Gender Differences in Short-Term Multiscale Complexity of the Heart Rate Variability

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Abstract

Among the analytical methods estimating the complexity of the heart period (HP), the linear model-based multiscale complexity (MSC) approach allows the estimation of the complexity over time scales linked to the cardiac autonomic control, i.e. in the low frequency (LF, 0.04-0.15 Hz) and high frequency (HF, 0.15-0.4 Hz) bands. In this study we exploited MSC to evaluate the differences in the HP variability complexity during daytime (DAY) and nighttime (NIGHT) in 23 healthy females (WOMEN, age 36±6 yrs) and 21 males (MEN, age 35±5 yrs) performing a 24-hour Holter electrocardiogram. Parametric power spectral analysis was applied as well for comparison. Complexity indexes were computed regardless of the temporal scale (CI) and in the LF and HF bands (CI_{LF} and CI_{HF}, respectively). We found that the power spectral indexes did not differentiate WOMEN and MEN, while CI and CI_{LF} were higher in WOMEN during DAY. The higher HP complexity in females could be explained by a lower sympathetic drive and more complex hormonal regulation than males. We conclude that MSC was more powerful than power spectral analysis in detecting gender differences in HP variability. In addition, as cardiac control differs between females and males, preventive and therapeutic interventions should take gender differences into account.

1. Introduction

The analysis of the heart period (HP) is one of the most widely applied tools to typify the cardiac neural autonomic control of healthy and pathological subjects. Traditionally, this analysis is based on the study of the HP oscillations in two frequency bands: the high frequency (HF, from 0.15 to 0.4 Hz) and the low frequency (LF, from 0.05 to 0.15 Hz) bands [1]. The power in LF band is linked to both vagal and sympathetic controls, while the HF power is a marker of vagal modulation directed to the sinus node [2, 3]. Among the several analytical methods exploited to evaluate cardiac control over short recordings of about 300 HP values, complexity analysis plays an important role [4]. Recently, the short-term complexity of the HP variability has been assessed via a model-based multiscale complexity (MSC) method [5] that allows the estimation of the complexity of short-term HP series over time scales specifically linked to the cardiac autonomic control, i.e. in the LF and HF bands [5, 6].

In the last years, the gender medicine approach is gaining more and more attention [7]. However, when assessing cardiac neural control via HP variability analysis, a few studies checked gender differences [8]. Among those studies the majority is based on traditional power spectral analysis, is carried out in the well-controlled conditions of the laboratory and does not compare diurnal and nocturnal periods [8, 9].

We hypothesize that the study of the HP variability complexity in females and males using MSC [5] could provide more insights about cardiac neural control and gender differences compared to the more traditional power spectral analysis. Thus, the aim of this study is to perform MSC analysis of HP variability during daytime (DAY) and nighttime (NIGHT) in a group of young healthy women (WOMEN) and men (MEN) undergoing 24-hour Holter electrocardiogram monitoring. MSC indexes are compared to more traditional power spectral assessment.

2. Population and experimental protocol

The WOMEN group was composed by 23 healthy young females, while the MEN group comprised 21

Table 1. Demographic and clinical features of the enrolled population.

Index	WOMEN (n=23)	MEN (n=21)
Age [yrs]	36±6	35±5
BMI [kg·m^{-2}]	23.7±2.8	24.4±3.0
Smokers [%]	22	24
Sleep [hours]	6.2±1.20	6.2±1.1
Physical activity [%]	26	43
Physical activity [hours·week^{-1}]	2.7±0.9	3.8±2.6

WOMEN: female group; MEN: male group; BMI: body mass index. Interval variables are expressed as mean±standard deviation. Categorical variables are expressed as percentage.

healthy young men. At enrolment a detailed clinical evaluation was performed to verify the healthy status of the included subjects and to collect the demographic and clinical information reported in Table 1. Age, body mass index, percentage of light smokers, slept hours per night and physical activity habits were similar in the two groups. Each participant underwent a 3-lead 24-hour Holter electrocardiogram (360° eMotion FAROS, MegaElectronics, Finland; Sylco srl, Monza, Italy) during a regular working day. Participants were asked to avoid heavy physical activity in the 48 hours preceding and during the recording. Sampling rate was 500 Hz. The study adhered to the principles of the Declaration of Helsinki and was approved by the local Ethics Committee (2131CE). Each subject signed a written informed consent.

3. Methods

3.1. Beat-to-beat time series extraction

The modified lead II was chosen for analysis. HP was measured as the temporal distance between two consecutive R-wave peaks. Detections were checked and ectopic beats were corrected by means of cubic spline interpolation (maximum 5% of total samples). Segments of 2500 consecutive HP intervals were selected during DAY (from 1:00 p.m. to 5:00 p.m.) and during NIGHT (from 1:00 a.m. to 4:00 a.m.). Within the assigned segments short-term analysis was iterated, with 80% overlap, over windows of 300 consecutive HP values after linear detrending. The median of the distribution of all computed indexes was taken as representative marker [10]. HP mean (μ_{HP}) and variance (σ^2_{HP}) were calculated and expressed in ms and ms^2, respectively.

3.2. Power spectral analysis

Autoregressive (AR) power spectral analysis was performed on the HP series. The coefficients of the model were estimated via Levinson-Durbin recursion. Akaike information criterion was used to choose the model order in the range between 8 and 16. The HP series was decomposed into power spectral components. The sum of the power spectral components whose central frequency dropped in the HF band was labelled as HFa_{HP} and considered to be as a marker of the cardiac vagal modulation [2, 3]. HFa_{HP} was expressed in ms^2.

3.3. MSC analysis

The method is fully described in [5]. Briefly, the HP series was described as a realization of an AR process, that describes the current value HP_n as a linear combination of p past values plus a sample of a realization of a random zero mean Gaussian white noise w_{HP}. The same method utilized for spectral analysis was followed to identify the AR coefficients and optimize the model order within the same range. The variance of w_{HP}. was estimated as the variance of the prediction error derived by subtracting from the original value HP_n its estimate derived from the AR

Table 2. Time and frequency domain indexes of HP variability in WOMEN and MEN during NIGHT and DAY.

Index	WOMEN		MEN	
	DAY	NIGHT	DAY	NIGHT
μ_{HP}, [ms]	776.67±87.91	911.55±126.87 #	793.59±90.42	950.10±118.29 #
σ^2_{HP} [ms^2]	2132.13±1133.99	3547.35±4764.75	2501.76±1519.20	3518.19±2445.53
HFa_{HP} [ms^2]	388.26±345.19	1277.22±1742.20 #	286.67±262.09	1043.41±1149.51 #

WOMEN: female group; MEN: male group; DAY: daytime; NIGHT: nighttime; HP: heart period; μ_{HP}: HP mean; σ^2_{HP}: HP variance; HF, high frequency; HFa_{HP}, absolute power of HP in the HF band. Results are shown as mean±standard deviation. The symbol # denotes $p<0.05$ vs NIGHT within the same group.

Table 3. Complexity markers of HP variability in WOMEN and MEN during DAY and NIGHT.

Index	WOMEN		MEN	
	DAY	NIGHT	DAY	NIGHT
CI	0.31±0.09	0.38±0.17 #	0.22±0.09 *	0.34±0.09 #
CI_{LF}	0.16±0.05	0.18±0.03	0.14±0.05 *	0.16±0.04 #
CI_{HF}	0.20±0.07	0.20±0.05	0.23±0.08	0.21±0.05

WOMEN: female group; MEN: male group; DAY: daytime; NIGHT: nighttime; HP: heart period; CI: complexity index; HF: high frequency; CI_{HF}: complexity index of HP in the HF band; LF: low frequency; CI_{LF}: complexity index of HP in the LF band. Results are shown as mean±standard deviation. The symbol * indicates $p<0.05$ vs MEN within the same period of analysis, while the symbol # denotes $p<0.05$ vs NIGHT within the same group.

model. The variance of the prediction error is known to be linked to the complexity of the AR process [4]. It was taken as complexity index (CI). CI ranged from 0 to 1, where 0 is null complexity and 1 maximum complexity.

Then, the poles were derived from the transfer function from w_{HP} to HP series, and their modulus and phase were calculated. The poles whose phase, converted into frequency and expressed in Hz, dropped in the LF or HF band were labeled as LF or HF, respectively. The average position from the unit circle of all identified LF and HF poles was calculated in the complex plane. The average distance from the unit circle of LF and HF poles was taken as an CI of HP in the LF and HF bands and labelled as CI_{LF} and CI_{HF}, respectively. CI_{LF} and CI_{HF} were bounded between 0 and 1: the higher CI_{LF} and CI_{HF}, the higher the complexity of the HP series and the higher the unpredictability.

3.4. Statistical analysis

The differences in demographic and clinical features between WOMEN and MEN were tested by unpaired t test, or Mann-Whitney rank sum test when appropriate, in case of continuous variables and by χ^2 test in case of categorical ones. Two-way repeated measures analysis of variance (one factor repetition, Holm-Sidak test for multiple comparisons) was performed to evaluate the difference between WOMEN and MEN within the same period of analysis (i.e. DAY or NIGHT) and between different periods of analysis within the same group. Statistical analyses were carried out using Sigmaplot, Systat Software, Inc., Chicago, IL, version 11.0. A $p<0.05$ was always considered significant.

4. Results

Table 2 shows the results of time and frequency domain HP indexes in WOMEN and MEN as a function of the experimental condition (i.e. DAY and NIGHT). μ_{HP} and HFa_{HP} increased during NIGHT both in WOMEN and MEN. σ^2_{HP} did not vary between groups and experimental conditions. No differences were detected between WOMEN and MEN for none of the considered index.

Table 3 shows the results of CIs in WOMEN and MEN during DAY and NIGHT. CI increased during NIGHT in both WOMEN and MEN and was higher in WOMEN than in MEN during DAY. CI_{LF} increased during NIGHT only in MEN and was higher in WOMEN than in MEN during DAY. As to CI_{HF}, no differences between groups and experimental conditions were detected.

5. Discussion

The main findings of the study can be summarized as follows: i) time, frequency and complexity analyses differentiated DAY and NIGHT regardless of the gender; ii) time and frequency domain indexes were similar in WOMEN and MEN regardless of the period of analysis; iii) the complexity of the HP variability was higher in WOMEN than in MEN during DAY; iv) the differences between WOMEN and MEN in HP variability complexity were due to different complexity at the LF scale.

We first applied the MSC analysis to assess HP complexity in LF and HF bands from 24-hour Holter electrocardiographic traces. We found that MSC analysis was more powerful than time and frequency domain analyses in detecting differences of the cardiac control in females and males. Indeed, while $\mu_{HP,}$ σ^2_{HP} and HFa_{HP} were similar in WOMEN and MEN regardless of the period of analysis, HP complexity was higher in WOMEN than in MEN. This finding was significant only during DAY, with a tendency during NIGHT. This result is in agreement with other studies suggesting a higher HP complexity in WOMEN over short-term recordings during DAY [11, 12]. The original finding of this study is that this result was due to a higher short-term complexity of the cardiac control in the LF band, thus suggesting that the mechanisms involved in raising the HP complexity in women operates in this band. Previous studies suggested that the higher complexity in females is due to the more complex hormonal regulation than in males, mainly due to the effects of estrogen [11, 13]. The higher sympathetic drive detected in young healthy males compared to females [14-16] might have contribute to keep low the complexity of cardiac control in males. Indeed, cardiac control

complexity has been found to be lower in conditions shifting sympatho-vagal balance towards a sympathetic dominance [4, 5]. It is worth noting that these differences could vary across the life cycle [8, 13].

As expected the circadian variation of time and frequency domain HP variability indexes were detected in both groups. Indeed, μ_{HP} and HF_{aHP} increased during NIGHT. The HP complexity increased during NIGHT [10] as a likely effect of a more dominant vagal control [17]. Remarkably, MSC analysis attributed the modification of the HP complexity during NIGHT again to contributions in the LF band. This finding suggests that sympathetic control might have an important role in modulating HP complexity even when its activity is known to be limited such as during NIGHT.

Future studies should include subjects of different age, as the ageing process is known to dramatically impact on the cardiac control and on gender difference [13, 18]. The use of methods accounting for nonlinearities of cardiac control might add additional insights [19].

6. Conclusion

In the present study we assessed gender differences of HP complexity as assessed in the LF and HF bands via a MSC analysis. At difference with the more traditional power spectral analysis, complexity analysis highlighted important gender differences. More specifically, WOMEN were characterized by a higher HP complexity during DAY compared to MEN and this result was evident only in the LF band. Differences were attributed to a combination of lower sympathetic control and a more complex hormonal regulation than males. Therefore, we suggest to perform MSC analysis, together with more traditional analyses, when assessing gender differences in HP variability. These findings could guide clinicians through the choice of differentiate preventive and therapeutic interventions in relation to gender.

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