Effects of an Anthroposophical Remedy on Cardiorespiratory Regulation

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Running title:
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Context The human organism has the inherent ability to regulate and coordinate physiological functions to establish well-being. If this ability is disturbed, eg, in cases of orthostatic syndrome with purely functional disorders, an herbal remedy based on anthroposophical medicine may be able to regulate such rhythmic disturbances.

Objective To determine the effect of the anthroposophical herbal remedy on stimulating the ability to regulate and coordinate physiological functions in healthy subjects.

Design Double-blind, placebo-controlled, randomized trial.

Participants Ninety-nine healthy subjects; 49 received the remedy, 50 received the placebo.

Intervention Oral administration of the remedy for 4 weeks, 20 drops 4 times daily.

Main Outcome Measures Cardiorespiratory interaction was analyzed by 2 measures: the heart-respiratory ratio and the phase-coordination ratio of heartbeat and respiration. They were calculated from heart rate and respiratory rate, which were derived from 24-hour electrocardiogram recordings before and after the administration of the remedy. Improved normalization of these measures during nighttime sleep after administration of the remedy indicates a stimulation of regulation.

Results Oral administration of the remedy resulted in an improved normalization of heart-respiratory ratio, phase-coordination ratio and heart rate during nighttime sleep. These results were not observed in the placebo group.

Conclusions The remedy stimulates the regulation of cardiorespiratory interaction during nighttime sleep. Furthermore, improved normalization indicates a general improvement of the regulatory processes of functional rhythms.

Introduction

The human organism has many inherent functional rhythms. The most obvious, heart beat and respiration, have been studied in detail (e.g. by analyzing heart rate variability[1] and characteristic features of respiration[2]). The circadian variations of heart rate and respiratory rate show that heart rates seem to share a similar circadian profile[3] whereas respiratory rates are more distinct for each individual[4] (see Figure 1).
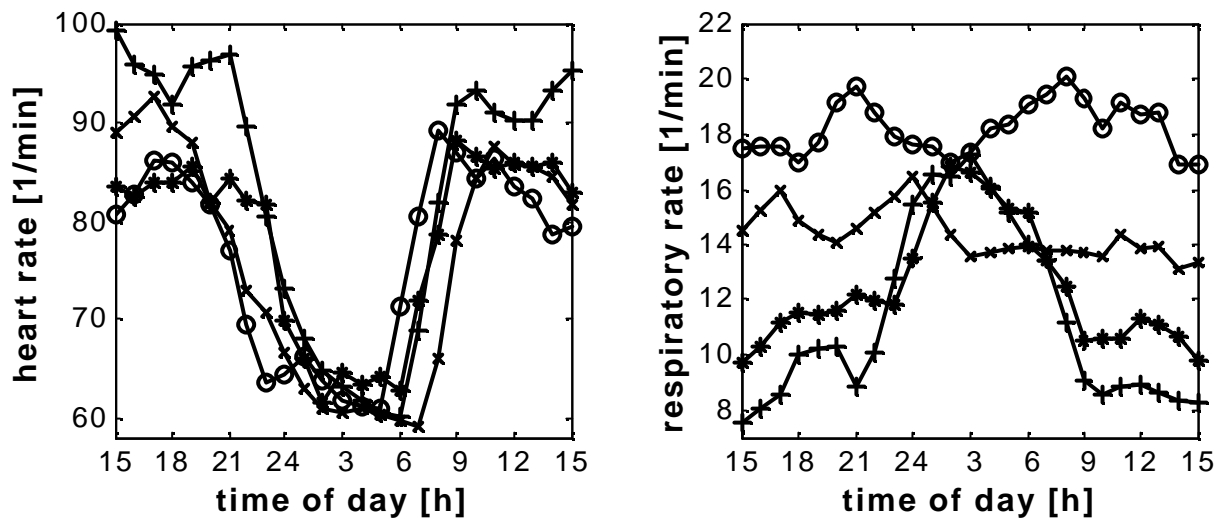

Figure 2:   Circadian variation of heart rate and respiratory rate of 4 healthy subjects. Heart rates show comparable profiles for all subjects; respiratory rates are more individualized.

Furthermore, the ratio of heart rate and respiratory rate (further denoted as heart-respiratory ratio) also shows a circadian profile. This profile has two characteristic features. (1) During the day it shows a considerable individual variation due to different activities and the subjects' physiological constitution. (2) These individual deviations are minimized during night time sleep: the mean heart-respiratory ratio of all subjects is 4[5-7], i.e. during sleep each respiratory cycle is accompanied by 4 heart beats on average (see Figure 2). This feature is called 'normalization'[5]. It is based on self-regulatory processes and helps in the organism's recovery and relaxation[8]. Although the heart-respiratory ratio is a relatively rough measure that can be calculated simply it can be used as a prognostic factor in diseases such as myocardial infarction[9].

Information about the cardiorespiratory interaction obtained by the heart-respiratory ratio can be refined by analyzing the synchronization between heart beat and respiration[10]. These techniques take into account the temporal distance between inspiratory onset and successive R-waves during the respiratory cycle. They give more detailed information about cardiorespiratory interactions, e.g. after myocardial infarction[11]. Another refined technique calculates the 'phase-coordination-ratio' that was recently introduced by our group[7,12]. this technique analyzes typical heart rate patterns resulting from in-phase modulations of heart rate by respiration through respiratory sinus arrhythmia. In healthy subjects during nighttime sleep the phase-coordination ratio correlates strongly with the heart-respiratory ratio and also

tends to the integer 4^{7}. Compared to the heart-respiratory ratio the phase-coordination ratio also increases the amount of information about cardiorespiratory interactions[13].
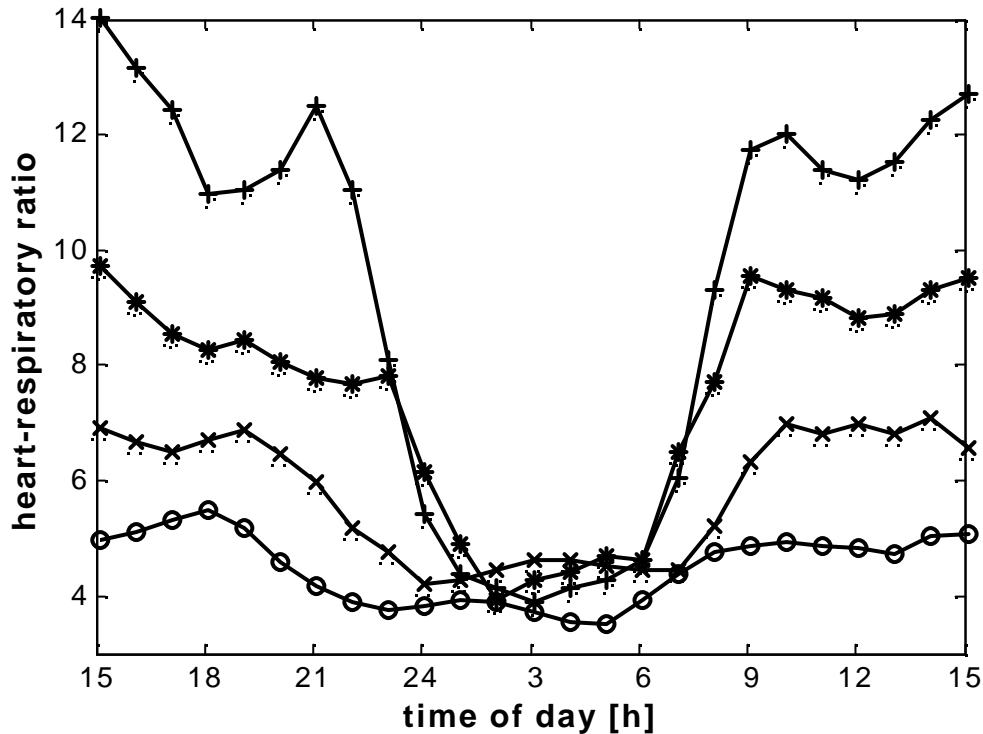

Figure 2: Circadian variation of heart-respiratory ratio for the same 4 subjects. Note that during nighttime sleep, the mean ratio for all subjects tends to 4.

In this study, the heart-respiratory ratio and the phase-coordination ratio were applied to investigate the effect of an herbal product (POH), consisting of extracts from Primula officinalis, Onopordon acanthium and Hyoscyamus niger (Cardiodoron®*). This product is used in anthroposophical medicine to treat purely functional disturbances of the cardiovascular system (e.g. orthostatic syndrome) and 'to regulate the rhythmic system' that comprises all functional rhythms in the human organism, particularly heart rate and respiration[14]. This indication implies that the interaction and coordination between closely related rhythms is as important as the quality of the separate rhythms. Thus POH should have an effect on heart beat and respiration as well as their interaction, especially during nighttime sleep when normalization processes take place. Therefore we tested the hypothesis that an oral administration of POH for 4 weeks alters cardiorespiratory interaction as quantified by heart-respiratory ratio and phase-coordination ratio especially during nighttime sleep in healthy subjects.

Methods

Subjects

Data from a previously published randomized controlled double blind study were re-analyzed[15]. Ninety-nine healthy subjects without any history of cardiovascular or pulmonary diseases in the age of 20 to 41 years (mean ± SD: 28.6 ± 7.0; 46 males) were included. Forty-nine subjects took POH and 50 received placebo. No additional cardiovascular medication was allowed. The placebo consisted of a water dilution with 24 vol.-% alcohol. All subjects gave their informed written consent. The study was approved by the local ethics committee.

Procedure

Before taking POH two successive 24-hour electrocardiograms (ECGs) were recorded. In the following, POH or placebo were then taken for 28 days (4 x 20 drops / day). A third 24-hour ECG was recorded on day 30 to evaluate physiological effects of POH. A final 24-hour ECG was recorded on day 44, 14 days after stopping the intake of POH. The study flowchart is shown in Table 1. All subjects kept a diary in which, in particular, the sleeping times were noted.

Day	Treatment
1	24-hourECG A
2	24-hour ECG B
3-30	POH intake (4 x 20 drops/day)
30	24-hour ECG C
44	24-hour ECG D

Table 1: Cardiorespiratory regulation study flow chart (ECG: electrocardiogram).

Heart rate and cardiorespiratory interaction

24-hour ECGs were recorded using Oxford FD3 solid state recorders with simultaneous R wave detection (Oxford, Abingdon, UK). An Oxford Excel ECG analyzer permitted the automatic evaluation of heart rates and visual inspection of the automatically detected R waves. The R times of all heartbeats were written to a binary data file for further analysis.

Instantaneous heart rates were calculated from each 24-hour ECG, and respiratory rates were extracted from respiratory sinus arrhythmia (RSA), i.e. the sinus-like frequency modulations of heart rate by respiration[7]. This allowed calculation of the heart-respiratory ratio as the average of the mean heart rate and the momentary RSA cycle length which is equivalent to respiratory rate. The heart-respiratory ratio served as a simple measure of cardiorespiratory interaction because the ratio is calculated regardless of the temporal distance between the onset of inspiration and successive R waves. Mean heart rate, respiratory rate and heart-respiratory ratio were calculated for each minute of the recording.

A second technique to quantify aspects of cardiorespiratory interaction used the instantaneous acceleration and deceleration from heartbeat to heartbeat, derived from the R waves in the ECG. Each acceleration and deceleration was coded and subsequently united to form patterns[12]. If heart beat and respiratory rhythm are synchronized, i.e. the sinus-like frequency modulations of heart rate by respiration are in-phase, typical patterns predominantly recur. Many of these recurrent patterns can be unambiguously assigned to a ratio between heart rate and respiratory rate. These ratios are used to calculate the phase-coordination ratio. Further details are given in the literature.

Statistics
The goal of the study was to gauge the effects of POH on cardiorespiratory interaction as quantified by the heart-respiratory ratio and phase-coordination ratio. Any effect of POH should become obvious during the normalization process that occurs during nighttime sleep. This normalization of the 2 ratios has 2 characteristic features: (1) the parameters tend toward the mean of the group ("normal" value), and (2) the direction and strength of these changes depend on their initial value.

The mean and standard deviation of all parameters were calculated for the sleeping period from 1 a.m. to 5 a.m. if not stated otherwise in the diary. Thus the circadian variations of cardiac activity were taken into account and comparable levels of activity in all subjects were assured. Because heart-respiratory ratio and phase-coordination ratio had skewed distributions, they were log-transformed before further evaluation. All calculations were made with Matlab 6.0 (The Mathworks, Natick, Mass, USA).

Normalization was quantified by a regression analysis. The difference of a parameter (e.g., heart-respiratory ratio) between 2 ECG recordings was plotted against its initial value for all subjects. This led to diagrams in which the direction and strength of change between the 2 ECG recordings became visible. In such a diagram the linear dependence is quantified by the Pearson correlation coefficient r and serves as a measure of the strength of normalization. The normalization of a parameter manifested in a negative correlation coefficient; ie, initial values above the mean have a negative difference (they decrease) and initial values below the mean have a positive difference (they increase). The more likely the normalization, the more the correlation coefficient tends toward -1 (perfect normalization). In the absence of normalization the correlation coefficient tends to zero (no normalization). The probability of rejecting the null-hypothesis of zero correlation (no normalization present) was calculated. A P value $<.05$ was considered statistically significant.

Results

Table 2 lists the mean and standard deviation of all parameters. The average heart rate was 60.4 (POH) and 61.7 beat per minute (placebo); the average respiratory rate was 15.8 (POH) and 15.9 (placebo) breaths per minute. Both the heart-respiratory ratio and the phase-coordination ratio were approximately 4. These results demonstrate virtually no group differences nor any systematic changes in the time course from ECG A-D in any of the parameters.

To explore normalization processes between two ECG recordings the differences were plotted against the initial values (see examples in Figures 3 and 4). The means of the differences are always approximately 0 as noted by the dashed lines.

On the other hand, the corresponding correlation coefficients were all negative as shown in Table 3. The correlation coefficients for heart rate, heart-respiratory ratio and phase coordination ratio show three important findings: (1) the correlation coefficients are greater after the administration of POH than after placebo. (2) in the POH group, the correlation coefficients are greater for differences from baseline ECG A and B to ECG C than from baseline ECG A and B to ECG D. Therefore the normalization effect of POH was stronger immediately following the use of the product than two weeks later. (3) Additionally, in the POH group all correlation coefficients are statistically significant compared to placebo.

ECG	heart rate [1/min]		respiratory rate [1/min]		heart-respiratory ratio		phase-coordination ratio	
	POH	Placebo	POH	Placebo	POH	Placebo	POH	Placebo
A	60.9 ± 7.7	62.5 ± 7.1	15.7 ± 2.1	15.8 ± 2.2	3.98 ± 1.22	4.08 ± 1.20	4.05 ± 1.18	4.15 ± 1.16
B	60.0 ± 7.4	61.7 ± 7.7	15.6 ± 2.3	15.8 ± 2.2	3.97 ± 1.22	4.04 ± 1.21	4.05 ± 1.18	4.10 ± 1.16
C	60.2 ± 6.6	61.5 ± 8.3	15.9 ± 2.3	16.1 ± 2.2	3.90 ± 1.20	3.96 ± 1.21	3.98 ± 1.16	4.01 ± 1.17
D	60.4 ± 7.8	61.0 ± 8.5	15.9 ± 2.2	15.9 ± 2.1	3.90 ± 1.21	3.97 ± 1.22	3.98 ± 1.17	4.03 ± 1.17

Table 2: Mean and standard deviation of all parameters for the night-time periods. ECG A and B denote recordings before intake of the medicament, ECG C was recorded on the last day of intake and ECG D two weeks after the intake ended.

	r (heart rate)		r (respiratory rate)		r (heart-respiratory ratio)		r (phase-coord. ratio)	
	POH	Placebo	POH	Placebo	POH	Placebo	POH	Placebo
A vs. C	-0.58***	-0.08	-0.06	-0.20	-0.44**	-0.13	-0.45**	-0.20
A vs. D	-0.38**	-0.10	-0.02	-0.37**	-0.38**	-0.10	-0.43**	-0.21
B vs. C	-0.52***	-0.20	-0.24	-0.15	-0.43**	-0.22	-0.50***	-0.18
B vs. D	-0.31*	-0.17	-0.27	-0.36*	-0.36*	-0.18	-0.48***	-0.15

* p<.05   ** p<.01   *** p<.001

Table 3: Correlation coefficients (Pearson's r) of nighttime parameters between two ECGs. Asterisks denote levels of significance.
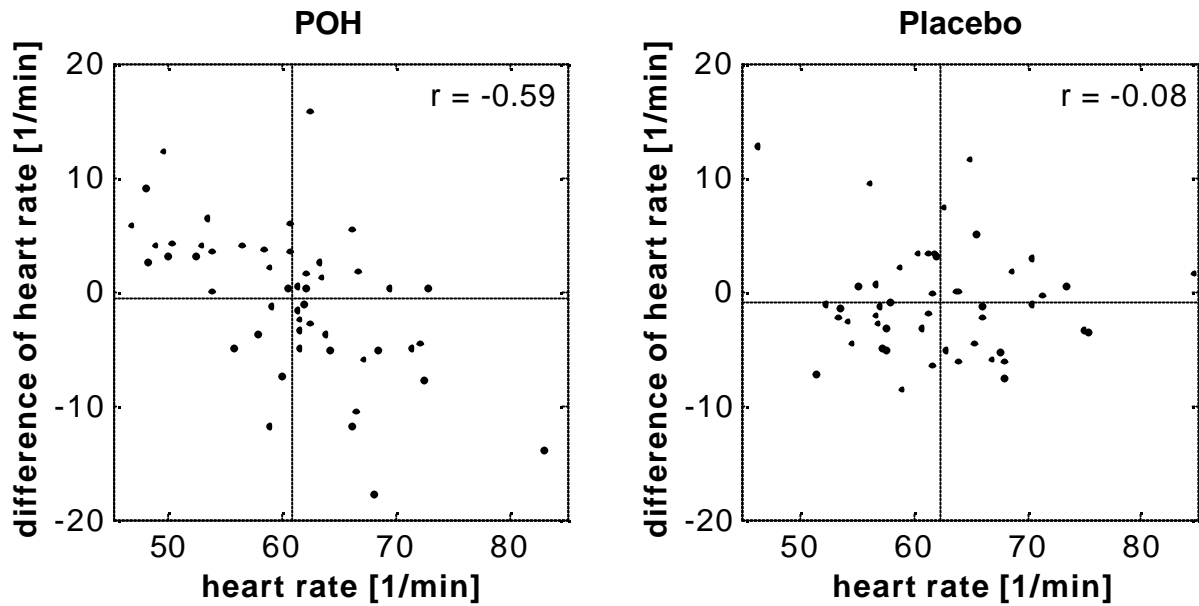
Figure 3: Comparison of heart rates in groups receiving POH and placebo. Note lack of correlation in placebo group. Dashed lines indicate mean of initial heart rate and mean of difference; *r*=Pearson's correlation coefficient.
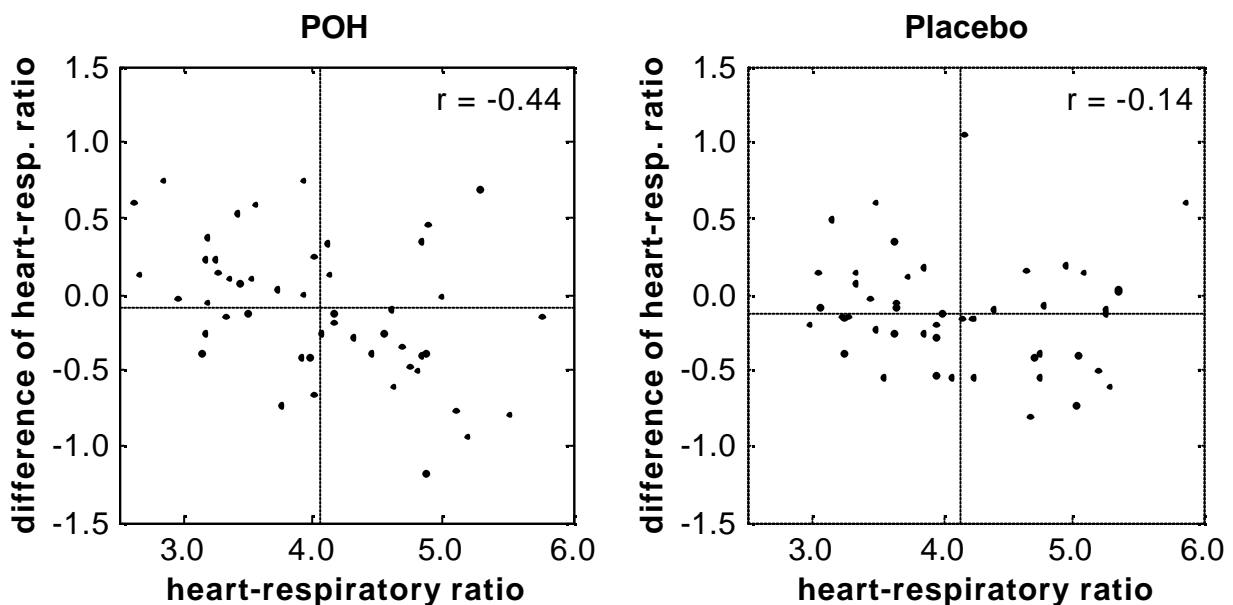

Figure 4: Comparison of heart-respiratory ratios in groups receiving POH and placebo. Note lack of correlation in placebo group. Dashed lines indicate mean of initial heart-respiratory ratio and mean of difference; *r*=Pearson's correlation coefficient.

Discussion

In a previously published randomized controlled study we investigated the use of POH in healthy subjects with respect to spectral parameters of heart rate variability. After the administration of POH the high frequency-component during the night was increased in a subgroup[15], i.e. the modulation of heart rate by respiration (respiratory sinus arrhythmia) was increased in these subjects. Furthermore, POH altered the heart rate which led to the question of whether cardiorespiratory interaction also was affected. In this paper, our analysis focused on the cardiorespiratory interaction. Heart-respiratory ratio and phase-coordination ratio served as parameters to quantify cardiorespiratory interaction. Heart rate and respiratory rate were analyzed to explore the influences of changes in the cardiorespiratory interaction.

After the administration of POH neither the mean nor the standard deviation of the parameters differed between the groups, nor did the time course of each group show changes in the values before and after. But in the POH group heart rate, heart-respiratory ratio and phase-coordination ratio showed a normalization, i.e. a negative linear correlation between the differences of before and after using the medication and the before values.

The respiratory rate did not normalize, so the normalization of the heart-respiratory ratio was mainly caused by the heart rate's normalizing[6,7]. The cardiorespiratory normalization was seen best immediately after POH intake was stopped because the correlation coefficients were largest between baseline ECG A (and B) to ECG C (see Table 3, first and third row). Two weeks later the normalization tended to disappear because the correlation coefficients between baseline ECG A (and B) to ECG D decreased (see Table 3, second and forth row). These results indicate that POH enhanced the normalization during nighttime sleep. The phase-coordination ratio showed similar results. Therefore, the improved normalization was characterized by a change of coordination between heart beat and respiration toward the integer ratio 4.

During nighttime sleep the normalization of the heart-respiratory ratio and the phase-coordination ratio toward the integer frequency ratio of 4 demonstrates that self-regulatory processes take place in the human organism. Self-healing and recovery processes are based on these self-regulations[8]. As POH improved the normalization, self-regulation of the rhythmic system was improved. Thus POH is able to support recovery processes of the rhythmic system and therefore strengthens self-healing processes. Although we did not investigate this, the involved vegetative regulations of the autonomous nervous system may be affected when the normalization process is altered.

The normalization process could be interpreted as a spontaneous 'regression to the mean'-artefact. But an artefact regression should have been also observed in the placebo group because both groups were comparable with respect to their means and standard deviations in baseline ECG A and B. Therefore, the results strongly suggest that POH normalized heart rate and cardiorespiratory coordination whereas placebo did not. Obviously, the respiratory rate was not similarly affected by POH. The two significant correlations in the placebo group are the only significant correlations in the placebo group. Thus these linear correlations in the placebo group seem to be caused by chance.

In an earlier study on POH in patients suffering from orthostatic syndrome (i.e. dysregulation of the rhythmic system) the medicament also led to a normalization of the heart-respiratory ratio to the integer 4 in the supine position[16]. As the orthostatic syndrome manifests itself through large fluctuations of heart rate and respiratory rate[17] POH apparently affected both rhythms. Although the methods used to determine the heart-respiratory ratio in the stated

study are not comparable to the methods used in the present study, the early results demonstrated in symptomatic patients that the stimulation of self-regulatory processes by POH may also induce changes in both rhythms.

In conclusion, the results of the heart-respiratory ratio and phase-coordination ratio shows that POH stimulates self-regulatory processes, i.e. the interaction of heart beat and respiration is more coordinated. This is expressed in an improved normalization towards the integer ratio 4 during nighttime sleep. This kind of stimulation is supposed to enhance self-healing and recovery capabilities. As POH has only been studied in healthy subjects and in patients suffering from orthostatic syndrome it remains to be shown if a stimulation of self-regulatory processes by POH is also advantageous in combination with standard therapies for more severe heart diseases such as chronic heart failure or coronary artery disease.

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