Autonomic cardiac activity in adults with short and long sleep onset latency

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***Abstract*— Autonomic cardiac activity during sleep has been widely studied. Research has mostly focused on cardiac activity between different sleep stages and wakefulness as well as between normal and pathological sleep. This work investigates autonomic activity changes during sleep onset in healthy subjects with long and short sleep onset latency (SOL). Polysomnography (PSG) and electrocardiography (ECG) were simultaneously recorded in 186 healthy subjects during a single night. Autonomic activity was assessed based on frequency domain analysis of RR intervals and results show that the analysis of RR intervals differs significantly between the short SOL and the long SOL groups. We found that the spectral power in the low frequency band (LF) was significantly higher in the long SOL group compared to the short SOL group in the first 10 minutes in bed intended to sleep. There was no significant difference for LF and the spectral power in the high frequency band (HF) 10 minutes before and after sleep onset between the two groups. Only in the short SOL group there was a significant increase in HF from the first 10 minutes in bed intended to sleep to 10 minutes before SO, while LF decreased significantly in both groups. The effect of time (5.5-min bin) on the heart rate variability (HRV) features around sleep onset showed that both LF and HF differed significantly during the period surrounding sleep onset only in the short SOL group.**

I. INTRODUCTION

Sleep problems, in particular the difficulty initiating sleep are becoming more prevalent [1] and worldwide one third of the adults is affected occasionally by sleeplessness symptoms [1], [2]. The effects of sleep problems have been associated with different health consequences such as increased risk of hypertension, obesity, depression, heart attack, and stroke [3]. Many factors can be associated with the difficulties in falling asleep such as increased levels of stress and physiological hyperarousal [5]. The process to falling asleep is a transition between two states: wakefulness, and usually, Non Rapid Eye Movement (NREM) sleep [7]. The standard definition of sleep onset (SO) is based on polysomnographic (PSG) recording and changes observed in electroencephalography (EEG), electrooculography (EOG) and electromyography (EMG) and can be annotated with a precision of seconds [7]–[9]. However, PSG recording is labor intensive and cannot provide long-term monitoring of sleep especially for people suffering from problems initiating sleep. This is due to the fact that many electrodes are attached to the human body and its obtrusiveness might have a negative impact on the subject's ability of falling asleep.

Studies have shown that the transition from wakefulness to sleep is associated with changes in the autonomic nervous system [7], [10]–[13]. Heart rate variability (HRV) can be expressed by a set of objective measures that provide information regarding the dynamics of the autonomic nervous system (ANS). Several studies have shown that heart rate (HR) and blood pressure (BP) decrease during SO [10], [13], [14]. Research has mostly focused on HRV features averaged per hour between different sleep stages and wakefulness [10], [12], [14] as well as between normal and pathological sleep [7]. The aim of this work is to study autonomic activity changes during the first 10 minutes in bed intended to sleep and 10 minutes before and after SO because we expect that these changes occur in a shorter time scale. In particular, this study investigates whether autonomic activity expressed by spectral power of HRV differs between healthy adults with long and short sleep onset latency (SOL).

II. MATERIAL AND METHODS

A. Data

The data set used in this work comprises four data sets collected in four different studies. The first data set consists of a subset of the data collected in the SIESTA project in the period from 1997 to 2000 [15] and we used 192 standardized PSG recordings of healthy subjects (101 female) with a mean ± standard deviation (SD) age of 51.4 ± 19.3 years. All subjects had a Pittsburgh Sleep Quality Index (PSQI) [4] score of less than 6. None of the subjects were using or had a history of drug and/or alcohol use. In addition, none were working at night, or had been diagnosed with a medical (or mental) disorder interfering with the aim of the study [15], [16]. The PSG recordings of all participants were scored according to the R&K guidelines [8] by two trained somnologists from different sleep centers and revised by a third expert who took the final decision in case of disagreement [15], [16]. More details regarding the study design are described by Klosh et al. [15].

The second data set was collected in 2014 and consists of 13 healthy subjects (6 female) with a mean age of 52.7 ± 8.0 years. All subjects had a PSQI score of less or equal

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than 7 and a mean body mass index (BMI) index lower than 30 kg/m^2 (for details regarding the study design see [16]). The third data set was collected in 2015 and consists of 34 healthy (22 female) subjects with a mean age of 51.7 $\pm$ 6.9 years and a BMI index lower than 37 kg/m^2 (for details regarding the study design see [16]). The fourth data set was collected in 2009 and consists of single-night PSG recordings from 8 healthy (7 female) subjects with a mean age of 29.6 $\pm$ 10.9 years and a BMI index lower than 31 kg/m^2.

The PSG recordings of all participants in the latter three data sets were scored by a trained somnologist according to the AASM guidelines [9]. None of the healthy subjects were using sleep, antidepressant or cardiovascular medication, recreational drugs, nor had they been diagnosed with a sleep (or mental) disorder.

For the purpose of this study, a subject was included in the analysis if he/she experienced a sleep onset latency of at least 10 minutes from the moment subjects went to bed intended to sleep. Furthermore, in order to eliminate the effect of multiple night monitoring our analysis was performed on the first night of PSG recording. After applying these inclusion criteria, the resulting data set consists of 186 (102 female) subjects with a mean age of 50.9 $\pm$ 17.54 years and a mean BMI index of 24.75 $\pm$ 3.6 kg/m^2. This data set was divided in two groups based on the SOL according to quantitative criteria for insomnia [6]: subjects with SOL greater than 30 minutes form the long SOL group, comprising 77 subjects (48 female) while the remaining comprise the short SOL group with 109 subjects (54 female). The subjects of both groups did not differ significantly with regard to age and gender (Mann-Whitney U test and Fisher's exact test). BMI was significantly higher in the short SOL group compared to the long SOL group (Mann-Whitney U test).

B. Sleep onset definition

Frequency domain HRV features were computed during the first 10 minutes in bed intended to sleep and 10 minutes before and after SO. SO was defined as the first epoch of three consecutive 30-s epochs scored as non-awake and usually N1 sleep stage or any other deeper sleep stage [8]. The R&K definition [8] was chosen due to the fact that it requires a longer duration of sleep to be defined as onset compared to the AASM definition [9] of SO: 1.5 minutes instead of 30 seconds.

C. Feature extraction

ECG signals from the PSG were high-pass filtered with a cut-off frequency of 0.8 Hz and then normalised with regard to mean and amplitude. R-peaks were detected based on the algorithm proposed by Kathirvel et al. [17] and then post-processed for precise QRS localization by using the algorithm of Fonseca et al. [18]. Ectopic RR intervals longer than 2 s, shorter than 0.3 s or shorter than 0.6 times their previous value were excluded. The resulting RR interval time series was re-sampled at a sampling rate of 4 Hz using linear interpolation. The power spectral density was estimated with an auto-regressive model [19]. We extracted two frequency domain features using a sliding window of 11 epochs centered on each 30-s epoch, guaranteeing sufficient data (5.5 minutes) to capture the changes in autonomic activity as recommended by [20]. The features consist of the logarithmic spectral powers in the low frequency band (LF) from 0.04 to 0.15 Hz and in the high frequency band (HF) between 0.15 to 0.4 Hz [20]. The LF and HF were normalized by dividing the power in each band by the difference between total power and very low frequency spectral power.

Given the fact that the sliding window is centered in every 30-s epoch, the first value of the 10 minutes vector before SO corresponds to -7.25 minutes and the last value corresponds to -2.75 minutes before SO, yielding a total of 10 values of each HRV feature (see Figure 1). Accordingly for after SO the first value and last value of the 10 minutes vector correspond to +2.75 minutes and +7.25 minutes. The mean value of the HRV feature values in the first 10 minutes in bed intended to sleep, before and after SO was computed.

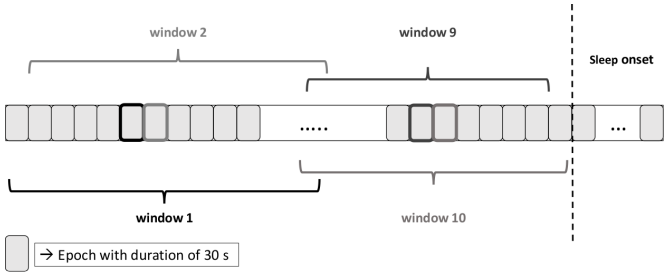

Fig. 1. HRV feature extraction by using a sliding windows of 5.5 minutes centered on each 30-s epoch.

D. Statistical analysis

The mean value of each HRV feature during the three examined periods (the first 10 minutes in bed intended to sleep, before and after SO) was compared between the two SOL groups using the non-parametric Mann-Whitney U test. This test was chosen due to non-normal distributions (as determined by ShapiroWilk W tests). Statistical significance was established for $p < 0.05$. Effect size was computed by probability of superiority (PS). The expected value of this statistic is, under the null hypothesis that there is no difference between the groups, PS = 0.5. The further away PS is from 0.5 the larger the observed effect. Hodges-Lehmann estimates ($HL\Delta$) and Moses 95% confidence intervals (CIs) were computed to compare the differences between two parameters [21].

In addition, median values and standard errors (SE) of LF and HF as a function of time in 5.5-min bins during the transition to sleep were calculated (Figure 2 and 3). This measure represents the evolution of LF and HF over time of all the subjects in each group. Friedman's non-parametric test was used to analyze the effect of time (5.5-min bin) on each of LF and HF features in each group. This test is a non-parametric repeated measure one way ANOVA. Friedman's test was chosen due to non-normal distributions (as determined by ShapiroWilk W tests). A Wilcoxon test was used for post-hoc pairwise comparison of

LF and HF, followed by a Bonferroni correction for multiple comparisons at a significance level of $p < 0.05$.

III. Results

A. Comparisons of HRV features

LF was significantly higher in the long SOL group than in the short SOL group in the first 10 minutes in bed intended to sleep (U = 4814, $p < 0.05$, PS = 0.575 with median difference of $HL\Delta$ = 0.092 (95% CI: 0.090, 0.093)) but not before SO (U = 4477.0, $p > 0.05$, PS = 0.533 with median change of $HL\Delta$ = 0.039 (95% CI: 0.038, 0.042)) and after SO (U = 4578.0, $p > 0.05$, PS = 0.545 with median change of $HL\Delta$ = 0.063 (95% CI: 0.061, 0.066)).

The median value of LF decreased significantly from the first 10 minutes in bed intended to sleep (median = -0.645) to 10 minutes before SO (median = -0.667) in the short SOL group, z = 2092.0, $p < 0.05$, with PS = 0.176. Furthermore, a significant reduction in LF was also observed in the long SOL group, from the first 10 minutes in bed intended to sleep (median = -0.513) to 10 minutes before SO (median = -0.608), z = 1103.0, $p < 0.05$, with PS = 0.187.

HF was not significantly lower in the long SOL group compared to the short SOL group in all three examined time periods (*the first 10 minutes in bed intended to sleep:* U = 4050, $p > 0.05$, PS = 0.483 with median change of $HL\Delta$ = -0.030 (95% CI: -0.032, -0.028), *before SO:* U = 4047.0, $p > 0.05$, PS = 0.482 with median change of $HL\Delta$ = -0.027 (95% CI: -0.029, -0.025) and *after SO:* U = 3865.0, $p > 0.05$, PS = 0.461 with median change of $HL\Delta$ = -0.066 (95% CI: -0.069, -0.066)).

The median value of HF increased significantly from the first 10 minutes in bed intended to sleep (median = -1.025) to 10 minutes before SO (median = -0.968) in the short SOL group, z = 2086.0, $p < 0.05$, with PS = 0.176. A statistically significant increase in HF was not observed in the long SOL group, z = 1341.0, $p > 0.05$, with PS = 0.226.

B. Effect of time on HRV features

A Friedman's test of differences among repeated measures of LF was conducted and showed in the short SOL group a significant difference in LF depending on which time was measured (χ^2 = 15.95, $p < 0.01$). A post-hoc analysis with Wilcoxon signed-rank tests with a Bonferroni correction of LF showed a significant decrease from -7.25 min (median = -0.592) to +2.75 min (median = -0.677), z = 2156, $p < 0.05$ and increase from +2.75 min (median = -0.677) to +7.25 min (median = -0.602), z = 2665, $p < 0.05$. There were no significant differences between the remaining pairs. In the long SOL group a Friedman's test of differences among repeated measures of LF did not show significant differences (χ^2 = 2.66, $p > 0.05$).

A Friedman's test showed, in the short SOL group, a significant difference in HF (χ^2 = 20.13, $p < 0.001$). A post-hoc analysis of HF with a Wilcoxon signed-rank test with a Bonferroni correction showed a significant increase from -7.25 min (median = -0.985) to -2.75 min (median = -0.933), z = 2119, $p < 0.05$, a significant increase from -7.25 min (median = -0.985) to +2.75 min (median = -0.835), z = 1826, $p < 0.005$ and a significant decrease from +2.75 min (median = -0.835) to +7.25 min (median = -0.942), z = 2008, $p < 0.05$. There were no significant differences between the remaining pairwise comparisons. In the long SOL group a Friedman's of HF did not show significant difference (χ^2 = 2.70, $p > 0.05$).

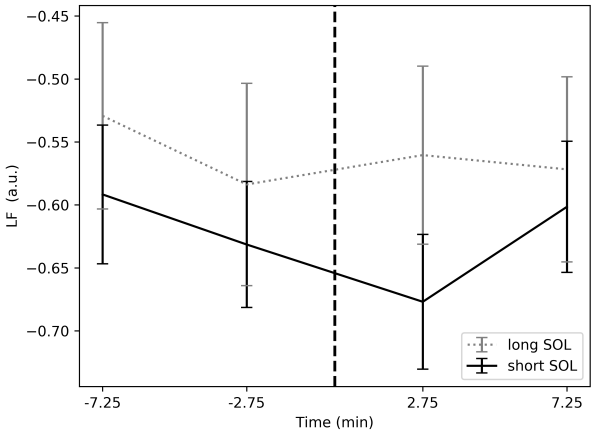

Fig. 2. The median values and standard errors (SE) of LF as a function of time in 5.5-min bins. The black dashed line denotes sleep onset.

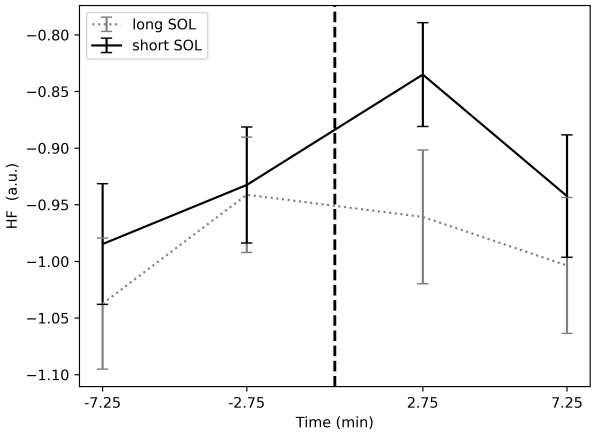

Fig. 3. The median values and standard errors (SE) of HF as a function of time in 5.5-min bins. The black dashed line denotes sleep onset.

IV. Discussion

The results show that LF differs significantly between the short SOL and the long SOL groups. However, significant differences (between or within groups) are not always found in all three examined time periods or HRV features. We found that there is a statistically significant difference in LF between the two groups in the first 10 minutes in bed intended to sleep. In particular, LF was significantly higher in the long SOL group compared to the short SOL group. In addition, only in the short SOL group there was a significant increase in HF from the first 10 minutes in bed intended to sleep to 10 minutes before SO, while LF decreased significantly in both groups. The effect of time on the HRV features showed that both LF and HF (before and after SO but also during the 10 minutes before or after SO) differed

significantly around the process of falling asleep only in the short SOL group (consistent with the main tends in the literature [7], [10], [12]).

The transition to sleep is a combination of physiological, cognitive and behavioral alterations. In this study we focused on the autonomic nervous system changes as expressed by the spectral power of HRV. In accordance with the literature, HF reflects the respiration-driven modulation of sinus rhythm, and has been used as an index of tonic vagal drive [2], [20]. LF is seen as a marker of sympathetic modulation, especially when expressed in normalized units [2], [20]. However, some researchers support that LF reflects both sympathetic and parasympathetic activity [2], [20].

Under the assumption that LF reflects sympathetic activity, the results of this study suggest that subjects with problems initiating sleep (long SOL) are more aroused in the first 10 minutes they intended to sleep as compared to subjects in the short SOL group (LF significantly higher). This hypothesis seems to be supported also by the fact that significant reduction in LF from the first 10 minutes the subjects intended to sleep to 10 minutes before SO was higher in the long SOL group. This hyperarousal could explain the mechanisms underlying the long SO. Nevertheless, this was not seen by HF feature since there was no significant difference found between the two groups. This could be due to the fact that subjects included in this study have a broad age range and it is known that there is a significant reduction of parasympathetic activity with age [22]. This fact could have increased the variability of HF between subjects and groups and decrease the group differences. Decreased LF and increased HF during the transition from wakefulness to sleep was observed only in the short SOL group. This suggests that there is lower variability in the HRV features of the long SOL group compared to the short SOL group, probably related to hyperarousal state mentioned earlier.

As mentioned above, our study includes a broad age range of participants. Limitations to our study include the fact that the analysis was not performed per age group so the broad age range of participants could increase the variability of the feature in both groups and thus decrease the possibility to show group differences. Additionally, we investigated only one definition of SO. It would be insightful to compare different definitions of sleep onset latency with the goal of assessing which would yield, from an autonomic cardiac perspective, the largest differences between the two groups. Furthermore, a possible physiological explanation for the significant difference in BMI between the two groups can be investigated. An extension of the study including more HRV features as well as pathological sleep such as insomnia would be interesting to explore if there is an association with the chronic aspect of the disorder.

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