Heart Rate Variability and Cardio-respiratory Coupling During Sleep in Patients Prior to Bariatric Surgery

R. Trimer · R. Cabiddu · R. G. Mendes · F. S. M. Costa · A. D. Oliveira Jr · A. Borghi-Silva · A. M. Bianchi

R. Trimer (✉) · R. G. Mendes · A. Borghi-Silva
Cardiopulmonary Physiotherapy Laboratory, Physiotherapy Department, Federal University of São Carlos, Rodovia Washington Luís, KM 235-SP 310, São Carlos 13565-905, São Paulo, Brazil
e-mail: retrimer@hotmail.com

R. Trimer
CAPES Foundation, Ministry of Education of Brazil, Brasília, DF 70040-020, Brazil

R. Cabiddu · A. M. Bianchi
Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, Via Golgi, 39, 20133 Milan, Italy

F. S. M. Costa · A. D. Oliveira Jr
Sleep Institute of São Carlos, Rua Padre Teixeira, 1152, São Carlos 13560-000, São Paulo, Brazil

Introduction

Obesity was declared a global epidemic by the World Health Organization and is associated with increased cardiac risk and higher indices of morbidly and mortality; moreover, it is considered as major risk factor for the development of ob-structive sleep apnea (OSA) [1–4]. The prevalence of OSA in obese patients is nearly twice that of normal-weight adults [4–6].

OSA associated to obesity can be responsible for autonom-ic dysregulation, with impaired heart rate variability (HRV) that could contribute to myocardial ischemia or arrhythmias [7–10]. A better understanding about autonomic cardiac reg-ulation, respiratory variations, and cardio-respiratory coupling (CRC) in obese patients that will undergo bariatric surgery would be important to manage the pre- and postoperatory period. Thus, CRC indices may provide valuable insight into different aspects of the cardiorespiratory interaction, which the HRV investigation is not able to address [11]; moreover, they may provide additional information about surgery risks and perioperative complications, useful to support clinicians in the decision about interventions to decrease possible

complications and minimize risks as, for instance, the application of CPAP therapy [5, 6, 10].

During sleep, HRV is affected by sleep stage organization and by the presence, of apnea events. Respiration changes during sleep as well, becoming deeper and more regular during deep sleep, and shallower and more frequent during rapid eye movement (REM) sleep [11]. However, it is not known how severity of obesity affects the cardiac autonomic nervous system during sleep and if sleep stage organization influences HRV in obese patients. Given the fact that OSA in obesity is considered a major risk factor for cardiac autonomic impairment, we hypothesized that a more drastic HRV impairment would be found as severity of obesity increased.

Therefore, the aim of the study was to determine if the severity of obesity alters the autonomic cardiac regulation and the cardio-respiratory coupling during sleep using spectral analysis of HRV and respiration variability signals in patients prior to bariatric surgery.

Methods

Subjects

Consecutive patients referred to our sleep medicine clinic for preoperative evaluation of excessive daytime somnolence prior to bariatric surgery were included in the study. In order to classify the patients according to their level of obesity, the following BMI grading system was implemented [12]: severely obese (BMI, 35–39.9 kg/m^2), morbidly obese (BMI 40–49.9 kg/m^2), and super obese (BMI>50 kg/m^2). The patients completed a questionnaire concerning possible daily or nocturnal symptoms, intoxications, medication, and medical history. The inclusion criterion was the presence of a normal electrocardiogram (ECG) during wakefulness. A group of eutrophic subjects, who were referred with suspect of OSA, not confirmed after polysomnography, with apnea–hypopnea index (AHI) <5 matched for age and sex, were also included in the present study (control group). The exclusion criteria were previous or current cardiovascular diseases, pulmonary disorders, diabetes mellitus, and substance abuse; patients who were on antihypertensive treatment or had a diagnosis of hypertension or of periodic limb movements during sleep (PLMS) were also excluded from the study.

Signal Processing

Nocturnal polysomnographic (PSG) recordings were obtained from all subjects. Signals were acquired using Icelera Fast-Poli 26i (Homed, São Paulo, Brazil) device and included electroencephalogram, electro-oculogram, oronasal flow, nasal pressure, thoracoabdominal movement, ECG, snoring, and body position [13]. A sleep specialist analyzed the data and visually scored PSG recordings for sleep staging and apnea events detection. Total sleep time, number and duration of REM periods, and number and duration of arousals were also measured [14].

Sleep stages, hypopneas, apneas, and arousals were scored using the standards recommended by the American Academy of Sleep Medicine [15]. OSA was diagnosed on the basis of the AHI, calculated by dividing the total number of apneas and hypopneas occurred over the whole night by the number of hours of sleep [16]. R peaks were detected on each ECG signal using the Pan–Tompkins algorithm [17]. The respirogram was extracted from each respiration signal by sampling it in correspondence of each R peak identified in the ECG signal [18].

HRV Analysis

On both the tachogram and the respirogram, 5-min long stationary and free of artifacts portions were manually selected during wakefulness, sleep stages S2 and S3, and REM. Autoregressive (AR) analysis was performed on each tachogram and respiration portion to obtain an AR model to calculate the signal power spectral density (PSD). The Akaike Information Criterion (AIC) was used to choose the model order and the Yule–Walker equations were implemented to calculate the model coefficients [19]. The PSD was decomposed into single spectral components, following the method described in Baselli's study [20].

Spectral components of interest were identified on the HRV signal spectrum, namely, the power in the low frequency band (LF, 0.04–0.15 Hz), and the power in the high frequency band (HF, 0.15–0.4 Hz); normalized LF (LF_{nu}) and normalized HF (HF_{nu}) were computed as follows:

$$LF_{nu} = \frac{LF}{Pt - VLF} \quad (1)$$

$$HF_{nu} = \frac{HF}{Pt - VLF} \quad (2)$$

where PT is the total spectral power, and VLF is the power in the very low frequency band (VLF, <0.01 Hz).

The values of the power in the LF and in the HF bands and the LF/HF ratio were calculated for each HRV signal, while for the respirogram, only the HF component was considered. A bivariate analysis was conducted on the tachogram and the respirogram portions, in order to obtain the cross-spectrum between them. The coherence between the signals in the HF band and the percentages of coherent and not-coherent power between the signals were also calculated. Average values were

calculated on all subjects for LF power, HF power, LF/HF ratio, HF band coherence, and percentage of tachogram power coherent and not coherent with respiration.

Statistical Analysis

The results were compared using a Kruskal–Wallis one-way analysis of variance on ranks test, with post hoc Dunn's, in order to identify statistically significant differences in the tachogram LF and HF power and LF/HF ratio values, in the respirogram HF power and in the tachogram–respirogram coherence in the HF band during different sleep stages.

Spearman's correlation was applied between clinical data and HRV indices. Differences were considered significant when $p<0.05$. The analyses were performed with Sigma Plot version 11.0 (Systat Software, Germany).

Results

Sixty-five consecutive patients were evaluated prior to bariatric surgery. Of these, 50 patients were referred to our sleep clinic for preoperative evaluation. Twelve patients were excluded from the present study due to poor quality of the ECG signal, and nine were excluded due to poor quality of the respiration signal. The remaining 29 patients were included in this study. Seven of them were classified as severely obese (SO), 13 as morbidly obese (MO), and 9 as super obese (SOP). Ten eutrophic subjects without OSA composed the control group. Patients' characteristics are shown in Table 1.

As expected, in our population we found higher AHI, T90, and ODI in all obese patients when compared to controls, and we also found a strong correlation between BMI and ODI (r=0.68) and between BMI and AHI (r=0.7) in morbidly obese patients. The OSA stratification by BMI is presented in Table 2.

Figure 1 shows the HRV spectral indices during wakefulness and different sleep stages. As expected, the control group presented changes in the HRV indices during different stages of sleep with higher values of LF/HF ratio during stage S2 and REM sleep when compared with wakefulness ($p<0.5$). The same behavior did not characterize the obese patients' HRV, which can be interpreted with altered sympatho-vagal modulation during sleep in these patients.

We observed that severely and super obese presented lower values of LF/HF ratio and LF in the REM phase and higher HF when compared to controls. We observed that the morbidly obese group presented lower values of LF/HF ratio and LF in sleep stage S2 and higher HF when compared to controls (Fig. 2).

The bivariate analysis results are shown in Fig. 3. We observed that the coherence between the tachogram and the respirogram in the HF band progressively increases with synchronization of sleep and decreases during REM sleep in the control group. We could not observe the same behavior in obese patients. Super-obese patients presented lower percentage of tachogram power coherent with respiration in sleep stage S3 when compared to controls and a higher percentage of tachogram power not coherent with respiration ($p<0.05$).

We also correlated the HRV indices with clinical parameters, with the aim to investigate if all obese patients had the same risks. We observed that in morbidly obese patients T90 presented a negative correlation with the LF/HF ratio and LF_{nu} in the REM phase (r=−0.76) and with the LF/HF ratio and LF_{nu} in stage S2 (r=−0.63); we observed that BMI presented a negative correlation with the LF/HF ratio and LF_{nu} in stage S3 (r=0.66). Super-obese patients presented a strong negative correlation between ODI and LF/HF ratio and LF nu in the REM phase (r=−0.88).

Table 1 Patients' characteristics: clinical and polysomnographic parameters

	Controls n=10	Severely obese n=7	Morbidly obese n=13	Super obese n=9
Age (years)	39±9	41±12	37±10	38±6
Male %	2 (20 %)	1 (14 %)	6 (31.5 %)	5 (55 %)
BMI (kg/m^2)	26±3	37±1*	43±3*$^{\#}$	54±3*$^{\#\dagger}$
AHI (h^{-1})	4.3±2	22±20*	29.7±33*	62.7±35*$^{\#\dagger}$
Basal saturation %	95.5±2	95.7±2	95.8±1	94.3±3
Mean saturation %	93.5±1.5	92.2±1.7	91.9±1.4	88.7±2.5*
T90 (min)	3±5	31±35*	48±73*$^{\#}$	174±101*$^{\#\dagger}$
ODI (h^{-1})	4±2	18±15*	26±28*	74±28*$^{\#\dagger}$

BMI body mass index, *AHI* apnea hypopnea index, *T90* time spent with saturation under 90 %, *ODI* oxygen dessaturation index

*$p<0.05$, significant difference with control group; $^{\#}p<0.05$, Significant difference with severely obese; $^{\dagger}p<0.05$, significant difference with morbidly obese

Discussion

Morbid obesity is associated with multiple comorbidities and may increase perioperative risk in bariatric surgery [21–23]. A better understanding about autonomic cardiac regulation, respiratory variations, and cardio-respiratory coupling in these patients is important to manage the pre- and postoperatory period, since patients with OSA have been shown to have increased preoperative risk and mortality and specific perioperative measures have to be taken [6, 10, 22]. The present study was undertaken to investigate possible relationships among severity of obesity, HRV signal and respiration variability signal during sleep and to investigate the effects of the autonomic nervous modulation during different sleep stages in these patients.

Table 2 OSA stratification in obese patients

BMI	Non OSA	Mild OSA	Moderate OSA	Severe OSA
Severely obese (35–39.9 kg/m^2)	1 (15 %)	3 (42 %)	–	3 (42 %)
Morbidly obese (40–49.9 kg/m^2)	1 (7 %)	4 (31 %)	5 (38 %)	3 (23 %)
Super obese (>50 kg/m^2)	1 (11 %)	–	–	8 (89 %)
Total (*n*)	3	7	5	14

BMI body mass index, *OSA* obstructive sleep apnea

The main finding is that we detected an altered cardiac autonomic regulation and an altered cardio-respiratory coupling in severely, morbidly, and super-obese patients that will be undergoing bariatric surgery, and we found a relationship among autonomic impairment, severity of obesity, and OSA parameters.

Obesity is the most important reversible risk factor for the development of OSA [24], and severity of obesity is associated with severity of OSA [25]. Obesity, specifically abdominal obesity, is associated with increased risk of hypertension, diabetes, hyperlipidemia, sleep apnea, coronary heart disease, and stroke [26, 27]. Bariatric surgery represents an alternative treatment for obesity and has been recommended by several authors as a way to reduce medical comorbidities and decrease cardiovascular risk factors and OSA severity [28, 29].

In our study, all obese patients presented higher AHI, T90, and ODI than controls, and super-obese patients presented higher values than severely and morbidly obese patients, and 89 % of super obese were diagnosed with severe OSA. We found a strong correlation between BMI and ODI (r=0.68) and between BMI and AHI (r=0.7) in morbidly obese patients. The increasing severity presumes that this translates into increasing perioperative risk with regard to airway management, postoperative airway obstruction, hypoventilation, and apnea [30, 31]. Obesity can alter respiratory physiology by two main mechanisms: the effect of excessive tissue on the upper airways and on the pulmonary function and the effects of obesity on neurologic control of upper airway and respiratory pump muscles [32].

Recent reports have suggested that OSA may worsen the effect of obesity on cardio-metabolic risk and that it could represent an additional burden on metabolic dysfunctions associated with obesity [6, 25]. The mechanisms through which OSA may worsen metabolism are complex. It may trigger several pathological mediating pathways like sympathetic activation, neurohumoral changes, glucose homeostasis disruption, inflammation, and oxidative stress through chronic intermittent hypoxia [33, 34].

In healthy subjects, we found changes in HRV indices, with a LF power decrease during deep sleep and increase during

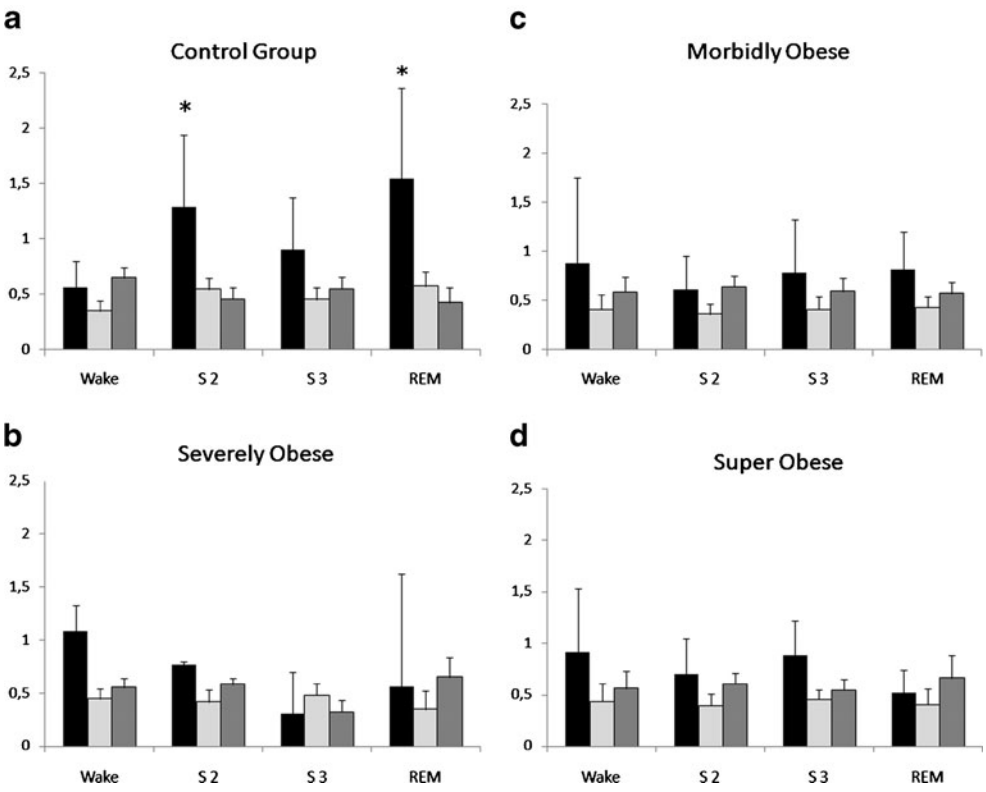

Fig. 1 HRV indices during different sleep stages (mean±SD). **a** Control group. **b** Severely obese. **c** Morbidly obese. **d** Super obese. *S2* Stage 2, *S3* stage 3, *REM* rapid eye movement. *Black bars* LF/HF ratio, *light gray bars* HF_{nu}, *dark gray bars* LF_{nu}. *p<0.05, difference with wakefulness

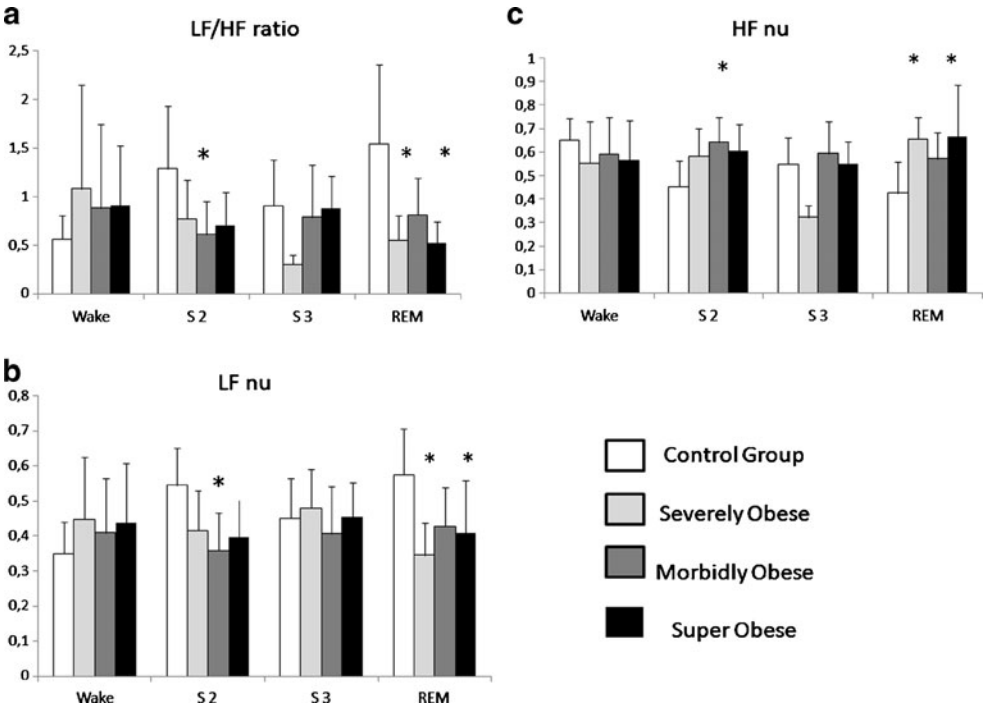

Fig. 2 HRV indices in obese patients (mean±SD). **a** LF/HF ratio. **b** LF_{nu}. **c** HF_{nu}, *S2* stage 2, *S3* stage 3, *REM* rapid eye movement. *White bars* control group, *light gray bars* severely obese, *dark gray bars* morbidly obese, *black bars* super obese. *$p<0.05$, difference with control group

REM sleep, suggesting a diminished sympathetic modulation during deep sleep as compared to the wakefulness state and an augmented sympathetic tone during the REM phase. The HF behavior was indicative of an increased vagal drive to the heart during deep sleep, which decreased during REM sleep.

The expected change in the sympatho-vagal balance during sleep, which in healthy subjects markedly decreases during deep sleep [11], and increases during REM sleep, was not observed in obese patients. When we analyzed sleep stages, we observed a marked decrease in LF/HF ratio and LF_{nu} HRV indices in sleep stage S2 in morbidly obese patients and in sleep stage S3 and REM sleep in severely and super-obese patients when compared to controls. Our results could be explained by the fact that different degrees of

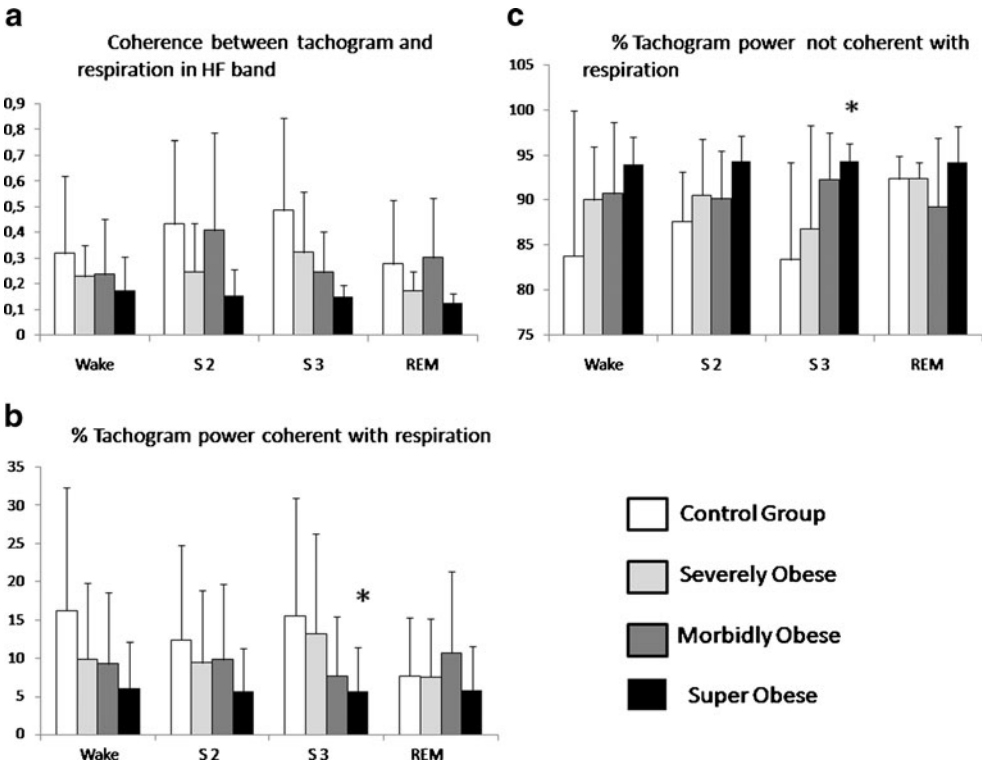

Fig. 3 Coherence between HRV and respiration. **a** Coherence between tachogram and respiration in the HF band. **b** Percent tachogram power coherent with respiration. **c** Percent tachogram power not coherent with respiration. *S2* Stage 2, *S3* stage 3, *REM* rapid eye movement. *White bars* control group, *light gray bars* severely obese, *dark gray bars* morbidly obese. *Black bars* super obese. *$p<0.05$, difference with control group

visceral fat characterize patients with different BMI values [33, 34, 36].

Obese patients did not present the same behavior as controls. We could not observe differences between sleep stages and between sleep and wakefulness in the obese patients groups, which can be interpreted with poor sympatho-vagal modulation during the sleep.

Obesity itself has been shown to alter autonomic activity, and weight gain has been proved to decrease HRV [35]. Increased adiposity has been linked to decreased sympathetic responsiveness [36], alteration of both sympathetic and parasympathetic activities, and decreased isolated parasympathetic activity.

A bivariate analysis was conducted to take into account the cardio-respiratory coupling during the different sleep stages. The correlation between cardiac and respiratory rhythms has been widely acknowledged [37]. The HF range of the HRV signal coincides with the respiratory rhythm; thus, the HF component provides information about respiration frequency and its modulation [38].

The investigation of cardiac and respiratory synchronization can provide useful indications about the way these systems interact. In normal subjects, the cross-spectrum between the tachogram and the respirogram presents a more pronounced peak centered in the HF band during sleep stages S2 and S3 as compared to that of the wake state, whereas the peak markedly decreases during REM sleep.

The peak becoming more pronounced during deep sleep stages is indicative of a more regular respiratory rhythm, synchronized with heart activity; the presence of a less pronounced peak during REM sleep is indicative of a less regular respiratory rhythm and a lower synchronization between respiration and heart activity, in line with previous studies [11]. We observed that super-obese patients presented a lower percentage power coherent with respiration in stage S3 when compared to controls.

Cardio-respiratory coordination during sleep changes in pathological conditions, as demonstrated in patients affected by OSA [37] or sleep disordered breathing [38]. In a large cohort study [38], which evaluated cardio-respiratory coordination during sleep, they observed a significant reduction in phase coupling in severe OSA when compared to mild and non-OSA subjects. They also observed no effect of age and BMI on phase coupling, but it is worth noticing that in that study the mean BMI was 34±8. Our study, to our knowledge, is the first to investigate cardio-respiratory coordination during sleep in severely obese patients, and this could explain our different results.

Clinical Implications

Altered cardiac autonomic regulation and altered cardio-respiratory coupling in patients that will be undergoing bariatric surgery, quantified by polysomnographic analysis, can add information about possible surgical risks [6, 10, 20, 22]. These analyses, together with the screening of OSA, may provide additional diagnostic indices for this population, able to improve not only resource allocation and management but also to facilitate patients' recovery by guiding medical strategies [39]. Future clinical studies are necessary to evaluate these analyses prognostic value over time and the effects of the application of non invasive ventilation before and after bariatric surgery and weight loss.

Limitations of the Study

As this was a retrospective study, standardization and accuracy may be compromised. Information regarding exercise, dietary habits, leptin, or insulin sensitivity, all of which are known confounders, was unavailable.

Finally, we did not have all anthropometric variables, such as neck circumference, percentage of body fat, or waist/hip ratio for all subjects, which could be additional information of body composition in order to better characterize the sample size of the present study.

Conclusions

Patients prior to bariatric surgery presented altered cardiac autonomic regulation with lower spectral indices of HRV and respiration variability signal in all sleep stages.

Severely, morbidly, and super-obese patients presented an altered cardio-respiratory coupling during sleep, and these alterations were found to be related with severity of obesity and OSA parameters.

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Conflict of Interest The authors have indicated no conflicts of interest in this study.

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