

## CARDIAC TONE IN SLEEP RELATED ALVEOLAR HYPOVENTILATION

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## Increased Sympathetic and Decreased Parasympathetic Cardiac Tone in Patients with Sleep Related Alveolar Hypoventilation

Jose-Alberto Palma, MD<sup>1</sup>; Elena Urrestarazu, MD, PhD<sup>1</sup>; Jon Lopez-Azcarate, EngD, PhD<sup>2</sup>; Manuel Alegre, MD, PhD<sup>1,2</sup>; Secundino Fernandez, MD, PhD<sup>3</sup>; Julio Artieda, MD, PhD<sup>1,2</sup>; Jorge Iriarte, MD, PhD<sup>1</sup>

<sup>1</sup>Sleep Unit and Clinical Neurophysiology Section, University Clinic of Navarra, Pamplona, Spain; <sup>2</sup>Neurophysiology Laboratory, Neurosciences Area, CIMA, University of Navarra, Pamplona, Spain; <sup>3</sup>Department of Otolaryngology, University Clinic of Navarra, Pamplona, Spain

**Objective:** To assess autonomic function by heart rate variability (HRV) during sleep in patients with sleep related alveolar hypoventilation (SRAH) and to compare it with that of patients with obstructive sleep apnea (OSA) and control patients.

**Design:** Cross-sectional study.

**Setting:** Sleep Unit, University Hospital of University of Navarra.

**Patients:** Fifteen idiopathic and obesity related-SRAH patients were studied. For each patient with SRAH, a patient with OSA, matched in age, sex, body mass index (BMI), minimal oxygen saturation (SatO<sub>2</sub>), and mean SatO<sub>2</sub> was selected. Control patients were also matched in age, sex, and BMI with patients with OSA and those with SRAH, and in apnea/hypopnea index (AHI) with patients with SRAH.

**Interventions:** N/A.

**Measurements and Results:** Time- and frequency-domain HRV measures (R-R, standard deviation of normal-to-normal RR interval [SDNN], very low frequency [VLF], low frequency [LF], high frequency [HF], LF/HF ratio) were calculated across all sleep stages as well as during wakefulness just before and after sleep during a 1-night polysomnography. In patients with SRAH and OSA, LF was increased during rapid eye movement (REM) when compared with control patients, whereas HF was decreased during REM and N1-N2 sleep stages. The LF/HF ratio was equally increased in patients with SRAH and OSA during REM and N1-N2. Correlation analysis showed that LF and HF values during REM sleep were correlated with minimal SatO<sub>2</sub> and mean SatO<sub>2</sub>.

**Conclusions:** Patients with SRAH exhibited an abnormal cardiac tone during sleep. This fact appears to be related to the severity of nocturnal oxygen desaturation. Moreover, there were no differences between OSA and SRAH, supporting the hypothesis that autonomic changes in OSA are primarily related to a reduced nocturnal oxygen saturation, rather than a consequence of other factors such as nocturnal respiratory events.

**Keywords:** Autonomic nervous system, heart rate variability, hypoxia, obesity hypoventilation syndrome, sleep apnea, sleep disordered breathing.

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## INTRODUCTION

Sleep related alveolar hypoventilation (SRAH) is characterized by decreased alveolar ventilation resulting in sleep related oxygen arterial desaturation in patients with normal mechanical properties of the lung. SRAH can be distinguished from central and obstructive sleep apnea (OSA) by the fact that OSA is defined by periodic alterations in the respiratory flow (i.e., apnea, hypopnea, or respiratory effort-related arousals [RERAs]) that are not typically present in SRAH, even though both conditions (sleep apnea and SRAH) may coexist.<sup>1</sup>

In the absence of pulmonary parenchymal or vascular pathology, lower airway obstruction, neuromuscular disorders, or kyphoscoliosis, the disorder is referred to as idiopathic SRAH. When severe obesity is present, it predisposes individuals to developing SRAH by increasing the burden on disadvantaged respiratory muscles, and then the disorder can be referred to as obesity-related sleep hypoventilation syndrome, and is usually included in the spectrum of obesity-related hypoventilation

(pickwickian syndrome).<sup>2,3</sup> Not all patients with SRAH have an increased body mass index (BMI), nor will all patients with obesity develop SRAH. The magnitude of obesity and SRAH is not sufficiently correlated to predict what will occur during sleep in individual patients.<sup>1</sup>

The chief feature of SRAH is reduced ventilation secondary to decreased tidal volume, resulting in hypercapnia, hypoxemia, and leading to a disruption of sleep architecture with increased fragmentation and awakenings. Hypoxemia may also give rise to arrhythmia during sleep.<sup>1</sup>

One of the simplest noninvasive methods to study changes in cardiovascular autonomic control is to measure heart rate variability (HRV), which can be defined as a physiologic phenomenon where the time interval between heartbeats varies. It is measured by the variation in the beat-to-beat interval. HRV reflects the relationship between the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS), and it has been reported to be a good predictor for future cardiovascular disease.<sup>4</sup> HRV can be analyzed by using a time- or frequency-domain analysis in several intervals (see Methods section).

There is evidence supporting the fact that the autonomic nervous system is dysregulated during sleep and wakefulness in patients with OSA even without evidence of cardiovascular disease. When HRV is analyzed, patients with OSA exhibit increased sympathetic activity and decreased parasympathetic activity.<sup>5,6</sup> The HRV improves after initiation of continuous positive airway pressure, even in the first night of treatment.<sup>7</sup> How-

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Address correspondence to: Dr. E. Urrestarazu and Dr. J.A. Palma, Sleep Unit, University Clinic of Navarra, Av. Pio XII, 36; 31008 Pamplona, Navarra, Spain; Tel: +34 948255400; Fax: +34 948 172294; E-mail: eurrestara@unav.es and jpalmaca@unav.es.

ever, it remains unclear whether the changes in HRV seen in patients with OSA are a consequence of the hypoxemia during sleep or, conversely, are a result of the dramatic fluctuations in intrathoracic pressure that occur during the repetitive nocturnal respiratory events (i.e. apnea, hypopnea, or RERAs).

In this regard, patients with SRAH represent a uniquely valuable group of individuals to explore this question, as they have significant oxygen desaturations during sleep but respiratory events are almost absent. We hypothesized that, if HRV changes are a consequence of hypoxemia (and not an effect of the changes in intrathoracic pressure during respiratory events), spectral components of HRV should not differ between patients with SRAH and those with OSA.

According to the hypothesis previously mentioned, our aim in this study was to evaluate nocturnal autonomic cardiovascular function in patients with SRAH using frequency- and time-domain HRV analysis during 1-night polysomnography (PSG) and compare it with that of patients with OSA and control patients. Further, we analyzed whether HRV changes differed depending on the different sleep stages (rapid eye movement [REM], N1-N2, N3, and wakefulness just before and after sleep), and whether HRV changes were correlated with any of the patients' characteristics such as body mass index (BMI), minimal oxygen saturation (SatO<sub>2</sub>), mean SatO<sub>2</sub>, or wake time after sleep onset (WASO).

Previous studies analyzing HRV have been reported in congenital central hypoventilation syndrome (Ondine's curse)<sup>8,9</sup> and in hypoventilation associated with chest wall deformities and neuromuscular disease<sup>10</sup>; however, no studies have investigated the spectral HRV components across sleep stages in patients with idiopathic or obesity-related SRAH in comparison with patients with OSA or healthy control patients. An understanding of the changes in HRV during sleep in patients with SRAH may offer insights into the pathophysiology of the autonomic nervous system disruption seen in patients with sleep related breathing disorders.

## METHODS

### Patients

This was a single-center cross-sectional study involving patients with idiopathic SRAH and obesity-related SRAH. For each patient with SRAH, a patient with OSA matched by age, sex, BMI, minimal SatO<sub>2</sub>, and mean SatO<sub>2</sub> was selected. Control patients with a normal PSG study were also matched in age, sex, and BMI to the remaining two groups and matched in apnea-hypopnea index (AHI) with patients with SRAH.

Patients were retrospectively selected from the sleep database of the Sleep Unit of the University Clinic of Navarra. Patients were either referred to the Sleep Unit from other departments within the University Clinic of Navarra (neurology, pulmonology, endocrinology, ear, nose, and throat, etc.) or from other hospitals of Spain. Most patients were referred because of primary complaints of poor nocturnal sleep, daytime sleepiness, morning headache, or other symptoms suggesting a sleep related breathing disorder. Before PSG studies, all patients completed a questionnaire to document clinically relevant data including current medications, current medical problems, alcohol, tobacco, and recreational drugs consumption, Epworth

Sleepiness Scale score, height, and weight. During each hospitalization, sitting systolic and diastolic blood pressures (SBP and DBP) were measured using a mercury sphygmomanometer just before the PSG study. Physical and neurologic examinations were performed to exclude other pathologies.

Inclusion criteria for patients with SRAH were (1) PSG showing more than 30% of total sleep time at an SatO<sub>2</sub> of less than 90%; (2) five or fewer scoreable respiratory events (i.e. apnea or hypopnea) per hour of sleep; (3) absence of periodic alterations of air flow; (4) absence of kyphoscoliosis and pulmonary, neurologic, muscular, or cardiac cause.

Inclusion criteria for patients with OSA were (1) five or more scoreable respiratory events (i.e. apnea or hypopnea) per hour of sleep; (2) evidence of respiratory effort during all or a portion of each of the respiratory events; (3) matching with patients with SRAH in terms of BMI, age, sex, minimal SatO<sub>2</sub>, and mean SatO<sub>2</sub>.

Inclusion criteria for control patients were (1) five or fewer scoreable respiratory events (i.e. apnea or hypopnea) per hour of sleep; (2) PSG showing more than 30% of total sleep time at an SatO<sub>2</sub> of more than 90%; (3) matching with patients with SRAH in terms of BMI, age, sex, and AHI.

Exclusion criteria for the three groups were (1) atrial fibrillation and other cardiac arrhythmias; (2) myocardial ischemia, cardiomyopathy or myocardial infarction; (3) cardiac pacemaker; (4) history of neurologic or psychiatric disorders; (5) thyroid diseases; (6) other sleep disorders such as periodic limb movement disorder, restless limb syndrome, or narcolepsy; (7) treatment with calcium channels blocker, beta-blockers, or any other drugs known to affect the autonomic nervous system; and (8) a previous diagnosis of congenital central hypoventilation syndrome.

### Data Acquisition and Handling

OSA and SRAH were diagnosed based on an overnight PSG study. PSG studies were performed using Lamont amplifiers, 20 bit, 32 channels, and dedicated inputs for electroencephalogram, tibial and chin electromyogram, oronasal flow, respiratory effort, oxymetry, heart rate, and body position. Sleep stage classification was performed following the current American Academy of Sleep Medicine (AASM) criteria,<sup>11</sup> and hypopneas, apneas, and arousals were scored using the standard recommended AASM scoring criteria.<sup>1</sup> We recorded data on the following features: total sleep time, percentage of sleep spent in REM, N1-N2, and N3; REM latency; WASO; number of periodic leg movements per hour; number of awakenings per hour; SatO<sub>2</sub>; minimal SatO<sub>2</sub>; number of oxygen desaturations per hour of sleep; and AHI.

### HRV Data Handling and Analysis

For each patient, we carefully selected several consecutive apnea-free, arousal-free, 10-min electrocardiogram (ECG) samples, from each sleep stage (REM, N1-N2, N3 and wakefulness before sleep [W-pre] and after sleep [W-post]). ECG was recorded with two derivations (V3 and V5), amplified, band-pass filtered (0.3-30 Hz), and digitized at 250 Hz. The beat series derived from the ECG segments was interpolated and resampled, using cubic splines, to obtain equally spaced RR intervals with an interpolation rate of 4 Hz.

**Table 1**—Sample characteristics

	SRAH (n = 15)	OSA (n = 15)	Controls (n = 15)	P
Age (y), mean ± SD	45.93 ± 11.56	51.35 ± 15.48	46.22 ± 12.01	0.51
Females, n (%)	15 (100%)	15 (100%)	15 (100%)	1.00
Postmenopausal, n (%)	9 (60%)	10 (66.6%)	9 (60%)	0.67
BMI (kg/m <sup>2</sup> ), mean ± SD	37.03 ± 10.52	35.63 ± 10.18	36.91 ± 11.06	0.82
Blood pressure (mm Hg), mean ± SD				
Systolic	122.36 ± 7.67	123.31 ± 15.29	119.59 ± 14.02	0.12
Diastolic	76 ± 6.92	75.54 ± 9.08	72.72 ± 8.18	0.31
Tobacco (cigarettes/day)	7.12 ± 10.23	13 ± 10.17	10 ± 16.27	0.25
Alcohol (U/day)	0.5 ± 0.9	1.1 ± 0.2	0.6 ± 0.2	0.43
Caffeine (100-mg dose/day)	2.6 ± 0.7	2.5 ± 1.2	2.6 ± 0.9	0.84

BMI, body mass index; OSA, obstructive sleep apnea; SD, standard deviation; SRAH, sleep related alveolar hypoventilation.

Sleep data in the form of digital files were collected using the Stellate Reviewer software program (Harmonie 6.0). The sleep segments were saved as text files from their digital recording in Stellate Reviewer Version 6 (Stellate Inc., Montreal, Canada). The text files containing the sleep data were converted into a Spike2 data file (S2R) using Spike2 (version 6.02, Cambridge Electronic Design Limited, Cambridge, UK). Then, two of the authors (JAP, EU) assessed HRV of each patient blinded to the PSG results using the S2R files in a HRV analysis program created with MatLab (Mathworks Inc., Natick, MA, USA) by one of the authors (JLA). Each ECG recording was manually inspected to avoid abnormal QRS wave morphology, ectopic cardiac beats, and movement artifacts, and to ensure that R-waves were correctly marked by the HRV analysis program to allow an accurate detection of R-R intervals.

The following HRV measures were computed in the time and frequency domain based on the measurement standards<sup>12</sup>:

#### Time Domain Measures

- Mean R-R: the mean normal-to-normal RR interval, in ms.
- The standard deviation of normal-to-normal RR interval (SDNN), reflecting the overall HRV, in ms.

#### Frequency Domain Measures

For HRV analysis in the frequency domain, RR time series were interpolated at 250 ms to obtain equidistant values. Then, fast Fourier transform was applied. We quantified HRV power in four frequency bands that have been associated with different physiologic rhythms<sup>4</sup>:

- Ultra low frequency (ULF) band (ULF power in the range of 0.0001 to 0.003 Hz), in ms<sup>2</sup>, which is associated with circadian variation, and variations in the activity of neuroendocrine system.
- Very low frequency (VLF) band (VLF power in the range of 0.003 to 0.04 Hz), in ms<sup>2</sup>, which reflects vagal and renin-angiotensin system effects on heart rate.
- Low frequency (LF) band (LF power in the range of 0.04 to 0.15 Hz), in ms<sup>2</sup>, which reflects a combination of sympathetic and parasympathetic influences and baroreflex function.<sup>13</sup>

- High frequency (HF) band (HF power in the range of 0.15 to 0.40 Hz), in ms<sup>2</sup>, which primarily reflects parasympathetic activity.
- We also considered the LF/HF ratio, a unitless measure thought to reflect sympathovagal balance or sympathetic modulations.<sup>12</sup>

#### Statistical Analyses

Comparisons of patients' characteristics and sleep characteristics in the three samples were made. The effect of sleep on the HRV variables across sleep stages and within the same sleep stage among the three groups was calculated by using analysis of variance (ANOVA), with Bonferroni correction for multiple comparisons, and the interaction where appropriate. The correlation between the clinical parameters of SRAH patients and the various measures of HRV was analyzed with Spearman correlation coefficient. In all cases, statistical significance was defined as  $P < 0.05$ . All statistical tests were performed using SPSS version 15.0.1 (SPSS Inc., Chicago, IL, USA).

#### Standard Protocol Approval

This study was approved by the Institutional Review Board (IRB) of the University of Navarra. The IRB specifically waived the need for consent of participants, as this was a retrospective study. Data were made anonymous by removal of direct identifiers from the data file (a variable was removed when it was highly identifying such as name, surname, or place of birth; other variables irrelevant for analyses were also removed).

## RESULTS

#### Sample Characteristics

Fifteen female patients with SRAH who fulfilled the inclusion criteria were selected. Fifteen female patients with OSA and 15 female control patients were also selected. All groups had similar age, BMI, and tobacco, alcohol, and caffeine intake levels. Eleven patients with SRAH had severe obesity (BMI  $\geq 30$  kg/m<sup>2</sup>), fulfilling criteria for obesity hypoventilation syndrome; the remaining four patients had a BMI  $\leq 25$  kg/m<sup>2</sup>, fulfilling criteria for idiopathic SRAH. Characteristics of patients

**Table 2**—Sleep characteristic in patients with sleep related alveolar hypoventilation, patients with obstructive sleep apnea, and control patients

	SRAH (n = 15)	OSA (n = 15)	Controls (n = 15)	P
REM (%), mean ± SD	19.47 ± 8.43	21.01 ± 10.78	20.65 ± 5.37	0.89
N1-N2 stages (%)	56.16 ± 13.52	55.27 ± 8.45	58.63 ± 14.11	0.60
N3 stage (%)	24.64 ± 12.79	23.72 ± 9.44	22.12 ± 7.87	0.77
REM latency (min)	134 ± 108.35	153 ± 87.01	139.77 ± 101.54	0.86
WASO (%)	9.54 ± 10.37	14.36 ± 10.34	8.24 ± 6.16	0.17
Periodic leg movement index	0	0	0	1.00
Awakening index (n°/h)	3.94 ± 2.69	6.5 ± 4.03	5.5 ± 4.96	0.16
AHI (n°/h)	3.28 ± 1.13	32.35 ± 31.38	4.07 ± 0.43	< 0.001
Minimal SatO <sub>2</sub> (%)	82.8 ± 3.36	82.42 ± 4.18	90.5 ± 3.12	< 0.001
Mean SatO <sub>2</sub> (%)	94.53 ± 0.99	94.57 ± 1.34	96.45 ± 1.43	0.005

AHI, apnea-hypopnea index; OSA, obstructive sleep apnea; REM, rapid eye movement; SatO<sub>2</sub>, oxygen saturation; SD, standard deviation; SRAH, sleep related alveolar hypoventilation; WASO, wake after sleep onset.

with SRAH, patients with OSA, and control patients are summarized in Table 1.

Sleep structure was similar in all groups, including REM latency, percentage of REM, N1-N2 and N3 sleep, and periodic limb movement index. As expected, patients with OSA had a higher AHI when compared with patients with SRAH and control patients, whose AHI was similar. Patients with SRAH and those with OSA had a similar mean and minimal SatO<sub>2</sub>, but it was lower in comparison with control patients. WASO and the awakening index were higher in OSA patients, although the differences were not statistically significant. Sleep characteristics of all groups are summarized in Table 2.

### HRV Parameters

The ANOVA between-group analysis revealed that mean R-R intervals and SDNN were lower in patients with OSA and SRAH when compared with control patients in all sleep stages, although the differences did not reach statistical significance. Across sleep stages, no significant differences were observed in W-pre, W-post, and N3 stages. However, during N1-N2 stage, HF was lower in patients with OSA and SRAH ( $P = 0.006$ ), and the LF/HF was higher in patients with SRAH when compared with control patients ( $P = 0.014$ ). During REM, LF was higher in patients with OSA and SRAH than in control patients ( $P = 0.016$ ), as well as VLF ( $P = 0.030$ ). Conversely, HF was lower in patients with OSA and SRAH ( $P = 0.007$ ). The LF/HF ratio was increased in patients with SRAH when compared with control patients ( $P = 0.011$ ) but not with patients with OSA. No differences were seen when we compared the spectral values of patients with OSA against those with SRAH (Figure 1). For further details, see Table S1 in the supplemental material.

When studying the effects of sleep stage on HRV in patients with SRAH, the ANOVA within-group analysis only showed changes during REM, comprising a significant increase of ULF ( $P = 0.003$ ), and VLF ( $P = 0.003$ ) components. In patients with OSA, LF was higher during REM ( $P = 0.004$ ) and HF was higher during N1-N2 ( $P = 0.03$ ). In control patients, only significant increases in ULF ( $P = 0.002$ ) during REM and in HF during N1-N2 ( $P = 0.04$ ) were observed.

### Correlation Analysis

In patients with SRAH, mean SatO<sub>2</sub> was inversely correlated with LF during N1-N2, and LF and LF/HF during REM; it was positively correlated with HF during REM. Minimal SatO<sub>2</sub> showed a similar pattern, as it was inversely correlated with LF during N3, and LF and LF/HF during REM; and positively correlated with HF during REM. Figure 2 shows an example of this correlation analysis. The remaining features (BMI, AHI, and WASO) did not correlate in patients with SRAH with any of the HRV measures (Table 3).

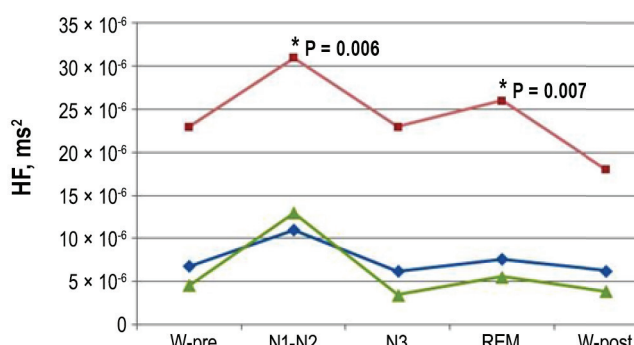
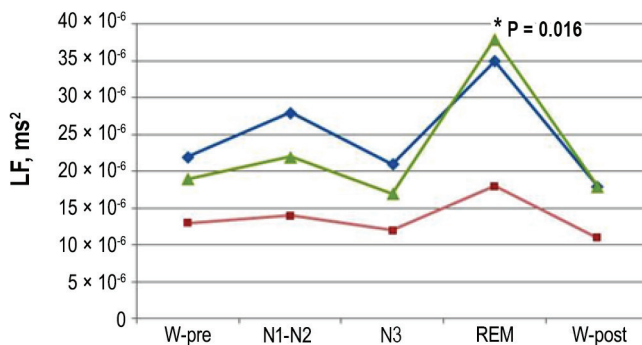
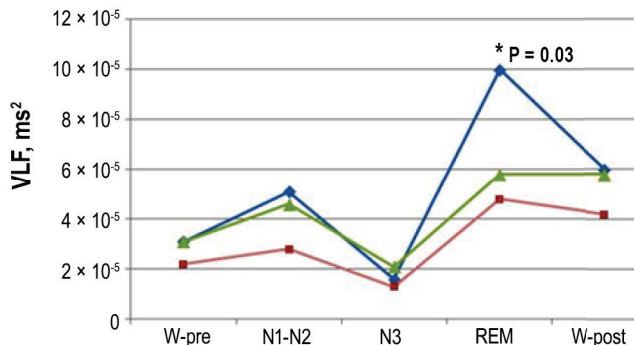
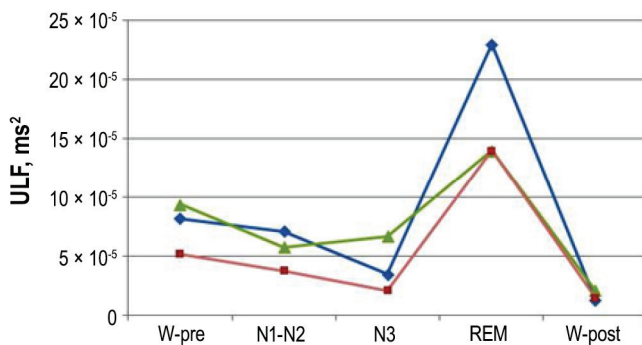
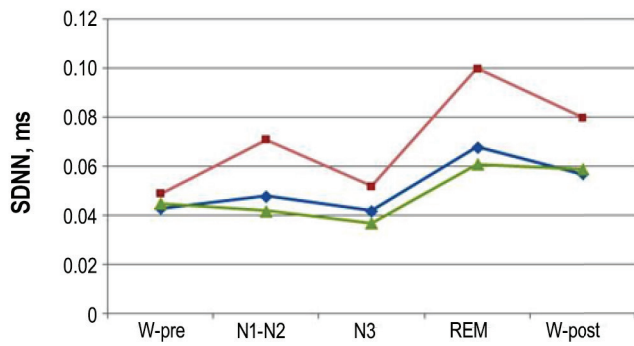
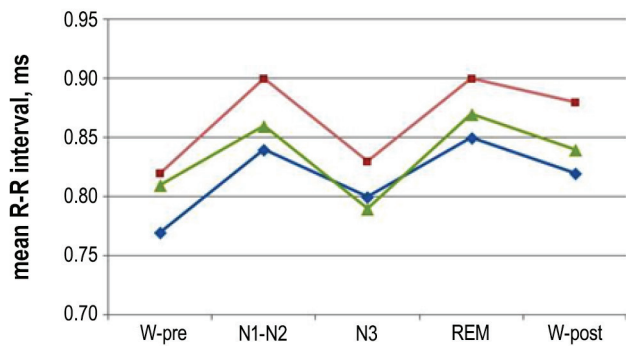
### DISCUSSION

In this work, we aimed to study HRV across sleep stages in a homogenous SRAH patient sample (free from medications, comorbidities and any other concurrent sleep related breathing disorders) and to compare it with a well-matched sample of patients with OSA and control patients. Another of our aims was to investigate whether the HRV differences were correlated with BMI, AHI, WASO, or oxygen saturation.

Our results revealed that patients with SRAH exhibit an increased LF heart rate (which is thought to be dependent on negative feedback of the baroreflex arch mediated by both SNS and PNS, and traditionally has been considered a measure of sympathetic activity) and decreased HF heart rate (which is modulated by PNS inputs only), suggesting an impaired cardiovascular tone during sleep, particularly during REM sleep, when compared with control patients with similar sleep structure, BMI, and AHI. Furthermore, when patients with SRAH were compared with a group of patients with OSA with similar sleep structure, BMI, mean SatO<sub>2</sub> and minimal SatO<sub>2</sub>, no differences were observed.

Moreover, in patients with SRAH, the LF band was inversely correlated with the mean and minimal SatO<sub>2</sub> values, but not with BMI or AHI. The HF band was directly correlated with the mean and minimal SatO<sub>2</sub> values, but not with the BMI or the AHI. The influence of BMI on HRV has remained controversial, with some studies finding that obese patients have changes in HRV,<sup>14,15</sup> whereas other investigations found no association.<sup>7</sup> This discrepancy might be a consequence of the fact that those studies finding changes in HRV in obese patients did not mea-

— Controls — SRAH patients — OSA patients



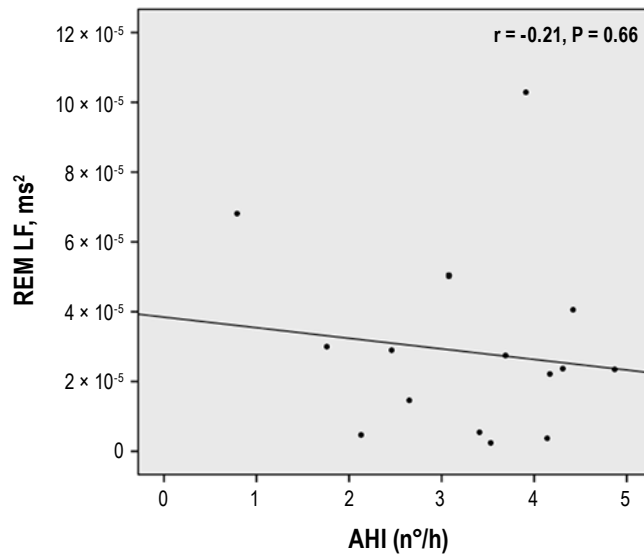
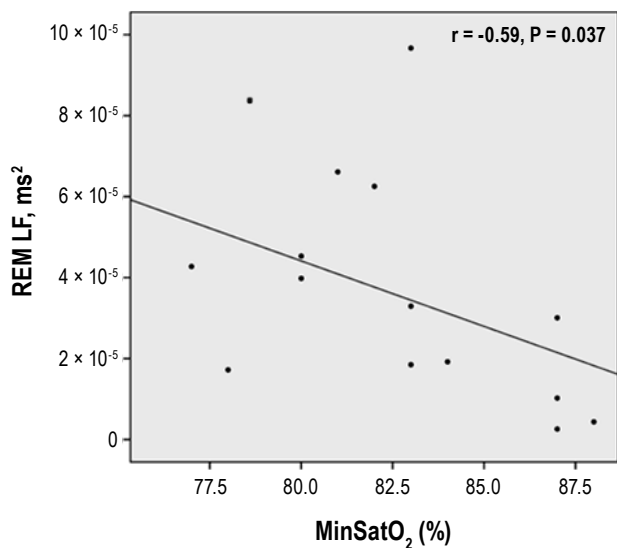
**Figure 1**—Mean R-R interval, standard deviation of the NN interval (SDNN), ultra low-frequency components (ULF), very low-frequency components (VLF), low-frequency components (LF), and high-frequency components (HF) during different sleep stages (N1-N2, N3, REM) as well as during wakefulness before (W-pre) and after (W-post) sleep in patients with SRAH, patients with OSA, and control patients. Asterisks indicate statistical significance, and the analysis of variance P value is given. OSA, obstructive sleep apnea; REM, rapid eye movement; SRAH, sleep related alveolar hypoventilation.

sure oxygen saturation nor were PSGs performed, and therefore the possibility that patients had sleep disordered breathing could not be excluded.

The individual effects of intermittent hypoxia and intrathoracic pressure swings on the sympathetic nervous system activity during sleep disordered breathing are difficult to disentangle.<sup>16</sup> We added further insight into the pathophysiology of abnormal autonomic tone during sleep observed in OSA patients. Our results suggest that the increased sympathetic and decreased parasympathetic tone observed in patients with OSA and SRAH might be a direct consequence of the hypoxemia during sleep; acute changes in intrathoracic pressure during nocturnal respiratory events (i.e., apnea and hypopneas that give rise to intrathoracic swings) probably have a minor rele-

vance in the dysregulation of cardiac autonomic control during sleep in patients with sleep disordered breathing.

Some authors have underlined the importance of increased intrathoracic pressure swings, which are an important feature of OSA, in the abnormal cardiac function.<sup>17,18</sup> Increased negative inspiratory intrathoracic pressures generated against the occluded upper airway increase left ventricular (LV) pressure and amplify LV afterload. These changes increase venous return, augmenting right ventricular (RV) preload, whereas OSA-induced hypoxemia will result in pulmonary vasoconstriction, thus giving rise to an increased RV afterload. These phenomena (i.e., RV distension and impairment of LV filling) can synergistically increase myocardial oxygen demand in the context of reduced tissue oxygen delivery during apnea-related hypoxemia.<sup>19</sup>



**Figure 2**—Examples of correlation analysis. Low-frequency (LF) heart rate variability during rapid eye movement (REM) sleep in relation to minimal oxygen saturation (SatO<sub>2</sub>) and apnea-hypopnea index (AHI). The y-axis is given in ms<sup>2</sup>. Significant increases in LF variability occurred with decreasing SatO<sub>2</sub> ( $r = -0.59$ ;  $P = 0.037$ ) but not with increasing AHI ( $r = -0.21$ ;  $P = 0.66$ ).

However, our results support the importance of hypoxia *per se*, independently of other phenomena, and nicely extends the findings by Sforza et al.<sup>20</sup> who found that, during REM sleep, hypoxic responsiveness does not account for the observed changes in intrathoracic pressure during apnea. In our study, autonomic disturbances were observed primarily during REM sleep. Additional experimental reports have emphasized the key role of hypoxemia in the autonomic changes seen in OSA.<sup>21,22</sup>

The arterial chemoreceptors, particularly the carotid bodies that operate as primary sensors for hypoxemia, and the ensuing carotid chemoreflex trigger a reactive oxygen species-mediated signaling that increases sympathetic activity, elevates blood pressure, and stimulates breathing, giving rise to arousal from sleep.<sup>23</sup> Upon arousal (which is a direct consequence of hypoxemia) autonomic activity, blood pressure, cardiac output, and heart rate rapidly increase, resulting in more increased cardiac oxygen demand at a time when arterial SatO<sub>2</sub> is at its lowest level.<sup>24</sup> In patients with OSA, repetitive apnea episodes aggravate the hypoxemia and CO<sub>2</sub> retention, both of which augment sympathetic activity and reduce parasympathetic activity.<sup>25,26</sup>

Our findings indicating that patients with OSA exhibit changes of spectral components of the HRV are mainly in accordance with previous reports showing that patients with OSA have an increased sympathetic predominance, primarily during REM sleep (where apneas and hypopneas, and also hypoxemia, predominate).<sup>27-30</sup> Although a similar mechanism might take place in patients with SRAH, the pathways by which nocturnal hypoxemia causes autonomic dysfunction in this population remain unclear.

Previous experimental studies clearly support the fact that hypoxemia elevates sympathetic basal activity.<sup>21,25,31</sup> Patients with congenital alveolar hypoventilation exhibit a decreased cortical thickness and extensive axonal injury as a conse-

quence of sustained hypoxia.<sup>32</sup> It is possible that autonomic neurons may be able to survive prolonged periods of mild hypoxia, but that damage occurs following more severe hypoxemia, even if this lasts only for a few min. This could explain why HRV was correlated both with the minimal oxygen saturation and the mean nocturnal oxygen saturation. Although bilevel pressure ventilation has been shown to improve oxygenation and sleep quality in obesity hypoventilation syndrome,<sup>33</sup> it is unknown whether the autonomic damage is reversible, and further studies to investigate the effects of treatment with noninvasive ventilation on autonomic function in patients with SRAH are required.

The similar HRV findings in patients with SRAH and those with OSA raises the question whether both conditions represent two stages of a clinical continuum of sleep disordered breathing, ranging from normality to severe OSA.<sup>34,35</sup> This vision is supported by the fact that upper airway collapsibility during sleep is variable (which would help to explain why not all patients with severe obesity develop OSA)<sup>36,37</sup>; and by the fact that nonapneic snorers as well as patients with upper airway resistance syndrome (two of the conditions also included in the continuum of sleep disordered breathing) exhibit alterations in HRV during sleep.<sup>38,39</sup> However, the initiating feature of OSA would be the obstructive episodes leading to hypoxia (and, in the long-term, diminished chemoreceptor responsiveness<sup>24</sup>), whereas the initiating feature of SRAH (and also in central sleep apnea<sup>40</sup>) would be the impaired chemoreceptor responsiveness *per se*, resulting in diminished drive to breathe, hypoventilation, and hypoxemia.

This is the first study to analyze the HRV both in idiopathic and obesity-related SRAH, as previous studies have only investigated patients with congenital central hypoventilation syndrome<sup>8,9</sup> and hypoventilation associated with chest wall deformities and neuromuscular disease.<sup>10</sup> These previous studies, as with the current study, also found that autonomic dysfunction

appears to be related to the severity of oxygen desaturation, although patients with less severe nocturnal oxygen desaturation had significant abnormalities in comparison with those with no oxygen desaturation.<sup>10</sup>

The observed differences of HRV in patients with SRAH when compared with control patients cannot be attributed to differences in BMI, AHI, or sleep structure, as both groups had similar characteristics. Remarkably, we were able to select control patients with severe obesity (BMI  $\geq$  30 kg/m<sup>2</sup>) without respiratory abnormalities, which confirms that the magnitude of obesity and SRAH are not sufficiently correlated to predict whether an obese individual will develop sleep disordered breathing.

Why all patients with SRAH in our sample were found to be women is unclear. The main reason is probably the sample selection: after patients with cardiovascular and other comorbid diseases, patients taking drugs, and patients with artifacted ECG recording were excluded, only a sample composed of women remained. However, epidemiology of idiopathic SRAH is poorly characterized, so it is not well known whether, in this particular condition, a female preponderance exists. Among patients with OHS, male patients have been reported to have a slightly increased frequency than women,<sup>41</sup> although some studies have analyzed samples with more women than men.<sup>2</sup>

This fact is related to one of the limitations of this research: because all patients were female, we were unable to analyze the differences in HRV according to sex. This would be an interesting analysis in patients with SRAH, as it has been shown that healthy women have a higher parasympathetic tone than men<sup>42</sup> and that non-REM to REM excitatory cardiac responses are more marked in women than in men, regardless of their hormonal status.<sup>43</sup> Hormonal mechanisms are also important, as women exhibit sleep disordered breathing syndrome less frequently than men before but not after menopause, suggesting that progesterone and estrogens may exert a protective effect<sup>44,45</sup> although the exact mode of action through which these hormones affect breathing is not completely understood. In our sample, the frequency of postmenopause was similar among the three groups, so differences could not be attributed to hormonal status.

Because this was a cross-sectional study, the prognostic value of our findings is unclear, although in other conditions, autonomic dysfunction as measured by HRV has been reported to be a marker of morbidity and mortality.<sup>46-48</sup> It is therefore likely that HRV analysis may provide a tool for prognostic evaluation in patients with SRAH, but this warrants additional prospective studies.

In conclusion, HRV is abnormal in patients with SRAH, and appears to be related to the severity of nocturnal oxygen desaturation. Moreover, there were no differences between patients with OSA and patients with SRAH, supporting the hypothesis that HRV changes seen in patients with OSA may be primarily related to lower nocturnal oxygen saturation rather than a consequence of intrathoracic changes during nocturnal respiratory events. Further studies are needed to elucidate whether the abnormal autonomic function has prognostic significance, and whether it is affected by the treatment of SRAH.

**Table 3**—Spearman correlation coefficient (rho) between different measures and heart rate variability parameters in patients with sleep related alveolar hypoventilation

	W-Pre				
	BMI	AHI	MinSat	MeanSat	WASO
R-R	0.08	-0.001	0.01	-0.08	-0.39
SDNN	-0.24	-0.39	0.23	-0.37	-0.31
ULF	-0.16	-0.41	0.09	-0.15	0.19
VLF	-0.41	-0.18	-0.03	0.09	0.14
LF	-0.26	-0.27	-0.18	0.14	-0.21
HF	-0.18	0.07	-0.09	-0.19	0.18
LF/HF	0.03	-0.16	-0.12	-0.31	-0.14
	N1-N2				
	BMI	AHI	MinSat	MeanSat	WASO
R-R	-0.06	-0.28	-0.26	-0.21	-0.51
SDNN	-0.13	0.19	0.12	0.06	0.14
ULF	0.25	0.17	-0.29	-0.09	-0.06
VLF	-0.1	-0.02	0.2	0.06	-0.04
LF	-0.14	0.17	-0.39	<b>-0.62<sup>a</sup></b>	0.05
HF	-0.12	0.21	0.18	0.12	0.28
LF/HF	0.09	0.26	-0.26	-0.32	0.41
	N3				
	BMI	AHI	MinSat	MeanSat	WASO
R-R	-0.31	-0.17	-0.03	-0.14	-0.38
SDNN	0.24	-0.06	-0.41	-0.13	-0.11
ULF	0.38	0.19	-0.49	0.09	-0.15
VLF	0.12	-0.09	-0.39	0.08	-0.29
LF	-0.06	-0.09	<b>-0.55<sup>a</sup></b>	-0.29	-0.14
HF	0.3	0.03	0.11	0.41	0.11
LF/HF	0.13	0.18	0.08	-0.08	0.23
	REM				
	BMI	AHI	MinSat	MeanSat	WASO
R-R	0.3	0.21	-0.35	-0.55	0.21
SDNN	0.03	-0.41	-0.38	-0.25	0.12
ULF	-0.01	0.36	-0.37	-0.24	0.09
VLF	-0.02	0.41	-0.03	0.03	0.1
LF	-0.07	-0.21	<b>-0.59<sup>a</sup></b>	<b>-0.61<sup>a</sup></b>	0.06
HF	0.04	-0.19	<b>0.51<sup>a</sup></b>	<b>0.58<sup>a</sup></b>	-0.03
LF/HF	-0.05	0.15	<b>-0.52<sup>a</sup></b>	<b>-0.51<sup>a</sup></b>	0.18
	W-Post				
	BMI	AHI	MinSat	MeanSat	WASO
R-R	0.16	-0.14	0.01	0.02	0.18
SDNN	0.4	-0.21	-0.45	0.01	0.24
ULF	0.12	0.23	0.3	-0.42	-0.08
VLF	0.29	-0.16	0.07	-0.26	-0.01
LF	0.42	-0.42	0.16	-0.05	-0.38
HF	0.38	-0.27	-0.22	-0.23	-0.43
LF/HF	0.19	0.08	-0.39	-0.32	0.49

<sup>a</sup>P < 0.05. AHI, apnea-hypopnea index; BMI, body mass index; HF, high frequency; LF, low frequency; minSat, minimum saturation; meanSat, mean saturation; REM, rapid eye movement; SDNN, standard deviation of normal-to-normal RR interval; ULF, ultra low frequency; VLF, very low frequency; WASO, wake after sleep onset; W-Post; wakefulness after sleep; W-Pre, wakefulness before sleep. Significant values are in bold.

## DISCLOSURE STATEMENT

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**SUPPLEMENTAL MATERIAL**

**Table S1**—Heart rate variability in patients with sleep related alveolar hypoventilation, patients with obstructive sleep apnea, and control patients

	W-pre		
	SRAH	OSA	Controls
R-R mean (ms), ± SD	0.77 ± 0.12	0.81 ± 0.08	0.82 ± 0.08
SDNN (ms), ± SD	0.043 ± 0.03	0.045 ± 0.018	0.049 ± 0.022
ULF (ms <sup>2</sup> ), ± SD	0.000082 ± 0.00011	0.000094 ± 0.00016	0.000052 ± 0.00051
VLF (ms <sup>2</sup> ), ± SD	0.000031 ± 0.000029	0.000031 ± 0.000016	0.000022 ± 0.000021
LF (ms <sup>2</sup> ), ± SD	0.000022 ± 0.000027	0.000019 ± 0.000015	0.000013 ± 0.000013
HF (ms <sup>2</sup> ), ± SD	0.0000068 ± 0.000014	0.0000046 ± 0.0000056	0.000023 ± 0.000017
LF/HF (ms <sup>2</sup> ), ± SD	1.02 ± 0.89	1.22 ± 1.49	0.91 ± 0.92
	N1-N2		
	SRAH	OSA	Controls
R-R mean (ms), ± SD	0.84 ± 0.13	0.86 ± 0.09	0.90 ± 0.08
SDNN (ms), ± SD	0.048 ± 0.03	0.042 ± 0.012	0.071 ± 0.052
ULF (ms <sup>2</sup> ), ± SD	0.000071 ± 0.000082	0.000058 ± 0.000048	0.000038 ± 0.000021
VLF (ms <sup>2</sup> ), ± SD	0.000051 ± 0.000054	0.000046 ± 0.000047	0.000028 ± 0.000021
LF (ms <sup>2</sup> ), ± SD	0.000028 ± 0.000026	0.000022 ± 0.000034	0.000014 ± 0.000048
HF (ms <sup>2</sup> ), ± SD	<b>0.000011 ± 0.000016<sup>b</sup></b>	<b>0.000013 ± 0.000018<sup>b</sup></b>	<b>0.000031 ± 0.000058<sup>b</sup></b>
LF/HF (ms <sup>2</sup> ), ± SD	<b>1.8 ± 1.4<sup>c</sup></b>	<b>1.5 ± 1.3<sup>c</sup></b>	<b>0.6 ± 0.4<sup>c</sup></b>
	N3		
	SRAH	OSA	Controls
R-R mean (ms), ± SD	0.8 ± 0.12	0.79 ± 0.06	0.83 ± 0.11
SDNN (ms), ± SD	0.042 ± 0.022	0.037 ± 0.029	0.052 ± 0.043
ULF (ms <sup>2</sup> ), ± SD	0.000035 ± 0.000046	0.000067 ± 0.00012	0.000021 ± 0.000012
VLF (ms <sup>2</sup> ), ± SD	0.000016 ± 0.000012	0.000021 ± 0.000033	0.000013 ± 0.000011
LF (ms <sup>2</sup> ), ± SD	0.000021 ± 0.000016	0.000017 ± 0.00002	0.000012 ± 0.000042
HF (ms <sup>2</sup> ), ± SD	0.0000062 ± 0.0000067	0.0000035 ± 0.0000046	0.000023 ± 0.000034
LF/HF (ms <sup>2</sup> ), ± SD	1.3 ± 1.5	0.9 ± 1.7	1.0 ± 0.3
	REM		
	SRAH	OSA	Controls
R-R mean (ms), ± SD	0.85 ± 0.15	0.87 ± 0.08	0.90 ± 0.9
SDNN (ms), ± SD	0.078 ± 0.052	0.061 ± 0.024	0.1 ± 0.08
ULF (ms <sup>2</sup> ), ± SD	0.00023 ± 0.00028	0.00014 ± 0.00015	0.00014 ± 0.00012
VLF (ms <sup>2</sup> ), ± SD	<b>0.0001 ± 0.0001<sup>a</sup></b>	<b>0.000058 ± 0.000062<sup>a</sup></b>	<b>0.000048 ± 0.000031<sup>a</sup></b>
LF (ms <sup>2</sup> ), ± SD	<b>0.000035 ± 0.000027<sup>d</sup></b>	<b>0.000038 ± 0.000015<sup>d</sup></b>	<b>0.000018 ± 0.000022<sup>d</sup></b>
HF (ms <sup>2</sup> ), ± SD	<b>0.0000076 ± 0.0000025<sup>e</sup></b>	<b>0.0000056 ± 0.0000036<sup>e</sup></b>	<b>0.000026 ± 0.00008<sup>e</sup></b>
LF/HF (ms <sup>2</sup> ), ± SD	<b>1.6 ± 1.2<sup>f</sup></b>	<b>1.1 ± 1.7<sup>f</sup></b>	<b>0.24 ± 0.3<sup>f</sup></b>
	W-post		
	SRAH	OSA	Controls
R-R mean (ms), ± SD	0.82 ± 0.11	0.84 ± 0.07	0.88 ± 0.07
SDNN (ms), ± SD	0.057 ± 0.02	0.059 ± 0.01	0.08 ± 0.11
ULF (ms <sup>2</sup> ), ± SD	0.000013 ± 0.00008	0.000021 ± 0.00041	0.000015 ± 0.00014
VLF (ms <sup>2</sup> ), ± SD	0.00006 ± 0.00004	0.000048 ± 0.000042	0.000052 ± 0.000051
LF (ms <sup>2</sup> ), ± SD	0.000018 ± 0.000015	0.000018 ± 0.000025	0.000011 ± 0.000018
HF (ms <sup>2</sup> ), ± SD	0.0000063 ± 0.0000067	0.0000039 ± 0.0000024	0.000018 ± 0.000091
LF/HF (ms <sup>2</sup> ), ± SD	1.06 ± 1.1	1.3 ± 1.3	0.90 ± 0.91

HF, high frequency; LF, low frequency; REM, rapid eye movement; SDNN, standard deviation of normal-to-normal RR interval; SRAH, sleep related alveolar hypoventilation; ULF, ultra low frequency; VLF, very low frequency; W-post, wakefulness after sleep; W-pre, wakefulness before sleep. Statistically different values are in bold.

<sup>a</sup>P = 0.030; Bonferroni: SRAH vs. controls: P = 0.038; OSA vs. controls: P = 0.041; SRAH vs. OSA: P = 1.

<sup>b</sup>P = 0.006; Bonferroni: SRAH vs. controls: P = 0.0142; OSA vs. controls: P = 0.040; SRAH vs. OSA: P = 1.

<sup>c</sup>P = 0.014; Bonferroni: SRAH vs. OSA: P = 0.36; OSA vs. controls: P = 0.012; SRAH vs. controls: P = 0.37.

<sup>d</sup>P = 0.016; Bonferroni: SRAH vs. controls: P = 0.015; OSA vs. controls: P = 0.106 SRAH vs. OSA: P = 1.

<sup>e</sup>P = 0.007; Bonferroni: SRAH vs. controls: P = 0.014; OSA vs. controls: P = 0.030; SRAH vs. OSA: P = 1.

<sup>f</sup>P = 0.011; Bonferroni: SRAH vs. controls: P = 0.012; OSA vs. controls: P = 0.14; SRAH vs. OSA: P = 0.