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Rationale, design and methods planned in a prospective study concerning the circadian rhythm of heart rate asymmetry in healthy subjects

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ABSTRACT

Heart rate asymmetry (HRA) is a physiological phenomenon caused by an unequal (asymmetric) contribution of heart rate decelerations and accelerations to the variability (variance) and microstructure of the heart rhythm of sinus origin. HRA has been studied in healthy people and patients with heart failure, diabetes, obstructive sleep apnoea, ischaemic heart disease, and survivors of myocardial infarction. HRA is a particular form of the heart rate variability (HRV) phenomenon related to the changes in the duration of cardiac cycles of sinus origin. HRV is influenced by physical activity, age, gender or time of day. It has been reported that HRA expression differs between day and night. However, its circadian rhythm has not been analysed so far. Moreover, the differences in HRA expression related to gender, level of physical activity or age have not been investigated either. With this study, we aim to explore the circadian rhythm of the HRA features, as well as the relation of the HRA expression to gender, physical activity, sleep pattern and body composition in a group of at least 100 healthy adults of both sexes aged between 19 and 60. This study might provide reference values for HRA as well as confirming or dismissing the existence of circadian rhythm of this physiological phenomenon.

Basic concept and hypotheses

Heart rate asymmetry (HRA) is a phenomenon caused by the different behaviour of heart rate (HR) accelerations and decelerations, which have unequal input to the short-, long-term and total heart rate variability (HRV) as well as the HR complexity and microstructure [1-5]. HRA was first discovered and described in the short-term HRV in 2006 by Guzik and Piskorski [1]. In the following years, these authors also reported asymmetric features of [1] the long-term and total HRV; [2] HR microstructure composed of monotonic runs of consecutive decelerations and accelerations; and [3] HR complexity measured by entropy derived separately from decelerations and accelerations [2,3].

In more detail, HR decelerations make a significantly higher contribution than accelerations to the short-term variance of RR intervals but a lower contribution to the long-term and total HRV in healthy people [1,4]. The analysis of the HRA microstructure has revealed that the number of deceleration runs is significantly lower than that of acceleration runs, and the longest monotonic runs are usually composed of accelerations but not decelerations [2,5]. Consequently, the heart rate entropy (a measure of complexity) derived from decelerations is lower than that from accelerations [2].

Since the first papers on HRA, there has been a growing interest in this phenomenon. HRA has been studied both in physiological and clinical studies. The HRA expression is reduced in patients with type 1 diabetes [4], heart failure [5], sleep apnoea [6,7], septic new-borns or people with emotional stress [8-10].

Many physiological phenomena are oscillatory, and some present a diurnal variation or circadian rhythm [11,12]. Our daily routines related to eating, working, leisure time and lifestyle behaviour have a specific repeated pattern and present typical features of diurnal variation [13]. The autonomic nervous system also shows the circadian activity [14,15]. The system's sympathetic part is usually more active during the day, whereas parasympathetic tone increases at night. Both the heart rate and respiratory rate go down at night and increase during the day [16]. Blood pressure usually increases when someone is awake and drops during sleep [17,18].

Studies in animals showed that the activity of potassium channels Kv1.5 and 4.2 is linked with circadian rhythm. A similar phenomenon occurs with the regulation of intracellular calcium concentration via the ryanodine receptor and multiple T-type calcium channels. In the sinus node of rats, the HCN4 protein and HCN4 mRNA concentrations change with the circadian rhythm. Remodelling of the ion channels leads to their different expression on the cells' membranes. Circulating fatty acids influence the activity of fatty acid dehydrogenase through transcriptional, translational and post-translational mechanisms [19]. Impairment of the natural clock or the function of clock genes such as CLOCK, BMAL1, Per, and Cry may cause hypertension, obesity, heart attacks, ischaemic strokes, and mood and mental disorders. Changes in the phosphorylation of eNOS during the day and night cycle lead to endothelial dysfunction [20-22].

It is assumed that our human physiological reactions have adapted to environmental stimuli which change during a day [23]. As already mentioned, HR and HRV are typical examples of the cardiovascular circadian rhythm (**Figure 1**) [24,25]. The HRA phenomenon is a specific part of HRV and as such should have similar behaviour, e.g. diurnal variation. However, HRA circadian rhythm has not yet been studied.

For this study, we hypothesise that some HRA features have a circadian pattern and thus should change their expression during day and night. Porta et al. partially showed that short-term HRA differs between day and night in patients with heart failure [26]. However, they have studied it neither in healthy people nor for all HRA features, nor with the methods dedicated to the circadian rhythm analysis.

Many natural oscillations are quite frequent, e.g. breathing occurs 12 to 18 times a minute (0.2-0.3 Hz), and spontaneous increases of arterial pulse pressure known as Mayer waves appear every 10 seconds (0.1 Hz) [28]. Some other oscillations are rarer and can be spotted once every 24 hours [27]. It is relatively easy to observe oscillations appearing twice or more times during 24 hours, but oscillations present once a day may be inappropriately identified with the 24-hour ECG recordings. According to the Nyquist theorem, when it comes to studying slow oscillations present once a day (0.000012 Hz), the recording should last at least

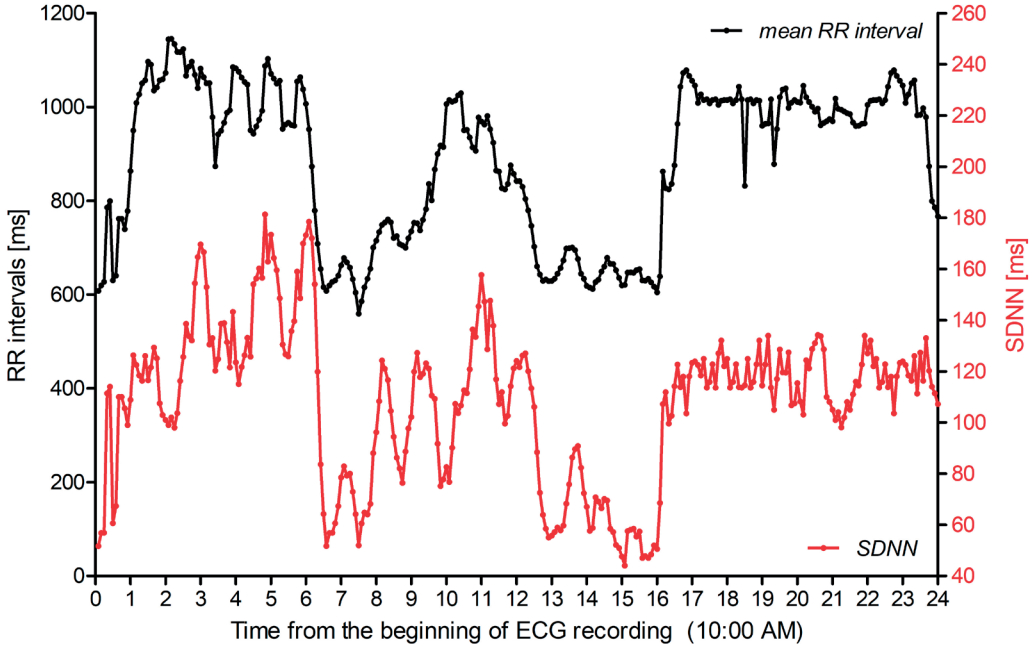

Figure 1. Oscillations of 5-minute means of RR intervals and values of the standard deviation of normal-to-normal RR intervals (SDNN) in a 24-hour ECG recording acquired from a healthy 20-year-old male

48 hours [29]. For HRA, some very long acceleration and deceleration runs appear only once a day or even less frequently. Runs composed of 16 consecutive decelerations or 20 consecutive accelerations are just two examples [2]. Whether more prolonged deceleration and acceleration runs may occur in the 48-hour ECGs is uncertain.

There is a known effect of ageing on HRV – most of the variance-based parameters become reduced with advancing age [30,31]. Further, sex differences in HRV have also been reported [32]. However, neither effect of age nor sex on HRA have been studied so far. We hypothesise that both factors might contribute to the expression of the HRA phenomenon. Usually, HRV is reduced in overweight and obese people, but it increases in individuals who are more active and sleep longer [33-36]. Yet, the relationships between HRA and body composition, level of physical activity, and sleep duration and quality have never been investigated.

The analysis of the asymmetric properties of the HR microstructure has shown that the number of acceleration runs is usually higher than that of deceleration runs [13]. Additionally, the longest runs in the same people come from accelerations rather than decelerations. Previous studies on the HRA microstructure used a lower sampling frequency of 200 Hz for the 24-h Holter ECGs, which translates into a precision of RR intervals of 5 ms [2]. There was a substantial number of so-called neutral runs (up to 6-7% of all beats), i.e. such consecutive RR intervals which have identical duration. For instance, the neutral run of three is composed of four consecutive RR intervals, with the first as the reference for the 2nd, the 2nd for the 3rd, and the 3rd for the 4th RR interval. RR intervals before the 1st and the 4th RR intervals must be different. In total, however, the number of comparisons showing no change for this particular neutral run equals three. The following time series of RR intervals is more explanatory: 1,000 ms (1st RR interval), 1,000 ms (2nd RR interval), 1,000 ms (3rd RR interval), and 1,000 ms (4th RR interval). For more details on the HRA microstructure please refer to references 2 and 5.

As discussed in the previous study [2], the neutral runs seem to be an artificial effect of low sampling frequency rather than a genuine physiological phenomenon. Therefore, studying the distribution of acceleration and deceleration runs in Holter ECGs recorded at a much higher frequency of at least 4,000 Hz (precision of 0.25 ms), i.e. over 20 times higher than in the original paper, should result in a lower number of, or even no, neutral runs, and more precise description of the asymmetric features of the heart rate microstructure.

Study aims

Based on the above reasoning, we have proposed several study aims, which are summarised in **Table 1**. The whole study is designed as a prospective piece of work, in a group of healthy people with a wide age range who will undergo the 48-hour Holter ECG recording.

Research plan, material and methods

Our methodological aim is to collect at least 100 good-quality 48-hour Holter ECG recordings from men and women of a wide age range. We intend to achieve equal gender distribution; therefore, the same number of men and women will be recruited. Additionally, to preserve an equal contribution of age to our results, we intend to collect at least 20 ECG recordings of the 48-hour duration from men and women in each of the following age groups:

- 19-29 years;
- 30-39 years;
- 40-49 years; and
- 50-60 years.

The quality of Holter ECG recordings is unpredictable, and correcting technical artefacts is sometimes impossible. To avoid methodological problems related to an insufficient statistical power secondary to poor quality of recorded ECGs, we plan to examine up to 200 healthy people. In this way, we will increase the likelihood of collecting 100 good-quality 48-hour ECGs.

Each participant will go through a standard clinical interview and examination, body composition analysis, the 48-hour Holter ECG, transthoracic echocardiography, and estimation of daily activity performed with a sports watch. All gathered data will be stored in digitised form and later used for mathematical and statistical analyses. **Table 2** shows the inclusion criteria for all participants.

The study was approved (708/18) by the Bioethics Committee at Poznan University of Medical Sciences, Poznan, Poland.

Body composition analysis

The body composition will be measured using the total body impedance with the TANITA MC180-MA medical device (Tanita, Japan); four different electrical current frequencies will be employed. This test makes it possible to determine body mass, body fat percentage, lean and water mass, and basal metabolic rate [37].

48-hour Holter ECG recording

To acquire the 48-hour ECG with at least 4,000 Hz sampling frequency, it is necessary to employ the Medilog® DARWIN 2 Enterprise system with the 3-lead ECG recorder Medilog AR12plus (Schiller, Switzerland). Such ECG recordings will be col-

Table 1. The study aims of this project

	We intend to explore:
1	the circadian rhythm of different features of HRA;
2	the gender differences in the HRA expression;
3	the relationship between the HRA expression and body composition;
4	the association between the HRA expression and daily activity;
5	the link between the HRA expression and duration and quality of sleep;
6	the distribution of acceleration and deceleration runs in recordings of at least 4,000 Hz sampling frequency.

Table 2. Inclusion criteria for individuals enrolled in this study

The following inclusion criteria will be required from each study participant:
Voluntary participation;
Accepting all study conditions and signing informed consent;
Feeling healthy;
No known chronic diseases or any acute illness in the past three months;
No history of myocardial infarction, cerebral stroke, neoplasm, atrial fibrillation or flutter, pulmonary embolism;
Not taking medications (except for hormonal contraception, nutrients and typical supplements such as vitamins and minerals);
No past surgeries or interventions related to the cardiovascular, respiratory or nervous system;
Normal findings in physical examination, resting 12-lead ECG and transthoracic echocardiography.

lected from all healthy participants with normal results for their resting ECG, blood pressure measurement and transthoracic echocardiography. In addition to standard Holter ECG analysis such as arrhythmia, ST-segment and QT analysis, the reconstructed respiratory curve will be analysed so as to identify potential episodes of apnoea and hypopnea. For this purpose, the ECG-Derived Respiration monitoring (EDR) index will be employed, i.e. a parameter derived from the analysis of the R wave amplitude variation. An EDR value above 20 is considered as a severe risk of apnoeas in the subjects [38-41].

Each Holter recording will first be automatically analysed and then reviewed manually to correct, if necessary, inappropriately-identified RR intervals. Finally, the duration of each RR interval and information about its origin, i.e. from the sinus node, atria or atrioventricular junction, or ventricles, or labelled as a technical artefact, will be exported to ASCII files for further analysis of HRV and HRA.

Daily activity, duration, and quality of sleep

The daily activity, duration, and quality of sleep of each participant will be monitored and recorded using the M430 POLAR Running Watch (Polar Electro, Finland). This sports watch will be placed on the wrist of each individual and programmed with personal details such as age, gender, and current body weight. After 48 hours, the data recorded by each sports watch will be uploaded to the PolarFlow service to retrieve the following information:

These data will be used for further analysis.

Heart rate variability analysis

For the HRV and HRA analysis, we will use the set of parameters defined in a specific HRV guideline [42,43] or papers on HRA published by our team.

The list of HRV and HRA methods applied for the measurement of many possible parameters is shown in Table 3 [1,2,44-46].

Data collection

All data will be, after coding, placed and stored in a specialised electronic data capture form prepared with the use of the REDCap environment. The REDCAP project is available for scientific research at Poznan University of Medical Sciences at redcap.ump.edu.pl.

Statistical analysis

Data distribution will be analysed using the Shapiro-Wilk test. A summary of the data will be presented, with the mean, standard deviation, median, and 25th-75th percentiles.

For the analysis of associations between different HRV and HRA features and the remaining parameters, nonparametric Spearman, parametric Pearson, and linear regression models will be used.

The binomial tests will be applied to study whether or not specific asymmetric features are present.

For the analysis of the circadian rhythm of HRA and HRV we intend to use the time series analysis methods for correlated series to avoid variation, inflation, and loss of statistical significance.

Measurable effects and expected results

We plan to gather for our database at least 100 good-quality ECGs of 48-hour duration with a sampling frequency of at least 4,000 Hz. These recordings will be equally distributed between men and women and across consecutive age decades between 19 and 60 years old. We intend to use such a database not only for HRA and HRV measurements, but also for other newer and emerging methods related to the RR interval analysis.

As we have developed several different methods for the quantitative and qualitative analysis of HRA, we believe that, with this database, it will be possible to establish reference values for various measures of HRA. One of our primary goals is to study the circadian pattern of HRA – we hope to explore this issue and find specific answers. Additionally, we will be able to compare the HRA expression between men and women, so as to investigate any association between age, body composition, quality of sleep, real daily activity, and HRV and HRA. With our results, we should also be able to answer the question regarding the value of high sampling frequency for the HRV and HRA analysis, and define reference values for such sampling. Most of these aspects have never been studied for HRA, and, in many cases, neither for HRV.

Based on our previous experience and the available literature, we expect that:

- 19-29 years;
- 30-39 years;
- 40-49 years; and
- 50-60 years.
- number of steps a day;
- total distance walked;
- duration and quality of sleep;
- number of burned calories.
- the circadian rhythm of HRA exists;
- women have a weaker expression of HRA than men;
- HRA expression attenuates with ageing;
- more active people have higher values of HRV and stronger HRA expression;
- HRA expression and HRV values are related to the duration of sleep, and potential episodes of sleep apnoea;
- higher sampling frequency will reduce the number of so-called neutral runs and improve the differentiation between heart rate accelerations and decelerations.

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Conflict of interest statement
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