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Clinical Study

Autonomic Cardiovascular Control in Hyperthyroid Women during Sleep

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Hyperthyroidism is characterized by hyperadrenergic symptoms (i.e., tachycardia, anxiety, and increased metabolic state). Although hyperthyroid patients often complain about an impairment of sleep, no data are available on sleep characteristics and autonomic cardiovascular control during sleep in these patients. We aimed to assess sleep qualitative indices and autonomic cardiovascular regulation during sleep in hyperthyroidism (Hyperthyr) and after treatment. Six subjects with a first diagnosis of Graves' disease or hyperfunctioning nodule underwent a complete polysomnographic study (PSG) at the time of diagnosis and after the treatment, when they became euthyroid (Euthyr). ECG and respiratory signals were extracted and samples of consecutive 250–300 beats were analyzed using linear spectral and nonlinear entropy analysis of heart rate variability (HRV), during the different sleep stages. Heart rate was decreased and total power increased in Euthyr compared to Hyperthyr, both during wake and sleep; no changes of the sympathovagal balance were observed. Entropy analysis showed that regularity index was reduced in Euthyr compared to Hyperthyr, suggesting changes in the complexity of the cardiovascular control. Periodic leg movements (PLM) were reduced in Euthyr compared to Hyperthyr. In conclusion, hyperthyroidism seems to be associated with an increased sleep fragmentation, due to PLM and an altered cardiac autonomic control.

1. Introduction

Hyperthyroidism (Hyperthyr) is a pathological condition characterized by an overproduction of thyroid hormones manifesting with clinical symptoms and signs of an hyperadrenergic activation, such as tachycardia, anxiety, and weight loss.

It has been reported that Hyperthyr is associated with an alteration of cardiac autonomic nervous system (ANS) control, namely, a predominant sympathetic modulation associated with a reduced parasympathetic modulation [1–4]; however, conclusive results are still lacking.

Sleep is a physiological process essential for life. Physiologically, sleep can be divided into two different stages, non-REM (NREM) and REM sleep. NREM sleep is characterized by the absence of rapid eyes movements and it can be identified into light sleep (N1 and N2) and deep sleep (N3). Interestingly, it has been shown that ANS fluctuates among the different sleep stages: a progressive reduction of sympathetic modulation and an increase of parasympathetic control are described during NREM sleep while, on the opposite, REM sleep is associated with important surges of sympathetic activity [5–9].

The analysis of autonomic cardiovascular modulation using spectral analysis of heart rate variability (HRV) has been widely used as a noninvasive tool able to provide reliable information on the autonomic cardiac regulation [10–12]. HRV analysis has also been applied for the assessment of autonomic control during different sleep stages [13, 14]. In the last years, an increasing interest has been focused on

the evaluation of the complexity of cardiovascular system, which cannot be adequately assessed using the classical linear tools. The use of entropy-derived non linear indices, such as sample entropy, approximate entropy, corrected conditional entropy, and Shannon entropy [15, 16], has been proposed. Indeed, both physiological and pathological conditions seem to be characterized by a decrease of HRV complexity during aging and diseases; in addition, in healthy subjects a gradual increase of sympathetic modulation during graded tilt progressively leads to attenuation in complexity [17]. Most importantly, these cardiovascular complexity indices can provide important information for risk stratification in patients with an increased risk of sudden cardiac death [18].

Hyperthyroid patients often complain about bad sleep quality or insomnia; however, no data are available in literature regarding sleep characteristics and cardiovascular autonomic control during sleep in these patients.

Therefore, aim of the present study is the assessment of sleep characteristics and cardiovascular autonomic control by means of HRV during different sleep stages in hyperthyroid patients before and after suppressive therapy.

2. Methods

2.1. Experimental Protocol. The study was approved by our Institution's Review Board. An informed consent was obtained from all patients enrolled in the study.

We enrolled six caucasian female subjects, with a first diagnosis of Graves' disease caucasian disease or single hyperfunctioning nodule; mean BMI was 24 ± 1.1 kg/m^2. All the subjects were non-smokers, they did not assume any drugs, and they did not have any overt cardiovascular, respiratory, or metabolic disease.

The mean age was 47 ± 16, and all subjects were females; mean thyroid hormone levels at the diagnosis were as follows: TSH 0,01 ± 0,003 mcg/mL, FT3 14 ± 12 pg/mL, and FT4 35 ± 29 pg/mL.

A polysomnographic study (PSG) was performed at the moment of the first diagnosis of hyperthyroidism, before starting the suppression therapy with Methimazole (Hyperthyr). A second one was performed once the normal thyroid hormones profile had been restored after the treatment (Euthyr).

2.2. Sleep Studies. A PSG was performed in all subjects using a computer-assisted device (Pamela, Medatec, Brussels, Belgium). The electrocardiogram, electroencephalogram, electrooculogram, and submental and tibial electromyogram were recorded with surface electrodes using standard techniques. A nasal cannula and thoracic and abdominal belts with attached piezoelectrodes were used to record airflow and ventilator effort, respectively. Oxyhemoglobin saturation was recorded by finger pulse oximetry. The transducer and lead wires allowed normal position changes during sleep. Bedtime and awaking time were at each subject's discretion, and the study was terminated after final awakening. PSG studies were scored by a sleep expert according to standard criteria [19, 20].

2.3. Data Analysis. ECG and respiratory traces were divided according to the different sleep stages. Four different stages can be identified: wakefulness (W), N2, N3, and REM sleep. For each sleep stage, consecutive samples of 250–300 beats were selected avoiding any nonstationary segment and periods with irregular breathing.

After the detection of QRS complexes, the apex of the R wave was located using a parabolic interpolation. QRS detection was checked to avoid missed beats and incorrect detection of R waves. The time series obtained were linearly detrended. Spectral analysis and entropy-derived measures were performed on the time series divided according to the different sleep stages among the two states. The respiratory traces were resampled at 128 Hz and the respiratory rate was assessed from the respiratory signal. Spectral analysis variables and entropy-derived indices were calculated for each sample according to the different sleep stages.

2.4. Spectral and Entropy Analysis of Heart Rate Variability. Using an autoregressive model, we applied spectral analysis of HRV to evaluate cardiac autonomic control. In each time series, three main rhythmical components can be identified: very low frequency (VLF), low frequency (LF), and high frequency (HF) oscillations. VLF, with a frequency band below 0.04 Hz, is marker of very low oscillations, such as circadian rhythms and hormonal fluctuations. LF component, frequency band bounded between 0.04 and 0.15 Hz, is marker of sympathetic modulation and HF component, frequency band above 0.4 Hz and synchronous with respiration, is marker of parasympathetic modulation.

These oscillations are characterized by specific frequency band and amplitude and both LF and HF can be expressed in absolute values of power (ms^2) and in normalized units (nu), which represent the relative value of each spectral component. Normalized units can be calculated as follow: LF nu = [LF absolute units/(total power − VLF power)] and the HF nu = [HF absolute units/(total power − VLF)]. The sympathovagal balance is expressed by the calculation of the ratio between LF and HF power (LF/HF), considered a marker of the sympathetic-vagal balance (lower the LF/HF, lower the sympathetic modulation and vice versa) [21].

The mathematical details of entropy measures have been published elsewhere [15, 17, 22]. Briefly, the entropy-derived measures were used to assess the complexity of the autonomic cardiovascular control. From a specific entropy-derived index, the Corrected Conditional Entropy, it is possible to derive an index of regularity, Ro, that can be calculated by dividing the Corrected Conditional Entropy by the Shannon entropy. Ro ranges from 1, meaning maximum regularity and lowest complexity of the time series, to 0, lowest regularity and maximum complexity.

2.5. Statistical Analysis. Data are presented as mean ± standard deviation. SigmaPlot 11 (Systat Software Inc., Chicago, IL, USA) was used for the statistical analysis.

A two-way ANOVA analysis for variance for repeated measures was performed to evaluate differences between

Table 1: Linear and nonlinear parameters during wake and sleep in Hyperthyr and Euthyroid subjects.

	Wake	N1-N2	N3	REM
Hyperthyr ($n = 6$)				
HR (bpm)	82 ± 13	81 ± 12	84 ± 13	83 ± 11
TP (ms^2)	863 ± 822	857 ± 1050	829 ± 74	887 ± 41
VLF (ms^2)	376 ± 566	254 ± 469	387 ± 812	404 ± 551
LF (ms^2)	207 ± 441	281 ± 691	151 ± 394	158 ± 243
HF (ms^2)	236 ± 369	239 ± 328	167 ± 269	177 ± 290
LF nu	26 ± 30	34 ± 25	26 ± 31	33 ± 26
HF nu	53 ± 21	46 ± 20	47 ± 29	48 ± 30
LF/HF	0.99 ± 1.5	1.2 ± 2.1	2.7 ± 7.9	1.5 ± 1.6
Ro	0.37 ± 0.14	0.32 ± 0.08	0.33 ± 0.13	0.33 ± 0.12
Euthyr ($n = 6$)				
HR (bpm)	75 ± 10*	73 ± 10*	76 ± 13*	71 ± 12*
TP (ms^2)	1489 ± 1464*	2099 ± 6205*	1261 ± 1614*	1749 ± 2028*
VLF (ms^2)	599 ± 415	645 ± 1363	652 ± 1187	558 ± 801
LF (ms^2)	204 ± 228	699 ± 2557	233 ± 393	635 ± 1020
HF (ms^2)	5488 ± 768	693 ± 2393	316 ± 432	494 ± 737
LF nu	40 ± 39	54 ± 34	40 ± 36	47 ± 36
HF nu	49 ± 31	38 ± 29	43 ± 28	48 ± 33
LF/HF	0.5 ± 0.7	1.7 ± 2.4	1.7 ± 5.1	2.0 ± 3.4
Ro	0.23 ± 0.08*	0.23 ± 0.15*	0.27 ± 0.15*	0.27 ± 0.11*

Data are presented ±SD. HR: heart rate; TP: total power; VLF: very low frequency; LF: low frequency; HF: high frequency; nu: normalized units; Ro: regularity index. * $p < 0.05$ versus Hyperthyr.

the two states (Hyperthyr versus Euthyr). A $p < 0.05$ was considered statistically significant.

3. Results

The spectral analysis results are summarized in Table 1. As shown in Figure 1, heart rate (HR) was significantly lower in Euthyr compared to Hyperthyr during wake (75 versus 82 bpm, $p < 0.05$) and during N1, N2, and N3 (73 versus 81, 76 versus 84 and 71 versus 83, respectively, $p < 0.05$). Total variability significantly increased in Euthyr during W and sleep (see Figure 2), while no changes have been observed in LF and HF components (see Table 1). Respiratory frequency was similar among the two states during wake and sleep.

As to entropy-derived measures, Ro, index of regularity of the heart period time series, was significantly lower in Euthyr compared to Hyperthyr during W, N1, N2, and N3 (see Table 1).

The sleep quality analysis of polysomnographic studies revealed that Euthyr had significantly lower periodic leg movements compared to Hyperthyr. No other sleep quality indexes were significantly different among the two states (see Table 2).

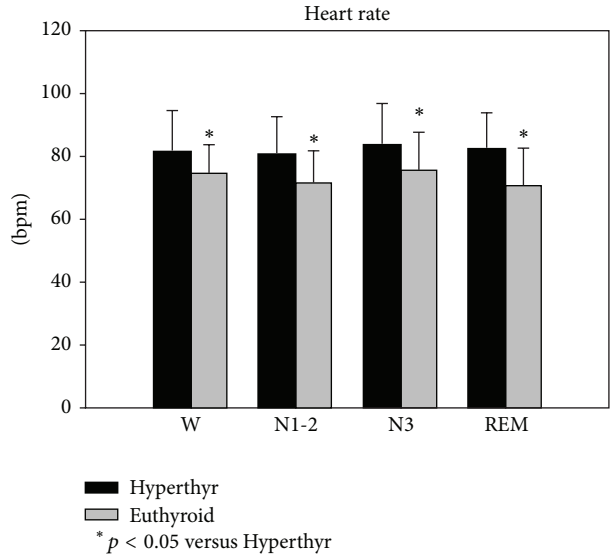

Figure 1: Heart rate (HR) during wake and different sleep stages in the two states, Hyperthyr and Euthyroid subjects. HR is significantly lower in the Euthyroid during wakefulness and sleep. * $p < 0.05$.

4. Discussion

The main findings of the present study are the following. First, autonomic cardiovascular control during sleep is characterized by a decreased mean HR and increased total variability during wake and throughout sleep in Euthyr compared to Hyperthyr; second, entropy analysis shows that in Euthyr regularity of ANS control is reduced both during wake and sleep, suggesting important changes in the complexity of the cardiovascular control; third, qualitative analysis of sleep parameters revealed that Euthyr subjects have reduced

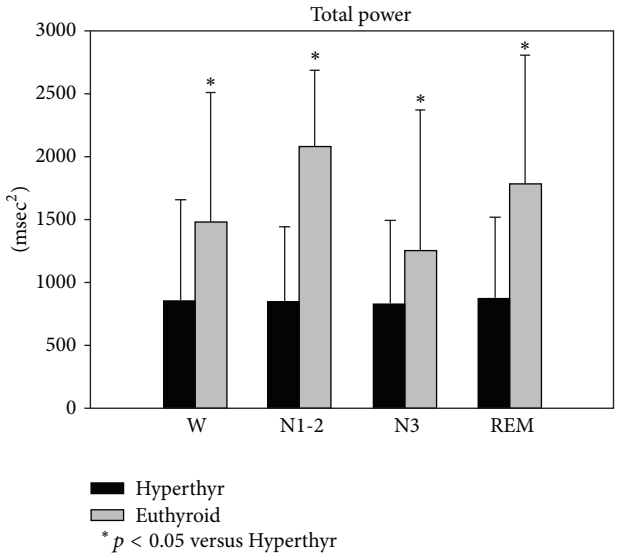

Figure 2: Total power during wake and sleep in the two states, Hyperthyr and Euthyroid subjects. Total power is significantly higher in the Euthyroid during wakefulness and sleep. * $p < 0.05$.

Table 2: Sleep parameters in Hyperthyr and Euthyroid subjects extracted from the analysis of polysomnographic studies.

	Hyperthyr	Euthyroid
TIB (min)	478 ± 35.8	471.8 ± 73
SPT	481.3 ± 33.2	444.8 ± 83.8
Sleep efficiency	90.6 ± 3.3	92 ± 3.5
N1	6.5 ± 4.3	5.0 ± 1.7
N2	56.9 ± 7.5	62.9 ± 11.1
N3	9.8 ± 6.8	9.8 ± 6.8
REM	16.6 ± 7.3	15.3 ± 6.4
PLM/h	9.8 ± 6.9	6.0 ± 4.0*
Arsl/h	8.0 ± 5.4	6.2 ± 3.1
Awake + arousal/h	8.9 ± 5.5	6.6 ± 3.2
AHI	1.7 ± 1.5	1.4 ± 1.3
Mean SaO_2	95.7 ± 0.9	96.1 ± 0.8

Data are presented ±SD. TIB: time in bed; SPT: sleep period time; PLM: periodic leg movements; Ars/h: arousals per hour; AHI: apnea/hypopnea index. * $p < 0.05$ versus Hyperthyr.

leg movements compared to Hyperthyr, thus suggesting an improvement of sleep quality after the treatment.

Hyperthyroidism is characterized by augmented levels of thyroid hormones, Which cause signs and symptoms similar to a hyperadrenergic state; these clinical features are due to the sympathomimetic action of thyroid hormones [3].

In Hyperthyr, an alteration of ANS regulation has been described: in fact, previous studies showed an increased sympathetic and a decreased parasympathetic modulation during Hyperthyr [1–4]. Interestingly, hyperthyroid subjects anecdotally reported reduced sleep quality.

However, considering the key role played by the ANS in Hyperthyr and in the regulation of sleep, no data are available on the autonomic cardiovascular control during sleep in Hyperthyr. Therefore, we aimed to assess HRV using spectral analysis and entropy-derived index in a group of Hyperthyr subjects during wake and sleep at the time of diagnosis (Hyperthyr) and after the suppression treatment, when they returned to normal thyroid hormones levels (Euthyr).

Our data revealed that Euthyr subjects are characterized by reduced mean HR both during wake and throughout the sleep stages (N1-2, N3, and REM); since therapy suppresses the effect of thyroid hormones that mimic sympathetic activation, this result was quite expected. However, evaluating the autonomic profile, we observed a significant increase of total variability in Euthyr compared to Hyperthyr both during wake and sleep, with no changes in terms of sympathetic and parasympathetic components, as shown by the LF and HF components. Interestingly, although some papers reported an altered autonomic cardiovascular modulation in hyperthyroidism [1–3], no HRV data during sleep in Hyperthyr have been reported.

Therefore, our data seem to suggest that Hyperthyr condition is characterized by an altered autonomic cardiovascular control with respect to Euthyr, namely, a reduced total variability, that is considered an index of the ability of the ANS to react and respond to external and internal stressors stimuli [11, 12], without affecting the sympathetic and parasympathetic regulation of sleep stages.

In the last years, an emerging literature focused on the evaluation of autonomic cardiovascular regulation in terms of regularity or, its opposite, complexity. The higher is the complexity of the autonomic cardiac system, the higher is the capability of the different subsystems that regulate a variable (such as the function of the sinus node) to counteract different stressors; on the opposite, pathological conditions are associated with increase in the regularity of the system, as it has been demonstrated for aging and cardiovascular patients [17, 18].

For the first time, we showed that, compared to Hyperthyr, Euthyr condition is associated with changes in the regularity of the cardiovascular control, suggesting that this state is characterized by a capability of the cardiovascular system to better respond to external perturbations both during wake, NREM and REM sleep, as suggested by the significant reduction of Regularity Index from Hyperthyr to Euthyr.

Periodic leg movements are associated with changes in heart rate and autonomic cardiac control [23–25] and, clinically, with impaired quality of sleep. In the present study, in addition to the autonomic changes described previously, sleep analysis showed that the number of periodic leg movements was significantly reduced in Euthyr compared to Hyperthyr. To our knowledge, this is the first evidence supporting the hypothesis that hyperthyroid state is associated with worse sleep quality; this poorer quality of sleep can be related to the presence of leg movements, which could, per se, alter the physiological sleep process. However, after the suppression therapy, the return to Euthyr state is characterized by a more physiological and restoring sleep, as shown by the significant reduction of leg movements in this state.

Further studies are needed in order to better evaluate the reciprocal relation between Hyperthyr condition and autonomic cardiovascular control during sleep and the possible autonomic differences that can predict the response to therapy.

Conflict of Interests

The authors declare that they have no conflict of interests.

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