Assessment of cardiovascular autonomic function in the anaesthesia population

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Chapter 5

Short-term heart rate variability in healthy adults

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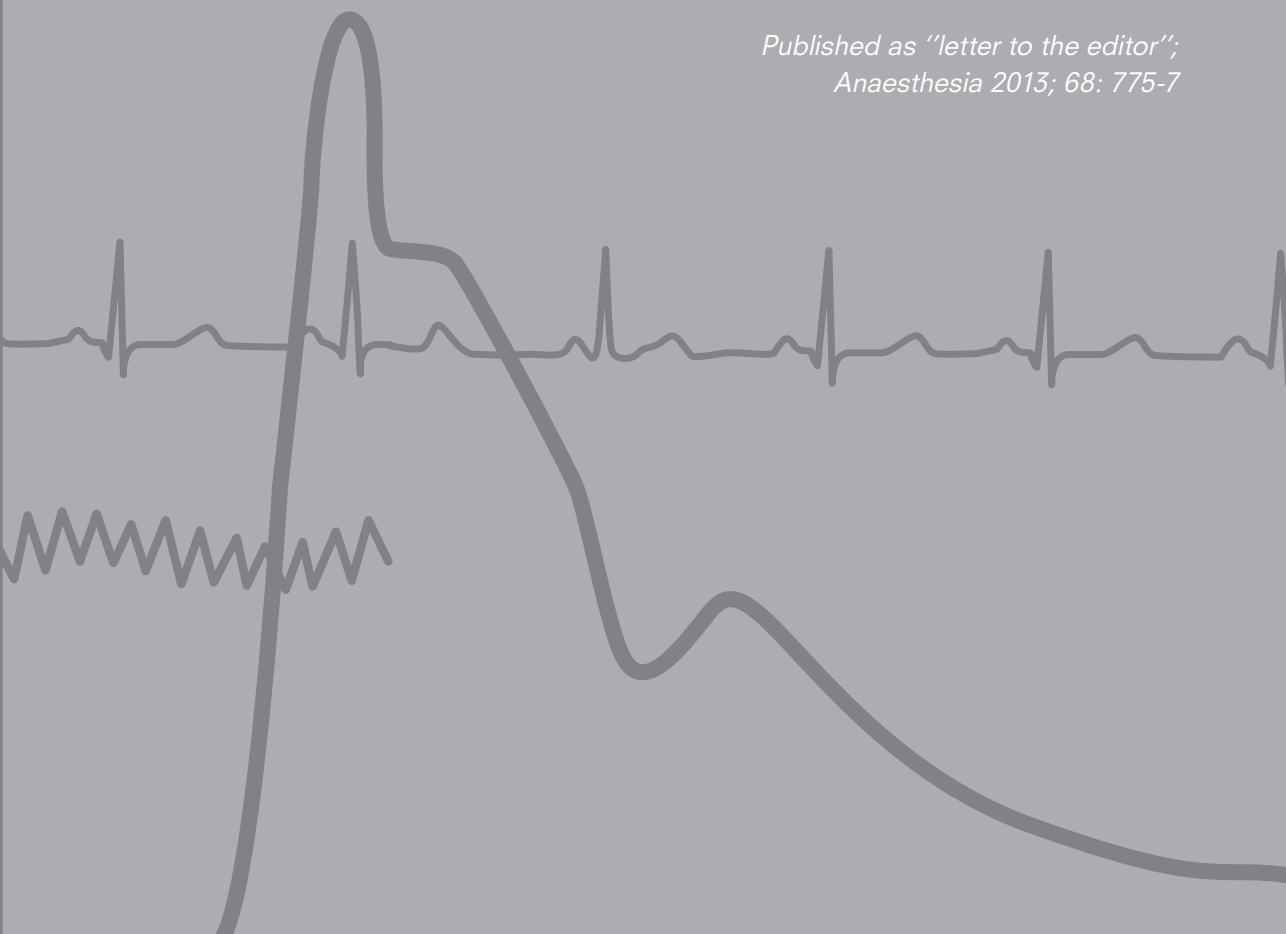


ABSTRACT

Introduction: Standardised heart rate variability (HRV) analysis is used as a diagnostic and prognostic tool for cardiovascular as well as perioperative risk stratification. The lack of reference values for young and middle-aged subjects however limits implementation of HRV analysis in the clinical setting. With this study we aimed to define reference values, and to define the influences of gender and age for short-term heart rate variability in the young and middle-aged population.

Methods: Ninety-three healthy subjects (18-50 years) were studied during standard test conditions. Short-term HRV was assessed using an ECG monitor. Data represent mean ±SD or median with 10^{th} and 90^{th} centiles. To determine gender and age differences Student's t-test or Mann-Whitney U-test were used. Pearson and Spearman's rank correlation coefficients were used to determine correlations between age and HRV parameters

Results: All parameters for heart rate variability, except for the LF/(LF+HF), showed significantly higher values for men then for woman (mean normal-to-normal (1014 ±183 vs 896 ±121 ms), standard deviation of normal-to-normal (65.3 (36.6-97.6) vs 49.4 (29.9-91.3) ms), root mean square of successive differences between normal-to-normal (55.8 (24.2-98.7) vs 41.5 (21.5-87.0) ms), very low frequency (1282 (438-4390) vs 785 (259-2090) ms^2), low frequency (1025 (361-2983) vs 487 (206-1365) ms^2), high frequency (1311 (405-3491) vs 763 (203-3981) ms^2) and total spectral power, respectively). Age showed no influence on the baseline characteristics and HRV parameters and showed no significant correlations in a range between -0.21 and 0.27.

Conclusions: This study provided reference values for short-term heart rate variability in healthy adults, which may support further implementation of this tool in patient risk stratification.

INTRODUCTION

A decline in heart rate variability (HRV) has been shown to be associated with cardiovascular morbidity and mortality [1-3]. In particular, under conditions of stress, such as anaesthesia and surgery, alterations in heart rate variability may be of predictive value for patient outcome [4-6].

Standardised heart rate variability analysis is well accepted as diagnostic and prognostic tool for cardiovascular as well as preoperative risk stratification [1, 5-6]. However, the accurate 24-hour heartbeat recordings that are recommended for heart rate variability analysis prohibited implementation of this method as standard screening in the preoperative setting [7]. The analysis of short-term heart rate variability, which requires a 5-minute recording of heartbeat variations at rest in supine position, has been shown to provide a simple alternative to assess cardiovascular autonomic function [8]. As a consequence, interest in the clinical use of heart rate variability in anaesthesia and critical care is increasing [9-15]. Moreover, there is more emphasis on the use of pulse rate variability as an alternative for measuring heart rate variability in the diagnosis of early autonomic dysfunction [16-17].

The implementation of short-term heart rate variability or pulse rate variability in the preoperative assessment setting requires insight into reference values in adults, with further specification of gender and age [8]. However, short-term heart rate variability reference values for young and middle-aged adults are currently lacking [8]. In the present study we therefore determined reference values for short-term heart rate variability in young and middle-aged, healthy adult subjects, and investigated the influence of gender and age on these reference values.

METHODS

Subjects

The Institutional Human Subjects Committee of the VU University Medical Centre Amsterdam approved this study (NL26318.029.08) and all participants gave written informed consent. The study population consisted of 93 healthy subjects aged 18-50 years, and typically included students, employees and staff of the VU University and VU University Medical Centre. Subjects with a history of cardiovascular disease and/or treatment, diabetes mellitus, or body mass index (BMI) < 15 or > 35 kg/m^2 were excluded.

Study design

HRV measurements were performed in the morning (08:00 am - 12:00 am) in a room with a quiet ambiance and temperature of 19-22^{o}C [15-16, 18]. Subjects were studied in supine position after overnight fasting (nil per mouth from 00:00 am) and refraining from smoking. Participants were connected to a standard ECG monitor and a non-invasive continuous finger arterial blood pressure measurement device (Nexfin HD, BMEYE, the Netherlands) to obtain continuous blood pressure waveforms and R-R intervals [18]. After stabilisation of heart rate and blood pressure, the R-R intervals, systolic and diastolic blood pressure were recorded during five minutes of spontaneous breathing to analyse short-term heart rate variability.

Heart rate variability analysis

R-R intervals were derived from the ECG signal using a QRS detector (sample rate 1000 Hz). The data were visually inspected for premature or irregular beats and movement artefacts. The R-R intervals were analysed by spectral analysis using the Fast Fourier Transformation with commercially available software (Kubios HRV version 2.0, University of Kuopio, Finland) [19].

HRV analysis comprised evaluation of mean R-R intervals (mean NN), the standard deviation of normal-to-normal (i.e. sinus rhythm) R-R intervals (SDNN) and the root mean square of successive differences between normal-to-normal R-R intervals (RMSSD). Furthermore, the very low (VLF; 0.0-0.04 Hz), low (LF; 0.04-0.12 Hz) and high frequency band (HF; 0.12-0.4 Hz) and the total spectral power were determined from all sinus rhythm R-R intervals. The ratio of the low frequency power to the total of LF and HF (LF/(LF+HF) was determined as well. Data represent mean ± SD or median with 10th and 90th centiles.

Statistical analysis

SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) was used to carry out all statistical analyses. To determine the differences in HRV parameters between gender and age, different gender and age groups were created (male - female; ≤ 30 years - > 30 years). Skewness and kurtosis analysis as well as the Kolmogorov-Smirnov test were used to calculate the normality of the data in the different groups. A Student's T-test or Mann-Whitney U-test was used for parametric or non-parametric data analysis respectively, to determine differences in baseline characteristics and HRV parameters between different groups. The Chi-square test was used to determine differences in gender in the different age groups. Pearson or Spearman's rank correlation coefficients were used for parametric or non-parametric data respectively, to determine the correlation between age and all HRV parameters. A P-value of <0.05 was considered as statistically significant.

RESULTS

Study population

The study population (n=93) consisted of slightly more males (55.6%). The study population had an average age of 28 ± 8 years and a body mass index (BMI) of 22.6 ± 2.6 kg/m^2. Mean systolic and diastolic blood pressure was 108 ± 12 mmHg and 64 ± 8 mmHg, respectively, with a mean heart rate of 64 ± 10 beats per minute (bpm).

Among men (n=50) and women (n=43), there were no differences in age (29 ± 9 vs 29 ± 8 years), systolic blood pressure (110 ± 11 vs 105 ± 12 mmHg) and diastolic blood pressure (64 ± 7 vs 65 ± 8 mmHg), respectively. Male subjects had a slightly higher BMI (23.1 ± 2.3 vs 21.9 ± 2.8 kg/m^2; P=0.01) and lower resting heart rate (59 ± 9 vs 69 ± 9 bpm; P<0.001) than female subjects.

Heart rate variability analysis

The study population (n=93) showed a mean NN of 941 ± 167 ms with a SDNN of 59.1 (34.7-96.9) ms and a RMSSD of 49.0 (23.4-92.4) ms. The VLF, LF and HF power showed values of 1011 (329-3381) ms^2, 734 (247-2389) ms^2 and 989 (343-3573) ms^2, respectively, and a total power of 3540 (1211-8004) ms^2. The LF-to-LF+HF ratio was 0.41 ± 0.18.

Heart rate variability was stratified for male and female subjects as shown in Table 1. Heart rate variability parameters were higher in men

then in woman, except for the LF-to-LF+HF ratio. A comparison between age groups (≤ 30 years (n=61) versus > 30 years (n=32)) showed no difference in baseline characteristics, except for body mass index (22.1 ± 2.1 vs 23.5 ± 3.1 kg/m^2 in younger and older subjects, respectively). HRV parameters were similar among age groups (Table 2).

Table 1.
Heart rate variability stratified by gender.

HRV parameters	Males	Females	P-value
N	50	43	
Mean NN, ms	1014 ± 183	896 ± 121	<0.001
SDNN, ms	65.3 (36.6-97.6)	49.4 (29.9-91.3)	0.01
RMSSD, ms	55.8 (24.2-98.7)	41.5 (21.5-87.0)	0.03
VLF power ms^2	1282 (438-4390)	785 (259-2090)	0.01
LF power ms^2	1025 (361-2983)	487 (206-1356)	<0.001
HF power ms^2	1311 (405-3491)	763 (203-3981)	0.04
Total power ms^2	4447 (1295-8999)	2273 (862-6635)	0.001
LF/(LF+HF)	0.44 ± 0.18	0.39 ± 0.17	n.s.

Data represent mean ± SD or median with 10th and 90th centiles.

Table 2.
Baseline characteristics and heart rate variability stratified by age.

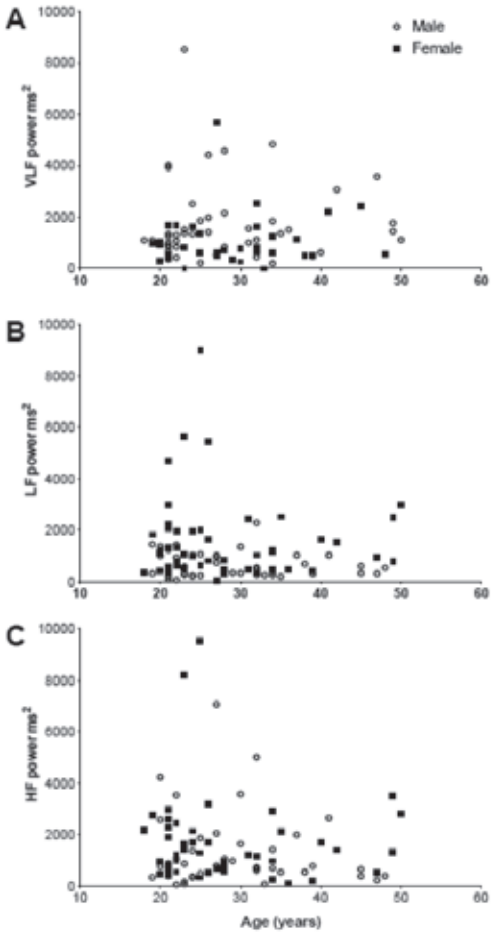
HRV parameters	18-30 years	31-50 years	P-value
N	61	32	
Mean NN, ms	941 ± 175	993 ± 149	n.s.
SDNN, ms	60.8 (35.5-98.0)	56.3 (32.6-95.0)	n.s.
RMSSD, ms	50.8 (24.5-98.9)	42.9 (20.4-84.6)	n.s.
VLF power ms^2	969 (301-4006)	1126 (458-2909)	n.s.
LF power ms^2	813 (225-2178)	576 (252-2481)	n.s.
HF power ms^2	1072 (358-4111)	887 (208-3353)	n.s.
Total power ms^2	3594 (1224-8905)	3379 (1111-7551)	n.s.
LF/(LF+HF)	0.40 ± 0.17	0.45 ± 0.18	n.s.

HRV, heart rate variability; Mean NN, mean normal-to-normal R-R intervals; SDNN, standard deviation of normal-to-normal R-R intervals; RMSSD, root mean square of successive differences between normal-to-normal R-R intervals; VLF, very low frequency (0.0-0.04 Hz); LF, low frequency (0.04-0.12 Hz); HF, high frequency (0.12-0.4 Hz); n.s., not significant. Data represent mean ± SD or median with 10th and 90th centiles.

Figure 1, panels A-C, represents scatter plots of the association between age with VLF (panel A), LF (panel B) and HF (panel C) for male and female subjects. Pearson and Spearman's rank correlation coefficients ranged from -0.10 and 0.23 for males and -0.21 to 0.27 for females, suggesting no relation between age and HRV parameters.

Stratification into four gender-age groups revealed more differences among HRV parameters. In both age groups, HRV values were higher in male subjects when compared to female subjects (Table 3), suggesting that gender differences could not be explained by age.

Figure 1.
Association of VLF (panel A), LF (panel B) and HF (panel C) with age. Data represent white circles (males) and black squares (females).



VLF = very low frequency (0.0-0.04 Hz) band of the heart rate variability; LF = low frequency (0.04-0.12 Hz) band of the heart rate variability; HF = high frequency (0.12-0.4 Hz) band of the heart rate variability.

Table 3.
Baseline characteristics and references values for heart rate variability for males and females stratified by gender and age.

HRV parameters	Males	Females	P-value	Males	Females	P-value
	18-30 years	18-30 years		31-50 years	31-50 years	
N	n=34	n=27		n=16	n=16	
Mean NN, ms	992 ± 200	878 ± 110	0.01	1060 ± 133	925 ± 136	0.01
SDNN, ms	63.5 (37.3-136.7)	52.3 (28.4-100.2)	n.s.	74.0 (33.5-100.6)	44.5 (31.4-85.6)	0.02
RMSSD, ms	52.4 (30.4-139.4)	44.9 (18.7-90.1)	n.s.	58.1 (19.6-90.0)	37.9 (20.1-89.0)	n.s.
VLF power ms²	1179 (417-4508)	745 (247-1746)	0.01	1408 (377-3963)	858 (403-2448)	n.s.
LF power ms²	934 (348-5042)	592 (174-1375)	0.01	1101 (388-2659)	428 (230-1408)	0.003
HF power ms²	1363 (464-5720)	886 (159-4810)	n.s.	1285 (167-5474)	688 (194-3364)	n.s.
Total power ms²	4163 (1351-15671)	2287 (771-8096)	0.03	4893 (1035-8906)	1849 (1117-6802)	0.02
LF/(LF+HF)	0.42 ± 0.17	0.37 ± 0.17	n.s.	0.48 ± 0.19	0.42 ± 0.16	n.s.

BMI, body mass index; Mean NN, mean normal-to-normal R-R intervals; SDNN, standard deviation of normal-to-normal R-R intervals; RMSSD, root mean square of successive differences between normal-to-normal R-R intervals; VLF, very low frequency (0.0-0.04 Hz); LF, low frequency (0.04-0.12 Hz); HF, high frequency (0.12-0.4 Hz); n.s., not significant. Data represent mean ± SD or median with 10^{th} and 90^{th} centiles.

DISCUSSION

Until now there were no reference values for short-term HRV available for healthy subjects, which limits the implementation of short-term heart rate variability in clinical practice. The present study therefore investigated normal ranges for short-term heart rate variability for young and middle-aged (18-50 years) adults [8].

Consistent with data in older subjects, we found particular differences between male and female subjects for the sympathetic as well as for the parasympathetic component of heart rate variability [3, 6, 8]. In contrast, other investigators particularly showed a larger difference between male and female gender for sympathetic parameters, such as the very low and low frequency power, when compared to parasympathetic parameters [20]. This may suggest a higher sympathetic activity in men, while muscarinic activity may play a more important role in the regulation of heart rate variability in female subjects [21]. However, this hypothesis is debatable and not consistent with previous data in young and middle-aged adults [22]. Van Hoogenhuyze and colleagues hypothesised that sex differences are due to the differences in mean heart rate, which are supported by our data [23]. The higher the heart rate, the shorter the R–R interval, which has a nonlinear inverse relation with heart rate. Shorter R–R intervals are likely to present less variation in absolute if not relative terms [4]. In our population the resting heart rate was significantly lower in male subjects, which may explain the higher references values for the VLF, LF and HF part of the HRV spectrum. Other possible explanations of the HRV differences may include differences in hormone status, such as androgen or oestrogen levels, different resting levels of catecholamines, or plasma cholesterol levels, but this was not within the scope of our investigation [21, 25-26].

Interestingly, we found no differences in HRV parameters between subjects with a lower age (≤ 30 years) or higher age (31-50 years). In contrast, other studies showed a decline of HRV with age [3, 6, 8, 20]. Nevertheless, these studies were mostly carried out in older subjects, while our investigation included healthy subjects. Based on the clinical usage of heart rate variability, we arbitrarily created age groups of ≤ 30 years and > 30 years. Although this division could be discussed, we found no strong association between age and short-term HRV values in our population. The subjects included were randomly selected, but predominantly Caucasian, and their lifestyle was relatively healthy when compared with the general Dutch population [27]. Although a comprehensive anamnesis was carried out to determine the medical history of subjects, we did not

analyse their glucose and cholesterol status, which may have influenced the heart rate variability.

The present study provides normal ranges for short-term heart rate variability analysis in the clinical setting, such as the perioperative period, operating room or intensive care [2-3, 8-16]. Recently, interest in the investigational and clinical use of heart rate variability, especially in anaesthesia and critical care, has increased [3, 8-16]. The use of heart rate variability or pulse rate variability for research or clinical risk stratification, for example for the perioperative period of intensive care, can now be validated using our reference values for young and adults. Future studies that focus on the practical implementation of heart rate variability for young and middle-aged patients in specific clinical settings and elucidate causes of the differences between men and woman are warranted.

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