1	-0.3 ± 0.1	0.2 ± 0.2	3.56 <sup>*</sup>	2.20
ln LF (wpc)	0.4 ± 0.2	0.2 ± 0.1	0.1 ± 0.1	0.2 ± 0.2	0.5 ± 0.1	3.48 <sup>*</sup>	1.74
ln HF (wpc)	0.8 ± 0.2	0.2 ± 0.1 <sup>§</sup>	0.1 ± 0.2 <sup>‡,§</sup>	0.3 ± 0.1	0.9 ± 0.1	3.67 <sup>*</sup>	5.70 <sup>†</sup>
LF (nu)	-1.3 ± 2.0	-1.3 ± 0.7	-1.8 ± 1.1	-2.5 ± 1.5	-2.0 ± 1.6	2.06	0.12
HF (nu)	1.3 ± 2.0	1.3 ± 0.7	1.8 ± 1.1	2.5 ± 1.5	2.0 ± 1.6	-2.06	0.12
LF/HF	-4.2 ± 0.7	0.5 ± 1.4	1.0 ± 1.6	-1.1 ± 1.7	-4.0 ± 2.8	-4.45 <sup>†</sup>	3.91 <sup>*</sup>

Values are expressed as mean ± standard error. Conf.: contrast between confinement and non-confinement (paired-samples t-test); Day: contrast between measurement days (repeated measures ANOVA followed by Tukey HSD post-hoc test); RRM, mean of RR interval duration (ms); SDNN, standard deviation of RR intervals (ms); RMSSD, square root of the mean squared differences of successive normal RR (ms); TP, total area power; VLF, very low frequency power; LF, low frequency power; HF, high frequency power; wpc, wavelet power coefficients; nu, normalized units. \* p<0.05; † p < 0.01; ‡ different from pre; § different from post.

## Captions for figures

**Figure 1.** Physiological mechanisms underlying heart rate variability. Respiratory rhythm is associated with high frequency changes of heart rate, mediated by parasympathetic activity; the baroreflex function is associated with low frequency changes of heart rate, mediated by sympathetic and parasympathetic activity; while less settled processes like temperature regulation or endocrine systems are related with very low frequency changes of heart rate, with dependence on the presence of parasympathetic outflow. The analysis of the power of these rhythms permits inferences on the function of sympathetic and parasympathetic activity. Several structures are involved in the central autonomic control of these mechanisms, including the insular cortex, prefrontal cortex, hypothalamic areas, amygdala, midbrain and pons areas and medullary nuclei. P: parasympathetic; S: sympathetic; VLF: very low frequency; LF: low frequency; HF high frequency.

**Figure 2.** Typical example of a 24-hour recording of RR intervals standardized to a mean of zero and a standard deviation of one (light grey line). The corresponding 20-minute interval averaged signal (black thin line) and a square wave fit are also shown (black thick line).  $T_{\text{down}}$  and  $t_{\text{up}}$  represent the transience time to the low and high heart rate periods, as indicated by the square wave fit, with the sleep period (light grey area) within them.

Figure 1  
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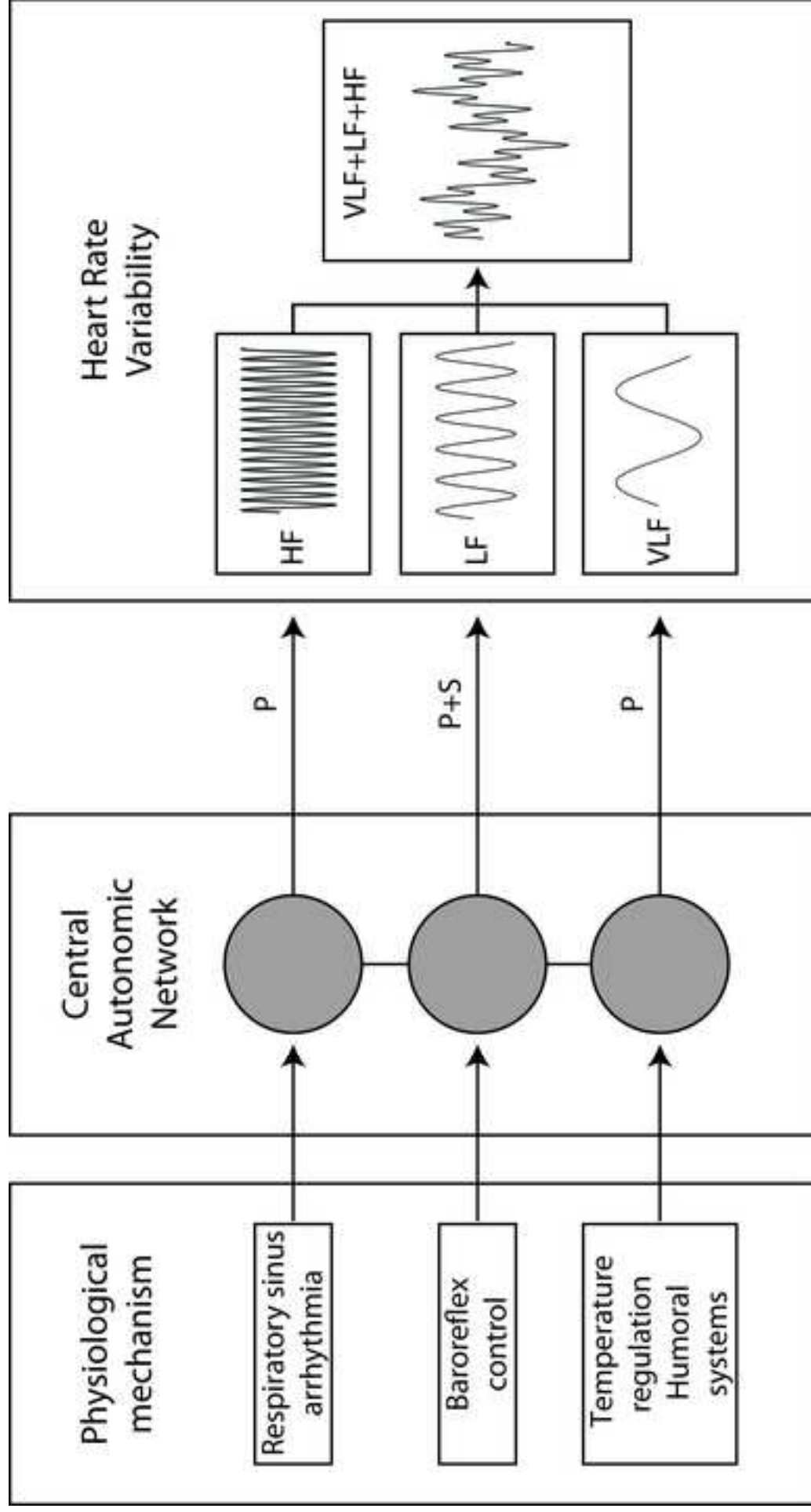


Figure 2  
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