35th Annual International Conference of the IEEE EMBS
Osaka, Japan, 3 - 7 July, 2013

Influence of age and gender on complexity measures for short term heart rate variability analysis in healthy subjects

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Abstract—**Short-term heart rate variability (HRV) analyses (less than 30min) are suitable for ambulatory care and patient monitoring and can provide an almost immediate test result. Short-term 5 min HRV indices from nonlinear dynamics were determined from 782 females and 1124 males from the KORA S4 database. We applied various fractal and complexity measures with focus on entropies and investigated the influence of age in terms of five age decades (25-34, 35-44, 45-54, 55-64 and 65-74 years) and gender on these HRV indices. The analyses revealed significant modifications of the indices especially by age but partly also by gender especially in the younger groups. These results should be considered in future studies applying nonlinear dynamics, especially if major age and gender differences between the investigated groups are expected.**

I. Introduction

Over the last decades, the importance of heart rate variability (HRV) as a tool for assessing the autonomic nervous system activity in many different diseases and conditions has steadily increased. In addition to frequently used long-term HRV analysis, short-term HRV analysis has progressively been applied in recent years due to its suitability for ambulatory care and short-term patient monitoring and to receive test results almost immediately. A limitation of short-term HRV analysis is the sparse availability of studies providing statistically relevant values for nonlinear HRV indices from healthy subjects. To achieve a high degree of acceptance of the HRV assessment in clinical practice, it is essential to determine information about age- and gender-related HRV indices.

Several studies demonstrated particularly age-related but also gender-related variation in long-term HRV as serious influence on the majority of linear and nonlinear HRV indices [1, 2]. Methods of nonlinear dynamics (NLD) providing a considerably extended and complex analysis of long-term HRV gained considerably in importance in recent years [3, 4] and were also partially used in the field of short-term HRV analysis [5, 6]. However, valid information for short-term HRV indices of nonlinear dynamics is rarely available because only relatively small numbers of subjects were enrolled [4, 7].

In the previous study, Voss et al. [8] investigated age dependencies of HRV indices from 5-min duration ECG recordings of 1906 healthy subjects of the population-based KORA S4 study [9]. The study's results revealed significant variations of the majority of examined short-term (5-min) HRV indices. However, gender dependencies of HRV indices were not investigated in this study.

Therefore, this study has the following objectives: first, to determine the gender dependency of nonlinear short-term HRV indices (according to [8]), especially entropy values, and second, to provide information about age- and gender-related short-term HRV indices based on a representative healthy population.

II. Methods

A. Study population and preprocessing

In this study, HRV analysis was performed on 5-min resting ECG recordings (lead II and lead V2 simultaneously, 500 Hz sample rate) of 1906 healthy subjects from the population-based KORA S4 database [9]. The cohort consisted of 782 females and 1124 males between the ages of 25 and 74 years.

We extracted time series of heart rate (tachogram) consisting of beat-to-beat intervals (RR-intervals) from the ECG recordings. In a further step, normal-to-normal (NN) interval time series were obtained by application of an adaptive filter [10] on the tachograms which detects and replaces ectopic beats and artifacts or disturbances by interpolated "normal" beats.

B. Statistical analyses

Univariate statistical analyses were performed using the statistical software SPSS 19 for Windows. Non-normal distribution for most of the HRV indices was proven after normality testing using the Kolmogorov-Smirnov test. For this reason, from the descriptive statistics, median values and interquartile ranges were calculated for all HRV indices, subdivided into males and females.

Two tests were performed to determine the age and gender dependency of investigated HRV indices. Test I investigated the age dependencies of HRV indices within the five age groups 25-34, 35-44, 45-54, 55-64 and 65-74 years separately for females and males using the Kruskal-Wallis test followed by Mann-Whitney U tests. Test II investigated the gender dependence within the different age decade using the Mann-Whitney U test.

C. Time Domain (TD)

From time domain (TD) the following standard HRV indices according to the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Task Force, 1996) were calculated as a limited reference: meanNN [ms] (mean value of NN

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interval time series) and sdNN [ms] (standard deviation of NN interval time series).

Additionally, the following entropy from time domain was estimated [11]: shannon_h [bit] - Shannon Entropy calculated on the basis of the class probabilities p_i (i = 1,…,n with n - number of classes) of the NN interval density distribution.

D. Symbolic Dynamics (SD)

The traditional symbolic dynamics (SD) method provides a simple description of the system's dynamics by coarse-graining of time series [12]. In this study, NN interval time series were transformed into strings of symbols of the specific alphabet A = {0, 1, 2, 3}. Afterwards, the symbol strings were transformed into word sequences each consisting of three successive symbols. Based on the probability distribution of the 64 (4^3) possible word types, the following SD indices were calculated: shannon_SD [bit] (Shannon entropy of the word distribution, complexity measure), forbword [arb. units] (forbidden words - number of seldom ($p < 0.001$) or never occurring word types), wpsum02 [arb. units] (relative portion of words consisting only of the symbols '0' and '2', measure for decreased HRV), wsdvar [arb. units] (standard deviation of word sequence), phvar5/plvar20 [arb. units] (portion of low-variability patterns in the NN interval time series (> 5 ms/< 20 ms) and fwrenyi4 [bit] (Renyi entropy of the word distribution with $\alpha = 4$).

E. Detrended Fluctuation Analysis (DFA)

Peng et al. [13] introduced the Detrended fluctuation analysis (DFA) quantifying fractal and complex scaling properties of time series by integrating NN interval time series y(k) (k = 1,…,N with N - length of time series) dividing them into equal and non-overlapping segments of length n. In each segment, the local trend $y_n(k)$ is determined by least-squares fitting and subtracted from y(k) and root-mean-square fluctuation values F(n) are calculated and scaling exponents are estimated as the slope of the double-log plot of F(n) against n. Applying DFA as reference method, following indices were determined [13]: α1 [arb. units] (short-term fractal scaling exponent calculated over n = 4-16 beats) and α2 [arb. units] (long-term fractal scaling exponent calculated over n = 16-64 beats).

F. Compression Entropy (CE)

Firstly, Baumert et al. [14] quantified the complexity of NN interval time series by compression entropy (CE). CE allows a lossless data compression using a sliding window technique, searching for, and encoding, matching sequences between the window (w) and a look-ahead buffer (b) leading to the index $H_c^{w,b}$ [arb. units] as the ratio between the length M of the compressed time series and the length L of the original time series).

G. Segmented Poincaré Plot Analysis (SPPA)

Voss et al. [15] introduced the Segmented Poincaré plot Analysis (SPPA) based on traditional Poincaré plot Analysis. Here, the cloud of points is rotated 45 degrees clockwise around the main focus of the cloud of points and segmented into 12x12 equal rectangles whose size depends on SD1 (height) and SD2 (width). Based on the occurrence of points in each rectangle, a 12x12 probability matrix was estimated. From the single probabilities we calculated most important row probabilities (SPPA_r_6/SPPA_r_7 [arb. units]) and the Shannon entropy of the 12x12 probability matrix (SPPA_entropy [bit]).

H. Multiscale Entropy (MSE)

Costa et al. [2] introduced the multiscale entropy analysis (MSE) based on the evaluation of sample entropy (SampEn) [16]. For a given one-dimensional discrete time series multiple consecutive coarse-grained time series are constructed determined by the scale factor τ. Coarse-grained time series for scale τ were obtained by averaging of τ neighboring original values without overlapping. The length of each coarse-grained time series is N/τ. For scale 1, the coarse grained time series is simply the original time series (SampEn [bit]). MSE [bit] is calculated for each one of the coarse-grained time series (present study: τ =1-2). It should be mentioned that higher scales of MSE require longer time series.

III. Results

The descriptive statistics and the results of Test I and II are presented in table I.

A. Time Domain (TD)

Test I showed that, irrespective of the gender, there is a highly significant decrease of HRV over all ages (Kruskal-Wallis test), the highest significant changes occur between the age groups 2 and 3 (age range 35-54 years). No significant differences could be found between the age decades 55-64 and 65-74 years. Additionally, there are no significant gender differences of the TD indices presented (test II).

B. Symbolic Dynamics (SD)

Irrespective of the gender, there is a general decrease of complexity and variability over all age groups. Additionally, the decrease of complexity is most pronounced comparing males between 35-44 years and 45-54 years but there are nearly no (exception: wsdvar in males) meaningful changes of indices between the age groups 4 and 5 (age range 55 to 74 years). Test II showed no highly significant gender differences (≥**) on any of the SD indices.

C. Detrended Fluctuation Analysis (DFA)

The Kruskal-Wallis test (Test I) showed that there is a general increase of short- and long-term fractal correlation over all age groups. In the stepwise analysis of the age decades, the index α1 revealed a significant increase (at least *) between the age groups 1 to 3 (age range 25-54 years) but did not reveal significant differences when comparing the age decades 45-54 and 55-64 years and 55-64 and 65-74 years, respectively. Furthermore, index α2 was highly significantly different (**) only between males aged 35-44 years and 45-54 years. Additionally, with regard to gender (Test II), highly significant differences (≥**) on any of the DFA indices were not present.

D. Compression Entropy (CE)

Irrespective of the gender, there is a general decrease of $Hc^{3,3}$ as sign of decreased complexity (information) within the HRV time series (Test I). The decrease of $Hc^{3,3}$ is most pronounced (p=****) comparing males between 35-44 years and 45-54 years. However, there are no highly significant changes (≥**) of $Hc^{3,3}$ between the age groups 3 to 5 (age range 45 to 74 years). With regard to Test II, we observed no gender differences for the $Hc^{3,3}$ index.

E. Segmented Poincaré Plot Analysis (SPPA)

The SPPA index SPPA_r_7 (Figure 1) in females and index SPPA_r_6 in males showed a general age dependent influence (at least p=**, Test I) between the age decades. This age dependent influence on SPPA indices could not be found in differentiating between successive age decades using the Mann-Whitney U test. Applying Test II, there are significant (at least **) gender differences on SPPA_r_7 (Figure 1) in the age range 25-54 years. In the higher ages, the gender differences of the mentioned SPPA indices disappear. However, there is no meaningful gender and age influence on the SPPA_entropy index.

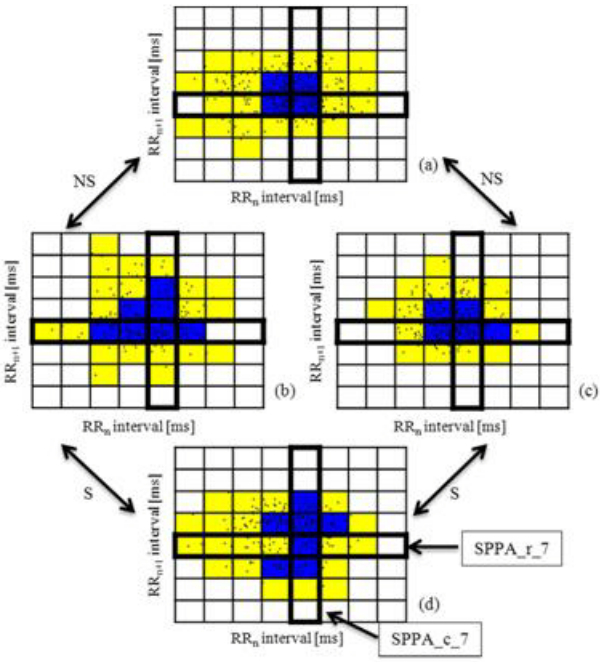

Figure 1. Examples of SPPA with marked 7th row (SPPA_r_7) and 7th column (SPPA_c_7); (a) from elder male, (b) younger male, (c) elder female and (d) younger female (NS – not significant; S – significant)

F. Multiscale Entropy (MSE)

Test I showed a general age dependent influence on all calculated indices in males and in females for scale1 and scale2 (at least **). No significant differences were found comparing the immediately succeeding age groups, with exception of the age group comparison 1-2 (age range 25-44 years). However, there is no meaningful gender difference (Test II).

IV. Discussion

Considering short-term nonlinear dynamics indices considerable age and gender dependencies could be observed in this study (Table 1). A general decline of HRV complexity with aging was proven. Both, age and gender influences on NLD HRV indices decrease with increasing age. As one major result we found significant differences of many nonlinear HRV indices between the younger age groups 1-3 (25-34, 35-44 and 45-54 years) in males and females. Comparing the elderly age groups 3-5 (45-54, 55-64 and 65-74 years) there are fewer differences noted. Additionally, it was shown that gender dependencies nearly disappear with aging. Especially above the age of 55 years, after the menopause in females (and males), gender differences on NLD HRV indices are marginal or absent.

Irrespective of the gender, the highest age related differences are present between the groups 2 and 3 (35-44 vs. 45-54 years) whereas the age groups 4 and 5 (45-54 vs. 55-64 years) reveal higher differences in females than in males.

These results are important for future analyses in the field of short-term HRV analysis applying a stronger focus on age- and gender-specific composition especially in the younger age decades. Comparing the age decades, we found only a few NLD HRV indices (e.g. SPPA_r_6) that are nearly not significant (or only marginal) different in females but significant in males, and vice versa (e.g. SPPA_r_7).

In addition to linear methods, nonlinear methods provide information regarding the dynamics and complex structure of interbeat time series. Complexity indices provide a possibility to quantify "irregularity" of time series. A high entropy value indicates a high level of complexity, and therefore, a low level of predictability. We could show a decrease in complexity with aging and a higher complexity of heart beat generation in females compared to males.

Age dependent alterations of HRV caused by modifications of the cardiovascular system with aging are not surprising and were found by Ferrari et al. [17]. He stated amongst others that aging is accompanied by significant cardiovascular modifications, both structural and functional. Fukusaki et al. [18] found that age-related changes in HRV reflecting vagal modulation of heart rate, were primarily mediated by aging per se and not by physiologic changes characteristic of normative aging. In the younger female groups probably estrogen plays an important role in gender-related autonomic differences [19].

The findings of this representative study on 1906 healthy subjects should be considered in future studies, especially if major age and/or gender differences between the considered groups are present.

Acknowledgment

The KORA research platform (KORA, Cooperative Research in the Region of Augsburg) (where required: and the MONICA Augsburg studies) was initiated and financed by the Helmholtz Zentrum München - German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research and by the State of Bavaria. This study was partly supported by grants from Deutsche Forschungsgemeinschaft (DFG-VO 505/8-2).

TABLE I. RESULTS OF KRUSKAL-WALLIS TEST AND MANN-WHITNEY U TESTS BETWEEN FEMALES OR FEMALES OF EACH TWO AGE DECADES (TESTS I) AND RESULTS OF MANN-WHITNEY U TESTS BETWEEN FIVE AGE MATCHED FEMALE AND MALE GROUPS (TESTS II); LEVEL OF SIGNIFICANCE: ****P<10^{-20}, ***P<10^{-10}, **P<BONFERRONI CRITERION=0.0007, *P<0.01, NS, NO SIGNIFICANCE; MA, METHOD OF ANALYSIS; TD, TIME DOMAIN; SD, SYMBOLIC DYNAMIC; DFA, DETRENDED FLUCTUATION ANALYSIS; CE, COMPRESSION ENTROPY; SPPA, SEGMENTED POINCARÉ PLOT ANALYSIS; MSE, MULTISCALE ENTROPY; AGE GROUPS: 1=25-34 YEARS, 2=35-44 YEARS, 3=45-54 YEARS, 4=55-64 YEARS UND 5=65-74 YEARS; MARKED LINES REPRESENT ENTROPIES.

		Test I: Females					**Test I: Males**					**Test II: Male vs. Female**				
		Kruskal-Wallis test	**Mann-Whitney U tests**				**Kruskal-Wallis test**	**Mann-Whitney U tests**				**Mann-Whitney U test**				
MA	***HRV-index***	***1-5***	***1***	***2***	***3***	***4***	***1-5***	***1***	***2***	***3***	***4***	***decades***				
			2	***3***	***4***	***5***		***2***	***3***	***4***	***5***	***1***	***2***	***3***	***4***	***5***
TD	meanNN	NS	NS	NS	*	NS	NS	NS	NS	NS	NS	**	NS	NS	NS	NS
	sdNN	****	NS	**	**	NS	****	*	**	*	NS	NS	NS	NS	NS	NS
	shannon_h	****	*	**	**	NS	****	*	**	*	NS	NS	NS	NS	NS	NS
SD	shannon_SD	****	**	**	**	NS	****	**	****	**	NS	*	*	NS	NS	NS
	forbword	****	*	**	**	NS	****	**	****	*	NS	*	*	NS	NS	NS
	wpsum02	****	*	**	*	NS	****	**	**	*	NS	NS	NS	NS	NS	NS
	wsdvar	****	*	**	**	NS	****	*	**	*	*	NS	NS	NS	NS	NS
	phvar5	****	**	**	*	NS	****	**	**	*	NS	NS	NS	NS	NS	NS
	plvar20	****	**	**	**	NS	****	**	****	**	NS	NS	*	*	NS	NS
	fwrenyi4	****	**	**	**	NS	****	**	****	**	NS	*	*	*	NS	NS
DFA	α1	***	**	*	NS	NS	****	**	**	NS	NS	*	*	*	*	NS
	α2	**	NS	NS	NS	NS	***	NS	**	NS	NS	NS	*	NS	NS	NS
CE	$H_c^{3,3}$	****	*	**	*	NS	****	**	****	*	NS	NS	NS	NS	NS	NS
SPPA	SPPA_r_6	NS	NS	NS	NS	NS	**	NS	NS	NS	NS	*	NS	NS	NS	NS
	SPPA_r_7	***	NS	NS	NS	NS	NS	NS	NS	NS	NS	****	**	*	NS	NS
	SPPA_ entropy	NS	NS	NS	NS	NS	*	NS	NS	NS	NS	NS	NS	NS	NS	NS
MSE	Entropy - scale1	**	*	NS	NS	NS	***	**	NS	NS	NS	NS	*	*	*	NS
	Entropy - scale2	**	NS	NS	NS	NS	***	NS	NS	NS	NS	NS	NS	NS	NS	NS

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