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Evaluation of modulations in heart rate variability caused by a composition of herbal extracts

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SUMMARY

The purpose of this prospective, placebo-controlled, randomized double-blind study was the examination of changes in the basic vegetative rhythms due to Cardiodoron®. This medicine is a composition of extracts of blossoms from Primula officinalis and Onopordon acanthium and from the herbs of Hyoscyamus niger. In its clinical use it is known as a modulating medicine in the treatment of functional disturbances of the cardiovascular system. With use of Holter monitoring, 24-h ECG recordings were obtained from 100 healthy subjects of whom 50 took the composition and 50 a placebo. Heart rate variability was evaluated from the 24-h ECGs by means of a power spectral analysis based on the Fast Fourier Transformation (FFT). Regulative influences of changes on the rhythmic system due to the medicine were found. After four weeks of medication half of the verum group showed a tendency to an increased variability in the low and high frequency range at night (LFn: 0.04 – 0.15 Hz, HFn: 0.15 – 0.4 Hz) in contrast to the placebo group. The mean heart rate at night (HRn) showed a tendency of normalization in the verum group: in subjects with a low HRn the heart rate was increased and in subjects with a high HRn the heart rate was decreased. This effect could not be observed in the placebo group. After two further weeks without any medication this difference between verum and placebo was abolished.

Keywords:
heart rate variability, spectral analysis, rhythmic system

ZUSAMMENFASSUNG

Ziel dieser prospektiven, randomisierten, Plazebo-kontrollierten Doppelblindstudie war die Untersuchung der Änderungen der vegetativen Rhythmen durch Cardiodoron®. Dieses Medikament ist eine Mischung von Auszügen aus Blüten von Primula officinalis und Onopordon acanthium und aus dem blühenden Kraut von Hyoscyamus niger. In der klinischen Anwendung wird es als modulierendes Medikament bei der Behandlung von funktionellen Herz- und Kreislaufstörungen eingesetzt. Von insgesamt 100 gesunden Probanden, von denen 50 das Verum und 50 ein Plazebo einnahmen, wurden 24-Stunden-EKGs aufgezeichnet. Die Herzperiodenvariabilität wurde mit der Spektralanalyse, basierend

auf der Fast Fourier Transformation, aus dem 24-Stunden-EKG errechnet. Regulierende Einflüsse des Medikaments auf das Rhythmische System konnten erfaßt werden. Nach vierwöchiger Einnahme des Medikaments zeigte die Hälfte der Verum-Gruppe gegenüber der Plazebo-Gruppe eine Tendenz zu einer gesteigerten Variabilität in dem nächtlichen nieder- und hochfrequenten Bereich (LFn: 0.04 – 0.15 Hz, HFn: 0.15 – 0.4 Hz). Die mittlere nächtliche Herzfrequenz (HRn) zeigte ebenfalls in der Verum-Gruppe eine Tendenz zur Normalisierung: bei Probanden mit einer anfänglich niedrigen HRn stieg nach der vierwöchigen Einnahme die Herzfrequenz an und bei Probanden mit einer hohen HRn fiel sie ab. Dieser Effekt konnte in der Plazebo-Gruppe nicht festgestellt werden. Nach zwei weiteren Wochen ohne Medikation waren die Unterschiede zwischen beiden Gruppen nicht mehr vorhanden.

Schlüsselwörter:
Herzperiodenvariabilität, Spektralanalyse, Rhythmisches System

1. INTRODUCTION

In recent years chronobiological research revealed more and more of the complexity of rhythmical processes in man. This autonomous system of endogenous and spontaneous rhythms comprises physiological and pathological oscillation patterns, the so-called rhythmic system [1]. In the past there was a lack of methods to characterize this complex system and its location in the organism. Heart rate variability (HRV) as a method to characterize the heart rate from continuous 24-h ECG recordings has been established recently [2]. With this method even subtle effects of drugs which interact less strong on the rhythmic system can be measured. Thus slight alterations of rhythmic regulations in healthy subjects could be found [3].
In this study the effects of the composition of extracts of blossoms from Primula officinalis and Onopordon acanthium and from the herbs of Hyoscyamus niger known as Cardiodoron®* were investigated. It is clinically used as a modulating medicine in the treatment of functional disturbances of the cardiovascular system. Preliminary examinations of the acute administration of this composition of herbal extracts (5%, 1 ml injected subcutaneously 4 times in 24 hours) on the HRV resulted in a decrease of the very low frequency component at night [3]. In this study the orally given composition of herbal extracts was examined exploratory in order to find influences on the HRV in healthy subjects. An alcoholic dilution was used as a placebo.

2. METHODS

Subjects

From january to august 1997 100 subjects without any history of cardiovascular or pulmonary diseases in the age of 20 to 41 years (mean ± SD: 28,6 ± 7,0) were included into the randomized and double-blind study (46 males). Fifty subjects took the composition of herbal extracts and 50 a placebo for 28 days (4 x 20 drops / day). Any further cardiovascular medication was not allowed. One female subject (verum group) was excluded from the study. After all, 49 subjects in the verum and 50 subjects in the placebo group were evaluated.
The study lasted six weeks for each subject (see figure 1). The medication had to be taken from the 3rd to the 30th day. Four 24h-ECGs were recorded (on the 1st, 2nd 30th and 42nd day), further denoted as ECG A-D. The subjects were asked to have no vacation and to live a

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regular working life. Habits like smoking or non-smoking were to be kept for the duration of the study. All subjects gave their informed written consent. The study was approved by the local ethics committee.
All subjects kept a diary in which, in particular, the sleeping and waking times were noted. This allowed a differentiation of the data with respect to sleeping and waking periods. Most of the subjects slept at least from 1 a.m. to 5 a.m. at night. In 72 ECGs these times had to be corrected because of wakefulness. In this case the sleeping times were determined with the help of visual inspection of the mean heart rate.

Heart rate variability (HRV)
The 24h-ECGs were recorded with Oxford FD3 solid state recorders with simultaneous R wave detection. Automatic evaluation of heart rates was performed by an Oxford Excel ECG analyzer which also allowed the visual inspection of the automatically detected R waves. From each 24h ECG heart rate and the following frequency components were calculated for all 10 minute intervals: VLF: 0.004 - 0.04 Hz, LF: 0.04 - 0.15 Hz, HF: 0.15 - 0.4 Hz, TF (total): 0.004 - 0.4 Hz. The spectral analysis based on the methods of Bigger et. al. [4, 5]. Each 10-minute tachogram yielded integrated values in ms^2 units that correspond to the variance of the RR times.
To reduce information, taking the circadian variations of cardiac activity into account, the mean values for the times between 8 a.m. and 4 p.m. (daytime values) and between 1 a.m. and 5 a.m. (nighttime values) were calculated. The parameters were labelled 'd' and 'n' respectively.

Statistics
The statistical methods used in this paper are descriptive. Lower and upper quartiles, the median and, for reasons of comparison, the means and standard deviations of all distributions of the parameters are evaluated. To stabilize the values of the baseline ECG, the values of ECG A and ECG B are averaged. The values of ECG C and ECG D are divided through those of the averaged baseline ECG. Thus the values were interindividually standardized and comparable.
In this study we decided to explore the parameters of HRV in order to find differences between the verum group and the placebo group. Thus we did not intend to confirm a precise pre-defined hypothesis with a statistical test. Distributions of the parameters in the two groups are compared visually using empirical cumulative distribution functions (cdf). These are plotted for each relative HRV parameter separately in each group (cdf-plots). p-values of the Kolmogorov-Smirnov test are used solely to classify the differences in the distributions between the cdf-plots from the verum and the placebo group after four weeks of medication (ECG C).

3. RESULTS

Due to huge interindividual variations of the vegetative rhythms, no systematic differences in the time course of the means and the medians are observable. Nevertheless, the cdf-plots reveal subtle differences in the distributions of the relative HRV values. In figure 2 relative changes of the distributions of the parameters HFn and LFn between the mean baseline ECG and the ECG after four (ECG C) and six weeks (ECG D) are shown. Cdf-plots of all other distributions of the parameters do not contain any further information. After four weeks the parameters HFn and LFn exhibit differences in the cdf-plots of the verum and the placebo group (figure 2, left column). For the relative HRV parameters >1 the cdf-plots from the verum and the placebo group are well distinguishable. Two different results can be found. First, the upper part of the placebo groups cdf-plot of the parameter LFn is slightly shifted to

the left. On the other hand, the upper part of the verum groups cdf-plot of the parameter HFn shows a slight shift to the right. In all cases the median (0.5 on the p-axis) is approximately related to the value 1 (i.e. no change in HRV) on the 'relative change' axis. The parameter LFn exhibits the most probable difference ($p<0.077$, see table I) between the groups. After two further weeks without any medication all differences disappear (figure 2, right column).
To depict intraindividual changes of the parameters in the time course, for each subject of the verum group the values of ECG B, C, and D are plotted versus the value of ECG A, and a linear regression analysis $y = a \cdot x + b$ is performed (see figure 3). When plotting the mean nighttime heart rates (HRn) of ECG C vs. those of ECG A the slope of the regression is remarkably small (0.5). Thus high values of HRn tend to become lower and vice versa. This effect disappears after two further weeks.

4. DISCUSSION

A prospective randomized placebo-controlled double-blind study was carried out in 100 healthy subjects with respect to HRV. Fifty subjects took a composition of herbal extracts and 50 a placebo orally (4 x 20 drops / day). In a preliminary study the subcutaneously injected composition of herbal extracts (acute administration) decreased the VLF component of the HRV at night. This effect may be interpreted as a suppression of the sympathetic nervous system [3].
In this study the differences between the verum and the placebo group were generally small. After four weeks of oral administration the most striking difference was observed in the low frequency HRV at night (LFn) ($p<0.077$). This effect was not due to an increase of HRV in the verum group, but a slight decrease in the placebo groups HRV.
Previous investigations of low doses of hyoscyamine and scopolamine showed an increase in the parameter HF of the HRV because low doses yield an increase of the parasympathetic nervous system's activity [6, 7, 8, 9, 10, 11, 12]. The maximum vagomimetic effect was observed at a dose of 0.1 mg of hyoscyamine (injected intravenously) [14]. The present results show only a slightly elevated increase of the HF at night in those subjects who generally increased the HFn, compared with the 'HFn increase subjects' of the placebo group. Other subjects are not affected. This subtle result may be due to the fact that the concentration of hyoscyamine (scopolamine) is far lower in the investigated composition of herbal extracts than in the cited studies. Carefully, this finding could be interpreted as a conditional responder criterion: those subjects who show an increase in HFn tend to the elevated increase after administration of the herbal composition.
Plotting the values of HRn of the ECG C versus those of the ECG A for all subjects in the verum group, the slope of the corresponding linear regression further indicates tendencies of different interindividual response. After administration of the composition of herbal extracts, the regression slope of the mean heart rate at night tends to small values. This can be interpreted as normalization: in subjects with a low HRn the heart rate was increased and in subjects with high HRn the heart rate was decreased.
In conclusion, the composition of herbal extracts under consideration may have the ability to change the rhythmic system by adjusting the heart rate and thus the interplay between the two branches of the autonomic nervous system at night. The present results may possibly be due to the combination of the herbal extracts contained in the composition. This is in accordance with the finding of other authors that organisms can be retuned when a mild medicine is given over longer periods of time [1, 14]. Moreover, the findings show that effects are observable only in a responding subgroup of healthy young subjects. Though the study gives hints which subjects are responders, universal responder criteria have to be further evaluated.
The current approach of HRV is linear. Linear methods are often extended by non-linear tools giving a deeper insight into the dynamics of heart rate [15]. Secondly, this study shows that,

observing intraindividual and interindividual changes, different information are obtained. Taking this into account, further clinical studies have to demonstrate that the described effect will also take place in patients suffering from dysregulation of the rhythmic system.

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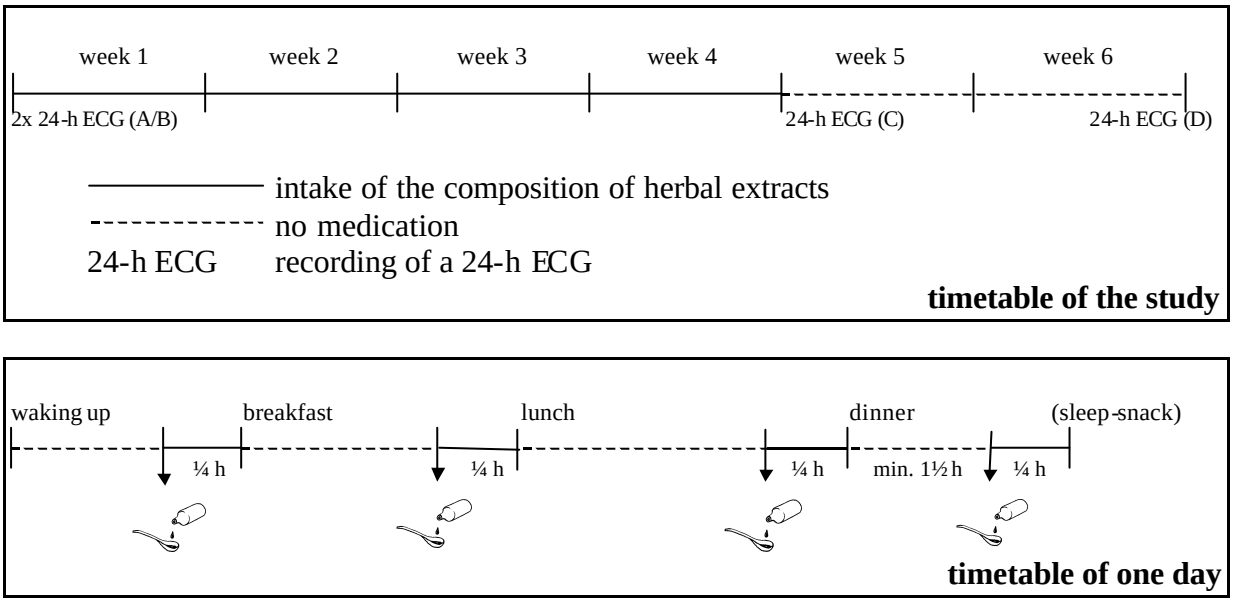

Figure 1: Timetable of the study and timetable for one day during intake of medication.

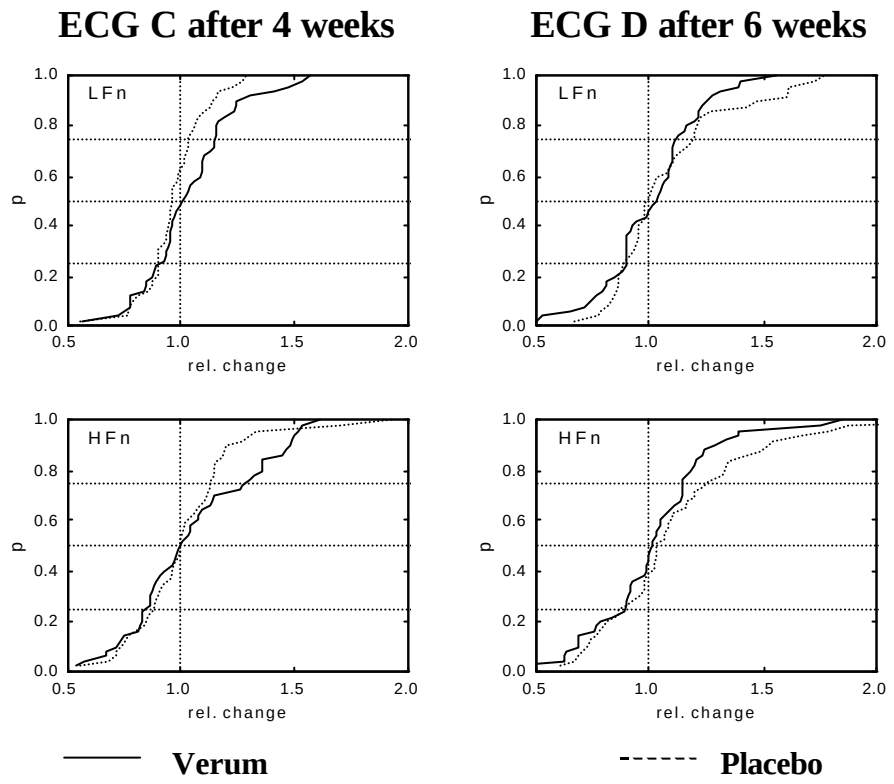

Figure 2: Plots of empirical cumulative distribution functions of the parameters LFn and HFn. Left column: ECG C after 4 weeks; right column: ECG D after 6 weeks (solid line: verum group, streaked line: placebo group).

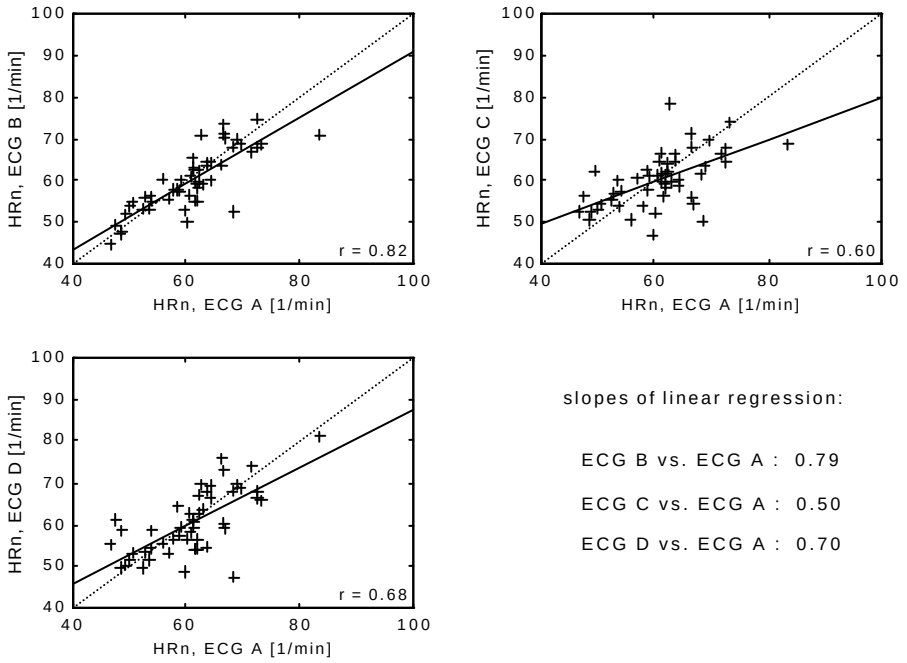

Figure 3: Nighttime heart rates (HRn) of the verum group's subjects of ECG A vs. ECG B, ECG C and ECG D. Streaked line: identity (i.e. reproducibility), solid line: linear regression $y = a \cdot x + b$. Spearman rank-order correlation coefficient is indicated by value of r.