The analysis of heart rate variability does not provide a reliable measurement of cardiac sympathetic activity

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Introduction

The measurement of heart rate variability has been described as a tool to assess the autonomic regulation of the heart [1-3]. A separation between cardiac sympathetic and cardiac parasympathetic activity is supposed to be provided by the spectral analysis of heart rate variability. Experimental studies revealed a link between heart rate variability in the low-frequency band (0.02-0.15 Hz) and sympathetic activity[3,5]. The high-frequency band (0.15-0.8) is supposed to reflect vagal tone[2,6,7]. A suggested clinical application for the analysis of heart rate variability is the risk stratification for arrhythmic events in patients after myocardial infarction [8-10].

Essential for the clinical use of heart rate variability measurements are a sufficient reproducibility of the heart rate variability data and a clear-cut relation between changes in heart rate variability data and changes in the cardiac autonomic activity. A well known discrepancy in this respect is the reduction of heart rate variability in all spectral bands during physical exercise [11-13]. This reduction is in contrast to the assumption that the LF band reflects sympathetic activity which obviously increases during exercise.

In our studies we determined the reproducibility of heart rate variability measurements under different physiological conditions. The impact of physical exercise on heart rate variability was investigated during exercise tests of different intensity and during a pharmacological exercise simulation - vagal withdrawal by infusion of atropine and sympathetic activation by the additional infusion of catecholamines. To ensure steady state conditions of cardiac autonomic activity during the measurement of heart rate variability all data were derived from short (5 min) recording periods.

Methods and Protocols

The ECG lead II was digitized and recorded with high temporal resolution (1 ms) on an AT compatible computer (16 MHz; numeric coprocessor). RR intervals were calculated from the recorded data. Artifacts, extrasystoles and the postextrasystolic beats were manually removed and the gaps in the signal were filled with interpolated data. The RR time series was then converted to a time series with equidistant data points (2 Hz) [14]. Frequency components below 0.02 Hz were removed by digital filtering. Segments of 256 s each were transformed into the frequency domain by fast Fourier transformation. Heart rate variability in the respective frequency band was calculated as the integral under the power spectrum.

Abbreviations used:

LF : heart rate variability in the low frequency band
HF : heart rate variability in the high frequency band
CV : coefficient of variation
HR : heart rate
SBP : systolic blood pressure; DBP : diastolic blood pressure
E : epinephrine; NE : norepinephrine

All data are presented as means ± SD. The differences between and within the experimental procedures were analyzed by the non-parametric Friedman test. When significant (p < 0.05) differences were detected, the Wilcoxon test was applied to compare single mean values.

Study 1: The protocol consists of heart rate variability measurements under the following conditions: A) supine position followed by standing, and B) sitting followed by standardized cycle ergometry (40, 80 and 120 W for 5 min each) and a subsequent recovery period. Blood pressure was measured in each phase of the protocol using sphygmomanometry. Ten healthy volunteers (age 37 ± 7 years) participated in this study, and for each volunteer each protocol was repeated 6-10 times in weekly intervals. To estimate the reproducibility, the CV was calculated intraindividually for each condition. For comparison we also calculated the CV of heart rate, blood pressure and the inspiration to expiration ratio of heart rate.

Study 2: Six healthy male individuals (age 31 ± 3 years) performed three different steady state exercise tests on a bicycle ergometer. In order to achieve comparable conditions for all volunteers, the workload was adjusted individually with respect to the exercise-induced heart rate response: control without cycling (EX0), cycling with a target heart rate of 150 bpm (EX150), and cycling with a target heart rate of 150 bpm (EX150). The three exercise tests were performed on different days. During the steady state phase of exercise, plasma catecholamines were determined from venous blood samples by the HPLC method. In a second protocol, atropine was infused intravenously followed by the additional infusion of epinephrine and norepinephrine. The epinephrine to norepinephrine ratio was determined individually for each volunteer and was the same as during the EX150 ergometry. The infusion rate of atropine was increased until a heart rate of 100 bpm was reached and then kept constant. The infusion rate of the catecholamines was increased until the diastolic blood pressure had increased by 30 mmHg or had reached 120 mmHg, or until the systolic blood pressure had increased by 70 mmHg or had reached 200 mmHg. The infusion rate was then kept constant and heart rate variability was assessed. Blood samples for plasma catecholamine determination were drawn at rest, during the infusion of atropine, and immediately before stopping the infusion of atropine and catecholamines. Blood pressure was measured during the exercise protocols and during the atropine/catecholamine infusion.

Results

Study 1: HR and DBP increased from the supine to the standing position (HR: 73±13 to 87±10 bpm; DBP: 79±11 to 88±9 mmHg). SBP remained unchanged. LF was increased (5.1±3.6 to 13.6±12.4 bpm²) and HF tended to decrease (4.1±5.2 to 2.3±2.6 bpm², n.s.). During cycling ergometry, HR and SBP increased (HR: 83±12 to 139±13 bpm; SBP: 12±13 to 159±19 mmHg). DBP was decreased (84±10 to 75±8 mmHg). Heart rate variability in both frequency ranges decreased (LF: 10.4±7.3 to 1.3±0.8; HF: 2.4±2.2 to 0.5±0.2 bpm²). Compared to the pre-exercise phase, HR remained increased during recovery (94±13 bpm) and HF remained decreased (1.5±1.1 bpm²).

The repeated measurements of heart rate variability revealed a high intrindividual CV of heart rate variability data under all tested conditions whereas the CV of heart rate and blood pressure were low, indicating a good reproducibility of these measurements. The CV for the inspiration to expiration ratio of heart rate was 4.6±1.9 %.
The mean values ± SD of the CV for all measured parameters and all conditions are given in Table 1. Figure 1 shows all measured data of one representative volunteer. To compare the scatter of the data independent from the absolute values all data were normalized to the mean of the corresponding control condition (supine, sitting).

<table>
<thead>
<tr>
<th>Table 1 CV [%]</th>
<th>means ± SD</th>
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<tbody>
<tr>
<td></td>
<td>supine</td>
</tr>
<tr>
<td><strong>HR</strong></td>
<td>7.8 ± 1.8</td>
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<tr>
<td><strong>SBP</strong></td>
<td>5.5 ± 1.4</td>
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<tr>
<td><strong>DBP</strong></td>
<td>7.2 ± 1.3</td>
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<tr>
<td><strong>LF</strong></td>
<td>43.5 ± 22.6</td>
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<tr>
<td><strong>HF</strong></td>
<td>38.2 ± 7.3</td>
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</tbody>
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![Figure 1](image1.png)

*Figure 1: Representative data from one volunteer. All data are normalized to the mean value "supine" and "sitting", respectively.*

![Figure 2](image2.png)

*Figure 2: Changes in LF and HF during EX100. Values are means ± SD (n=6).*

**Study 2:** During EX2 all parameters remained unchanged. During EX100 HR increased from 69 ± 9 to 101 ± 4 bpm and during EX150 from 70 ± 8 to 157 ± 5 bpm. SBP increased from 118 ± 9 to 130 ± 9 mmHg during EX100 and from 120 ± 7 to 169 ± 21 mmHg during EX150, respectively. DBP was not changed during EX100 and decreased from 78 ± 5 to 65 ± 4 mmHg during EX150. LF and HF decreased from rest to exercise during EX100 and EX150 (Fig. 2). LF was lowest during EX150. Plasma concentrations of E and NE increased from rest to EX100 (E: 0.049 ± 0.025 to 0.113 ± 0.089; NE: 0.29 ± 0.15 to 1.21 ± 0.55 ng/ml).

During the infusion of atropine HR increased from 67 ± 6 to 95 ± 10 bpm. Blood pressure remained constant. LF and HF decreased considerably (Fig. 3). E and NE did not change. During the additional infusion of norepinephrine and epinephrine HR increased further to 123 ± 6 bpm. SBP increased from 118 ± 4 to 186 ± 16 mmHg and DBP from 83 ± 5 to 105 ± 7 mmHg. The remaining heart rate variability was completely suppressed (Fig. 3). E and NE were increased (E: 0.026 ± 0.007 to 0.269 ± 0.185; NE: 0.15 ± 0.10 to 2.77 ± 0.94 ng/ml).

**Discussion**

In both studies we investigated heart rate variability as determined from short recordings of heart rate. These short periods are characterized by a steady state condition of autonomic activity. In our first study, orthostatic load and ergometric exercise were used as defined physiological perturbations. With repeated measurements of heart rate variability we estimated the reproducibility of the results. Both, changes in mean values and in most of the individual measurements during the induced physiological perturbations were in accordance with the literature[7,11,12,15]. LF increased and HF decreased during orthostatic load. These changes can be interpreted as a reduction of vagal activity and an increase in sympathetic activity as part of the baroreflex. Although the direction of changes in heart rate variability was almost the same for all volunteers, the amount of changes scattered remarkably.

During exercise, we observed - like other investigators [11-13] - a substantial reduction in both spectral bands. This reduction in the LF range is at discrepancy to the established increase in sympathetic activity during exercise. The recovery period was characterized by a persistently increased HR and a decreased HF, indicating a persisting reduction of vagal activity after exercise. In contrast, the CV of heart rate, blood pressure, and the inspiration to expiration ratio of heart rate did not exceed the maximal CV of 8% which was proposed in the "European guidelines for exercise testing" [16]. It remains unknown whether the reduced heart rate variability in patients may result in a better reproducibility of heart rate variability data.

In our second study we investigated the influence of exercise on heart rate variability. The exercise-induced tachycardia is
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mediated both by an initial rapid vagal withdrawal and at higher levels of workload by a more delayed increase in sympathetic activity [17,18]. Humoral factors such as circulating catecholamines may play a more dominant role than direct neural input in sustaining the tachycardia [19]. In our study we observed changes in heart rate variability during exercise which are in accordance with the literature [11-13]. During the pharmacological exercise simulation by infusion of atropine and catecholamines, we intended to achieve the same heart rate as in EX100. Yet, the pressor action of the infused catecholamines limited the maximal infusion rate. Thus, the maximal achieved heart rate during the infusion of catecholamines remained lower than during EX100.

The profound suppression of LF during exercise and during the pharmacological exercise simulation does not support the assumption that LF solely reflects sympathetic activity [4,5]. On the contrary, our data indicate that LF is influenced by both vagal and sympathetic activity, as previously proposed by other investigators [7,20,21]. The substantial reduction in heart rate variability during EX100 as well as during infusion of atropine point to a major impact of vagal activity on both LF and HF. The further reduction in LF during EX100 and during the infusion of atropine and catecholamines can be explained by an additional negative feed-back of circulating catecholamines on sympathetic heart rate control. Likewise, a negative relationship between spectral and nonspectral measurements of heart rate variability and plasma norepinephrine was reported in patients with congestive heart failure [22]. High plasma norepinephrine levels were accompanied by low values of heart rate variability.

Conclusion

We conclude that the poor reproducibility of heart rate variability data together with the unclear relation between LF and sympathetic nervous activity do not support a clinical use of heart rate variability measurements to assess cardiac sympathetic activity. This conclusion was further corroborated by a recent collaborative study of our group and the department of anaesthesiology of the university of Düsseldorf in which patients undergoing epidural anesthesia had no significant attenuation of the LF increase during tilt [23].

References


