Heart Rate Variability During Sleep in Patients with Vasovagal Syncope

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CINTRA, F., ET AL.: Heart Rate Variability During Sleep in Patients with Vasovagal Syncope. ***Background:*** *There are a few studies showing no significant heart rate variability (HRV) over a 24-hour period in vasovagal syncope (VVS) patients, but no research has examined HRV and its sympathetic and parasympathetic components during rapid eye movement (REM) and non-REM sleep. The authors hypothesized that REM sleep might be a critical state in which VVS patients would show abnormal responses.*

Objectives: *To analyze the sympathetic and parasympathetic components of HRV during REM and SWS in patients with VVS compared to normal subjects, and in patients with positive HUTT compared to negative ones.*

Methods: *Thirty-seven VVS patients and 20 normal age-matched controls were submitted to polysomnography with 24-hour Holter monitoring to assess HRV. Time and frequency domain techniques were carefully performed for 24 hours and during Stages 3 and 4 of REM and non-REM sleep. Variation of sympathetic activity index (VSAI) was defined as the difference in the low frequency (LF) component of HRV between REM and Stages 3 and 4 of non-REM sleep. An analysis of variance was performed to compare patients and controls; patients with positive and negative head-up tilt testing.*

Results: *The LF component was lower in syncope compared to normal patients (1,769.54 ± 1,738.17, 3,225.37 ± 2,585.05, respectively, $P = 0.03$). There was a significant decrease in VSAI in the syncope group compared to the control group (−539.39 ± 1,930.78, 1,268.10 ± 2,420.20, respectively, $P = 0.01$). The other sleep variables analyzed including very LF, high frequency, low frequency/high frequency and time domain parameters did not reach statistical significance. Syncope patients also showed an increase in slow wave sleep (28.2 ± 10.5, 19.7 ± 7.8, $P = 0.01$).*

Conclusions: *VVS patients exhibited sympathetic suppression during REM sleep. Possible mechanisms are discussed in this article. (PACE 2005; 28:1310–1316)*

syncope, REM sleep, heart rate variability, sympathetic activation

Introduction

Syncope is defined as acute and transitory loss of consciousness associated with loss of postural tonus and spontaneous recovery. Neurally mediated syncope or vasovagal syncope (VVS) is probably the most prevalent cause of this disorder.[1,2] The pathophysiology of VVS is not properly understood, but the involvement of mechanoreceptors, autonomic alterations, and high catecholamine levels[3–7] has been described. Postural triggered reflex is a common feature in these patients and is usually assessed by head-up tilt testing (HUTT).[8]

HRV has been used as an alternative technique to analyze autonomic nervous system (ANS). Some studies failed to show significant changes over a 24-hour period in syncopal children;[9] on the other hand, discordant autonomic alterations have been reported when HRV was performed during HUTT.[10–12] Moreover, there are no studies analyzing HRV during REM and non-REM sleep.

It is known that there is a tonic increase in parasympathetic activity during REM and non-REM sleep. However, there have also been findings of bursts of high-amplitude sympathetic activity during REM sleep compared to wakefulness in normal subjects,[13,14] characterizing a special state in which ANS components interaction is particular. Thus, the integrity of all mechanisms involved in ANS activation is then necessary. Since we acknowledge that REM sleep pursues a distinct ANS control, and VVS may be due to an increase in susceptibility to the autonomic reflex, the authors hypothesized that altered ANS behavior is likely to occur during this sleep state. Therefore, we

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decided to assess the HRV during REM sleep and slow wave sleep (SWS) in VVS patients.

Methods

Population

All patients aged 16–55 years referred consecutively to the syncope clinic at the Cardiology Department of the Federal University of São Paulo over a 4-month period were invited to be participants in the study. After clinical, cardiac, and electrophysiological evaluation a sample was selected using the following criteria:

- Typical VVS clinical history, including short syncope episodes, prompt recovery, occurring at least twice in the last 3 months, preceded by a typical prodromic phase (diaphoresis, nausea, blurred vision, weakness, dizziness).
- Normal 12-lead electrocardiogram (ECG) and thorax X-ray;
- Absence of cardiac structural disease, respiratory diseases, respiratory sleep disorders and major sleep disorders, diabetes, obesity, neurological and psychiatry disease, and use of medications.
- Body mass index lower than 25 kg/m^2.

A total of 37 patients were selected and signed the informed consent form. The control group consisted of 20 normal age- and gender-matched volunteers. They were submitted to the same clinical evaluation as the patients and had no history of medical diseases or previous syncope symptoms.

The study was approved by the Ethical Committee of the Federal University of São Paulo.

Head-Up Tilt Testing

HUTT was performed in a quiet and comfortable room at a constant temperature of 22°C, during a 45-minute period of inclination at an angle of 70°, without drug sensitization, and after a initial 20-minute period of stabilization in supine position in all syncope patients. Patients were instructed to fast for at least 4 hours. There was continuous 12-lead ECG monitoring (BARD® system version 2.57, USA) and blood pressure measurements with esphigmomanometer were taken every 2 minutes during HUTT. When symptoms were referred, blood pressure measurements were taken shortly afterward.

HUTT was considered positive if it triggered the syncope or presyncope symptoms associated with hypotension and/or bradycardia.

Polysomnography and Holter Monitoring

All subjects went to bed at their usual bedtime, and had a minimum of 7 hours of polysomnography (PSG) recordings. The following sleep variables were collected and stored using amplifiers and preamplifiers (Meditron™) and a dedicated computerized 20-channel sleep system (Sonolab® Meditron, São Paulo, Brazil) with a sampling rate of 256 Hz per second per channel. A total of 4 electroencephalogram (EEG) leads, two electrooculogram channels, two electromyogram channels (chin and both legs), and an ECG channel were recorded. Respiration was monitored as follows: (a) nasal cannula with flow measured using a pressure transducer, (b) mouth thermocouple to monitor mouth flow, and (c) two channels for chest and abdominal efforts with calibrated inductive respiratory plethysmography; and pulse oximetry was obtained using a Nellcor™ oximeter (Oakland, CA).

The three-channel Holter recordings were obtained during 24-hours with a DMI-Cardios Holter system with a sampling rate of 200 Hz per channel. The ECG signal was synchronized with the sleep PSG signals.

Heart Rate Variability Analysis

ALTAIRPC® software version 6.00B (Burdick, Milton, WI) was used to perform HRV analysis. A careful manual review was performed in order to exclude artifacts or arrhythmias from the analysis.

Time Domain Analysis

During continuous ECG recording, each QRS complex was detected, and the normal-to-normal (NN) intervals determined. Five time-domain indexes were derived: the standard deviation of all NN intervals (SDNN); the standard deviation of the average NN intervals (SDANN) calculated over 5-minute periods throughout the recording; the mean of the standard deviation of the 5-minute NN intervals over the entire recording (SDNN index); the root mean square of the difference between successive NN intervals (RMS) and the proportion of adjacent normal NN intervals differing by >50 ms (pNN50).

Frequency Domain Analysis

Artifact-free stable sleep Stages 3 and 4 non-REM Sleep (SWS) and 5-minute REM sleep periods were selected. Spectral indexes for HRV were computed by fast Fourier transforms using 5-minute Hanning windows. We choose the central 5-minute period of the longest abovementioned sleep stages. The power densities in the very low frequency (VLF, 0.0033–0.04 Hz), low frequency (LF, 0.04–0.15 Hz), and high frequency (HF, 0.15–0.4 Hz) components were calculated by integrating the power spectral density in the respective frequency bands. Normalized power spectra LF/HF were also calculated. Results were expressed in ms^2/Hz

Variation of Sympathetic Activity Index

The variation of sympathetic activity index (VSAI) was defined taking the difference between LF values during REM and SWS-non-REM sleep, according to the following formula:

$$VSAI = LF\,REM - LF\ SWS\text{-}non\text{-}REM.$$

Data Analysis

Visual scoring of sleep stages, recognition of respiratory events, and identification of all other sleep phenomena such as body or leg movements, as well as HRV calculations were performed by two researchers blind to the patient condition.

The following PSG variables were analyzed: total sleep time (TST), sleep efficiency (sleep time/recording time $\times$ 100), percentage of sleep time for non-REM and REM sleep stages, apnea/hypopnea index (apnea + hypopnea/hour), arousals/hour, periodic leg movement/hour, and minimal oxygen saturation.

Statistical Analysis

Data are shown as mean and standard deviations. Symmetry, kurtosis, and distribution were calculated for all variables. One-way analysis of variance (ANOVA) test was used to compare sleep variables, HRV, VSAI, demographic data for syncope patients and normal controls, and HUTT positive versus negative patients. Correlations between LF during REM sleep and VSAI with HUTT positivity were assessed by a means of Spearman correlation test. After applying the ROC curve to calculate the best cut-off points, the sensitivity, specificity, predicitive values, and Cohen K coefficient of VSAI and LF to recognize syncope diagnostic were also calculated.

Significance level was set at $P < 0.05$.

Results

Thirty-seven VVS patients (10 male and 27 female) and 20 normal controls (8 male and 12 female), mean ages (24.43 ± 10.28 and 22.18 ± 2.10, respectively, $P = 0.86$) were studied. All patients showed normal results on echocardiogram and ergometric testing. The mean number of syncope episodes was 2.82 ± 2.00, and the duration of symptoms was 10.40 ± 10.04 months. Twenty-five patients had positive HUTT. Data for 11 patients and 4 controls were excluded from the HRV analysis due to technical problems with EEG and ECG data collection, or lack of consecutive 5-minute REM sleep and SWS stages during the entire sleep period.

Most parameters followed a normal distribution, but not VLF and RMS. These variables were then normalized.

Sleep Parameters Results

VVS patients showed higher SWS percentage of total sleep time than controls. There were no significant differences on other sleep parameters analyzed (Table I). None of the subjects presented abnormal periodic leg movements or episodes of significantly reduced oxygen saturation.

Time Domain Results

No significant differences were found for any of the variables analyzed: NN mean, SDNN, SDANN, RMS, PNN50 across the syncope and control groups (Table II) and HUTT positive versus negative (Table III).

Frequency Domain Results

A significant difference in the LF component of HRV during REM sleep was found. The LF component was lower in syncope patients compared to normals ($1{,}769.54 \pm 1{,}738.17$, $3{,}225.37 \pm 2{,}585.05$, respectively) [$F(1,39) = 4.6$, $P = 0.03$].

Table I.

Sleep Parameters for Syncope and Control Groups

	Syncope (n = 37)	Controls (n = 20)	P
Arousal index per hour	7.50 ± 5.04	4.60 ± 2.80	NS
Slow wave sleep (%)	28.2 ± 10.50	19.70 ± 7.80	0.01 F(1,55) = 7.3
REM sleep (%)	14.20 ± 6.90	15.60 ± 6.20	NS
Total sleep time (minutes)	384.11 ± 51.23	381.20 ± 61.70	NS
Wake time after sleep onset (%)	16.47 ± 10.00	17.40 ± 10.00	NS
Sleep efficiency (%)	83.97 ± 10.06	82.50 ± 10.00	NS

ANOVA, $P < 0.05$.

Table II.

Twenty-Four-Hour HRV Time Domain Analysis Parameters for Syncope and Control Groups

	Syncope (n = 26)	Controls (n = 18)	P
NN mean	883.70 ± 108.70	913.40 ± 139.80	NS
SDNN	168.26 ± 48.46	193.70 ± 58.30	NS
SDANN	133.53 ± 46.99	158.9 ± 46.20	NS
SDNN index	87.53 ± 24.24	95.80 ± 31.90	NS
rMSSD	78.03 ± 36.83	81.00 ± 44.60	NS
pNN50	29.85 ± 15.83	32.10 ± 14.90	NS

ANOVA, $P < 0.05$.

Differences in the other variables analyzed (VLF, HF, and LF/HF) did not reach statistical significance during REM and non-REM sleep between syncope and control groups (Table IV), and HUTT positive and negative (Table V). There was no significant correlation between LF during REM sleep and HUTT positivity ($R = 0.11$).

Variation in Sympathetic Activity Index

There was a significant decrease in VSAI in the syncope group compared to the control group ($-539.39 \pm 1{,}930.78$, $1{,}268.10 \pm 2{,}425.20$, respectively) [$F(1,35) = 6.27$, $P = 0.01$] (Fig. 1). No difference was found between HUTT negative and positive, nor was there a significant correlation between VSAI and HUTT positivity ($R = 0.05$).

The sensitivity, specificity, predictive positive and negative values of VSAI, and LF during REM sleep, isolated, and combined are shown in Table VI. One outlier control subject was removed from this calculation.

Discussion

This is the first study evaluating the two components of the ANS during sleep in patients with VVS. In the current protocol, patients and controls were studied in both physiological states: sleep and wakefulness. Sleep was similar in overall terms in both groups. This is an important result since arousal index could directly influence sympathetic tone during sleep.[15] However, VVS patients showed significantly increased percentage of SWS. This finding has not yet been reported in the literature.

The authors used HRV technique to investigate possible ANS abnormalities in VVS patients. Some studies using HRV analysis seem to show different results. Alehan et al.,[16] who analyzed HRV in children with VVS at rest and during HUTT, found that a positive HUTT response was more likely in subjects who had an increase in sympathetic tone immediately prior to testing. Hosaka et al.[17] used HRV analysis to investigate the mechanisms underlying abnormal HUTT response in VVS patients, and found an increase in baseline parasympathetic tone. However, in the present study, when 24-hours time domain HRV analysis was performed, no differences were found, as in other reports.[9] A possible explanation is that a reflex abnormality may not be detected when analyzing such a long window of time. Indeed we found a significant LF range alteration when performing 5-minute frequency domain HRV in a particular state, REM sleep. The LF range of HRV may have controversial physiological interpretation, since both sympathetic and parasympathetic components are involved. However, it has been accepted that an increase in its power is a direct consequence of sympathetic activation already observed in several clinical circumstances.[18,19] As previously described, the LF usually increases during REM compared to NREM sleep,[14,20] as observed in our control subjects. However, in the VVS patients, the LF component is decreased during REM sleep, suggesting an alteration of the sympathetic activation. If patients are unable to physiologically increase their sympathetic tone,

Table III.

Twenty-Four-Hour HRV Time Domain Analysis Parameters for HUTT Positive and Negative Syncope Patients

	HUTT Positive (n = 18)	HUTT Negative (n = 7)	P
Mean heart rate	69.95 ± 9.77	71.12 ± 6.55	NS
SDNN	163.38 ± 40.83	187.00 ± 77.95	NS
SDANN	128.72 ± 40.05	155.60 ± 77.57	NS
SDNN index	85.33 ± 20.20	88.60 ± 27.94	NS
rMSSD	76.50 ± 33.02	73.20 ± 40.92	NS
pNN50	28.64 ± 14.49	29.24 ± 14.82	NS

ANOVA, $P < 0.05$.

Table IV.

HRV Power Density (ms^2/Hz) Results During REM Sleep for Syncope and Control Groups

	Syncope (n = 25)	Controls (n = 16)	P
VLF	4,166.32 ± 6,918.76	7,791.70 ± 17,075.80	NS
LF	1,769.54 ± 1,738.17	3,225.37 ± 2,585.05	0.03
HF	2,577.20 ± 3,557.06	2,557.20 ± 3,442.7	NS
LF/HF	2.48 ± 3.50	3.00 ± 3.90	NS

ANOVA, $P < 0.05$.

this may partially explain the autonomic reflex during syncope episodes. In fact, Krediet et al. have reported a possible vasovagal reflex occurring and interrupting sleep in 13 patients.[21] We also acknowledge that a reduced LF component is a more complex finding and might also involve the parasympathetic component, since the normalized LF/HF was not significant, but the HF band did not change. Therefore, the authors utilized an index of LF component variation across SWS and REM sleep as a possible marker of abnormal ANS activity during sleep. In normal conditions, this index should be positive, as observed in the control group, but was significantly negative in the VVS group. Both parameters of HRV, LF, and VSAI, exhibited good sensitivity and specificity compared with the clinical judgment diagnostic of VVS as gold standard.

Cardiovascular reflex control is complex, and both cardiopulmonary and baroreflex might be involved in VVS mechanisms.[22] We believe that studies assessing cardiorespiratory coupling and baroreflex behavior during REM sleep would provide further data on the mechanisms through which LF component is altered in VVS patients.

Table V.

HRV Power Density (ms^2/Hz) Results During REM Sleep for HUTT Positive and Negative Syncope Patients

	HUTT Positive (n = 18)	HUTT Negative (n = 7)	P
VLF	4,071.94 ± 7,091.87	5,830.20 ± 8,807.43	NS
LF	1,951.76 ± 2,048.32	1,218.70 ± 618.28	NS
HF	2,598.52 ± 4,015.13	1,479.40 ± 1,120.46	NS
LF/HF	2.92 ± 3.98	1.05 ± 0.65	NS

ANOVA, $P < 0.05$.

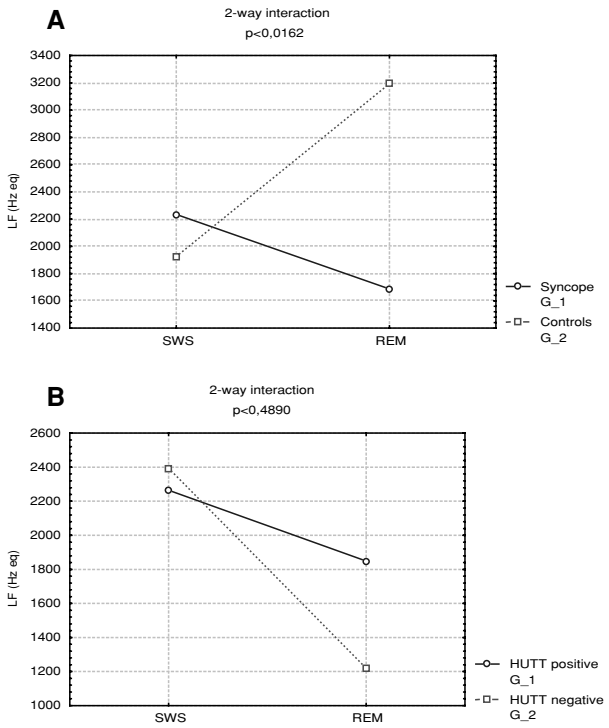

Figure 1. *(A) Low frequency component of HRV for syncope and control groups during NREM and REM sleep. (B) Low frequency component of HRV for TT-positive and TT-negative syncope patients, during NREM and REM sleep.*

Moreover, a sympathetic reduction in VVS has been found using other ANS assessments. Some studies[7,23] have shown this drop in sympathetic tone performing muscle nerve sympathetic activity. Lewis et al.[24] have observed peripheral sympathetic inhibition induced by either HUTT or lower-body negative pressure.

β-blockers have been widely used to treat VVS, by attenuating sympathetic effects. There are reports showing that β-blockers are not effective in controlling syncope (5 of 6 controlled prospective and long-term trials).[25–30] The only double-blind placebo controlled study, performed by Madrid et al.,[28] evaluated Atenolol treatment efficacy in patients with VVS and showed a trend toward a better evolution in the placebo group ($P = 0.09$). The role of sympathetic ANS is more complex, and its suppression, is involved in some degree in the physiopathology of syncope, as also suggested by our results.

Interestingly, HRV abnormality in REM sleep is independent of HUTT positivity in the VVS group. Finally, the lack of HUTT data in controls,

Table VI.

Sensitivity, Specificity, and Related Results of VSAI and LF During REM Sleep

Variable	Cut-Off Point*	Sensitivity	Specificity	PPV	PNV	KAPPA
VSAI	808	87.0	57.1	76.9	72.7	0.460
REM1LF	2,580.5	84.0	56.3	75.0	69.2	0.417
Combined (both positive)	–	48.6	75.0	78.3	44.1	0.204
Combined (at least 1 positive)	–	62.2	60.0	74.2	46.2	0.207

*Obtained from ROC curve.
PPV = predictive positive value; PNV = predictive negative value.

and the relative small number of subjects are limitations of this study.

Conclusion

Sympathetic suppression was observed in VVS patients during REM sleep. This finding may play a role in VVS physiopathology. Interestingly, sympathetic changes during REM sleep did not correlate with HUTT positivity.

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