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Acute effect of different types of physical exercise on sleep patterns

Efeito agudo de diferentes tipos de exercício físico no padrão do sono

Marcio Vinicius Rossi^{1,2}, Daniel Alves Cavagnolli^{1,2}, Alexandre Paulino Faria^{1,2}, Sionaldo Eduardo Ferreira³, Renata Guedes Koyama^{1,2}, Alberto Bailone Neto^{1,2}, Lígia Mendonça Lucchesi⁴, Sergio Tufik^{2,4}, Marco Túlio de Mello^{1,2,4}

ABSTRACT

Objective: Many studies assessing the effects of physical exercises on sleep patterns have been conducted in recent years, but no consensus has been reached in the literature due to methodological differences relating mainly to exercise duration and intensity. Moreover, most of protocols used only aerobic exercises. This paper aimed to assess the sleep pattern before and after different types of physical exercise in a sample of sedentary volunteers. **Methods:** The sample consisted of 102 volunteers (40 males and 62 females) aged 28 ± 7 . The experimental protocol involved three types of acute physical exercise: resistance exercise (with load on each type of device equivalent to 50% of 1 repetition maximum test – 1RM), aerobic (30 minutes treadmill at 60% of VO_{2peak}) or interval (ergocycle, 10 repetitions of 35 seconds at load equivalent to 140% of that reached on the maximum effort test). To assess the possible effects of acute exercise on sleep patterns, volunteers' polysomnograms (PSG) were recorded previously (basal) and on the day they performed physical exercise. **Results:** Though many studies show an increase in slow-wave sleep and decrease in REM sleep amount after physical exercise, the present study found no significant differences between polysomnograms variables on the exercise day and basal values for any of the three types of exercises. **Conclusions:** A single session of physical exercise at moderate intensity did not alter sleep patterns in sedentary "good sleepers", regardless of type of exercise. This was probably due to the low volume and/or intensity of physical exercise used in the present study.

Keywords: Exercise; Sleep/physiology; Sleep, REM; Polysomnography; Physical fitness; Circadian rhythm; Body weight/physiology

RESUMO

Objetivo: Nos últimos anos, muitos estudos foram realizados com o intuito de verificar os efeitos do exercício físico no padrão do sono. Porém, devido às diferenças metodológicas empregadas, principalmente com relação à duração e intensidade do exercício físico, ainda não há um consenso na literatura sobre a sua real influência no sono. Além disso, a grande maioria dos estudos utiliza apenas o exercício aeróbico como protocolo. Este trabalho objetivou verificar o padrão do sono por

meio das variáveis polissonográficas de indivíduos sedentários, com boa qualidade de sono, antes e após a realização de diferentes tipos de exercícios físicos. **Métodos:** Foram selecionados 102 voluntários, 40 homens e 62 mulheres com idade média de $28,54 \pm 6,97$ anos. O protocolo experimental consistiu na realização de três tipos de exercício físico realizados de forma aguda: exercício resistido (com carga obtida em cada aparelho equivalente a 50% do teste de 1 repetição máxima – 1RM), aeróbio (realizado em esteira, durante 30 minutos a 60% do VO_{2pico}) ou intervalado (realizado na bicicleta, com 10 repetições de 35 segundos e carga equivalente a 140% da carga máxima atingida no teste de esforço máximo). Os voluntários foram submetidos a um exame de polissonografia (PSG) antes (basal) e no dia da realização do exercício físico, no intuito de verificar os possíveis efeitos agudos do exercício físico no padrão do sono. **Resultados:** Embora muitos estudos apresentem um aumento do sono de ondas lentas e uma diminuição do sono REM após a prática do exercício físico, no presente estudo não foram observadas diferenças significativas entre os dados obtidos nas variáveis do sono da polissonografia realizada no dia do exercício físico quando comparados à basal em nenhum dos três tipos de exercício físico. **Conclusões:** De acordo com os resultados obtidos, uma única sessão de exercício físico de intensidade moderada, independentemente do tipo, não altera o padrão do sono em voluntários sedentários e com boa qualidade do sono, provavelmente em decorrência do baixo volume e/ou intensidade do exercício físico empregado no presente estudo.

Descritores: Exercício; Sono/fisiologia; Sono REM; Polissonografia; Aptidão física; Ritmo circadiano; Peso corporal/fisiologia

INTRODUCTION

Epidemiological studies have reported positive impacts of physical exercises on sleep quality⁽¹⁾. Physically active individuals presented lower frequencies of self-reported sleep complaints, better sleep quality and less daytime sleepiness^(2,3).

Many experimental studies have examined possible relations between physical exercise and sleep in recent years, but

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the actual mechanism involved in this effect is still a matter of debate⁽⁴⁻⁶⁾.

Although the most frequently observed effect of exercise is an increase in slow-wave sleep (SWS)⁽⁷⁻¹⁰⁾, some studies have found no such effect^(11,12). Increases in REM sleep latency and decreases in REM sleep have also been observed^(7,9,13). Moreover, physically active individuals showed longer total sleep time (TST) than sedentary individuals⁽¹⁴⁾.

Despite the effects mentioned above, a meta-analysis by Youngstedt et al.⁽⁶⁾ suggested that longer SWS and REM sleep latency, as well as longer TST and reduced REM sleep time, might be caused by acute physical exercises, but only to a limited or moderate extent. They also suggested that high intensity exercise was not associated with longer SWS, but rather with more wake time after sleep onset.

The lack of consensus in the literature in relation to the effects of exercise on the main sleep parameters may be due to differing methods used to describe exercise intensity and duration, or the fact that most samples consisted of athletes or physically active volunteers. Additionally, most protocols used aerobic exercises only. To the best of our knowledge, few researchers have examined the possibility of sleep patterns being altered after other types of exercise. Consequently, the objective of the present study was to assess the acute effect of different types of exercise on the sleep patterns of sedentary “good sleepers”.

METHODS

The study was authorized by the Research Ethics Committee at Universidade Federal de São Paulo (UNIFESP) (Ref. 0948/05). After being briefed on the study before the experimental protocol started, all volunteers signed an informed consent form.

Subjects

The sample was collected through advertising placed by the Press Office at UNIFESP and consisted of 102 adult volunteers (40 males and 62 females), mean age 28.54 ± 6.97 , all sedentary and good sleepers. Exclusion criteria were abnormalities in laboratory or clinical exams, electrocardiograms taken during rest and effort that contraindicated physical exercise, and sleep disorders as evaluated by a polysomnogram (PSG). Further exclusion criteria were Epworth Sleepiness Scale values ≥ 10 , apnea-hypopnea index (AHI) > 15 , AHI > 5 combined with snoring (2), or periodic leg movement (PLM) > 5 (1). After the clinical evaluation, individuals presenting lower values than those mentioned above were considered normal.

Experimental design

The experimental protocol carried out at the Psychobiology and Exercise Research Center (CEPE) of the Psychophar-

macology Incentive Fund Association (AFIP) consisted of three types of physical exercise – resistance, aerobic and interval – performed acutely at three schedule options (7:00 - 9:00, 13:00 - 15:00 and 18:00 - 20:00). The volunteers were allowed to choose the type of exercise and the exercise schedule. This was done to ensure that all volunteers liked the type of exercise done, but resulted in widely varying number of subjects in the experimental groups. Each volunteer chose only one type of exercise and one schedule. After the exercise protocol had been explained, each volunteer went through a basal evaluation consisting of an effort electrocardiogram (ECG), PSG, laboratory tests, general clinical evaluation and investigation of possible sleep complaints. Volunteers who did not present abnormalities in those exams, and therefore had their participation in the experimental protocol endorsed by the research center's doctor, proceeded to have their body composition measured. After three days adapting to the equipment, they did a maximum effort test (MET) for the aerobic and interval exercises, or a repetition maximum test (1RM) for the resistance exercise, and the results were used to prescribe the intensity of their exercise. All evaluations took place in a laboratory at controlled temperature (22-24°C) and 40-60% relative humidity. A second PSG was carried out on the exercise day, when the volunteers went about their regular activities before reporting to the laboratory at 21:00 for polysomnographic recordings (Figure 1).

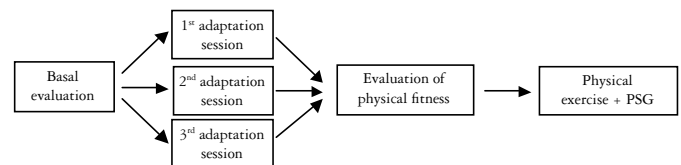


Figure 1: Chronogram of the evaluations carried out during the study. *Basal evaluation:* rest and effort ECG, PSG, blood tests, clinical and body composition evaluation. 1st, 2nd and 3rd adaptation sessions: familiarization with exercise equipment in 3 alternated days. Evaluation of physical fitness: MET or 1RM. Physical exercise + PSG: Physical exercise and PSG in late-evening.

Resistance exercise

The resistance exercises involving six muscle groups were done on the leg press (anterior leg muscles), lat machine (back muscles), leg curl (leg posterior muscles), chest press (chest muscles), abdominal crunch (abdominal muscles) and shoulder press (shoulder muscles), with equipment made by Technogym[®]. The exercise prescription parameter was based on a 1RM test⁽¹⁵⁾. The protocol consisted of one session of moderate physical exercise containing 3 series of 15 repetitions with a 90-second interval between series and a load of 50% 1RM test.

Aerobic exercise (Maximum oxygen uptake - VO_{2peak})

The aerobic exercise and MET were performed on a treadmill (Life Fitness® 9700 HR). The initial speed of 4 km/h was accelerated by 1 km/h every minute until exhaustion. A 1% grade was used to simulate the energy cost of outdoor running⁽¹⁶⁾. The VO_{2peak} was obtained by analyzing ventilatory alterations during MET with incremental load. The Quark PFT Ergo 4 (Cosmed®) metabolic analyzer was used to record data. The protocol consisted of one 30-minute session of moderate physical exercise with load and cardiac frequency (CF) equivalent to 60% of VO_{2peak} .

Interval exercise

Interval exercises and MET were done on ergocycles (Monark 824E®). The initial MET load was 80W for 3 minutes with subsequent increases of 40W every 2 minutes until exhaustion. The VO_{2peak} was obtained by analyzing ventilatory alterations of MET with incremental load. The Quark PFT Ergo 4 (Cosmed®) metabolic analyzer was used to record the data. The physical exercise was performed at a predetermined percentage of the MET maximum load with incremental loads, as shown in Table 1. The protocol consisted of one session of moderate exercise, carried out in 10 series with 4-minute intervals between series, with the volunteers pedaling at 80 rpm for 35 seconds and 140% of the maximum load obtained in the MET (adapted from Fernandez⁽¹⁷⁾).

Sleep parameters

Sleep parameters were recorded using the EMBLA S7000® sampling at 30-second intervals and classified as wakefulness, NREM and REM sleep stages I, II, III and IV using the criteria standardized by Rechtschaffen and Kales⁽¹⁸⁾.

Electroencephalographic recording was obtained by placing electrodes as in International System 10-20⁽¹⁹⁾. We used four electroencephalographic derivations, two electrooculogram channels, two electromyogram channels (submentonian and legs) and one ECG derivation.

We used a termistor and nasal canula to monitor the airflow, belts to monitor thoracic and abdominal effort, transcutaneous oximetry to record oxygen saturation and a sensor tracking the position of the trunk during sleep.

In addition to PSG, we used the Pittsburgh Sleep Quality Index (PSQI) as a standardized measure of the subjective sleep quality, sleep-related habits and occurrence of sleep disorders⁽²⁰⁾.

Statistical analysis

The Statistica 6.0 (StaSoft, INC®) software was used for the statistical analyses. Sample normality was rated by the Kolmogorov-Smirnov test. The comparison between basal and exercise data was made using the Student's t test for dependent samples with normal distributions. In the absence of normality of the sample, we used the Wilcoxon test. The 0.05 level of significance was used for all analyses, and the results are expressed as mean \pm standard deviation.

RESULTS

Experimental groups had similar age, height, and weight, but body mass index (BMI) was slightly, but significantly, higher in the aerobic group (Table 2). The table also shows VO_{2peak} for aerobic and interval exercises, and load (kg) for resistance exercises. The numbers of volunteers performing each type of exercise during each schedule are shown in Table 3. The PSQI and sleep parameters obtained on the basal PSG are shown in Table 4.

No significant differences were detected between basal sleep variables and those on the exercise day for any of the three types of exercise (Table 4).

DISCUSSION

No significant differences were detected between sleep parameters recorded on the day of physical exercise and basal values, regardless of the type of exercise performed.

Contrasting with our findings, several studies have found an increase in SWS^(7-10,21,22) and a decrease in REM sleep^(7,9,13,21) after acute physical exercise.

Most of these studies used athletes as volunteers, and their polysomnographic recording were usually made during training periods or after competitions or marathons involving intense effort and very high energy expenditure^(10,21).

Some findings suggest that the volume of physical exercise has to be increased to cause significant alterations in sleep^(6,10). The intensity and duration of physical exercise

Table 1: Description of physical exercise

	Physical exercise			
	Load	Number of series	Number of repetitions	Interval between series
Resistance	50% 1RM	3	15	90s
	Load	Warm up	Exercise	Cool down
Aerobic	60% VO_{2peak}	5-min walk	30 min	5-min walk
	Load	Number of series	Interval between series	Time in each series
Interval	140% MET load	10	4 min	35s

Load, volume and intensity of exercise prescribed for volunteers.

Table 2: Basal characteristics of the sample that performed physical exercise

	Resistance	Aerobic	Interval	p-value
n	70	19	13	
Age	29±7	29±7	27±6	0.71
Body Mass (kg)	64.8±11.4	70.8±2.6	66.6±12.5	0.13
Height (m)	1.68±0.09	1.68±0.02	1.66±0.09	0.82
BMI (kg/m ²)	22.74±2.45*	24.98±0.74	23.84±3.06	0.00
VO _{2peak} (mL.kg.min ⁻¹)	-	35.16±1.95	32.31±9.18	-
Chest press (kg)	42.54±18.90	-	-	-
Leg press (kg)	101.80±47.55	-	-	-
Lat machine (kg)	43.80±17.84	-	-	-
Leg curl (kg)	48.34±17.18	-	-	-
Shoulder press (kg)	23.52±13.34	-	-	-
Abdominal crunch (kg)	32.27±12.73	-	-	-

Descriptive analysis of the sample shown as mean ± standard deviation.

Note: VO_{2peak} data for two volunteers in the interval group were not used due to a malfunction in the ergospirometric device.

*Difference between resistance and aerobic groups.

Table 3: Number of volunteers in each training schedule

	Resistance	Aerobic	Interval
Morning	18	5	3
Afternoon	26	4	3
Evening	26	10	7

Total number of volunteers in each training schedule for each type of exercise.

Table 4: Comparison between sleep variables (basal *versus* exercise) for each group

	Resistance			Aerobic			Interval		
	Basal	Exercise	p-value	Basal	Exercise	p-value	Basal	Exercise	p-value
PSQI	5.05±2.45	-	-	5.06±2.01	-	-	4.77±2.95	-	-
Sleep latency (min)	10.2±12.2	8.8±13.3	0.09	10.1±10.6	12.5±21.4	0.60	14.5±17.5	10.4±14.3	0.28
Latency to REM sleep (min)	94.9±36.0	94.7±39.0	0.97	87.2±40.6	78.4±28.4	0.35	94.9±34.9	103.8±60.2	0.54
TST (min)	369.94±45.81	375.2±42.1	0.41	372.1±41.7	360.1±56.8	0.38	385.4±41.8	360.7±53.6	0.20
Sleep efficiency (%)	89.7±6.2	90.7±6.13	0.10	89.5±5.0	87.6±9.2	0.36	88.8±6.9	89.3±8.7	0.88
Stage 1 (%)	3.0±1.9	2.9±1.91	0.80	4.0±3.0	3.8±2.8	0.72	3.1±1.7	2.9±1.9	0.73
Stage 2 (%)	53.4±6.9	53.9±6.4	0.53	53.2±6.7	53.2±7.3	0.98	53.3±7.2	52.6±7.0	0.73
SWS (%)	24.03±6.0	24.9±11.8	0.60	23.1±6.6	21.4±6.0	0.38	23.1±6.5	24.5±6.2	0.46
REM sleep (%)	19.6±4.9	19.7±4.4	0.96	19.7±6.3	21.6±6.0	0.11	20.5±3.1	20.0±3.9	0.69
Wakefulness (min)	31.7±18.7	30.0±21.1	0.59	34.3±23.4	36.9±25.8	0.69	34.5±23.1	32.0±22.3	0.81
Arousals (h)	12.09±6.04	12.36±6.78	0.79	11.38±2.57	12.56±4.39	0.33	11.28±4.91	15.10±6.60	0.10
AHI	3.05±2.2	3.38±5.25	0.58	3.35±2.51	4.03±3.24	0.31	2.93±2.25	4.21±3.79	0.23
Apnea index	0.1±0.8	0.15±0.96	0.45	0.19±0.29	0.28±0.44	0.44	0.18±0.22	0.29±0.82	0.67
Hypopnea index	2.73±1.98	2.95±4.77	0.70	3.15±2.27	3.76±3.12	0.34	2.75±2.07	4.13±3.81	0.18
Mean oxygen saturation (%)	96.06±1.06	96.18±1.37	0.40	96.09±1.02	96.31±1.32	0.35	96.17±0.79	96.08±1.53	0.82

Data shown as mean ± standard deviation.

PSQI: Pittsburgh Sleep Quality Index.

The Student's t test was used for dependent samples.

For sleep latency and sleep efficiency variables in the resistance group and sleep latency in the interval group, we used the Wilcoxon test ($p < 0.05$). No significant differences were observed between basal sleep variables and their values after acute physical exercise.

in the present study were not sufficient to cause significant alterations in sleep parameters, especially SWS and REM sleep, since sedentary volunteers cannot be prescribed high-intensity or high-volume exercise to without previous adaptation (training).

After physically active individuals exercised on an ergo-cycle at an intensity equivalent to 60% of VO_{2peak} for one hour, researchers observed longer SWS and reduced REM sleep (30). On the other hand, the present study found that doing aerobic exercise at 60% of VO_{2peak} for 30 minutes did

not affect sleep parameters. The differing results may be due to the different durations of exercise.

On similar lines to our study, others found no significant differences in sleep parameters after exercise^(12,23,24), but the methods used to rate type, volume and intensity of exercises varied. Oda and Shirakawa⁽²⁴⁾ found no significant differences in sleep parameters of sedentary individuals after 40 minutes of moderate or intense aerobic exercise from 21:20 to 22:00.

Few researchers have examined the effects of resistance exercise on the sleep pattern in humans, and no other study in the literature has focused on interval exercises, so our protocol was the first to involve this type of exercise.

Studies of resistance exercise have focused mainly on the elderly, and assessed the chronic effects of a physical exercise program⁽²⁵⁻²⁷⁾. Again, Montgomery et al.⁽¹²⁾ studied weightlifters doing resistance exercise and evaluated the effect on their sleep. However, they did not find differences in sleep architecture after strength training in the evening.

Consequently, our initial hypothesis was that there would be no improvement in volunteers' sleep quality after acute physical exercise, since all were "good sleepers" as assessed by PSG. We expected a change in sleep architecture without impairment of quality. In this case, we can discuss "ceiling and floor effects", i.e. the more the initial sleep impairment, the more the potential for improvement⁽²⁸⁾. Since only "good sleepers" were used in our study, the range of alteration in sleep parameters was very narrow.

Despite different characteristics in terms of how they were performed and, therefore, different physiological alterations during their performance, the different types of physical exercise did not affect sleep architecture.

As previously discussed, many studies showing alterations in sleep parameters sampled physically active individuals or athletes, and their PSGs were recorded after competitions or sessions of very high-volume physical exercise at very high levels of intensity. No significant alterations were detected in sleep parameters in studies that used only sedentary individuals doing exercises for less than one hour, particularly in relation to SWS and REM sleep. In fact, alterations in SWS and REM sleep seem to take place when the exercise induces observable physical stress.

Our sample consisted of sedentary volunteers, so we had to use a lower volume of exercise, otherwise the physical stress for these individuals might have been more intensive than for athletes or physically active individuals, even if relative intensity was the same. Our protocol did not exceed a moderate level of intensity in order to avoid health.

The screening process for the present study excluded 60 volunteers before the experimental protocol started, so a convenience sample was used. Therefore, the number of

volunteers and the variability of the data did not allow us to compare results for exercises in the three different schedules, or to compare the results from the three different types of exercise. These will be the objectives of a future study, when we will have data from more volunteers available.

The present study found that acute physical exercise, whether resistance, aerobic or interval, did not influence sleep-related parameters in sedentary "good sleepers". Therefore, sedentary individuals may undertake moderate exercise programs without impairing sleep quality during the initial phases of training, as long as the volume and the intensity are controlled. Further research with larger samples is required to examine the real effects of exercise on sleep patterns, and must involve varying volumes and intensities of exercise.

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Dopaminergic and noradrenergic drugs revert cocaine-induced erection in paradoxical sleep-deprived rats

Drogas dopaminérgicas e noradrenérgicas revertem a ereção induzida por cocaína em ratos privados de sono paradoxal

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ABSTRACT

Objectives: Evidence suggests that paradoxical sleep deprivation induces dopaminergic supersensitivity and noradrenergic subsensitivity. Previous studies have demonstrated that 96 h of paradoxical sleep deprivation enhance cocaine-induced penile erection (PE) and ejaculation (EJ). The present study investigated the influence of the dopaminergic agonist apomorphine and noradrenergic antagonist propranolol in reverting genital reflexes potentiated by cocaine. **Methods:** Rats were exposed to 96 h of paradoxical sleep deprivation and received acute and chronic intraperitoneally injections of apomorphine (120, 240 and 480 µg/kg) or propranolol (2, 4 and 8 mg/kg) before being challenged with cocaine (7 mg/kg). Acute or chronic apomorphine (240 and 480 µg/kg) administration reduced the proportion of animals that displayed erection. **Results:** acute propranolol administration induced a decrease in the proportion of animals displaying penile erection only at the lowest dose. Penile erection frequency decreased after acute and chronic propranolol treatment. **Conclusion:** This study indicates that dopaminergic supersensitivity and noradrenergic subsensitivity have critical roles in the regulation of sexual reflexes.

Keywords: Sleep deprivation; Cocaine; Sexual behavior, animal; Ejaculation/drug effects; Penile erection/drug effects; Genitalia, male/drug effects; Dopamine/therapeutic use; Apomorphine/therapeutic use; Propranolol; Animals; Rats

RESUMO

Objetivos: Evidências sugerem que a privação de sono paradoxal induz supersensibilidade dopaminérgica e subsensibilidade noradrenérgica. Estudos prévios demonstraram que 96 h de privação de sono paradoxal potencializam a ereção peniana e ejaculação induzida por cocaína. O presente estudo investigou a influência do agonista dopaminérgico apomorphine e do antagonista noradrenérgico propranolol na reversão dos reflexos genitais potencializados pela cocaína. **Métodos:** Ratos foram submetidos a 96 h de privação de sono paradoxal e receberam administrações intraperitoneais agudas ou crônicas de apomorfina (120, 240 e 480 µg/kg) ou propranolol (2, 4 e 8 mg/kg) antes de serem testados com cocaína. Administrações agudas e crônicas de apomorfina (240 e 480 µg/kg) reduziram a proporção de animais que apresentaram ereção. **Resultados:** Administração aguda de propranolol

induziu diminuição na proporção de animais que apresentaram ereção peniana, apenas na menor dose. A frequência de ereção peniana diminuiu após tratamento agudo e crônico com propranolol. **Conclusão:** Este estudo indica que a supersensibilidade dopaminérgica e a subsensibilidade noradrenérgica possuem papéis fundamentais na regulação dos reflexos sexuais.

Descritores: Privação de sono; Cocaína; Comportamento sexual animal; Ejaculação/efeitos de drogas; Ereção peniana/efeitos de drogas; Genitália masculina/efeitos de drogas; Dopamina/uso terapêutico; Apomorfina/uso terapêutico; Propranolol; Animais; Ratos

INTRODUCTION

There is great interest in the consequences of paradoxical sleep deprivation (PSD) techniques⁽¹⁻⁴⁾. Most consequences are thought to be controlled by central neurotransmitter systems and have been implicated in several behavioral alterations. Therefore, it is reasonable to predict that the behavioral alterations observed after PSD result from changes in the modulation of brain neurotransmitters occurring after selective sleep loss.

Experiments involving PSD employing the water tank technique have shown that this procedure alters behaviors that can be induced by drugs, acting on many neurotransmitter systems. A number of studies have reported a marked behavioral supersensitivity to directly- and indirectly-acting dopamine agonists after being subjected to a period of PSD⁽⁵⁻¹⁰⁾. These findings have led to the hypothesis that modification in sensitivity to a dopaminergic drug by PSD is due to functional hyperactivity of the dopaminergic system. Furthermore, downregulation of the noradrenergic system has been reported⁽¹¹⁾.

Among the behavioral alterations investigated in PSD rats, sexual behavior has drawn increased attention in recent years. Our laboratory group has consistently studied

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the stimulatory effect of PSD in male rats on genital reflexes such as penile erection (PE) and ejaculation (EJ). It has been shown that dopaminergic drugs such as cocaine⁽¹²⁾, methamphetamine⁽¹³⁾ and other dopaminergic agonists^(14,15) enhance the effect of PSD. Additionally, noradrenergic mechanisms have been reported to be involved in PE induced by sleep deprivation and cocaine⁽¹⁶⁾.

Pharmacological studies have been performed in an attempt to identify the neurotransmitter systems involved in the regulation of sexual behavior in male rats. Although the effect of dopaminergic agonists in facilitating male sexual behavior is well documented⁽¹⁷⁻²⁰⁾, the role of noradrenergic transmission is less clear and has received less attention.

Considering that dopaminergic^(5,8) and noradrenergic⁽¹¹⁾ receptor sensitivity is altered by PSD, that both systems are related to sexual function⁽¹⁷⁾, and that dopamine and noradrenaline play relevant roles in genital reflexes induced by cocaine in PSD rats, the present study was designed to determine whether a dopaminergic agonist (apomorphine) and noradrenergic antagonist (propranolol) could revert the occurrence of spontaneous genital reflexes potentiated by cocaine in PSD rats.

METHODS

Subjects

Naïve male Wistar rats were bred and raised in the animal facility of the Department of Psychobiology of the *Universidade Federal de São Paulo*. The animals were housed in a colony maintained at 22°C with 12:12 h light:dark cycle (lights on at 07:00) and allowed free access to food and water inside standard polypropylene cages. Rats were maintained and treated in accordance with the guidelines established by the Ethical and Practical Principles of the Use of Laboratory Animals⁽²¹⁾. The experimental protocol was approved by the Ethical Committee of UNIFESP (CEP N. 482/02).

Paradoxical sleep deprivation

The procedure consisted of placing ten rats in a tiled water tank (123 x 44 x 44 cm) for 96 hours. The tank contained 14 platforms (6.5 cm in diameter) rising 1 cm above the water surface, thus allowing the rats to move around by leaping from one platform to another. At the onset of each paradoxical sleep episode, the animal experiences a loss of muscle tone and falls into the water, thus being awakened. When platforms of this size are used, previous work from this laboratory demonstrated that paradoxical sleep is completely abolished during the four-day period⁽²²⁾. Slow wave sleep is significantly reduced but does not lead to rebound sleep. It therefore seems appropriate to refer to these animals as being paradoxical sleep deprived rather than being exclusively

deprived of sleep. The cage control group was maintained in the same room as the experimental rats throughout the study and showed normal patterns of paradoxical sleep, slow wave sleep and wake. Throughout the study, the experimental room was maintained under controlled temperature and a light:dark cycle. Food and water were available *ad libitum*, with chow pellets and water bottles provided on a grid located on the top of the tank. The water in the tank was changed daily throughout the PSD period. The duration of 96 hours of PSD was chosen since it has been shown that most genital reflexes are produced during this period of time⁽¹²⁾.

Drugs

Cocaine hydrochloride (Sigma Chemical Co., St. Louis, MO, USA) was freshly dissolved in a vehicle of 0.9% sterile saline solution for injection. Apomorphine and propranolol (Sigma Chemical Co., St. Louis, MO, USA) were freshly dissolved in a vehicle of 0.9% sterile saline solution and two drops of Tween. The injection volume for all systemic studies was 1 mL/kg, and the route of administration was intraperitoneal injection.

Experimental design

The rats were subjected to PSD (n=10-11/group). In acute treatment, each group was administered with apomorphine or propranolol and was returned immediately to the tank. One hour later, the animals were administered intraperitoneally with cocaine (7 mg/kg) and placed immediately in the observation cages for the evaluation of genital behaviors. In chronic treatment, rats were administered with apomorphine (120, 240 and 480 µg/kg) or propranolol (2, 4 and 8 mg/kg) twice per day (09:00 and 16:00) every day during the 4 days of the PSD protocol. The PSD + cocaine group was pretreated with sterile saline. Rats were randomly distributed into seven distinct treatment groups (apomorphine: APO and propranolol: PRO): (1) PSD+coc; (2) PSD+APO120; (3) PSD+APO240; (4) PSD+APO480; (5) PSD+PRO2; (6) PSD+PRO4; (7) PSD+PRO8. At the end of the PSD period, rats were placed in wire mesh cages for behavioral observations.

Penile erection evaluation

The animals were observed in experimental wire mesh cages (15 x 31 x 26 cm) containing neither water nor food. The behavioral observations were carried out between 08:00 and 11:00 in a temperature-controlled room by trained observers with inter-rater reliability established in previous studies. The observers were unaware of group assignments of the rats under observation.

Penile erection (PE) was counted only when the rat stood on its hind limbs, bent its body forward, bent its

head down to reach the genital area, held and licked its penis in full erection and displayed hip movements. The erect penis was always visible. The proportion of rats displaying genital behaviors, the frequency of PE (total number of genital reflexes divided by the number of rats) and latency (time elapsed between the injection to the first genital reflex) were assessed for 60 minutes. Each animal was tested only once.

Statistical analysis

For statistical analysis of the proportion of animals displaying PE (expressed in percentage), the Chi-square method was used to assess differences between groups. Homogeneity of variance was assessed by the Bartlett test, and normal distribution of the data was assessed by the Kolmogorov-Smirnov test. When the Bartlett test showed absence of homogeneity of variance, data were square transformed. One-way analysis of variance (ANOVA) was used to analyze the frequency and latency data to determine possible group effects. In order to make specific group comparisons, the *post hoc* Tukey test was performed. Values shown are expressed as mean \pm standard error of mean (SEM). The value of $p < 0.05$ was used as the criterion for statistical significance.

RESULTS

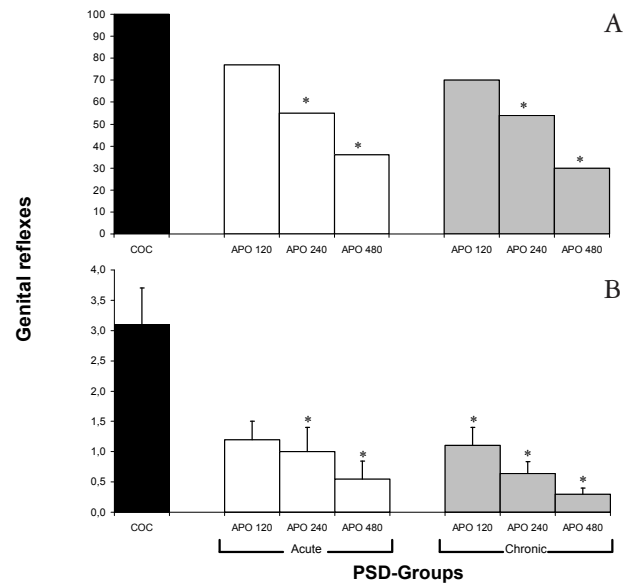
Effects of acute and chronic apomorphine administration

Figure 1 shows the effect of acute and chronic apomorphine administration in PSD+coc rats. As expected, a single cocaine injection (7 mg/kg) increased the proportion and frequency of PE after four days of PSD. Chi-square analysis indicates that there was no significant difference in the proportion of PE in rats that received the lowest dose of apomorphine (120 $\mu\text{g}/\text{kg}$). However, the high doses (240 and 480 $\mu\text{g}/\text{kg}$) administered acutely and chronically reduced PE compared to the PSD+coc group, as showed in Figure 1A.

As shown in Figure 1B, one-way ANOVA revealed significant group effects in the frequency of PE after acute and chronic apomorphine treatment [$F_{(6,64)} = 5.61$, $p < 0.001$]. Tukey *post hoc* test showed that acute (240 and 480 $\mu\text{g}/\text{kg}$) and chronic (all doses) apomorphine administration decreased the frequency of PE as compared to PSD+coc rats ($p < 0.05$). No statistically significant alteration was found in latency to first erection after acute or chronic apomorphine administration [$F_{(6,35)} = 1.58$, $p = 0.18$] (data not shown).

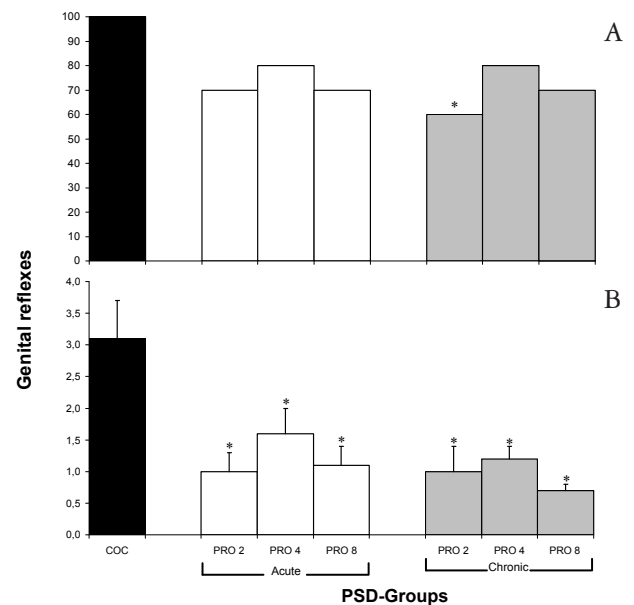
Effects of acute and chronic propranolol administration

In PSD+coc rats, chronic propranolol administration (2 mg/kg) induced a decrease in PE proportion. In the other propranolol groups, there was no significant alteration in the



* $p < 0.05$ relative to vehicle (ANOVA followed by Tukey test). Data are expressed as mean \pm SEM ($n = 10/\text{group}$).

Figure 1: Effects of acute and chronic apomorphine (APO 120, 240 and 480 $\mu\text{g}/\text{kg}$) administration on the proportion of animals (expressed in percentage) displaying PE (A) and on the frequency (number of genital events per rat) of penile erection (PE) in paradoxical sleep-deprived rats challenged with cocaine (B).



* $p < 0.05$ relative to vehicle (ANOVA followed by Tukey test). Data are expressed as mean \pm SEM ($n = 10/\text{group}$).

Figure 2: Effects of acute and chronic propranolol (PRO 2, 4 and 8 mg/kg) administration on the proportion of animals (expressed in percentage) displaying genital behaviors (A) and on the frequency (number of genital events per rat) of penile erection (PE) and ejaculation (EJ) in paradoxical sleep-deprived rats challenged with cocaine (B).

proportion of animals displaying erection when compared to PSD+coc animals, as shown in Figure 2A.

Figure 2B shows the effects of acute and chronic propranolol administration on PE frequency in rats challenged with cocaine. The ANOVA followed by Tukey test [$F_{(6,63)}=3.72$, $p<0.004$] revealed that the PE frequencies observed in the acute and chronic propranolol groups were significantly lower than PSD+coc rats. Examination of PE latency and one-way ANOVA revealed no significant difference between the groups after acute or chronic propranolol treatment [$F_{(6,47)}=1.04$, $p=0.41$] (data not shown).

DISCUSSION

These results demonstrate that acute and chronic apomorphine administration in rats challenged with cocaine reduces the proportion of animals displaying erection and PE frequency. Acute propranolol administration induced a decrease in PE proportion only at the lowest dose. However, PE frequency decreased after both acute and chronic propranolol treatment.

Several systems play critical roles in the regulation of male sexual behavior. It was recently demonstrated that dopaminergic agonists have facilitator properties for PE and may also enhance sexual drive⁽¹⁷⁾. Dopamine has facilitator effects on sexual motivation, copulatory proficiency and genital reflexes. It is well recognized that sexual stimulation leading to PE is controlled by different areas in the brain⁽²³⁾. Apomorphine induces dose-dependent increases in PE in PSD-treated rats (13) but does not modify EJ. In addition, the response to apomorphine decreased by increasing the drug doses. This biphasic effect of apomorphine has been previously shown⁽²⁴⁻²⁶⁾.

Studies suggest that the adrenergic system may exert a relevant function in male copulatory behavior⁽²⁷⁾. Systemic administration of subtype selective adrenoceptor agonist and antagonist allows discrimination of the roles of these receptors in the modulation of sexual behavior in male rats. Previous investigations have found that agonist and antagonist α -1, β -1, β -2 and antagonist α -2 reduce genital reflexes, and that only α -2 agonist does not induce alterations in sexual behavior⁽¹⁶⁾.

Cocaine, considered by most to be the world's most addictive drug, produces its powerful euphoric effect by acting on monoamine neurons to produce acute psychomotor activation and long-term changes, including psychosis and addiction. These effects are the result of cocaine-induced activity in dopaminergic pathways that project to the neostriatum and nucleus accumbens⁽²⁸⁾. Although cocaine has a variety of pharmacological actions, one of its major activities is binding the DA transporter to prevent dopamine uptake into presynaptic neurons, thus increasing synaptic concentrations of dopamine⁽²⁹⁾. This leads to behavioral effects in

animals and humans. However, an effect of cocaine on the noradrenergic system cannot be excluded⁽³⁰⁾.

In rats, cocaine administration induces a significant increase in stereotypical behavior⁽⁹⁾. PSD induces significant but heterogeneous effects in animals such as increased grooming. PSD has no effect on stereotypical behavior, locomotion or anxiety-like behaviors, but it significantly decreases rearing behavior. PSD potentiates the action of cocaine on stereotypical behaviors, suggesting alteration of central mechanisms. Thus, the behavioral effects of cocaine may be modified by PSD.

PSD induces a marked increase in percentage of rats displaying genital reflex events like PE and EJ after acute cocaine injection⁽¹²⁾. Evidence indicates that PSD results in dopaminergic supersensitivity^(5,8,31) and noradrenergic subsensitivity⁽¹¹⁾ and that central compounds alter the effects of PSD in rats⁽⁵⁻⁷⁾. Our group has observed increased stereotypical behavior induced by apomorphine⁽⁵⁾ and cocaine⁽⁹⁾ after 96 hours of PSD. The effects of cocaine⁽⁹⁾ and amphetamine⁽³²⁾ in PSD rats are consistent with previous findings that suggest participation of dopaminergic supersensitivity in behavioral alterations induced by PSD⁽⁵⁻⁷⁾. Facilitation of sexual behavior by cocaine⁽¹²⁾ and other dopaminergic drugs in PSD rats⁽¹⁰⁾ in addition to the present findings suggests that dopaminergic D_2 receptor supersensitivity may account for the PSD-induced effects on behavior altered by cocaine.

The aim of this study was to investigate whether a dopaminergic agonist and a noradrenergic antagonist could revert the occurrence of spontaneous genital reflexes potentiated by cocaine in PSD rats. The findings demonstrate that rats receiving acute and chronic treatment with apomorphine ($D_2>D_1$ dopamine receptors nonselective agonist) and propranolol (nonselective β -receptor antagonist) display reversion of dopaminergic supersensitivity and subsensitivity of the β -adrenergic receptor induced by PSD.

In summary, the present findings confirm our previous work, demonstrating that the combination of sleep deprivation and cocaine evokes a marked increase in genital reflexes in male rats, which suggests critical involvement of dopaminergic and noradrenergic systems in this phenomenon. Since sexual behavior and sleep are complex behaviors that result from a well-synchronized string of neurochemical events that in turn trigger a network of neurotransmitters, it can be assumed that any disruption of these elements may promote significant and broad consequences, such as peripheral and central nervous system alterations rather than modifying only two neurotransmitter receptor pathways.

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Metabolic parameters of rats prone to display wild-running of the audiogenic crisis and fights induced by REM-sleep deprivation

Parâmetros metabólicos de ratos propensos a demonstrarem corrida selvagem devido a crises audiogênicas e brigas induzidas por privação de sono REM

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ABSTRACT

Objective: Total sleep or selective REM-sleep deprivation (SD) increases aggressiveness. Rats that display fighting when submitted to sleep-deprivation are those that manifest wild running (WR), a panic-like flight that precedes tonic-clonic seizures induced by intense acoustic stimulation (audiogenic epilepsy). The incidence of WR-sensitive rats in the colonies around the world may reach 20%, which makes important to know the other characteristics of these animals for both sleep and other kinds of experimental research. Based on the report of their reduced body weight, we investigated some glucose metabolism parameters. **Methods:** Adult male *Wistar* rats were submitted to high-intensity acoustic stimulation (112dB, 60s) and then classified as WR-sensitive or WR-resistant rats. Glycemia and insulinemia, measured by glucometer and radioimmunoassay, respectively, and body weight were analyzed during three months. At the end of this period, intraperitoneal glucose and insulin tolerance tests were performed, and hepatic fat and glycogen content were also determined. **Results:** WR-sensitive rats showed proportionally less gain of body mass compared to the resistant ones ($p < 0.05$) in initial measurements, but this tendency did not sustain thereafter. Interestingly, fasting glycemia was significantly lower in the WR-sensitive group throughout the experiment, compared to WR-resistant rats. No significant differences between groups were found in insulinemia, peripheral glucose and insulin tolerance, and hepatic glycogen. However, WR-sensitive rats increased hepatic fat content significantly after a 12-hour fasting. **Conclusions:** Slow weight gain, decreased fasting glycemia and hepatic steatosis suggest a possible accelerated energetic metabolism or low resistance to food deprivation, which could partially explain the reduced body weight of WR-sensitive rats.

Keywords: Running; Sleep deprivation/physiopathology; Sleep deprivation/metabolism; Acoustic stimulation; Aggression; Panic/physiology; Blood glucose/metabolism; Adipose tissue/metabolism; Body weight; Seizures/metabolism; Epilepsy, reflex/physiopathology; Ener-

gy metabolism/physiology; Lactic acid/blood; Rats, Wistar; Animals

RESUMO

Objetivo: A privação total ou seletiva de sono REM aumenta a agressividade. Ratos que manifestam brigas quando submetidos a tal privação são os mesmos que manifestam a corrida selvagem (WR, *wild running*), uma fuga paniciforme que precede a convulsão tônico-clônica induzida pela estimulação sonora intensa (epilepsia audiogênica). A incidência de ratos sensíveis à WR nas colônias ao redor do mundo pode alcançar 20%, e isto torna importante conhecer as outras características desses animais tanto nos estudos de sono como em outras espécies de investigação experimental. Baseados no relato de que esses animais têm peso corporal reduzido, foram investigados alguns parâmetros do metabolismo da glicose. **Métodos:** Ratos *Wistar* machos adultos foram submetidos à estimulação acústica de alta intensidade (112 dB, 60s) e classificados como propensos ou resistentes à WR. A glicemia e insulinemia foram medidas por glicosímetro e por radioimunoensaio, respectivamente. O peso corporal foi avaliado por mais de três meses. Ao final do período, os testes de tolerância à glicose e à insulina administrada intraperitonealmente foram efetivados paralelamente às determinações do conteúdo hepático de gorduras e de glicogênio. **Resultados:** Os ratos propensos à WR mostraram ganhar relativamente menos massa corporal em relação aos animais resistentes ($p < 0,05$) no início das observações; entretanto, esta tendência não se manteve subsequentemente. De maneira interessante, a glicemia em jejum foi significativamente menor no grupo de animais propensos à WR quando comparados aos animais resistentes. Não foram encontradas diferenças significativas entre os grupos no tocante à insulinemia, tolerância à glicose e à insulina administrada periféricamente, assim como no glicogênio hepático. Contudo, os ratos propensos à WR aumentaram significativamente o conteúdo de gordura hepática após 12 horas de jejum. **Conclusões:** O ganho lento de peso, a redução das glicemias de jejum e a esteatose hepática sugerem a possibilidade de

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um metabolismo energético acelerado ou baixa resistência à privação alimentar, o que pode explicar parcialmente o peso corporal reduzido em ratos propensos à WR.

Descritores: Corrida; Privação do sono/fisiopatologia; Privação do sono/metabolismo; Estimulação acústica; Agressão; Pânico/fisiologia; Glicemia/metabolismo; Tecido adiposo/metabolismo; Peso corporal; Convulsões/metabolismo; Epilepsia reflexa/fisiopatologia; Metabolismo energético/fisiologia; Acido láctico/sangue; Ratos Wistar; Animais

INTRODUCTION

Sleep has an important restorative function and it is widely known that its deprivation may lead to aggressive and anti-social behaviors in humans⁽¹⁾. Dement⁽²⁾ established that such effect is determined by the suppression of the sleep state named Rapid Eye Movements-sleep (REM sleep), and this fact was subsequently observed by his group to also occur in rats⁽³⁾. Pharmacological manipulation of REM-sleep deprived (SD) rats disclosed the key role played by the central cholinergic and monoaminergic systems⁽⁴⁾. In addition, the hypothesis of dopaminergic hypersensitivity as an important mechanism responsible for the SD-induced aggressiveness and other effects was proposed⁽⁵⁾. The SD-induced fighting observed in rats is always defensive, and part of these episodes starts without an environmental detectable reason, according to Sandrin and Hoshino⁽⁶⁾. As panic attacks of the panic disorder present such characteristics, they hypothesized SD-induced fighting as a panic manifestation. The hypothesis was supported by the increase in SD-induced fighting promoted by hypertonic lactate administration⁽⁷⁾, a procedure used in panic disorder diagnosis⁽⁸⁾; whereas it is reduced by fluoxetine⁽⁹⁾, an antidepressant drug used successfully in the treatment of panic disorder⁽¹⁰⁾.

Panic is expressed by instinctive fight-or-flight behaviors⁽¹¹⁾. Interestingly, animals displaying panic-like fighting induced by SD also show a panic-like flight when they are submitted to high intensity acoustic stimulation⁽¹²⁾. This seems to indicate that part of the rats spontaneously exhibits an increased sensitivity for panic and express them when they feel threatened or submitted to conditions like SD. Suppression of REM sleep may be considered panicogenic because the number of panic-like flights induced by irritating electrolytic brainstem lesions increases proportionally to the SD period enhancement⁽¹³⁾.

The acoustic-induced flight is known as wild running (WR), since this episode is characterized by an explosive and uncontrollable running around the cage that may, sometimes, end with a tonic-clonic seizure. Such features lead it to be considered as an epileptic manifestation (audiogenic epilepsy) and to be used as an experimental model of epilepsy^(14,15), although no equivalent running occur in human epilepsies. Notwithstanding, it is possible to accept

that some pre-convulsive states are at the same time a panic state⁽¹⁶⁾. Indeed, antipanic procedures have shown to reduce the strychnine-facilitated WR in rats⁽¹⁷⁾.

Rats prone to display WR (WR-s) present some other peculiarities. They are reported to be more anxious when evaluated in the plus-elevated maze, to display higher behavioral inhibition index when exposed to predator odor⁽¹⁸⁾, and to have lower exploratory activity⁽¹⁹⁾. The assessment of other differences in WR-s rats figures to be nowadays important, since SD has been demonstrated to be involved and to affect multiple systems and processes of the organism. Audiogenic epilepsy is genetically determined and its spontaneous incidence may reach 20% of the population in rat breeding colonies around the world⁽²⁰⁾. Consequently, the probability of inclusion of WR-s animals in experimental samples is high, and it may introduce unknown bias that enhances the risk to obtain invalid conclusions. Indeed, as difference in body weight along WR-s ontogenetic development was previously reported⁽²¹⁾, such risk seems clear in studies involving glucose metabolism, appetite and energy expenditure, which seem to be the main factors involved in SD-related obesity and diabetes^(22,23). Additionally, it seems also important to point out that the knowledge of WR-s rat's characteristics is also interesting for other non-sleep-related studies. Overweight and obesity display a significant correlation with anxiety disorders⁽²⁴⁾, and the experimental approach to such subject using WR-s rats as a panic model evidently requires their full knowledge.

The present study aimed, therefore, to evaluate some aspects of the glucose metabolism of WR-s rats comparatively to WR-resistant (WR-r) rats kept in natural sleep condition in order to assess some pre-existing factor that contribute to sleep-deprivation-induced fighting. In order to do that, blood glucose and serum insulin levels, as well as the analysis of peripheral glucose and insulin sensitivity, were determined in both groups. In addition, hepatic fat and glycogen content were also determined.

METHODS

Subjects

The subjects were male adult Wistar albino rats, weighing 366 ± 56 g at the beginning of the experiments. They were bred at the UNESP Central Animal House in Botucatu (SP/Brazil) and maintained for at least one week before starting the experiments in our laboratory conditions. During this period, they were housed in groups of five animals in conventional polypropylene cages (40x32x16 cm) containing wood shavings on the floor, and with potable water and food (Labine chow) accessible *ad libitum*. Cages were kept at a temperature of $23 \pm 2^\circ\text{C}$ in a light/dark-cycle controlled

(12h/12h) room, being regularly cleaned every two days. The local Ethics Committee (CEP-FC) approved the procedures, which followed all the recommendations for ethical usage of animals stated by the *Colégio Brasileiro de Experimentação Animal* (COBEA).

Determination of WR susceptibility

The rats were initially tested for the wild-running susceptibility by means of the high-intensity acoustic stimulation routinely conducted in our laboratory. For this, the rat was placed in a wire mesh cage (23x32x23 cm) located inside a sound-proof chamber (33x25x19 cm) containing a ringing bell, an incandescent lamp bulb (60W), and a glass window through which complete visualization of the rat's behavior was possible. Fifteen seconds after the rat placement, the ringing bell was turned on, producing an acoustic continuous stimulation of 112 dB for up to 60 seconds, or until the rat emitted one clearly identifiable episode of WR. Operational definition of the WR behavior was previously described⁽²¹⁾, but briefly, it consisted of a high-speed circular running fit marked by galloping, jumping and collisions against the walls of the cage. The rats could exhibit the complete WR pattern in a short time span (two to four seconds) and when this occurred, the rat was categorized as WR-s and the stimulation was promptly interrupted. The WR-resistant (WR-r) rats behaved very differently in the trial, showing no signs of locomotor agitation or vigorous attempts to escape from the cage, thereby being used for comparisons with the WR-s animals.

After being tested, the two types of rats were distributed among home cages in such a way that each cage contained a similar number of WR-s and WR-r rats, already identified regarding their WR susceptibility with marks on the ears. Ten days were allowed for the recovery of the animals, during which no other experimental procedure was conducted.

Body weight measurements

The subjects were regularly weighed in an electronic balance for rats every two weeks, when all of them were 90, 104, 132, 146 and 160 days of age. Net body weights and weight gains over time were compared between the groups.

Blood glucose and serum insulin levels

Glucose and serum insulin levels were measured on the same days as when the animals were weighed. Fasted (12 hours) rats were anaesthetized with sodium thiopental (Thiopentax® 40mg/kg ip). After checking the absence of corneal and pedal reflexes, blood was collected from the tail of the rat for measurement of blood glucose levels with a glucometer ("one touch" - Johnson & Johnson). An additional blood sample (500 µL) was collected and the serum, obtained by

centrifugation, was used to measure the insulin levels by radioimmunoassay (RIA), utilizing a Guinea Pig anti-rat insulin antibody and rat insulin as standard. Another set of WR-s (n=11) and WR-r (n=11) rats had their blood collected without food deprivation for the measurement of glycemia in fed animals (day 160).

Intraperitoneal glucose tolerance test (ipGTT)

This test was performed, as previously described^(25,26), two weeks before the day of euthanasia in order to avoid interference in the measurement of metabolic parameters. Thus, the fasted (12 h) rats were anaesthetized at 146 days of age, as described above. After checking the absence of corneal and pedal reflexes, unchallenged blood samples (time 0) were obtained from the rat's tail. Immediately, 50% glucose (2 g/kg b.w., i.p.) was administered, and blood samples were collected at 30, 60, 90 and 120 minutes from the tail tip as to determine glucose concentrations.

Intraperitoneal insulin tolerance test (ipITT)

One week before euthanasia, the 153-day-old rats underwent ipITT, according to Rafacho et al.^(25,26). Briefly, the fed rats were anaesthetized and a sample of blood was collected from the tail tip for glucose measurement at time 0. Human recombinant insulin (Biohulin® N) equivalent to 2 units/kg of body weight was then administered by intraperitoneal injection. Further samples were collected at 5, 10, 20 and 30 minutes in order to measure blood glucose. The constant rate for glucose disappearance (*Kitt*) was calculated as previously described^(25,26).

Hepatic glycogen and lipids content

Determination of hepatic glycogen was performed in fed and fasted animals, according to Lo et al.⁽²⁷⁾ with some modifications^(25,26). For hepatic fat content measurement, a tissue fragment of around 100 mg was obtained and homogenized (Polytron PT 1200) in 7.5 mL methanol/chloroform-buffer (1:2, v/v). The samples were then maintained overnight at room temperature for lipid extraction and, on the day after, were filtered and washed with chloroform. After drying, the fat was measured with an analytical balance.

Data analysis

Results from the WR-resistant and WR-sensitive rats were compared by means of the following statistical tests: One-way ANOVA with *post-hoc* Bonferroni Multiple Comparison test was used for the repeated measures of glycemic and insulinemic levels; ipGTT, ipITT, hepatic fat and hepatic glycogen were analyzed by the Student's *t* test for two independent samples. Body weight and weight gain results yielded marked variable values, as they tended to increase

over time. Thus, they were compared in isolation for each measurement by the Student's *t* test. Two-way ANOVA with *post-hoc* Bonferroni Multiple Comparison test was used to analyze the glycogen and fat hepatic contents in the rats grouped by WR susceptibility and fed *versus* rats deprived from food. All tests were performed with the help of a specific computer software (Statistica/Statsoft and InStat), with a 5% level of significance.

RESULTS

Three WR-s rats died at around 132 days of age, probably due to vulnerability to anesthesia and blood collection or other unknown reasons, and data from one WR-r rat were missed. Therefore, until the fourth body weight measurement and serum collection, each group was composed of ten individuals. Subsequent results, including glucose and insulin tolerance tests, liver composition analyses were performed with seven WR-s rats and nine WR-r ones.

Body weight measurements

WR-r and WR-s rats exhibited a biphasic pattern of body weight variation characterized by a slow increment until 132 days old, and by a more intense weight gain thereafter. This aspect seemed to be more evident among the WR-sensitive rats, and coincided with the deaths of three sensitive animals. In order to avoid biased results during the last 14 days of weight evaluation, the percentage of weight gain was determined taking as 100% the weight at 90 days old (Figure 1). The weight gain of WR-s animals was found to be lower during the first two weeks ($t=1.787$; $df=13$, $p=0.048$). The following measurements showed a similar statistical trend ($t=1.390$; $df=13$; $p=0.09$), but this tendency was not sustained along the subsequent periods.

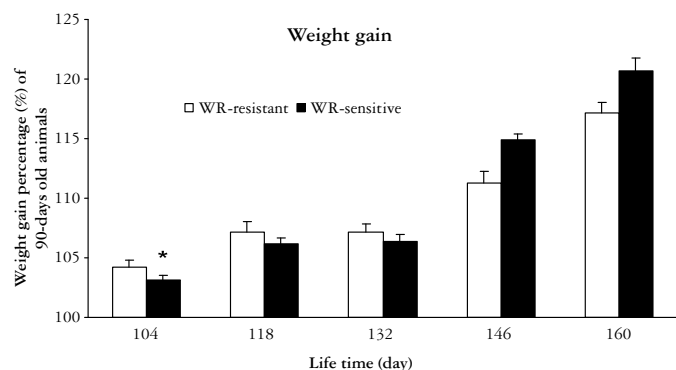


Figure 1: Percentage of weight gain from the 90 days of age in WR-sensitive and in WR-resistant rats. The asterisk indicates statistically significant difference (Student's *t* test, $p<0.05$).

Blood glucose and serum insulin levels

The blood glucose and serum insulin levels of each group are presented in Figure 2. The experimental groups differed

significantly [$F(1, 14) = 4.74$; $p<0.047$] regarding the fasting blood glucose levels, with the WR-s rats presenting a reduced mean blood glucose value along the repeated measures (83.4 ± 1.9 mg/dL) when compared to the WR-r rats (89.8 ± 1.4 mg/dL) (Figure 2A). However, the glycemia in fed status did not show statistical difference between WR-sensitive and WR-resistant groups, nor did the fasting serum insulin levels determined along the experiment (Figure 2B and C, respectively).

Intraperitoneal glucose tolerance test (ipGTT) and intraperitoneal insulin tolerance test (ipITT)

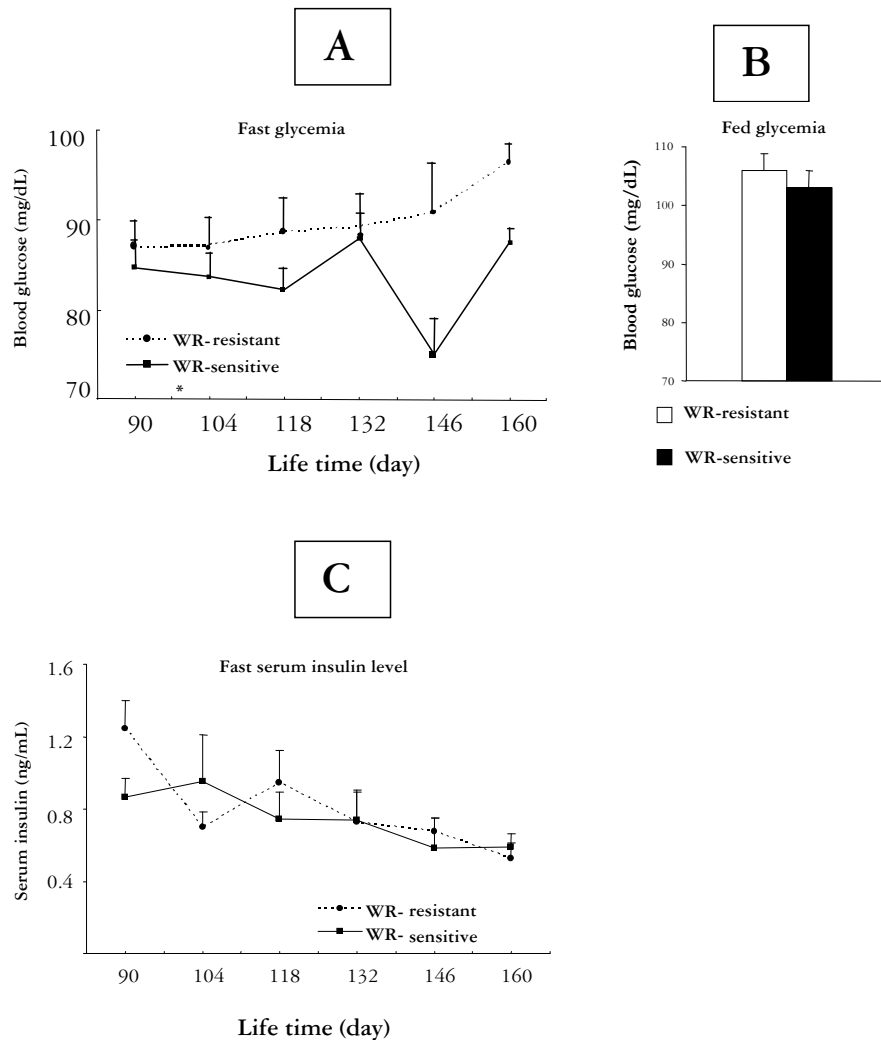
Figure 3 shows the results of glucose tolerance (upper panel) and of insulin tolerance (lower panel) tests. The mean blood glucose levels during *ipGTT* were similar for WR-r and WR-s rats (Figure 3A), and the area-under-curve (AUC) for the experimental groups were not statistically different (Figure 3B). The mean blood glucose levels during *ipITT* were similar along the experiment in both groups (Figure 3C), and the constant rate for glucose disappearance exhibited no differences between WR-r and WR-s rats (Figure 3D).

Hepatic glycogen and lipid content

The results of the hepatic glycogen and lipid determinations are presented in Figure 4. With regard to hepatic glycogen content, statistical analysis failed to show differences between WR-r and WR-s rats both in fasting and fed conditions. During 12 hours of food deprivation, the reduction of hepatic glycogen was significant both in WR-r ($t=2.498$; $p<0.05$) and WR-s ($t=2.706$; $p<0.05$) rats, according to the *post-hoc* Bonferroni Multiple Comparison tests. The hepatic lipid content observed in fasting and fed conditions did not present statistical difference between WR-r and WR-s rats. However, the average of hepatic fat content after the 12-hour fasting increased by 27 and 38% in WR-r and WR-s rats, respectively, and according to the *post-hoc* Bonferroni Multiple Comparison test, this was significant only for the WR-s rats ($t=2.669$; $p<0.05$).

DISCUSSION

Susceptibility to WR in rats showed to be associated with a trend to lower weight gain. Such characteristic cannot be attributed to the fail in insulin secretion and action, since these animals exhibit normal glucose and insulin sensitivity peripherally. When submitted to fasting periods, WR-s rats presented decreased blood glucose levels and hepatic steatosis, suggesting that they are somehow deficient in resisting to starvation. Based on such findings, it may be hypothesized that WR susceptibility is associated with a more accelerated metabolic rate or with reduced energetic stocking.



*significantly different *vs.* WR-resistant group. $p < 0.05$; ANOVA.

Figure 2: Fasting and fed blood glucose and serum insulin levels in WR-resistant and WR-sensitive groups. Note the significant reduction of glycemic values in WR-sensitive animals as compared to WR-resistant rats (A). Fed glycemia values did not differ between groups (160 day) (B), as well as insulinemia values (C). Data are means \pm S.E.M.

Reduced body weight has been observed in WR-s rats in a previous study; however, these rats were less manipulated and only weighed at 153 days of age⁽²¹⁾. In the present study, body masses were determined more closely and only a trend toward reduced weight gain in WR-s rats was detected until the fourth measurement. Beyond differences in experimental manipulations, homing condition, grouping only WR-s, may also be considered as responsible for the absence of a clear-cut weight difference. As WR-s animals are submissive, they eat less when kept with WR-r in the same cage⁽²¹⁾. After the fourth evaluation day, 33% of the animals of this group died, increasing artificially the mean weight gain due the elimination of low gain score animals. Thus, the data collected at the beginning of the experiment seems to be more representative of weight development. In addition, the deaths reduced the population density in the home-cages,

contributing to the weight gain of rats^(28,29). The death of WR-s rats was remarkable and probably occurred due to vulnerability to anesthesia. Although another unknown reason may be hypothesized, respiratory reflex inhibition promoted by thiopental seems to be the major factor, because its substitution by ketamine plus xylazine in our more recent study (unpublished data) showed to reduce the number of deaths significantly.

The study of glucose metabolism is frequently useful to assess the mechanisms underlying the regulation of body weight⁽³⁰⁾, as evidenced by the relationships between obesity and diabetes⁽³¹⁾. The WR-s rats are normoglycemic when fed, but exhibited decreased blood glucose levels after 12 hours of fasting. Such profile is not likely to be affected by the glycemic control exerted by the endocrine pancreas, because the insulin secretion was equivalent between the

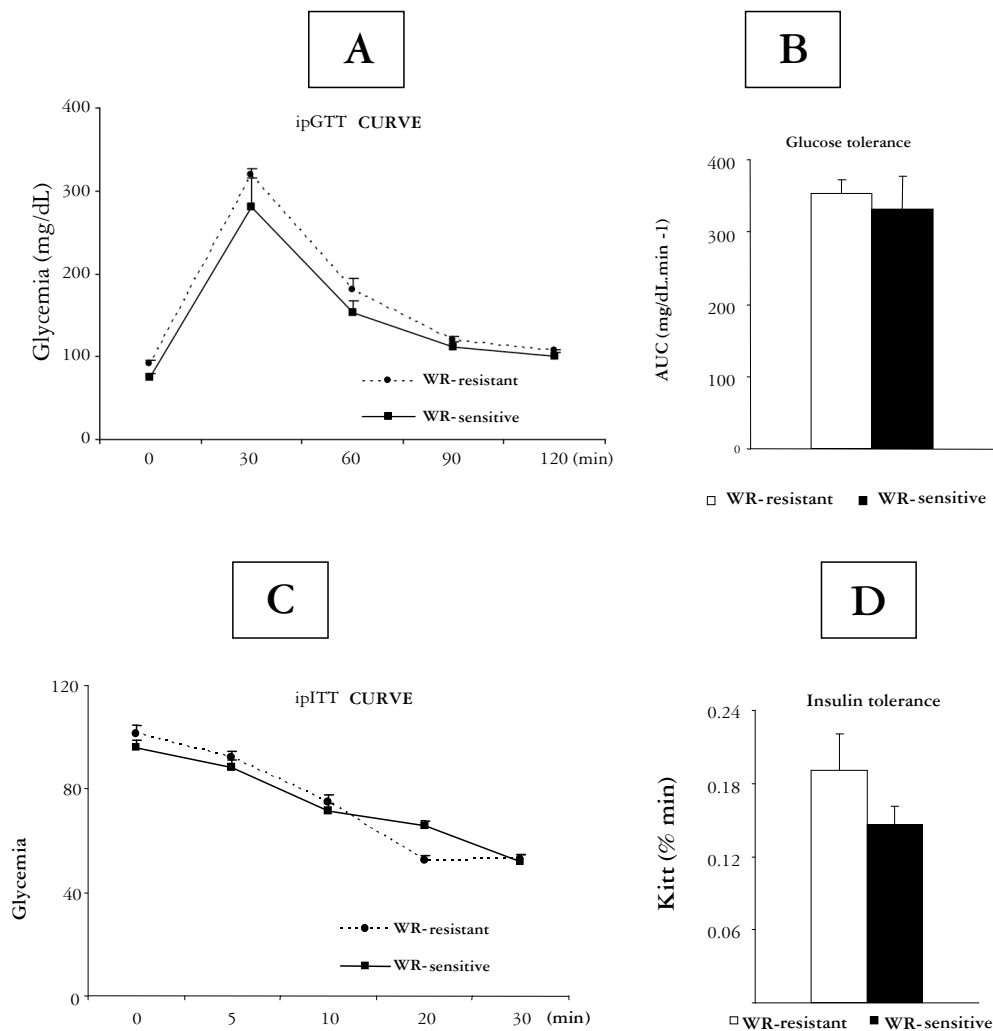


Figure 3: Intra-peritoneal glucose and insulin tolerance tests. Upper panels: the *ipGTT* curves (A) and area-under-curve (AUC) (B) for WR-sensitive and WR-resistant rats (right). Lower panels: *ipITT* curves (C) and the constant for glucose disappearance (Kitt) for the experimental groups (D). Data are expressed as Means \pm S.E.M.

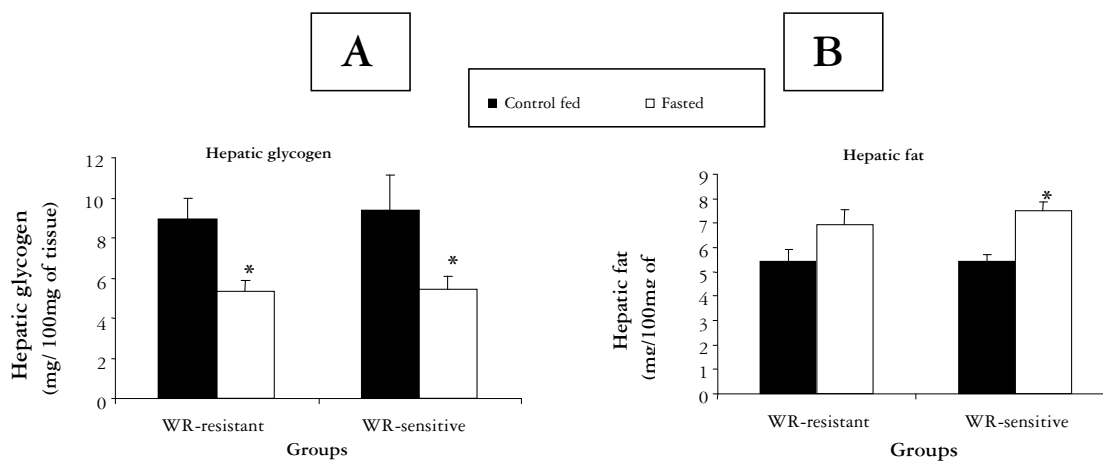


Figure 4: Hepatic glycogen (A) and fat (B) content in WR-resistant and WR-sensitive rats. Data are expressed as means \pm S.E.M. The asterisk indicates that fasted rats differ significantly from the control-fed rats according to ANOVA and *post-hoc* Bonferroni Multiple Comparison tests ($p < 0.05$).

groups. Differences in peripheral actions of insulin were discarded as well, since the sensitivity to insulin was similar in both types of rats. In this connection, the glucose tolerance also showed no alterations related to the WR susceptibility.

The hepatic content of glycogen and lipids may indicate the consumption rate of energetic substrates, since the liver mobilizes these reserves to provide constant supplies to the tissues⁽³²⁾. Botion and Doretto⁽³³⁾ found reduced contents of hepatic glycogen in audiogenic-prone rats without food deprivation, suggesting that abnormalities in the stocking or degradation could be associated with propensity to seizures. This was not observed in WR-s rats, comparatively to WR-r rats, of the present study. However, as expected, the glycogen storage reduced significantly between fed and fasting status in both groups, pointing to a demand of this substrate along this period. Therefore, fasting hypoglycemia observed in the WR-s rats of the present study is probably due to augmented energy consumption. In fact, being equal initial (fed state) and remaining (fasting state) hepatic glycogen content in both groups, lower blood glucose level may only result from its higher utilization. WR-s rats are more anxious, as cited before, and anxiety is an emotional state related to threatening danger⁽³⁴⁾, which is associated with increased circulating levels of catecholamines and corticoids. While catecholamines are known to trigger glycogenolysis in the liver, the corticoids activate gluconeogenesis, but the action of the catecholamines on the energy expenditure is present in other tissues, leading to increased usage of blood glucose. This could explain, at least partially, the reduced levels of blood glucose in this condition without alteration in peripheral insulin sensitivity and/or glucose tolerance. Increased levels of anxiety associated with a greater WR proneness in genetically selected strains seems to enhance more the energetic mobilization, reducing inclusive hepatic glycogen content, as observed by Botion and Doretto. Such metabolic frame fits the trend to reduced weight in WR-s rats.

In contrast to the WR-r rats, the WR-s rats showed increased hepatic fat content under 12-hour fasting, which can be interpreted as liver steatosis⁽³⁵⁾. Steatosis occurs due to the mobilization of fat acids from the adipose tissue with consequent triglyceride formation in the hepatocytes⁽³⁶⁾. This content is progressively converted into low-density lipoproteins (LDL) to be consumed by the muscles generally after 16 hours of starvation⁽³⁷⁾, but the WR-s animals presented steatosis earlier – after 12 hours. This could be explained by the rapid fat mobilization from the adipose tissue, or by the slow LDL synthesis in the liver. Botion and Doretto⁽³³⁾ reported that WARs present generally reduced lipid metabolism, with a slower lipolytic rate in the peripheral adipose tissue. If such deficit is associated with seizure proneness, it

may be hypothesized that WR-s rats presented steatosis due to slow LDL formation.

Therefore, the results observed herein such as the trend to slow weight gain, reduced fasting blood glucose levels, low resistance to food deprivation and hepatic steatosis converge to the suggestion of an accelerated metabolic rate in the WR-s rats. This hypothesis is feasible since our previous study showed that the susceptibility to WR may be interpreted as a propensity to display panic in rats^(12,21), and it is accompanied by higher levels of anxiety⁽²²⁾. Such emotional states have important metabolic outputs that include the release of catecholamines and corticoids⁽³⁸⁾. These hormones can increase the metabolic rate, activate catalytic reactions and affect ingestion^(25,39,40). Thus, future studies focusing on the investigation of metabolic rate, ingestion pattern and hormonal differences should be associated with WR susceptibility in rats.

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Prevalence of flight response in female rats: does it explain the reported gender difference in sleep deprivation related aggressiveness?

Prevalência da resposta de fuga em ratas: isto explica a diferença de gênero na agressividade da privação de sono?

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ABSTRACT

Objective: Rapid Eye Movement Sleep Deprivation (RSD) increases aggressiveness and is manifested in male rats as fighting episodes. The determination of the role played by such fights should constitute an important contribution toward assessing the adaptive function of this type of sleep. Nevertheless, female rats do not exhibit such behavior. Recent data indicate that RSD-induced fighting and wild-running flights are panic manifestations, thus advancing the hypothesis that female rats do not fight because their prevalent response in panic situations is flight. **Methods:** Therefore, 10 male and 12 female rats were acoustically kindled at 14 days of age, and their susceptibility to display wild-running was evaluated at 30, 60 and 90 days of age. **Results:** Six males and ten females produced respective totals of 12 and 30 wild-running episodes (chi-square test, $p=0.0003$), with mean (\pm standard error) of 0.60 ± 0.21 and 1.41 ± 0.24 episodes/rat. (ANOVA/MANOVA, $p=0.0169$). **Conclusion:** The results validate the hypothesis and are concordant with the higher frequency of panic attacks observed in women as compared to men.

Keywords: Sleep, REM; Sleep deprivation/physiopathology; Aggression/physiology; Panic/physiology; Rats

RESUMO

Objetivo: A privação do sono REM aumenta a agressividade expressa pelos ratos machos em forma de episódios de brigas. O esclarecimento do papel funcional destas brigas pode ser uma contribuição importante para a determinação da função deste tipo de sono. Apesar deste fato, as fêmeas não apresentam esse tipo de brigas. Dados recentes indicam que as brigas induzidas pela RSD e as fugas por corridas selvagens (*wild running*) dos ratos são manifestações de pânico. Com base neste dado, objetivou-se testar a hipótese de que as fêmeas não manifestam brigas induzidas por essa privação pelo fato de a fuga ser a manifestação prevalente de pânico. **Métodos:** 10 ratos machos e 12 fêmeas foram abrasados acusticamente aos 14 dias de idade e sua suscetibilidade para manifestar as corridas selvagens foram avaliadas com 30, 60 e 90

dias de idade. **Resultados:** Seis machos e dez fêmeas apresentaram, respectivamente, os totais de 12 e 30 episódios de corrida (teste qui-quadrado, $p=0,0003$), com média (\pm erro padrão) de $0,60\pm 0,21$ e $1,41\pm 0,24$ episódios/rato (ANOVA/MANOVA, $p=0,0169$). **Conclusão:** Os resultados validam a hipótese testada e são concordantes com a maior frequência de ataques de pânico que se observa nas mulheres em relação aos homens.

Descritores: Sono REM; Privação do sono/fisiopatologia; Agressão/fisiologia; Pânico/fisiologia; Ratos

INTRODUCTION

Sleep, composed of two different functional states of the central nervous system in mammals and birds, seems to play some important adaptive roles because total or selective deprivation of the state manifested by desynchronized waves in the electroencephalogram (paradoxical or REM-sleep) have been reported, among other effects, to increase aggressiveness which is expressed as anti-social behaviors in humans^(1,2). In male rats, such aggressiveness induced by REM-sleep deprivation (RSD) is expressed as an increase in the number of fighting episodes spontaneously displayed⁽³⁾ or induced by electrical footshocks⁽⁴⁾ or dopamine agonistic drugs⁽⁵⁾. The assessment of the nature and role played by such fights constitutes a key point for ascertaining the adaptive role of REM-sleep. Nevertheless, it was reported⁽⁶⁾ that such increase in aggressiveness does not occur in female rats treated with apomorphine at doses inducing fighting in male animals. Hormonal differences were advanced as the possible mechanism responsible for this intersexual difference. A substantial volume of data has documented that in males aggressiveness is expressed with greater intensity due to testosterone, whereas females

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display aggressiveness at similar intensities only in the early period of lactation⁽⁷⁾.

Fighting in rats may be offensive or defensive and can be determined by specific behavioral patterns assessed ethologically⁽⁸⁾. Ethograms of the fights induced by RSD in male rats have been shown to be always defensive, while some of them were found to initiate without a detectable environmental cause, suggesting that this behavior may be related to panic⁽³⁾. This possibility was supported by the reduction of fights with fluoxetine⁽⁹⁾, an antidepressant drug used in panic disorder treatment⁽¹⁰⁾, and by their increase promoted by lactate administration⁽¹¹⁾, a procedure used to trigger panic attacks and diagnose panic disorder⁽¹²⁾. The possibility of RSD-induced fights as panic manifestation makes it difficult to explain why female rats do not display it. The possibility of females being exempt from panic may be discarded because women reportedly display panic crises at a higher frequency than do men⁽¹³⁾.

Panic is expressed as flight or fight behavior. Male rats that fight when submitted to RSD are those that display wild running (WR), a flight response induced by intense acoustic stimulation⁽¹⁴⁾. Wild running episodes sometimes end with a tonic-clonic seizure, a fact that has led to their classification as pre-convulsive manifestations of audiogenic epilepsy⁽¹⁵⁾. Given that panicolytic procedures reduce this flight response while panicogenic ones augment it^(16,17), it seems that brainstem activation promotes both panic and convulsive manifestations when activation becomes excessive^(18,19). Accordingly, RSD was observed to facilitate panic attacks in panic disorder bearers⁽²⁰⁾ and to increase WR episodes proportionately to the sleep deprivation period in rats⁽²¹⁾. The conception of WR as a panic expression leads to the hypothesis that a female rat does not fight when subjected to RSD because its prevalent panic response is flight.

Aiming to find supportive data for this hypothesis, the present study evaluated whether female rats display some difference in the expression of wild-running flight, compared to males, when submitted to an equivalent panicogenic condition. For this, male and female rats were submitted to a high intensity acoustic stimulation (acoustic kindling) during the lactation period in order to render them prone to an audiogenic crisis. Wild-running parameters displayed in both sexes were evaluated at three moments during their development.

METHODS

Subjects

All procedures recommended by the *Colégio Brasileiro de Experimentação Animal* (COBEA) were followed, and the study started only after approval by the Local Ethics Committee.

Twenty-two Wistar rats were used. They were obtained by reproductive crossings of adult males and females provided by the Central Animal Breeding House (Biotério Central) of Universidade Estadual Paulista, Botucatu Campus. These adults had been previously tested for audiogenic crisis proneness and only the WR-resistant rats were bred. Only newborn rats weighing 15 g or more at 14 days old were selected for kindling. The animals were marked for individual identification, kindled and returned to the cage of their respective dam. They started to live in conventional polypropylene cages after weaning (21 days old), in groups of four animals with proximal ages. These cages were maintained in a silent room, with cyclic light (7:00-19:00) and controlled temperature (22-24°C). Food and potable water were kept *ad libitum* while cages were cleaned and wood shavings replaced on alternate days.

Kindling

Each animal was moved into a wire mesh cage (38x18x18 cm) of acoustic kindling when 14 days old and were kept inside a soundproof wooden box (44.5x38.5x33.0 cm) with a fluorescent lamp (40W) and a 125 dB, 10 KHz, sound-generating speaker. All these devices were maintained inside another soundproof cage. The continuous acoustic stimulation for 8 minutes was started 15 seconds after placing the animal in the cage and closing the soundproof wooden boxes. Acoustic stimulation parameters were chosen based on a kindling study reported in the literature⁽²²⁾. Ten males and 12 females were submitted to this acoustic kindling stimulation.

Audiogenic crisis evaluation

Audiogenic crisis was determined at 30, 60 and 90 days of age. Such evaluation was made in a translucent plexiglass cage (30.5x30.0x18.5 cm) maintained inside a soundproof wooden cage (48.0x48.0x28.0 cm) provided with a glass window and illuminated by an 11-watt incandescent light bulb for behavioral observation and video recording. Once inside the test cage, 15 seconds were allowed for exploration and a 103 dB, 200 Hz acoustic stimulation was presented for 60 seconds, as previously described⁽¹⁴⁾. WR was operationally defined as explosive high-speed running around the cage that evolves to galloping and then to jumping and collisions against cage walls. Seizures were defined as a generalized muscular contraction with postural hind-limb extension (tonic manifestation) and by intermittent strong kicking movements (clonic manifestation).

Data analysis

Wild Running frequencies computed in the male and female groups were compared by the chi-square test while

means were compared by ANOVA/MANOVA. The statistic program from Statsoft was used at 0.05 significance level.

RESULTS

All animals were found healthy at the end of observations, thus indicating that they tolerated the acoustic stimulation applied during kindling. The WR patterns were similar in males and females. The number of animals displaying WR increased progressively through evaluation moments; 4, 4 and 9 WR in the female group, respectively, at 30, 60 and 90 days of age, with many of them manifesting two or more running episodes in the same test. Corresponding numbers in the male group were 0, 2 and 4 episodes, respectively, at the same ages.

As shown in table 1, the proportions of WR-prone males (60%) and females (80%) were statistically equivalent. Twelve WR episodes were observed in all tests performed on male rats, whereas 30 WR episodes were counted in the 36 evaluations (3 tests *versus* 12 animals) of the female group. This difference was found to be significant ($p=0.0003$) and determined by the relatively large number of females that displayed WR at two or more different ages and in two or more episodes under the same test. The mean number of WR episodes displayed by males was significantly lower than the value found in the female group. Convulsive seizures at the end of WR episodes occurred in both sexes with equivalent frequencies and were not related to WR frequencies.

DISCUSSION

The acoustic kindling imposed in the present study can be considered effective because 60% of males and 83% of females were found to be WR-prone. These percentages of WR incidence are higher than those of spontaneous incidence that reach at maximum 20% of the population of rat colonies around the world⁽²³⁾. As these high incidences do not differ significantly between males and females, it may be concluded that male and female rats display equivalent susceptibility to acoustic kindling. Loss of internal cochlear capillary cells and disorganization of external ones, which are highly sensitive to acoustic stimulation⁽²⁴⁾, seem to be part of the mechanism responsible for the acoustic kindling presently observed. The concomitant involvement of the inferior colliculus in this process should be highlighted, because its lesion or chemical blockade antagonizes audiogenic crisis manifestation, whereas chemical or electrical stimulation facilitates it⁽²⁵⁾. The reason why acoustic stimulation for kindling was not effective in all animals submitted to it is the other aspect of the question concerning effectiveness. Acoustic kindling depends on a critical postnatal period of susceptibility in which tonotopic bands of frequencies develop in the inferior colliculus⁽²⁶⁾. Inter-individual differ-

Table 1: Wild-running parameters in male and female rats acoustically kindled at 14 days of age[§]

	Males	Females
Number of animals	10	12
Number and % of WR prone rats	6 (60%)	10 (83%)
Total number of WR episodes / number of evaluations	12/30	30/36*
Mean number of WR in the group (\pm standard error)	0.60 \pm 0.21	1.41 \pm 0.24**
Number of rats with WR plus seizures	2 (20%)	4 (33%)

[§]Wild-running (WR) evaluations were made at 30, 60 and 90 days of age using high intensity acoustic stimulation.

*Significant (chi-square test, $p=0.0003$); **significant (ANOVA/MANOVA, $F=6.2178$; $p=0.0169$).

ences in the development rate are common facts and explain non-kindled animals as stimulated when they were not in the critical period of susceptibility.

The main finding in the present study is the significantly higher number of WR episodes displayed by female rats compared to males submitted to the same procedures of kindling and evaluations. If one considers this behavioral pattern as a panic flight, as discussed before, it seems possible to state that, once rendered prone to panic manifestation and kept in similar panicogenic conditions, females display running crises more frequently than males. In other words, WR seems to be the most used defensive manifestation of female rats in threatening conditions that increase anxiety and culminate in panic. Prevalence of manifestation seems to be an adequate term, because greater frequency of use does not imply absence of the alternative manifestation. In fact, female rats fight aggressively during the first *post-partum* days⁽⁷⁾ or when grouped and submitted to electrical footshocks [K.H., personal observations]. Such prevalence seems to involve lower triggering thresholds of the neural circuitries, which promote readiness to flight and inhibit the fighting manifestation. These aspects of female rats seem to derive from an evolutionary selection conditioned by the presence of aggressive males. This may explain why female rats do not fight when deprived from REM sleep. This property seems to play a secondary adaptive role after the first lactation days, when litter movements and demands impose REM-sleep fragmentation and reduction⁽²⁷⁾. On the other hand, male rats that evolved under a selective pressure based on aggressiveness seem to have lower triggering thresholds for fighting, but higher ones for flight. When faced with overcrowding, specifically the sleep fragmentation and reduction imposed by its high competition level, increased aggressiveness may be advantageous.

The finding that female rats exhibit WR more frequently than males is concordant with some previous data demonstrating their higher susceptibility to an audiogenic crisis⁽²⁸⁾.

These data also corroborate the higher frequency of panic disorder crisis in women⁽¹³⁾. This aspect leads us to consider female rats prone to wild running as a potential valuable model to study the intersexual difference in panic disorder manifestation.

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Clinical and polysomnographic profile of sleep-disordered breathing patients according to the treatment indicated

Perfil clínico e polissonográfico de pacientes com transtorno respiratório obstrutivo do sono segundo o tratamento indicado

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ABSTRACT

Objective: To compare clinical and polysomnographic profiles of patients with obstructive respiratory sleep disorder according to the type of recommended treatment. **Methods:** A retrospective study of 131 patients treated at the sleep disorders outpatient clinic of Faculdade de Medicina do ABC, between August 2003 and July 2008. The indication of treatment considered both clinical and polysomnographic criteria. The patients were divided into clinical and surgical treatment groups. **Results:** Of the 131 patients, 59.5% were male and 40.5% were female with an average age of 48.9 ± 13.2 years. Clinical treatment was recommended for approximately 71.8% of the patients, and surgical treatment was recommended for approximately 28.2% with a prevalence of continuous positive airway pressure (CPAP) (60.6%). In both groups, there was male prevalence, and the average age was between forty and fifty years with no statistical significant differences between the groups. In the group receiving clinical treatment, the majority of the patients had moderate and severe obstructive sleep apneas (OSA). No statistical differences were found between the two groups in terms of clinical and polysomnographic variables. **Conclusion:** The majority of the patients were clinically treated with CPAP prevalence. However, almost one-third of the patients needed surgical intervention, with a high prevalence of anatomical abnormalities in this group. The type of recommended treatment was not influenced by clinical or polysomnographic parameters, which suggests that the presence of anatomical abnormalities in the upper respiratory tract or craniofacial region may be the main criterion for recommending surgical treatment.

Keywords: Sleep apnea, obstructive/surgery; Polysomnography; Positive-pressure respiration; Pharynx/surgery; Continuous positive airway pressure

RESUMO

Objetivo: Comparar o perfil clínico e polissonográfico em pacientes com transtorno respiratório obstrutivo do sono, segundo o tipo de tratamento indicado. **Métodos:** Estudo retrospectivo com 131 pacientes atendidos no ambulatório de transtornos respiratórios do sono da Faculdade de Medicina do ABC, entre Agosto de 2003 e Julho de

2008. A indicação do tratamento considerou critérios clínicos e polissonográficos. Os pacientes foram divididos em dois grupos: tratamento clínico e tratamento cirúrgico. **Resultados:** Dos 131 pacientes, 59,5% eram do sexo masculino e 40,5% eram do sexo feminino, com idade média de $48,9 \pm 13,2$ anos. Cerca de 71,8% receberam indicação de tratamento clínico e 28,2% de tratamento cirúrgico, sendo a pressão positiva contínua nas vias aéreas (CPAP, do inglês *continuous positive airway pressure*) a mais indicada (60,6%). Nos dois grupos houve predomínio de homens e a faixa etária média esteve entre a quarta e quinta décadas de vida, porém sem diferença estatística entre eles. No grupo submetido a tratamento clínico, houve predomínio de pacientes com Síndrome da Apneia Obstrutiva do Sono (SAOS) moderada e grave. Não houve diferenças estatísticas entre os dois grupos em relação às variáveis clínicas e polissonográficas estudadas. **Conclusão:** A maior parte dos pacientes foi tratada clinicamente, com predomínio da CPAP. Porém, quase um terço dos pacientes necessitou de intervenção cirúrgica, mostrando a alta prevalência de alterações anatômicas nesse grupo. A indicação do tipo de tratamento não foi influenciada pelos parâmetros clínicos ou polissonográficos, mostrando que a presença de alterações anatômicas sobre a via aérea superior ou craniofaciais talvez seja o principal critério de indicação do tratamento cirúrgico.

Descritores: Apnéia do sono tipo obstrutiva/cirurgia; Polissonografia; Respiração com pressão positiva; Faringe/cirurgia; Pressão positiva contínua nas vias aéreas

INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by recurring episodes of partial or total obstruction of the upper respiratory tract during sleep. The resulting irregular respiratory pattern causes oxyhemoglobin desaturation and interrupted sleep⁽¹⁾.

Defined by the presence of excessive daytime sleepiness and apnea-hypopnea index (AHI) greater than 5 per hour in polysomnography (PSG), the prevalence of OSA is estimated to affect 4% of middle-aged men and 2% of middle-aged women⁽²⁾.

Study carried out at Faculdade de Medicina do ABC – FMABC, Santo André (SP), Brazil.

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Clinically, OSA is characterized by snoring, pauses in breathing, excessive daytime sleepiness, cognitive changes (deficits in concentration and memory), mood fluctuations, nocturia, gastroesophageal reflux, fatigue, morning headaches, and decreased libido⁽³⁾.

Currently, OSA is considered a Public Health problem because it increases the risk of systemic arterial hypertension, cardiovascular complications, road accidents, and premature death if it is not treated⁽⁴⁾.

The physiopathology of the disease is multifactorial: it involves anatomical abnormalities in the upper airway tract and craniofacial region and neuromuscular changes in the pharynx^(5,6).

Obesity is the main factor associated with OSA, since the fatty tissue is deposited around the upper respiratory tract and predisposes it to collapse⁽⁷⁾.

OSA is diagnosed through the patient's clinical history, polysomnographic readings (PSG), and the criteria established in the 2005 International Classification of Sleep Disorders (ICSD)⁽⁸⁾.

The OSA treatment must be multidisciplinary and designed to eliminate obstructive respiratory events. This will restore normal sleep patterns and adequate arterial blood oxygen levels. Clinical measures, known as sleep hygiene, are first implemented in conjunction with recommendations of weight loss, hormonal illnesses treatment, sedative substances elimination (e.g., alcohol and tranquillizing medication), lateral decubitus, topical steroids usage when necessary, and anti-reflux measures.

The treatment of choice for OSA is continuous positive airway pressure (CPAP), which has been shown to reduce symptoms of daytime sleepiness, improve airflow, and increase quality of life⁽⁹⁾. However, given the difficulty of adaptation to the side effects, the adherence to this treatment is low and ranges between 46 and 80% of users⁽⁹⁾.

Other treatments have been proposed as alternatives to CPAP, such as the mandibular advancement splint (MAS). The action mechanism of MAS is the movement of the jaw forward, which prevents the tongue from falling back over the airway. This diminishes both snoring and apnea in some patients⁽¹⁰⁾.

Surgical treatment has been proposed for the correction of anatomical changes in the pharynx, nasal passages, base of the tongue, and craniofacial region. This presents a curative intent or can be used as an adjuvant to other therapies⁽¹¹⁻¹⁶⁾.

The objective of this study was to compare the clinical and polysomnographic profiles of patients with obstructive respiratory sleep disorder following the recommended treatment.

METHODS

We performed a retrospective study with 131 patients that were treated at the clinic of respiratory sleep disorders

from the Ear, Nose, and Throat Department of the Faculdade de Medicina do ABC between August 2003 and July 2008. These patients had their diagnosis confirmed through clinical and polysomnographic evaluations, besides the criteria of the International Classification of Sleep Disorders⁽⁸⁾.

All patients treated at this clinic were usually subject to a service protocol that included directed anamnesis, anthropometric data, physical examination, and basal polysomnography.

The recommended therapy for each patient accounted for the anamnesis data, anthropometric profile of patients, anatomical abnormalities in the upper respiratory tract, craniofacial abnormalities, and polysomnographic parameters. All of the patients were instructed regarding general recommendations (e.g., control of obesity and associated diseases), sleep hygiene (e.g., avoiding a supine position while sleeping), and the use of alcoholic beverages and sedatives. The therapeutic options considered included both clinical and surgical measures. When clinical treatment was the only proposed treatment, options included the use of CPAP, MAS, and sleep hygiene. Surgical treatment included surgeries on the upper respiratory tract or craniofacial region.

Once the patients were distributed into groups, they underwent retrospective analysis according to the protocol data. Statistical analyses were performed using Fisher's exact test, chi-square test and Wilcoxon signed-rank test.

RESULTS

Of the 131 studied patients, 78 (59.5%) were male and 52 (40.5%) were female (Figure 1). The average age was 48.9 ± 13.2 years. Regarding treatment, 94 patients (71.8%) were recommended for clinical treatment (CT group) and 37 (28.2%) were recommended for surgical treatment (ST group) (Figure 2).

The CT group was composed of 56 (59.6%) male patients and 38 (40.4%) female patients, with an average age of 52 ± 11 years (26-88 years), and an average body mass index (BMI) of 30 ± 5.8 kg/m². According to the polysomnographic results, 7 patients (7.5%) presented an AHI less than 5, 23 (24.5%) presented an AHI between 5 and 15, 25 (26.6%) presented an AHI between 15 and 30, and 39 (41.5%) presented an AHI greater than 30 (Tables 1 and 2).

The types of recommended treatment were: CPAP (60.6%), MAS (13.8%), and sleep hygiene exclusively (25.5%) (Figure 3).

The ST group was composed of 23 (62.2%) men and 14 (41.2%) women, with an average age of 39.2 ± 12 years, and an average BMI of 27.7 ± 4 kg/m². According to the polysomnographic results, 7 (18.9%) patients presented an AHI less than 5; 12 (29.7%) presented an AHI between 5 and 15; 8 (16.2%) presented an AHI between 15 and 30; and 10 (35.1%) presented an AHI that exceeded 30 (Tables 1 and 2).

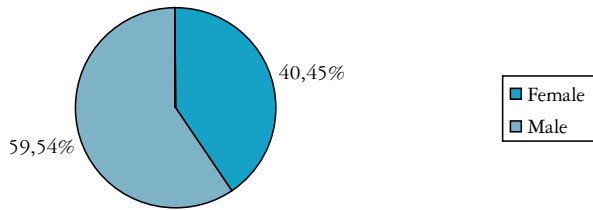


Figure 1: Distribution by gender.

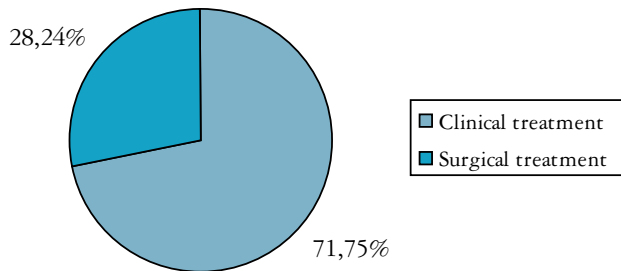


Figure 2: Distribution according to the type of treatment received.

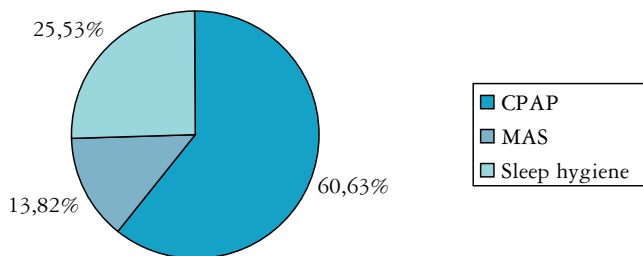


Figure 3: Types of recommended clinical treatment.

By comparing both groups of patients, no statistical significant differences were observed between the clinical and polysomnographic variables studied.

DISCUSSION

OSA is a chronic and progressive disease that causes a series of metabolic, cognitive, and cardiovascular changes, and it is currently regarded as a growing Public Health problem^(3,17). It presents a multifactorial etiology^(5,6), and several individual factors may be involved in its etiopathogenesis and severity. Thus, the treatment chosen in each case must be carefully analyzed, and the individual characteristics of each patient must be considered, including clinical factors, the presence of craniofacial abnormalities, and other aspects. Appropriate treatment is essential and fundamental to restore patient's quality of life.

The distribution of the groups, analyzed for gender, was not evident in this study, since similar percentages of men and women comprised both groups. However, the predominance of

Table 1: Apnea-hypopnea index: comparison between clinical and surgical group

AHI	Clinical group n (%)	Surgical group n (%)
< 5 (normal)	7 (7.45%)	7 (18.9%)
5-15 (mild)	23 (24.47%)	12 (29.7%)
15-30 (moderate)	25 (26.6%)	8 (16.2%)
> 30 (severe)	39 (41.49%)	10 (37.8%)

AHI: Apnea-hypopnea index; n: number of patients; p<0,05.

Table 2: Clinical data: comparison between clinical and surgical group

	Clinical group	Surgical group	p-value
Men	56 (59.6%)	23 (62.2%)	0.49
Women	38 (40.3%)	14 (41.2%)	0.49
Age	52 ± 11 years	39.2 ± 12 years	0.32
BMI	30 ± 5.8 kg/m ²	27.7 ± 4 kg/m ²	0.24

BMI: body mass index; Wilcoxon signed-ranked test.

male patients in the study coincided with findings in the literature that show a higher incidence of the disease in men^(2,18).

The patients in the current study were, on average, in their forties and fifties, which is an age range that is correlated with a greater prevalence of OSA, according to epidemiological data described in literature⁽¹⁸⁾. Although no statistical difference was observed, the CT group was composed of older patients, while the ST group was composed of younger patients. This can be explained by the fact that surgical treatment of OSA has better outcomes in young patients⁽¹⁹⁾ because they have not yet suffered the influence of neuromuscular factors that are present in the etiology of the disease in older patients. In addition, younger patients present fewer comorbidities, such as systemic arterial hypertension, *diabetes mellitus*, and arrhythmias. These are factors that have been shown to increase surgical risks^(10,20).

Due to the fat accumulation in the cervical region, obesity plays an important role in the physiopathology of OSA^(7,21). This fact, which is also associated with obstructive anatomical factors, tends to worsen the severity of the disease. In obese patients, surgery of the upper respiratory tract alone may not be effective in treating the disease. No statistical difference was observed between groups for BMI; however, the ST group was composed of patients with a lower BMI than the other patients.

Regarding the AHI for the CT group, the majority of the patients with moderate and severe OSA received clinical treatment. CPAP was the therapeutic option recommended for the majority of the patients in this group; it is also the treatment of choice for the disease according to literature^(20,22,23).

The objective of the surgical treatment in cases of OSA was curative in mild cases and adjuvant in severe cases⁽¹⁹⁾. Thus, nasal surgeries and tonsilectomies are equally capable of making the upper respiratory tract permeable, causing a reduction in the resistance level, and facilitating the use of

CPAP^(24,25). Therefore, one of the main factors related to the recommendation and success of OAS surgical treatment is the presence of anatomical abnormalities⁽²⁶⁾. Perhaps for this reason we did not encounter differences in the clinical and polysomnographic parameters between the two groups of patients.

Most of the patients received clinical treatment with a prevalence of CPAP, which is the main and most effective OSA treatment when adequately used. However, approximately one-third of the patients needed surgical intervention, and they displayed a high prevalence of anatomical abnormalities.

The type of recommended treatment was not influenced by the clinical or polysomnographic parameters, which showed that the presence or absence of anatomical abnormalities in the upper respiratory tract or in the craniofacial region was perhaps the main criterion for recommending a surgical OSA treatment.

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Correlation between subjective classification of snoring and the apnea-hypopnea index

Correlação entre a classificação subjetiva de ronco e índice de apneia e hipopneia

Marcos Marques Rodrigues¹, Ralph Silveira Dibbern¹, Carla Willemann Kruehl Goulart¹

ABSTRACT

Objective: Obstructive sleep apnea syndrome (OSAS) has gained increased attention in recent years, mainly due to the increased number of diagnosed cases and OSAS's relationship with other diseases. About 90% of the patients with OSAS snore. The objective of this paper was to investigate the relationship between the Stanford classification and the apnea-hypopnea index in patients with OSAS. **Methods:** Two hundred six patients were included in a longitudinal cohort study. The patients were evaluated and classified according to the Mallampati score, Stanford classification and the severity of their OSAS, as measured by the apnea-hypopnea index (AHI) using polysomnography. **Results:** A total of 168 patients who underwent polysomnography in the sleep laboratory were included in the final study. In a cross-tabulation of the Stanford classification for snoring and the AHI, the relative risk (RR) was 3.06 (95%CI 1.47 and 6.33). Therefore, we can infer that a patient with loud and intense snoring has a greater chance of developing moderate to severe OSAS. **Conclusion:** We concluded that there is a positive correlation between the intensity of snoring and OSAS severity.

Keywords: Snoring/classification; Sleep apnea syndromes/complications; Polysomnography/methods

RESUMO

Objetivo: A síndrome da apneia obstrutiva do sono (SAOS) é uma doença que vem ganhando importância nos últimos anos, principalmente pelo aumento dos casos diagnosticados e sua relação com outras doenças. O ronco está presente em cerca de 90% dos pacientes com SAOS. O objetivo deste trabalho foi verificar a relação entre a classificação de Stanford e o índice de apneia e hipopneia (IAH) em pacientes com SAOS. **Métodos:** Estudo de coorte histórica longitudinal. Foram avaliados e classificados 206 pacientes, de acordo com o Escore de Mallampati, Classificação de Stanford e a gravidade da SAOS pelo IAH na polissonografia. **Resultados:** Foram incluídos 168 pacientes que se submeteram ao exame de polissonografia no laboratório do sono. Na tabulação cruzada entre a Classificação de Stanford para ronco e o IAH, o Risco Relativo (RR) foi de 3,06 (IC95% 1,47 e 6,33). Portanto, podemos inferir que um paciente com ronco alto e intenso tem maior possibilidade

de desenvolver SAOS moderado a grave. **Conclusão:** Concluímos que há correlação positiva entre a intensidade do ronco e a gravidade da SAOS.

Descritores: Ronco/classificação; Síndromes da apneia do sono/complicações; Polissonografia/métodos

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) has been increasingly recognized and diagnosed in recent years. Accurate diagnosis and appropriate treatment are the key to managing a disease that has socioeconomic repercussions and complications, including increased incidence of cardiovascular diseases. The Western population is becoming increasingly overweight, and excess weight is associated with greater risk for developing OSAS and snoring^(1,2).

A large epidemiological study in the United States, involving 5,201 adult patients, showed that 19% of women and 33% of men older than 65 years old snore⁽³⁾. Within the general population, about 18% of men and 7% of women have snoring problems^(3,4).

Risk factors for OSAS and snoring include age between 40 and 65 years; male gender; obesity; smoking; alcoholism and sedentary lifestyle⁽⁵⁾. The main physical examination findings associated with OSAS include increased neck circumference, oropharyngeal obstruction, flaccid palate, nasal obstruction, turbinate hypertrophy, septal deformity, nasal cavity tumors, enlarged tonsils, macroglossia and retrognathia⁽⁶⁾. Anatomic findings such as vibration factors and collapsed upper airway have been described in studies that used cephalometry, computed tomography, magnetic resonance imaging and nasal fibroscopy⁽⁷⁾.

Most patients who consult a specialist complain primarily of snoring that bothers their partners. Snoring is present

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in 90 to 95% of patients who have OSAS and upper airway resistance syndrome (UARS)⁽⁸⁾.

Burschtin et al. reported a positive correlation between snoring intensity and OSAS severity, in which snoring intensity was assessed with a scale that grades snoring severity from 0 to 9. Patients with scores higher than 7 points are considered at high risk for OSAS⁽⁹⁾.

Guilleminault et al. studied snoring in 1,139 individuals by measuring sound levels with a decibel monitor. They observed a positive correlation between the intensity, in decibels, of snoring, daytime sleepiness and apnea-hypopnea index (AHI). They found that men snored louder than women, and men with body mass indexes (BMI) above 30 and snoring louder than 38 dB had a relative risk of 4.1 of developing AHI scores above 10⁽⁷⁾.

Several studies have associated snoring with OSAS, but few studies have evaluated the relationship between a subjective classification of snoring (the Stanford classification) and OSAS severity. Therefore, the objective of this study was to verify the relationship between the Stanford classification and apnea-hypopnea in patients with OSAS.

METHODS

This research project was approved by the Research Ethics Committee, under the Protocol Number 114/08. It was entered in the Clinical Trials registry under ID NCT00883376. The enrolled patients signed a consent form. A total of 206 patients were retrospectively evaluated. Patients were treated at the OSAS clinic of the Santa Casa de Limeira Hospital between August 2006 and October 2009. Patients whose primary complaint was habitual snoring were included in this study. Patients presenting Class III obesity (BMI \geq 40), craniofacial alterations, sedative or stimulant drug use, nasal obstruction caused by nasal polyps and/or nasal tumors were excluded from this study to avoid bias. All patients underwent an assessment protocol that included medical history, Epworth Sleepiness Scale, Scale of Subjective Snoring (Stanford)⁽⁸⁾, the Friedman classification and a complete ENT examination. Of the 206 patients initially included in the protocol, 168 patients were included in the study.

The Epworth Sleepiness Scale is widely used to assess daytime sleepiness. It consists of eight questions about the level of sleepiness the patient experiences in certain daily activities. Total score can range from 0 to 24 points; a score higher than 10 points indicates excessive daytime sleepiness⁽¹⁰⁾. The Friedman classification is used to evaluate oropharyngeal obstruction by evaluating tonsil size, the modified Mallampati classification and BMI. The Friedman classification uses grades ranging I to IV⁽¹¹⁾.

The patients underwent nasal fibroscopic exam using a Machida fiberscope with a 2.8-mm channel. The level of upper airway obstruction was classified according to the Fujita classification⁽¹²⁾. All 168 patients underwent nocturnal polysomnography in the sleep lab, in accordance with the American Academy of Sleep Medicine guidelines⁽¹³⁾. The following channels were fully monitored: eye movements, leg movements, airflow by nasal cannula and thermistor, chest movement, electroencephalogram, electrocardiogram, heart rate and oxygen saturation. Patients' disease severity was classified according to the criteria established by the American Academy of Sleep Task Force⁽¹³⁾.

The subjective snoring classification developed in Stanford⁽⁸⁾ assigns patients a grade from 0 to 10, based on the extent to which snoring affects their family relationships, especially with their spouses (Figure 1). Patients responded to this questionnaire in the presence of a spouse or family member.

Grade	0	1 to 3	4 to 6	7 to 9	10
Classification	No snoring	Mild	High	Very high	Intense
0 = no snoring					
1-3 = mild (does not disturb the partner during sleep)					
4-6 = high snoring (enough to disturb the partner)					
7-9 = very intense (disturbs people in other rooms)					
10 = the partner leaves the room					

Figure 1: Scale of subjective snoring (Stanford).

OSAS severity is classified by the American Academy of Sleep as follows: fewer than 5 AHI events/hour: no OSAS or primary snoring; Between 5 and 15 AHI events/hour: mild OSAS; Between 15 and 30 AHI events/hour: Moderate OSAS; More than 30 AHI events/hour: severe OSAS. In this study, we divided the subjects into four groups. Group I consisted of 85 patients with AHI scores below 15; i.e., patients with primary non-apneic snoring or mild apnea. Group II consisted of 83 patients with AHI scores above 15; i.e., patients with moderate to severe OSAS (Chart 1). The relative percentage of samples from both groups is shown in Figure 1. Group III consisted of 40 patients with mild to high snoring and Stanford scores below 7. Group IV consisted of 128 patients with loud, intense snoring that their spouses could not tolerate and Stanford scores greater than or equal to 7. Data are shown in Chart 2.

Chart 1: AHI intensity classification

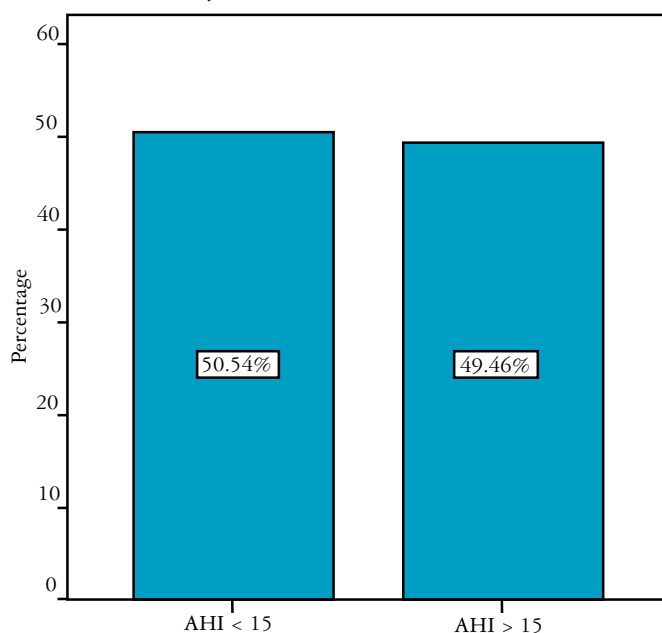
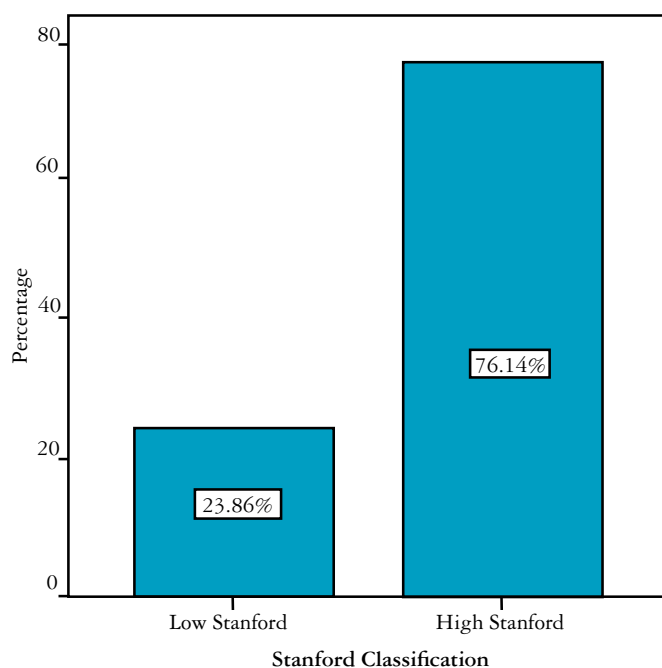


Chart 2: Percentage of the total study population grouped according to Stanford classification



RESULTS

The mean age of the subjects was 47.95 years (SD: 11; range: 17 to 77 years). Of the 168 patients, 90 (53.57%) were male and 78 (46.42%) were female. The average BMI was 29.42 kg/m² (SD: 5.55; range: 16.44 to 51.02 kg/m²). Patients had a mean Epworth Sleepiness Scale value of 11.25 points (SD 5.14). Snoring severity, based on the Stanford classification, averaged 8.16 points (SD 2.1). The data are available in Table 1.

Table 2 is based on the model for dichotomous variables. It contains cross-tabulations of the OSAS severity based on

Table 1: OSAS protocol data

	Stanford ^a	BMI ^b	Epworth ^c	Age
Average	8.16	29.42	11.25	47.95
Standard deviation	2.10	5.55	5.14	11.25
Minimum	2	16.44	0	17
Maximum	10	51.02	24	77

^aStanford subjective snoring value; ^bBody Mass Index; ^cEpworth Sleepiness Scale score

Table 2: Cross-tabulation of AHI and Stanford classification

	Group I AHI<15	Group II AHI>15	Total
Group III: Stanford<7	28	11	39
Group IV: Stanford≥7	57	72	129
Total	85	83	168

AHI (Groups I and II) and snoring intensity based on the Stanford classification (Groups III and IV).

The calculation of relative risk (RR) was based on data from Table 2. The RR was 3.06, with 95% confidence interval (95%CI) between 1.47 and 6.33. The calculations were performed and checked using SPSS 16.0 from the company SPSS Inc.

DISCUSSION

Snoring is a significant factor in OSAS; 90 to 95% of patients with OSAS snore⁽⁸⁾. There are few reports of patients with OSAS who do not snore. The primary cause of snoring is flaccidity of the oropharyngeal tissues, which causes vibration and partial blockage of the upper airway during sleep. OSAS occurs primarily when the upper airway collapses⁽⁵⁾.

Snoring was the main complaint of the patients analyzed in the ENT clinic, which is similar to what has been reported in the literature. Therefore, we must always be alert to complaints of snoring, which often indicate OSAS and/or increased upper airway resistance (UARS). The clinical examination of a patient with snoring should include polysomnography, a method suitable for diagnosing sleep breathing disorders.

Several studies have examined the correlation between snoring and OSAS. An important study by Chervin et al.⁽⁶⁾ showed a significant positive correlation between the intensity of snoring, in decibels, and the presence of OSAS. However, this study only related snoring intensity to the presence or absence of OSAS, and not to the severity of OSAS. In clinical practice, it is difficult to obtain a measurement of snoring in decibels because the polygraphs on the market do not offer such measure. A system with multichannel capability would be necessary to capture audio, and it should be able to filter out environmental noises and exclude them from the polysomnogram results.

Mair et al. discuss the feasibility of an acoustic assessment of snoring and its potential use to assess snoring and its source in the upper airways. The authors concluded that acoustic evaluation is useful for assessing and guiding the management of patients with palatal snoring, but they admit that standardization is necessary⁽¹⁴⁾.

We evaluated the correlation between the severity of snoring based on Stanford classification and the severity of OSAS, as determined by the AHI. This evaluation provides a practical in-office assessment of a patient's risk of developing a severe sleep breathing disorder. To develop the model, we used a longitudinal, historical cohort study to evaluate the possible influence and correlation of snoring intensity and OSAS severity. Applying the model of dichotomous variables, we found a relative risk of 3.06 (95%CI 1.47 to 6.33). Therefore, the correlation is positive and statistically significant.

Burschtin et al. found a positive correlation between snoring intensity and OSAS severity. The authors of that study assessed snoring subjectively with the Severity of Snoring Scale. As a measure of snoring severity, this questionnaire can provide a fast and easy indication of the severity of OSAS⁽⁹⁾. Subjective and standardized scales for evaluating snoring are useful in countries like Brazil, where acoustic means of analyzing snoring are not readily available or standardized.

Thus, snoring intensity is associated with sleep apnea, as the literature has shown. Most studies have associated snoring with the presence of sleep apnea and daytime sleepiness. When interviewing a snorer, physicians must seek details and try to quantify, even subjectively, the intensity of snoring.

As previously demonstrated, OSAS is a progressive and multifactorial disease. Anatomical, neuromuscular, connective tissue and genetic factors influence its evolution⁽⁶⁾. Therefore, physicians should be careful when treating patients with high Stanford scores; because of their high risk of sleep apnea, these patients should be referred for nighttime multichannel polysomnography.

A patient with a sleep breathing disorder and/or snoring should undergo a thorough, standard evaluation, including assessments of the upper airways (nasal endoscopy, Friedman classification), daytime sleepiness (Epworth Sleepiness Scale), BMI, age and medical history, as well as an ENT examination and a complete Type I polysomnography.

CONCLUSION

We concluded that snoring is linked to OSAS and seems to be associated with AHI scores. In situations in which there

is no established and standardized means of assessing snoring acoustically, the subjective snoring questionnaires provide a useful means of assessing patients with sleep breathing disorders. We must vigilantly evaluate all patients with primary snoring because OSAS is a progressive disease, and increased frequency or intensity of snoring can indicate worsening OSAS.

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Sleep in healthy older adults: a Brazilian sample

Sono em idosos saudáveis: uma amostra brasileira

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ABSTRACT

Objective: Few studies about sleep have been conducted in healthy older adults. The objective of this study was to describe behavioral and environmental factors that can provide a good quality of sleep in Brazilian healthy older adults. **Methods:** Healthy older adults without evidence of disease, not taking any medication and who were able to perform instrumental activities of the daily life were included in the study. They were submitted to full geriatric assessment and to The Pittsburgh Sleep Quality Index questionnaire. Forty patients (87%) had good sleep quality (PSQI < 5) and were selected to be studied. The following variables were collected: age, sex, education level, family income, employment status; subjective temperature sensation and ventilation conditions in the room; bed conditions; self-analysis of health status; number of awakenings during the night; daytime napping; television set in the sleep environment and types of nighttime TV programming watched; subjective latency and sleep duration; regularity of sleep onset/waking times; nocturia and sexual frequency. **Results:** Half of the sample presented overweight or were obese. Sixty per cent (n=24) had a good family income. Self-analysis of health status showed that all patients ranked their health as good, very good or excellent. No subjects referred bad or very bad health conditions. Over 90% of the subjects reported good bed and room conditions. Three-quarters of the sample had at least one episode of waking during the night and 70% reported daytime napping few days per week or daily. **Conclusions:** In conclusion, we found that adequate sleeping habits, as well as the absence of health disorders, apparently contribute to the results observed. Nocturia, naps and overweight did not affect sleep quality in healthy aged people.

Keywords: Sleep disorders/physiopathology; Sleep disorders/epidemiology; Aging/physiology; Attitude to health; Circadian rhythm; Sleep stages; Predictive value of tests; Questionnaires; Geriatric assessment; Middle aged; Brazil

RESUMO

Objetivo: Poucos estudos sobre o sono têm sido conduzidos em idosos saudáveis. O objetivo deste estudo foi descrever fatores comportamentais e ambientais que possam colaborar com a boa qualidade de sono de idosos saudáveis brasileiros. **Métodos:** Idosos saudáveis sem evidência de qualquer doença, sem utilizar qualquer medicação e com plenas funções nas atividades instrumentais de vida diária foram incluídos.

Quarenta deles (87%) tinham boa qualidade do sono (PSQI<5) e foram selecionados para o estudo. Foram avaliadas as seguintes variáveis: idade, sexo, nível educacional e renda familiar; sensação subjetiva de temperatura e de ventilação no quarto; condições da cama; autopercepção da condição de saúde; número de despertares noturnos; uso de televisão no quarto; tipo de programas televisivos que assiste à noite; latência e duração subjetiva do sono; regularidade de horários de dormir e acordar; noctúria e frequência de atividade sexual. **Resultados:** Metade da amostra tinha sobrepeso ou obesidade. Sessenta por cento (n=24) tinham boa renda familiar. Todos referiram boa, muito boa ou excelente autopercepção da saúde. Nenhum sujeito referiu-se à sua condição de saúde como ruim ou muito ruim. Mais de 90% dos sujeitos referiram boas condições do quarto e da cama de dormir. Três quartos da amostra tiveram ao menos um episódio de despertar à noite e 70% informaram cochilos diurnos alguns dias da semana ou mesmo diariamente. **Conclusões:** Conclui-se que adequados hábitos de sono, bem como a ausência de problemas de saúde, aparentemente contribuíram para os resultados observados. Noctúria, cochilos e sobrepeso não afetaram a qualidade do sono em idosos saudáveis.

Descritores: Transtornos do sono/fisiopatologia; Transtornos do sono/epidemiologia; Envelhecimento/fisiologia; Atitude frente à saúde; Ritmo circadiano; Fases do sono; Valor preditivo dos testes; Questionários; Avaliação geriátrica; Humano; Meia-idade; Brasil

INTRODUCTION

Many older adults and even physicians believe sleep difficulties are inevitable on old age. Aging has been reported to be related to subjective and objective changes in sleep quality such as decrease in sleep time⁽¹⁻³⁾. Subjectively, in several studies, older adults report waking up at earlier times, time spent in bed, increased sleep onset latency, nighttime awakenings, napping, and decreased total sleep compared to younger adults. However, most studies regarding sleep in older adults did not take into consideration co-morbidities that can affect sleep quality⁽⁴⁾. It also applies to medications, prostate enlargement and the use of diuretics that may affect sleep due to the desire to void at night. Chronic diseases such as depression and cognitive decline may be associated

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with sleep disorders. A longitudinal study of 50 healthy older adults that included evaluation by polysomnography found no significant difference between the older and the young control group, suggesting that aging is not necessarily synonymous of poor sleep quality⁽⁵⁾. The sleep pattern of healthy older adults with no evidence of illnesses and free of medication remains an open area for studying. Several studies have loose exclusion criteria due to the difficulty in selecting truly healthy older adults

The objectives of this study were to assess sleep quality in Brazilian healthy older adults and describe behavioral and environmental factors associated with a good quality of sleep.

METHODS

This was a cross-sectional descriptive study of subjective sleep quality in healthy older men and women, performed at the Geriatric Center of the University of Brasília. Ethics approval was obtained from the Research Ethics Committee at *Universidade de Brasília*. Participants were recruited from different institutions providing social activities for older persons (churches, community groups) and by advertisements in newspapers. The older adults interested in the study were contacted and meetings at the center to schedule an initial interview, if eligible. To be eligible for the study, the subjects should be 60 years old and older (legally considered elderly in Brazil), non-smokers, non-alcohol users or light drinkers (<3 drinks a week), for at least ten years with no evidence of major chronic illnesses, including diabetes, peripheral vascular disease, coronary artery disease, heart failure, lung disease, arthritis, depression or dementia. These diagnoses were based on a combination of self-report, medication use, and clinic evaluation. Subjects with chronic muscle or joint pain, physically handicapped, taking any medication, Mini-mental State Examination⁽⁶⁾ <24 or a score of 6 or more in the Geriatric Depression Scale⁽⁷⁾ were ineligible as well. All subjects had an extensive medical evaluation that included a brief cognitive examination. The term "Healthy Older Adults" refers to a subject without evidence of disease, not taking any medication and able to perform instrumental activities of the daily life. All individuals were living independently at the time of their participation in this study. All subjects had blood analysis that included blood count, lipids, sodium, potassium, blood urea nitrogen (BUN), liver enzymes, thyroid stimulating hormone, blood glucose and prostatic-specific antigen (PSA) for men. The following variables were collected: age, sex, education level, family income, employment status, subjective temperature sensation in the room (cold, neither too hot nor too cold or hot), subjective ventilation conditions in the room (airy, stuffy or intermediate), subjective bed conditions (comfortable, neither comfortable nor uncomfortable or uncomfortable), subjective self-analysis of health status (excellent, very good, good, bad or very bad),

number of awakenings in the night in the last month (none, once or more than once), daytime napping in the last month (never, few days per week, daily or weekends), television set in the sleep environment and types of nighttime TV programming watched (watches violent television programs or not), sleep latency in the last month (How long do you take to fall asleep? less than 15 minutes, between 15 and 30 minutes or more than 30 minutes), sleep duration in the last month (average), regularity of sleep onset/waking times and nocturia (defined as voiding two times or more per night) and sexual frequency (at least once per week, less than once per month or no sexual activity).

Body Mass Index (BMI) was calculated to measure the prevalence of overweight and obesity according to the criteria of the World Health Organization (obesity was defined as a BMI of ≥ 30 and overweight as a BMI >25 to less than <30).

The instrument used for the data collection about sleep quality was The Pittsburgh Sleep Quality Index (PSQI)⁽⁸⁾, an effective instrument used to measure the quality and patterns of sleep in the older adult. It differentiates "poor" from "good" sleep by measuring seven areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over the last month. Scoring of answers is based on a 0 to 3 scale. The PSQI global score is calculated by summing the scores for the seven subscales, resulting in a range of global scores from 0-21. A global sum of "5" or greater indicates a "poor" sleeper.

After we contacted about 400 volunteers, forty six older healthy adults were valued. Forty (87%) had good sleep quality (PSQI < 5). The group of poor sleepers showed the same social, behavioral and environmental profile, differing only in sleep parameters (Table 1).

Our exploratory analysis involves arraying descriptive data of good sleeping habits in these 40 healthy adults (21 men and 19 women), with average age of 68.3 ± 5.4 years.

Statistical analyses were performed using the Statistical Package for the Social Sciences Version 17 (SPSS). Chi-square test with Fisher's exact proportion was used to study a possible correlation between variables. A p value of <0.05 was considered significant and marked with a sign (*).

RESULTS

Only five percent of patients ($n=2$) were obese ($BMI \geq 30$), however 40% ($n=16$) were overweight. Sixty per cent of the sample had a family income between five and ten times the minimum wage (minimum wage in Brazil is around US\$ 3500.00 per year), a relatively high income in Brazil. The subjective self-analysis of health status showed that all patients ranked their health as good, very good or excellent, supporting our objective of studying older people in good

health. No subjects referred bad or very bad health conditions. Ninety-five percent esteemed intermediate to subjective temperature sensation and 90% described their bed conditions as comfortable. All but one subject had sleep latency less than 30 minutes in good sleepers group. Three-quarters of the sample had at least one episode of waking in the night and 70% reported daytime napping few days per week or daily (no differences between groups). Slightly less than half (47.5%) had no sexual activity.

DISCUSSION

One of the most interesting aspects of the present study is the low frequency of poor sleepers observed in a sample of forty-six healthy older adults (13%) as compared with other studies. It seems that nocturia, naps and overweight did not affect sleep quality in healthy elderly.

This sample were relatively well-off for Brazilian conditions, had good family income, good sleep hygiene, daytime napping and adequate sleep habits, which could justify a good sleep pattern. However, the group of poor sleepers showed the same social, behavioral and environmental profile, differing only in sleep parameters. Possibly, in this study, factors related to the environment or social conditions did not contribute to poor sleep.

Our sample did not differ from the profile of Brazilian elderly, considering most of the features described. Thus, it is likely that the quality of sleep was not influenced by co-morbidities, behavior or the environment. It could be termed as a "spotless sleep".

Three times more sleep disorders (insomnia) were observed in older people living in small communities in Brazil⁽⁹⁾. Much has been made of the often repeated fact that epidemiologic studies report as much as 50% of older adults complain of significant, chronic sleep disturbance⁽¹⁰⁾. Many sleep studies in older adults use different methods of assessment sleep, for example, studies on sleep physiology^(4,9,11,12), varying greatly from polysomnography, actigraphy, sleep diaries until information based upon phone calls⁽¹³⁾. These variables generate a number of biases when comparing different sleep data and tests. Age gaps have also been neglected in tests conducted with older adults. A 60-year-old adult is physiologically distinct from another one who is ninety. They certainly differ in their sleep pattern⁽¹⁴⁾. Many research projects may adopt more flexible exclusion criteria due to the difficulty in selecting truly healthy older adults.

The difficulties in finding healthy older volunteers to participate in research help justifying the scarcity of publications referring to this group⁽¹⁵⁾. Our rigid exclusion criteria may have resulted in selecting "super normal" individuals. The strict criteria that eliminated patients who were using medicines, including hypnotics, may have created a selection

Table 1: Characteristics of good sleepers compared to poor sleepers among the 46 study subjects.

Characteristics	Good sleepers	Poor sleepers
	n (%)	n (%)
Subjective temperature sensation in the room		
Cold	2 (5.0)	1 (16.5)
Neither too hot nor too cold	38 (95)	4 (67.0)
Hot	0	1 (16.5)
Subjective ventilation conditions in the room		
Airy	35 (87.5)	4 (67.0)
Stuffy	3 (7.5)	2 (33.0)
Neither too airy nor too stuffy	2 (5.0)	0
Subjective bed conditions		
Comfortable	36 (90.0)	6 (100.0)
Neither too comfortable nor too uncomfortable	4 (10.0)	0
Uncomfortable	0	0
Television set in the sleep environment		
No	28 (70.0)	4 (67.0)
Yes	12 (30.0)	2 (33.0)
Watches violent television programs at night		
No	32 (80.0)	3 (50.0)
Yes	8 (20.0)	3 (50.0)
Quantity of sexual activity		
At least once per week	13 (32.5)	2 (33.0)
Less than once per month	8 (20.0)	1 (17.0)
No sexual activity	19 (47.5)	3 (50.0)
Nocturia		
No	14 (35.0)	3 (50.0)
Yes	26 (65.0)	3 (50.0)
Sleep latency (subjective)*		
<15 min	28 (70.0)	3 (50.0)
Between 15 and 30 min	11 (27.5)	1 (17.0)
>30 min	1 (2.5)	2 (33.0)
Number of awakenings in the night		
None	14 (35.0)	1 (17.0)
Once	17 (42.5)	2 (33.0)
More than once	9 (22.5)	3 (50.0)
Daytime napping		
Never	3 (27.5)	3 (50.0)
Few days per week	9 (37.5)	2 (33.0)
Daily	8 (32.5)	1 (17.0)
Weekends	1 (2.5)	0
Kept regular routine bedtimes and waking times throughout the week and weekends		
Yes	38 (95.0)	5 (83.3)
No	2 (5.0)	1 (16.7)

*p<0.05.

bias when eliminated those who were healthy but had insomnia. Sleep disturbances tend to be associated with health complaints, thus implying that a good health status improves sleep^(16,17). Additionally, in our sample the proportion of men/women did not reflect the usual distribution in this age group. Men were overrepresented. Redline and colleagues concluded that men, but not women, show evidence of poorer sleep with aging⁽¹⁸⁾; however, other studies report more sleep disorders in women^(11,16), which could additionally explain our more favorable results. On the other hand, waking at night may be a consequence of prostate enlargement, a condition that may affect a predominantly male sample, and nocturia is a common cause of sleep disturbance⁽¹⁹⁾. Meanwhile, in our sample, sleep quality was not disturbed by nocturia, a finding which was also reported by Foley et al.⁽⁴⁾. Although healthy older people have a greater number of arousals during their nocturnal sleep period, their ability to reinitiate sleep remains intact and comparable to those of younger individuals⁽²⁰⁾.

The prevalence of obesity in the sample was lower than in the Brazilian population, where it reaches 12,5% in this age group⁽²¹⁾. This could contribute to our better results. Namyslowski et al. showed the lack of significant statistical correlations between BMI and all the sleep parameters studied in the overweight patients, as well as the statistical positive correlation between the BMI and Respiratory Disturbance Index in the obese cases⁽²²⁾. These findings could explain the good quality of sleep in our sample, in which overweight did not affect the quality of sleep.

Seventy per cent of the subjects reported a short sleep latency interval – less than 15 minutes – and for 39 subjects (97.5%), this interval was below 30 minutes. These findings are considered to be normal and confirm that the group had no difficulty in getting to sleep. Sleep latency over 30 minutes observed in one subject was not sufficient to establish poor quality sleep, because his sleep was regarded as good by himself and by PSQI.

The majority of the sample had no complaints about their sleep environment such as excessive heat, cold or noise that could interfere with their sleep pattern. Some studies report mixed results emphasizing the negative impact of environment condition⁽²³⁾, and others pertaining to the bed and room environment are considered to be the most important to older adults⁽¹⁵⁾. The better financial status of our sample when compared to the Brazilian average may explain the results, since it can be inferred they dwell in more comfortable houses.

Sleep pattern is highly influenced by poor sleep hygiene. In our study, there were no factors indicating such condition. The studied group presented good sleep hygiene, including non-smoking habits, low alcohol intake, a good sleep environment in the bedroom (adequate bed, temperature,

ventilation and noise level) and absence of television in the bedroom. Most individuals reported not having television in the bedroom and did not report watching television programs with violent content at night. Having a TV set in the bedroom has been linked to poor sleep quality in children⁽²⁴⁾, but this has not been confirmed in older persons. All these factors are related to good sleep quality in literature⁽²⁵⁾.

The sexual activity of participants in this study was higher than in a research executed by the National DST/AIDS Program, which verified that only 39.2% of the elderly were sexually active⁽²⁶⁾. There are few studies investigating quality of sleep and sexual frequency. An epidemiological survey in Finland found that satisfactory sexual life was reported to have positive effects on sleep⁽²⁷⁾.

Seventy percent mentioned day napping few days in the week, no more than 30 minutes of the day. The reported prevalence rates for habitual daytime napping in elderly populations is lower, ranging from 22 to 61%^(28,29). Napping is a controversial theme when studying sleep, but our study confirms that few authors attest that daytime naps is associated with a good subjective quality of sleep^(30,31).

Most of the older adults kept regular routine bedtimes and waking times throughout the week and weekends. Among young people, significant sleep schedule variation is observed, often deteriorating on weekends⁽³²⁾. This comparison reinforces the pertinence of good sleep hygiene in this study.

It is true that, with the aging, sleep quality and patterns can change, and such changes are gradual over a lifetime⁽¹⁰⁾. Normal aging is accompanied by changes in the sleep quality, quantity, and architecture. Specifically, there appears to be a measurable decrease in the ability to initiate and maintain sleep accompanied by a decrease in the proportion of the deeper, more restorative slow-wave sleep and REM sleep in the healthy elderly⁽³³⁾. Foley et al.⁽⁴⁾ argue that low quality of sleep among older adults is not related to aging *per se*, but a consequence of other conditions such as chronic diseases, environmental and psychological conditions. This study found that older people with sleep complaints that became healthy had improved sleep. This result shows a consistent relation between disease and sleep quality. Thus, an increase in the number of sleep complaints may be a marker of poor physical and mental health⁽¹⁷⁾. Distinguishing “normal” or physiologic age-related changes in sleep from “abnormal” or pathologic sleep can be problematic given the close association between sleep disorders and the higher prevalence of comorbid conditions in the elderly⁽³³⁾. Conversely, if comorbidities are present, it is clear that normal age-related sleep changes may well be exacerbated⁽¹⁰⁾.

Our study showed that a minority of healthy elderly had poor sleep quality, presenting lower frequency in rela-

tion to many other studies. Nocturia, naps and overweight did not affect sleep quality. These data do not allow refuting the hypothesis that aging causes poor sleep quality, but strengthens the theory. Individual history about sleep complaints during the life course would contribute to sleep understanding in our study, but unfortunately was not performed. Further studies with a larger sample size are needed to better understand the relationship between a healthy life and a healthy sleep in aging.

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Sleep-disordered breathing and heavy drinking: clinical features and polysomnographic findings

Transtornos respiratórios do sono e consumo de álcool: características clínicas e polissonográficas

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ABSTRACT

Objectives: The main objective of this study was to describe clinical features, particularly depressive symptoms, comorbidities, and polysomnographic characteristics of heavy drinkers with sleep disordered breathing (SDB). **Methods:** This was a cross-sectional study of 140 cases (92 males; mean age 54.6±8.2 years) referred for overnight polysomnography with suspicion of obstructive sleep apnea (OSA). Patients were questioned about clinical and demographic data and evaluated for depressive symptoms by the 17-item Hamilton Rating Scale for Depression (HRSD), excessive daytime sleepiness by the Epworth Sleepiness Scale (ESS) and comorbidity severity by the Charlson Comorbidity Index (CCI). **Results:** Fourteen patients were primary snorers [Apnea-Hypopnea Index (AHI)≤5; 10%] and 126 had OSA (AHI>5): 86 (61.4%) moderate/severe type (AHI>15). Heavy drinking was more common in male (p<0.005) and younger (p=0.01) individuals. Among heavy drinkers, there was a correlation between depressive symptoms and body mass index (BMI) (r=0.33; p=0.01) and this was more evident in women (r=0.68; p<0.005) than in men (r=0.53; p=0.02). Excessive daytime sleepiness (ESS≥10) was present in 57 cases (40.7%). ESS scores were positively correlated with arousals (r=0.24; p=0.02) and negatively with SpO_{2min} (r= -0.18; p=0.03). Heavy drinkers with AHI<15 presented higher ESS scores (p=0.03) and a trend of association remained after controlling for age and gender (p=0.08). **Conclusions:** In patients referred for polysomnography, heavy drinking is more common in younger male individuals. Depressive symptoms are related to BMI in heavy drinkers. More studies are warranted to clarify the influence of chronic heavy drinking on sleep abnormalities.

Keywords: Sleep apnea syndromes; Alcohol drinking; Alcohol beverages; Polysomnography; Comorbidity; Depression; Body mass index; Disorders of excessive somnolence

RESUMO

Objetivos: Identificar as características clínicas, comorbidades, sintomas depressivos e achados polissonográficos de portadores de transtornos respiratórios do sono associado ao consumo pesado de álcool. **Métodos:** Trata-se de estudo transversal envolvendo 140 indivíduos (92 homens; idade média 54,6±8,2 anos) encaminhados para exame

de polissonografia com suspeita de síndrome da apneia obstrutiva do sono (SAOS). A presença de sintomas depressivos foi avaliada por meio da escala de depressão de Hamilton (HAM-D 17 itens); hipersonolência diurna pela Escala de sonolência de Epworth (ESE) e gravidade das comorbidades por meio do Índice de Comorbidades de Charlson (ICC). **Resultados:** Quatorze indivíduos (10%) receberam diagnóstico de ronco primário [Índice de Apneia Hipopneia (IAH) ≤5] e 126 de SAOS (IAH>5), que foi classificada como moderada/grave (AHI>15) em 86 casos (61,4%). Consumo pesado de álcool foi mais comum em homens (p<0,005) e indivíduos mais jovens (p=0,01). Entre os bebedores pesados, os sintomas depressivos correlacionaram-se ao índice de massa corpórea (IMC; r=0,33; p=0,01), achado mais evidente no gênero feminino (r=0,68; p<0,005) do que no masculino (r=0,53, p=0,02). Sonolência excessiva diurna (ESE≥10) ocorreu em 57 casos (40,7%), correlacionando-se positivamente com o índice de despertares (r=0,24; p=0,02) e negativamente com SpO_{2min} (r= -0,18; p=0,03). Bebedores pesados com IAH<15 apresentaram escores mais elevados da ESE (p=0,03). **Conclusões:** Em casos encaminhados para exame de polissonografia, o consumo pesado de álcool é mais comum nos indivíduos mais jovens do sexo masculino. Nesse contexto, sintomas depressivos estão relacionados ao IMC. Outros estudos são necessários para elucidar os efeitos crônicos do consumo pesado de álcool sobre o sono.

Descritores: Síndromes da apneia do sono; Consumo de bebidas alcoólicas; Bebidas alcoólicas; Polissonografia; Comorbidade; Depressão; Índice de massa corporal; Distúrbios do sono por sonolência excessiva

INTRODUCTION

Obstructive sleep apnea (OSA) is an important clinical condition affecting around 4% of men and 2% of women⁽¹⁾, with more recent surveys showing even higher prevalence rates⁽²⁾. Sleep alterations, such as decreased sleep efficiency, increased number of arousals, nocturnal oxyhemoglobin desaturation, periodic leg movements, increased REM latency, and decreased amounts of slow wave sleep (stages 3 and 4 NREM sleep) and REM sleep have been reported in association with OSA⁽³⁻⁵⁾. Clinical and polysomnographic abnor-

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malities in OSA are known to be influenced by gender and mood disorders. For instance, men have more severe apnea-hypopnea index (AHI)⁽⁵⁾ and women present with more depressive symptoms⁽⁶⁾.

Previously, the clinical characteristics of long-term excessive use of alcohol in connection with OSA have not been sufficiently investigated. Alcohol consumption has been associated with both, a reduction of sleep latency and disruption of sleep and the latter can lead to daytime fatigue and sleepiness⁽⁷⁾. As regards to the relation of heavy drinking and sleep disordered breathing, previous studies have been contradictory. Alcohol has been shown to aggravate OSA⁽⁸⁾ while heavy drinking has been found not to be predictive of sleep disordered breathing⁽⁹⁾. Moreover, moderate alcohol ingestion is said not to influence continuous positive airway pressure (CPAP) therapy results⁽¹⁰⁾. Recently, serum gamma-glutamyl transferase (GGT), a marker of alcohol consumption, has been associated with increased nocturnal arterial oxygen desaturations suggesting a deleterious effect of alcohol in OSA⁽¹¹⁾. Other effects of alcohol consumption on various clinical conditions may also be considered contradictory. For instance, mild to moderate alcohol consumption has been claimed to have beneficial effects in coronary heart disease⁽¹²⁾, hypertension and cerebrovascular disease⁽¹³⁾; on the other hand, heavy alcohol ingestion has been connected with increased depression⁽¹⁴⁾ and worsening of sleep parameters⁽⁹⁾. The relevance of the relationship between heavy drinking and OSA is reinforced by the fact that stroke has been recognized in association with OSA^(15,16) and heavy drinking has been linked to stroke⁽¹⁷⁾. These findings highlight the importance of understanding the clinical and polysomnographic characteristics of patients with sleep disordered breathing and heavy drinking. More specifically, the frequency and severity of associated comorbidities might be of interest in this context.

The aim of this study was to evaluate the clinical and polysomnographic characteristics of patients with heavy drinking and sleep disordered breathing. Specifically, the pattern of associated comorbidity and depressive symptoms was investigated.

METHODS

Study design

This was a cross-sectional study of 150 consecutive patients referred for polysomnography with clinical suspicion of OSA. Cases with cancer, severe neurological, renal, hepatic, lung or cardiac diseases were excluded. Five individuals declined to participate in the study and five others were considered too ill to participate. Among the latter, three had dementia and two had suffered a recent ischemic stroke.

Thus, the final sample consisted of 140 patients. Cases included in the study were not involved in shift work and did not have recent hospitalizations for the last three months. A structured face-to-face interview was conducted prior to sleep study. All cases were submitted to overnight polysomnography. Those with AHI ≤ 5 events per hour of sleep were considered primary snorers. Obstructive sleep apnea was diagnosed in subjects with an AHI > 5 . These patients were further classified as having mild ($5 < \text{AHI} < 15$), moderate ($15 < \text{AHI} < 30$) or severe OSA ($\text{AHI} > 30$). Cases were divided into two groups for statistical purpose: snorers/mild OSA ($\text{AHI} \leq 15$) and moderate/severe OSA ($\text{AHI} > 15$). Cases were analyzed considering the presence/absence of heavy drinking. The protocol was approved by the local Research Ethics Committee and written informed consent was obtained in all cases.

Procedures

Demographic and clinical data were recorded using a closed-question data collection instrument. Body mass index (BMI) was calculated as the ratio between weight (kg) and squared height (m^2). Special emphasis was put on the history of heavy drinking and use of medication in the previous 30 days. Heavy alcohol drinking was considered present if, on a daily basis, more than 4 drinks for men and more than 3 drinks for women were reported, or more than 14 drinks for men and more than 7 drinks for women, on a weekly basis⁽¹⁸⁾.

Hamilton Rating Scale for Depression

Depressive symptoms were evaluated by the Hamilton Rating Scale for Depression - 17 item (HRSD)⁽¹⁹⁾. This scale takes into consideration several aspects such as anxiety (psychological and somatic), depressed mood, insomnia subdivided in early, middle and late insomnia among other mood-related questionings.

Epworth sleepiness scale

Daytime somnolence was assessed by the Epworth sleepiness scale (ESS), a questionnaire containing eight items that ask for expectation of dozing in eight hypothetical situations. Dozing probability ratings range from zero (no probability) to three (high probability). An ESS score of 10 or more indicates excessive daytime sleepiness⁽²⁰⁾.

Comorbidity Index Severity

Comorbidities were investigated using the modified Charlson Comorbidity Index (CCI)⁽²¹⁾. The CCI has been validated and is a strong predictor of clinical outcome in this population. The CCI is a composite score of multiple comorbid conditions, scores ranging from 1 to 6. The scale deals with

questions regarding organ system pathology such as the cardiovascular, respiratory, gastrointestinal, genitourinary, muscle-skeletal and neuro-psychological system. For the purpose of this study, the comorbid conditions were evaluated both by interview and confirmed by chart review and scored accordingly. However, age was not included in the index in order to examine the influence of age, independent of comorbidities.

Polysomnography

Standard overnight polysomnography (PSG) was performed on a digital polygraph (ALICE III®, Respiration Inc.). Polysomnographic recordings were set to begin at 10 p.m. (lights-out) and end at 6 a.m. (lights-on). Monitored variables included: electroencephalogram (C3, C4, O1, O2 referenced to contralateral ear electrodes), bilateral electrooculograms, submental electromyogram (EMG), two-lead electrocardiogram, pulse oximetry, bilateral *tibialis* EMG and airflow, using a nasal/oral thermocouple. Body position and thoracic and abdominal movements (inductance plethysmography) were also recorded. Sleep staging was performed by 30-s epochs, according to standard procedures. Polysomnography-derived parameters evaluated were AHI, minimum oxygen saturation (SpO_2 min), sleep latency, sleep efficiency, REM sleep latency, amount of REM sleep (% of total sleep time), amount of non-rapid eye movement (NREM) sleep (% of total sleep time), number of arousals and periodic leg movements. Arousal analysis and scoring of respiratory events during sleep were performed according to published criteria⁽²²⁾.

Apneas were defined as cessation of airflow for 10s or more and hypopneas as a reduction of inspiratory air flow of 50% or more associated with either oxygen desaturation of >3% or an arousal. Severity of sleep-disordered breathing was estimated by calculating the apnea index (AI; apneas per hour of sleep) and the apnea+hypopnea index (AHI; apneas plus hypopneas per hour of sleep)⁽²³⁾.

Statistical analysis

Statistical analysis was carried out using SPSS for Windows, version 16.0. For univariate analysis, we used the Fisher Exact Test for categorical variables, Student's *t*-test, or Mann-Whitney U test, as appropriate. Pearson correlation test was used between variables. Multivariate analysis was performed to estimate the independent contributions of variables. Variables with a *p* value ≤ 0.1 by univariate analysis were selected for entry into multivariate analysis. A two-tailed *p*-value <0.05 was considered to indicate a significant difference.

RESULTS

Patients of both genders ($n=144$; 65% of male gender), aged 19 to 81 years (mean age 54.6 ± 8.2 years) were included in the study. Fifty-three individuals (37.8%) were identified as heavy drinkers. Table 1 depicts clinical and demographic data of cases according to the presence or absence of heavy drinking. Patients who were heavy drinkers were younger ($p=0.01$) and predominantly of male gender ($p=0.003$). Table 2 summarizes clinical and polysomnographic characteristics of patients according to OSA severity and to the pres-

Table 1: Clinical and polysomnographic characteristics of patients with sleep-disordered breathing according to the presence/absence of heavy drinking

Variables	Heavy drinking n=53	Non-heavy drinking n=87	p-value
Age (years) Mean (SD)	41.1 (14.1)	47.4 (14.2)	^a 0.01*
Gender (male/female)	43/10	49/38	^b 0.003**
BMI mean (SD)	29.4 (5.9)	28.6 (5.9)	^a 0.41
HDRS scores mean (SD)	6.4 (4.2)	7.4 (5.6)	^c 0.26
ESS scores mean (SD)	10.6 (4.3)	9.6 (4.7)	^c 0.24
CCI mean (SD)	3.3 (1.6)	3.6 (2.1)	^c 0.28
Hypertension (Yes/No)	27/59	24/30	^b 0.14
Sleep latency (min) mean (SD)	11.8 (14.9)	13.2 (9.8)	^a 0.50
REM latency (min) mean (SD)	102.7 (58.6)	119.8 (69.3)	^a 0.13
Arousal index (events/h) mean (SD)	32.1 (17.9)	27.8 (16.2)	^a 0.25
Sleep efficiency (%) mean (SD)	86.9 (10.5)	84.8 (11.0)	^a 0.26
AHI (events/h) mean (SD)	28.9 (23.3)	26.1 (22.9)	^a 0.37
Mean SpO_2 (%) mean (SD)	92.4 (3.1)	92.8 (3.0)	^a 0.53
Minimum SpO_2 (%) mean (SD)	79.8 (10.0)	81.4 (8.7)	^a 0.32
$SpO_2 < 90\%$ (%TST) mean (SD)	16.2 (22.3)	13.6 (21.3)	^a 0.65

BMI: Body Mass Index; HDRS: Hamilton Depressive Rating Scale; ESS: Epworth Sleepiness Scale; CCI: Charlson Comorbidity Index; SpO_2 : peripheral oxygen saturation; REM: rapid eye movement; TST: Total Sleep Time.

^a Student's *t*-Test, ^b Fisher Exact Test, ^c Mann-Whitney Test.

* $p < 0.05$; ** $p < 0.01$

Table 2: Clinical and polysomnographic findings of individuals with obstructive sleep apnea according to disease severity and compared regarding the presence/absence of heavy drinking

Variables	IAH<15 (n=54)			IAH≥15 (n=86)		
	HD n=22	Non-HD n=32	p-value	HD n=31	Non-HD n=55	p-value
Age (years) mean (SD)	32.0 (6.6)	43.7 (13.0)	^a 0.001**	46.2 (14.6)	49.9 (14.7)	^a 0.25
Gender (male/female)	13/6	14/21	^b 0.04*	30/4	35/17	^b 0.02*
BMI mean (SD)	26.0 (3.7)	27.4 (5.0)	^a 0.5	31.3 (6.2)	29.4 (6.2)	^a 0.16
HDRS mean (SD)	7.0 (4.5)	8.7 (6.8)	^c 0.28	5.8 (4.5)	8.0 (5.0)	^c 0.04*
ESS mean (SD)	10.3 (4.1)	7.7 (4.4)	^c 0.03*	10.7 (4.4)	10.3 (4.8)	^c 0.68
CCI mean (SD)	3.0 (1.8)	3.6 (2.6)	^c 0.33	3.2 (1.7)	4.2 (1.9)	^c 0.01*
Sleep latency (min) mean (SD)	10.9 (7.4)	5.3 (4.6)	^a 0.29	16.4 (10.9)	16.8 (13.5)	^a 0.94
REM latency (min) mean (SD)	107.0 (50.8)	92.5 (33.8)	^a 0.68	119.3 (68.9)	87.5 (49.0)	^a 0.19
Arousal index mean (SD)	15.9 (5.7)	23.1 (17.1)	^a 0.39	33.7 (20.6)	26.7 (9.0)	^a 0.39
Sleep efficiency mean (SD)	88.8 (9.0)	82.1 (4.0)	^a 0.28	80.5 (9.7)	84.5 (10.0)	^a 0.32
AHI mean (SD)	8.9 (4.6)	7.0 (4.1)	^a 0.57	51.4 (21.0)	43.3 (26.9)	^a 0.61
Mean SpO ₂ mean (SD)	94.2 (1.1)	95.0 (0.0)	^a 0.2	91.0 (3.9)	90.1 (5.8)	^a 0.69
Minimum SpO ₂ mean (SD)	84.6 (5.7)	87.6 (1.8)	^a 0.4	73.0 (13.4)	76.7 (11.8)	^a 0.48
SpO ₂ <90% (%TST) mean (SD)	1.0 (0.95)	0.15 (0.03)	^a 0.19	29.0 (25.9)	19.8 (24.0)	^a 0.37

HD: Heavy Drinking; y: years, BMI: Body Mass Index; HDRS: Hamilton Depressive Rating Scale; ESS: Epworth Sleepiness Scale; CCI: Charlson Comorbidity Index; REM: rapid eye movement; AHI: Apnea+Hypopnea Index; SpO₂: peripheral oxygen saturation; TST: Total Sleep Time

^a Student's *t*-Test, ^b Fisher Exact Test, ^c Mann-Whitney Test

p*<0.05; *p*<0.01

ence/absence of heavy drinking. Eighty-six cases (61.4%) were diagnosed as moderate/severe OSA and 54 as primary snorers/mild OSA. Heavy drinkers from the group of snorers/mild OSA were younger (Student's *t* test, *p*=0.001), predominantly of male gender (Fisher Exact Test, *p*=0.04) and presented more daytime sleepiness (Mann-Whitney, *p*=0.03) than non-heavy drinkers from the same group. In this same group, after controlling for age and gender, ESS scores tended to be higher in heavy drinkers (*p*=0.08). In the moderate/severe OSA group, heavy drinkers were most predominantly of male gender (Fisher Exact Test, *p*=0.02; Table 2). Also, in the moderate/severe OSA group, non-heavy drinkers had more depressive symptoms (*p*=0.01) and higher comorbidity severity (*p*=0.04) than heavy drinkers. However, these differences did not remain significant after adjusting for age (*p*=0.54 and *p*=0.33, respectively). Among heavy drinkers, there was a correlation between HDRS scores and BMI (*r*=0.33; *p*=0.01, Table 3) and this was more evident in women (*r*=0.68; *p*<0.005) than in men (*r*=0.53; *p*=0.02). These findings remained after controlling for age (men: *r*=0.22; *p*=0.04 and women: *r*=0.36; *p*=0.008). Among all cases, scores of the HDRS were higher in female (9.1±6.1) than male (5.9±4.1; *p*<0.005) and this remained after controlling for age (*p*=0.008). Age was correlated with comorbidity severity (*r*=0.24; *p*=0.003), but not with depressive symptoms, in both groups (Table 3).

Overall, 17 individuals (12.1%) used sedatives, mostly benzodiazepines, and eight cases (5.7%) were on antidepressants (selective inhibitors of serotonin reuptake) without any

Table 3: Correlation coefficients between age, body mass index, and scores of Epworth Sleepiness Scale and Hamilton Depressive Rating Scale in heavy drinkers and non-heavy drinkers

Variables	Heavy drinking (n=54)		
	ESS	HDRS	CCI
Age	<i>r</i> = -0.099 <i>p</i> =0.37	<i>r</i> = -0.161 <i>p</i> =0.14	<i>r</i> =0.253 <i>p</i> =0.02*
BMI	<i>r</i> =0.107 <i>p</i> =0.32	<i>r</i> =0.33 <i>p</i> =0.01*	<i>r</i> =0.18 <i>p</i> =0.1
Variables	Non-heavy drinking (n=86)		
	ESS	HDRS	CCI
Age	<i>r</i> = -0.164 <i>p</i> =0.23	<i>r</i> =0.01 <i>p</i> =0.91	<i>r</i> =0.27 <i>p</i> =0.04*
BMI	<i>r</i> =0.141 <i>p</i> =0.31	<i>r</i> =0.212 <i>p</i> =0.12	<i>r</i> =0.069 <i>p</i> =0.62

ESS: Epworth Sleepiness Scale; HDRS: Hamilton Depressive Rating Scale; CIRS: Charlson Comorbidity Index; BMI: Body Mass Index.

p*<0.05; *p*<0.01

differences between heavy drinkers and non-heavy drinkers (Fisher Exact Test, *p*=0.81).

DISCUSSION

This data show that, among individuals with clinical suspicion of OSA, heavy drinkers are most predominantly young men. Also, among snorers and mild OSA subjects who are heavy drinkers, a trend for more daytime somnolence was found. We hypothesize that increased daytime sleepiness observed in snorers/mild OSA that are heavy drinkers may be secondary to more disrupted sleep in these individuals compared to non-

heavy drinkers. However, we were not able to demonstrate any differences in objective sleep parameters between these two groups. There are limitations to this study that need to be acknowledged: this is a cross-sectional evaluation of patients referred for sleep study and it is possible that these findings may not be representative for the general population. Other important issue is the potential influence of circadian rhythm abnormalities such as delayed sleep phase syndrome, a potential contributor to daytime sleepiness that was not evaluated in these cases. Although prospective studies are more suited for the investigation of chronic effects of heavy-drinking, they are costly, present difficulties with adherence to protocol and involve some ethical issues.

Using a different study design, Aldrich et al. looked for the prevalence of OSA in heavy drinkers and reported increased disease severity with ageing⁽⁹⁾. In the present study, cases that were older and had more severe OSA were not those identified as heavy drinkers. A possible explanation for this finding could be a greater awareness about the deleterious effects of heavy drinking among older individuals. After counseling, a follow-up of these patients including OSA severity and depressive symptoms evaluation may further clarify this issue. In this study, BMI was positively correlated with depressive symptoms in young heavy drinkers. This is in agreement with a previous report that points out the importance of body image on mood, particularly in young individuals⁽²⁴⁾. Others have reported an association between the BMI and depressive symptoms^(25,26). In this study population, depressive symptoms as evaluated by the HDRS were frequent, affected more women than men, and in most cases, remained untreated. This is also in agreement with a previous report showing that women with OSA present significantly higher levels of depression and anxiety than men⁽²⁷⁾. Recently, it has been shown that women with OSA complain significantly more of insomnia, restless legs, depression, nightmares, palpitations at night, and hallucinations than men⁽²⁵⁾. It has also been suggested that gender-related differences in symptom profile may be one explanation for the clinical under recognition of sleep disordered breathing in women^(26,28). Physicians involved in the care of patients with sleep disordered breathing should take notice of the necessity to investigate and diagnose more accurately depression in the obese and young cases with clinical suspicion of OSA.

In this study, AHI severity was not correlated with depressive symptoms. The relationship between depression and severity of OSA is controversial. Millman et al. reported that severity of OSA was associated with increased symptoms of depression⁽²⁹⁾. On the other hand, Pillar and Lavie did not observe any relationship between anxiety and depression and the severity of OSA in male patients, in agreement with our findings⁽²⁷⁾.

Our data do not support previous reports of an association between excessive daytime sleepiness and depressive symptoms in OSA^(30,31). Oxygen desaturation and high number of arousals, but not the AHI, were correlated to daytime somnolence, as assessed by the ESS. Previously, excessive daytime sleepiness has been associated with hypoxia⁽²⁶⁾ as well as snoring, poor sleep efficiency and increased total number of arousals⁽³²⁾.

In summary, this study shows that heavy drinking is common in young snorers/mild OSA male patients presenting for sleep laboratory studies and snorers/mild OSA that are heavy drinkers tend to have more pronounced daytime sleepiness. Among these young individuals, HDRS scores were correlated with the BMI and depressive symptoms were more severe in women.

CONFLICT OF INTEREST

The authors have nothing to disclose.

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Incidence of weight gain and obesity in night shift workers and the relationship of these factors with sleep

Incidência de ganho de peso e obesidade em trabalhadores de turno noturno e a relação destes fatores com o sono

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ABSTRACT

Objective: To evaluate the prevalence of obesity and weight changes in night shift workers and their relationship with sleep. **Methods:** Fifty night shift and twenty-six day shift workers were evaluated. They belonged to one of two groups: nurse technicians/assistants or nurses. The night shift started at 7:00 pm and ended at 7:00 am, while the day shift was either from 7:00 am to 1:00 pm or from 1:00 pm to 7:00 pm. Data were collected using sleep diaries, personal questionnaires, scales to measure weight, and height measurement to calculate body mass index (BMI). **Results:** There were significant differences between the day shift and the night shift groups in sleep latency (6m54s and 20m6s; $p < 0.001$), wakeup call (6h25m and 7h52m; $p < 0.001$), sleep duration (7h12m and 8h21m; $p = 0.002$), quality of nocturnal sleep (8.48 and 7.62; $p = 0.009$), and total nap time (34m48s and 1h30m; $p = 0.001$), respectively. The average BMI-1 (24.57; $p = 0.015$) and BMI-2 (25.63; $p = 0.033$) values from the day shift group were lower than those of the night shift group – BMI-1 (27.01) and BMI-2 (28.04). The frequency of physical activity was correlated with the difference in BMI ($r = -0.296$; $p = 0.0366$). **Conclusion:** The night shift workers showed a higher average BMI than day shift workers did. However, it was not possible to ascertain whether sleep alterations influenced the weight gain of night shift workers.

Keywords: Night work; Body mass index; Body weight; Personnel staffing and scheduling; Weight gain; Work schedule tolerance; Obesity; Sleep deprivation

RESUMO

Objetivo: Avaliar a prevalência de obesidade e a mudança de peso corporal em trabalhadores do turno noturno e sua relação com o sono. **Métodos:** Foram avaliados 50 trabalhadores noturnos e 26 diurnos distribuídos em: técnicas e auxiliares de enfermagem e enfermeiras. O horário de trabalho do turno noturno era das 19:00 às 7:00 e do diurno, das 7:00 às 13:00 ou das 13:00 às 19:00. Os instrumentos utilizados foram: diário de sono e informações pessoais, além de balança para pesagem e mensuração da altura para o cálculo do índice de massa corporal (IMC). **Resultados:** O padrão de sono dos grupos diurno e noturno mostrou diferença estatisticamente significante entre grupos

para latência do sono (6m54s e 20m6s; $p < 0,001$), horário de acordar (6h25m e 7h52m; $p < 0,001$), duração do sono (7h12m e 8h21m; $p = 0,002$), qualidade do sono noturno (8,48 e 7,62; $p = 0,009$), e cochilos (34m48s e 1h30m; $p = 0,001$), respectivamente. A média de IMC-1 (24,57; $p = 0,015$) e IMC-2 (25,63; $p = 0,033$) do turno diurno foi menor que do turno noturno, IMC-1 (27,01) e IMC-2 (28,04). A frequência de atividade física correlacionou-se com a diferença de IMC ($r = -0,296$; $p = 0,0366$). **Conclusão:** Os trabalhadores de turno noturno apresentaram média de IMC maior em comparação ao grupo diurno. Entretanto, não se pode afirmar que as alterações de sono influenciaram no ganho de peso no grupo do turno noturno.

Descritores: Trabalho noturno; Índice de massa corporal; Peso corporal; Admissão e escalonamento de pessoal; Ganho de peso; Tolerância ao trabalho programado; Obesidade; Privação do sono

INTRODUCTION

The current century has been marked by several transformations that directly affect the way of life of modern society. In order to meet constant market demands, a reorganization of labor into shifts has been developed to keep the service active for 24 hours⁽¹⁻³⁾.

The organization of shifts, especially the night shift, can have a strong impact on the physical, psychological and social well-being of workers due to a disparity between the endocrine circadian rhythm and environmental synchronizers (such as the light/dark cycle)⁽⁴⁻⁷⁾.

This desynchronization of the biological clock, combined with negative habits (such as smoking, a poor diet, a sedentary lifestyle and stress) can result in serious consequences for the worker's health such as fatigue, insomnia, somnolence, disorientation, gastrointestinal problems, cardiovascular problems, irritability and obesity^(4,7-9).

These effects may vary in duration and intensity, depending on individual factors (gender, age), work situation (ad-

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aptation and tolerance to shift work) and social conditions (living conditions, offspring)^(4,7).

Obesity is a multifactorial pathology with deep socio-environmental roots; therefore, its etiology is intrinsically related to the lifestyle of the individual over time. This suggests that the dysfunctional metabolic state of these workers could be one of the main causes of their weight gain. Therefore, this study propose to evaluate the incidence of weight gain and obesity in night shift workers and the relationship of these factors with sleep^(6,8).

METHODS

Seventy-six female nursing professionals who work in permanent shifts, either night (n=50) or day (n=26), participated in the study. The average age of participants in the night shift was 42±8 years and in the day shift was 42±9 years. The work rotation at the Hospital de Clínicas of the Universidade Estadual de Campinas (UNICAMP) was from 7:00 am to 1:00 pm, from 1:00 pm to 7:00 pm (day shifts), or from 7:00 pm to 7:00 am (night shift), with a work rotation of 12x36 hrs. The selected volunteers were seen by the occupational health control office in 2003 and remained with this service until the start of data collection (2006). The informed consent form was approved by the Research Ethics Committee of the School of Medical Sciences at UNICAMP (Project number: 385/2005, CAAE: 0190.0.146.000-05) and signed by every participant.

Participants were excluded if they were using corticosteroids or psychotropic drugs, if they had clinical diseases, if they were on vacation, or if they were day shift employees that worked or studied at night.

The employees answered a personal information questionnaire with categorical variables (physical activity, smoking and drinking habits, and marital status) and continuous variables (age, physical activity frequency, weight, height and BMI – body mass index). The weight, height and BMI measurements were recorded at two different times for the day and night shifts separately: in the first recordings, weight-1, height-1 and BMI-1 were obtained from records of the Occupational Safety and Health Division of the UNICAMP. A single researcher collected data from all participants during this period (2003). The participants, wearing light clothing and no shoes, were weighed and had their height measured after the work shift on a Filizola® balance.

A second set of measurements (weight-2, height-2 and BMI-2) was taken in 2006 from both shifts by the researcher, who used the same criteria of weighing (kg) and measuring height (m). The values were recorded and used to calculate BMI (kg/m²). Then, the gain or reduction in weight was calculated by finding the difference between the final and initial weights.

To evaluate the characteristics of the sleep-wake cycle, data were collected through a sleep diary for four weeks. The sleep diary consisted of 12 questions that the participants answered daily, including their bedtime and wake time, diurnal and nocturnal sleep quality, degree of well-being upon waking, manner of waking (spontaneous, with alarm clock or awakened by someone), and the time and number of naps taken. The participant took the diary home and was instructed to fill it in every day after waking. This sleep diary was developed and validated by the Multidisciplinary Group of Development and Biological Rhythms, ICB/USP⁽¹⁰⁾.

To describe the sample profile according to the studied variables, a frequency table was designed.

The averages of BMI-1 and BMI-2 were compared between the night and day shifts by the Mann-Whitney test.

The continuous variables from the sleep diary were compared between the day and night shifts by the Mann-Whitney test. For this analysis, the average bedtime (on the day off for the night shift workers), sleep latency, wake time and naps were obtained from the 30 days evaluated. Data from the weekends were not considered for either shift because night shift workers do not have weekends (only days) off.

The weight difference between the final (weight-2) and the initial (weight-1) measurements was calculated for the day and night shifts separately. With these values, the participants were divided into groups that lost weight and groups that gained weight. The chi-square test was used to evaluate these categorical variables.

Then, these groups were compared in relation to the pattern of sleep of participants and the length of time since working night shifts by the Mann-Whitney test.

The difference in BMI between the final and the initial measurements was associated with the frequency of physical activity by the Spearman correlation coefficient.

RESULTS

Table 1 shows the frequency and descriptive statistics of the variables used for sample characterization. The volunteers were grouped into day shift and night shift workers. The predominant age range was between 40 and 49 years old, with 69% working night shifts and 40% working day shifts. In relation to marital status, it was observed that the majority of workers in both shifts were married. As for smoking, 18% of night shift workers habitually smoked compared to 19% of day shift workers. A drinking habit was observed in 19% of day shift workers, whereas 20% of night shift workers reported alcohol consumption.

The night and day shift groups showed significant differences in sleep latency (p<0.001), wake time (p<0.001), nocturnal sleep duration (p=0.002), and nap (p=0.001) (Table 2). The night shift employees had a longer sleep latency

time, demonstrating a greater difficulty in falling asleep. When evaluating wake time, it was observed that day shift employees woke up earlier due to clinic activity that starts at 7:00 am. In relation to the duration of nocturnal sleep, the nocturnal group had a longer duration of sleep on their days off, possibly due to fatigue or tiredness (symptoms frequently seen in night shift workers).

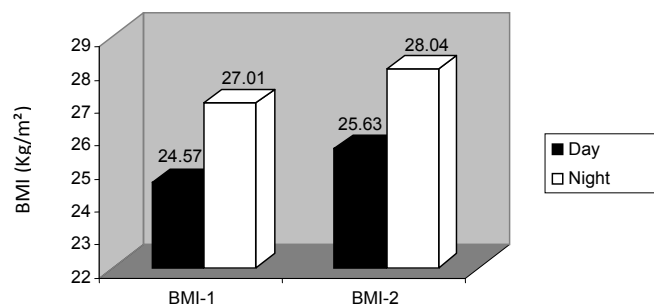
The evaluation of how the workers felt upon waking from nocturnal sleep was done through a visual analog scale with values from 0 (worse) to 10 (better). It resulted in an average of 7.62 for the nocturnal group and 8.48 for the day group ($p=0.009$), indicating that the sleep of the day group has better quality. The averages relating to how the participants felt at waking showed values 7.389 (SD 1.36) for the day group and 7.385 (SD 1.32) for the nocturnal group ($p=0.922$).

Figure 1 shows that the average BMI-1 (initial) values of the day and night shift groups were 24.57 and 27.01, respectively, showing a significant difference ($p=0.015$). The final BMI (BMI-2) was 25.63 for day shift workers and 28.04 for night shift workers ($p=0.033$).

It was observed that 78% of night shift workers and 84.6% of day shift workers gained weight during the study period, whereas 15.38% of day shift and 22% of night shift workers showed a weight reduction ($p=0.492$).

The night shift workers that gained weight had been working night shifts for an average of 13.87 years, compared to 11.18 years for workers that lost weight ($p=0.302$).

Looking at the BMI differences in individuals of the night group, a significant effect was found with the Spearman correlation coefficient ($r=-0.32356$; $p=0.0219$), showing that as the frequency of physical exercise per week increases, the BMI differences decrease; that is, although there is a tendency for night shift workers to gain weight, those that maintained physical activity instead had a stable or even reduced BMI by the end of the study period (Figure 2).



BMI-1: initial body mass index; BMI-2: final body mass index.

*Mean significant differences: BMI-1 ($p=0.015$) and BMI-2 ($p=0.033$).

The chi-square test was used.

Figure 1: Distribution of average values of BMI-1 and BMI-2 of day and night shift groups.

Table 1: Description of the characteristics of night shift and day shift employees

	Night shift (%)	Day shift (%)	p-value
Age			
<40 years	36	23	NS
40-49 years	40	69	0.043*
≥50 years	24	08	0.043*
Marital status			
Single	24	19	NS
Married	48	62	NS
Divorced	28	19	NS
Smoking			
Yes	18	19	NS
No	82	81	NS
Alcohol use			
Yes	19	20	NS
No	81	80	NS
Physical activity			
Yes	34	46	NS
No	66	54	NS

*Significant difference ($p<0.05$). The Mann-Whitney test was used.

Table 2: Average and standard deviations for bedtime, latency, waking time and nocturnal sleep duration, nocturnal sleep quality and how participants felt upon waking, by work shifts

	Work shifts	n	Mean (00h00m00s)	SD	p-value
Bedtime	Day	26	23h07m00s	00h52m55s	NS
	Night	50	23h11m00s	01h07m00s	
Latency	Day	26	00h06m54s	00h10m55s	*≤0.001
	Night	50	00h20m06s	00h10m02s	
Waking time	Day	26	06h25m00s	00h54m48s	*≤0.001
	Night	50	07h52m00s	01h41m00s	
Nocturnal sleep duration	Day	26	07h12m00s	01h03m53s	*0.002
	Night	50	08h21m00s	01h27m00s	
Nap	Day	7	00h34m48s	00h14m58s	*0.001
	Night	22	01h30m00s	00h42m07s	

* Significant difference ($p<0.05$). The Mann-Whitney test was used.

Table 3 compares the variables of the sleep diary: bedtime, latency, nocturnal sleep quality, waking time, sleep duration and nap duration, with the categorical variables weight gain and weight loss in the study period.

The night shift group was divided into subgroups according to weight gain and weight loss; the average bedtime was 11:03 pm for the weight loss group and 11:39 pm for the weight gain group ($p=0.092$).

The average sleep latency of the workers that gained weight was longer (25m24s) than that of the weight loss group (18m30s). These data were significantly different ($p=0.026$).

The average score for nocturnal sleep quality was 7.65 for the weight loss group and 7.52 for the weight gain group ($p=0.842$).

The average wake time was 7:49 am for the weight loss group and 8:04 am for the weight gain group ($p=0.981$).

The individuals from the weight gain group showed an average sleep duration of 7h58m48s, whereas the average sleep duration for the weight loss group was 08h27m36s ($p=0.343$). The nap duration showed an average of 1h33m36s for the weight loss group and 1h22m48s for the weight gain group ($p=0.987$).

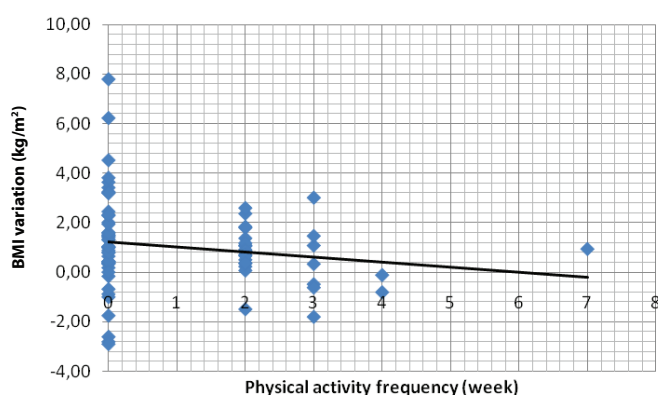


Figure 2: Correlation between physical activity frequency in a week and BMI variation. BMI difference: BMI 2- BMI 1. Spearman: ($r=-0.32356$; $p=0.0219$).

DISCUSSION

This study demonstrated that the night shift workers showed differences in sleep patterns and have a higher average BMI compared to the day shift workers. These data confirm other results found in the literature, describing the prevalence of obesity in night shift workers^(1,2,6,11) along with alterations in their sleep-wake cycles⁽¹²⁾. The sleep profile of these workers is characterized by difficulty in falling asleep at the desired time and a reduction of the efficiency and total duration of sleep. This can lead to both physical and psychological problems, neural disturbances, fatigue, nervousness, anxiety, depression, sexual problems and stress⁽²⁾.

This study observed that night shift workers had BMI in the overweight range, maybe because night shift workers show alterations in the sleep-wake cycle. They are chronically deprived of nocturnal sleep, thus promoting biochemical cascades that could perturb hormones that are released or altered during sleep. Examples of these hormones include growth hormone (which is secreted during deep sleep and regulates glucose synthesis), leptin (which is responsible for satiety), ghrelin (which stimulates appetite)⁽¹³⁻¹⁷⁾, cortisol (which inhibits the action of leptin and growth hormone⁽¹⁶⁾). During sleep deprivation, alterations might occur because the tired body stimulates feeding and decreases energy expenditure to increase energy reserves⁽¹⁸⁾, leading to an increase in weight gain⁽¹¹⁾.

When evaluating the weight gain in both shifts, it was observed that the night shift workers did not show greater weight gain than day shift workers during the study period. This finding agrees with another study that did not find any significant differences between the weight gains of night shift workers (0.3 kg) in comparison to day shift workers (0.6 kg) during the first phase of research (1980-1985). However, during the second phase of research (1985-1990), the results showed statistically significant differences. The weight gain of night shift workers was 2.2 kg and the weight gain of day shift workers was 1.3 kg. However, our findings showed similarities to the first phase of data

Table 3: Distribution of averages of the variables: bedtime, latency, waking time, sleep duration and nap duration, divided into the weight loss group and the weight gain group from the night shift employees

	Weight loss			Weight gain			p-value	
	n	Mean	SD	n	Mean	SD		
Bed time	11	23h03m00s	01h01m00s	Bed time	39	23h39m00s	01h22m00s	0.092
Latency	11	00h18m30s	00h08m24s	Latency	39	00h25m24s	00h13m30s	*0.026
Nocturnal sleep quality	11	7.65	1.29	Nocturnal sleep quality	39	7.52	1.59	0.842
Waking time	11	07h49m12s	01h33m36s	Waking time	39	08h04m12s	02h11m24s	0.981
Sleep duration	11	08h27m36s	01h31m12s	Sleep duration	39	07h58m48s	01h09m20s	0.343
Nap duration	06	01h33m36s	00h49m24s	Nap duration	16	01h22m48s	00h05m34s	1.000

* Significant difference ($p<0.05$). The Mann-Whitney test was used.

collection (short evaluation period); therefore, we suggest that the differences in the final results are due to the longer evaluation period used by the author⁽¹⁾.

Physical activity practiced regularly brings great benefits for both physical and mental health. The reduction in physical activity frequency is a risk factor that contributes to the development of obesity. Studies have verified that physical activity increases fat burning and reduces body mass^(11,19,20). In this study, it was observed that the weight difference decreased as the frequency of physical activity increased, meaning that these workers either gained little or maintained body mass. Consequently, it can be inferred that physical activity is essential to control obesity.

In addition to being important to increase energy expenditure, a study concluded that physical activity can modulate insulin and leptin signaling pathways (leading to a reduction of appetite), potentiating the effect of these hormones and interfering directly in the hypothalamus and in appetite control⁽²¹⁾.

In the analysis of the sleep patterns of the day and night groups, this study confirmed that the bedtimes of both groups were close to 11:00 pm, showing that when the night group workers sleep at night (on their day off), they do not show a habit of staying up late. This is in contrast with data found in another study⁽²²⁾.

The day shift group wakes up earlier than the night shift group as the start time for work is 7 am. The nocturnal sleep duration for the day group was shorter compared to the night group⁽²³⁾. This may be the result of sleep deficit because the night shift workers worked the night before, thus needing a longer nocturnal sleep duration than the day shift workers.

The nap, or short duration sleep, is a technique used to improve the alertness of employees during the night; it can be considered a possible strategic measure to compensate for fatigue. In this study, the results revealed that the night shift workers had a greater average naptime than the day shift workers. These findings are in agreement with another study that also demonstrated a greater average naptime for the night shift group. On the other hand, De Martino only observed naps in the day group, which is explained by the fact that sleep deficit also occurs when an individual wakes up too early⁽¹⁰⁾. The naps suggest tiredness and fatigue due to sleep deprivation⁽²⁴⁾, and can be a means of minimizing a possible sleep deficit.

The sleep deficit can result in alterations on metabolism and endocrine function, changing hormones responsible for feeding control, and this hormonal disparity can generate weight gain and obesity^(13-18,25).

The night shift workers showed a greater sleep latency time than that of the day shift group in this study, indicating a greater difficulty in falling asleep. Another study⁽¹⁰⁾ evaluated the sleep of the night groups and determined that this group of workers has difficulties in falling asleep quickly. In this study, the sleep latency time was compared between workers that gained weight and those that lost weight. The sleep latency time was confirmed to be higher in workers that gained weight than in the group that lost weight.

In conclusion, this study showed a higher prevalence of obesity in night shift workers in comparison to day shift workers. However, it cannot be confirmed that the sleep alterations influenced weight gain. The importance of physical activity in this group of workers must be emphasized in order to minimize the negative effects on the health of these individuals.

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Use of an oral appliance in a marked retrognathic and severe OSA patient. Three years follow-up: clinical report

Uso de um aparelho intraoral no tratamento da AOS grave em um paciente com severa alteração craniofacial. Três anos de acompanhamento: relato de caso

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ABSTRACT

The aim of this study was to show the efficacy of mandibular repositioning appliance (MRA) to treat severe obstructive sleep apnea (OSA) on a marked retrognathic patient that refused continuous positive airway pressure (CPAP) therapy. The apnea/hypopnea index (AHI) reduced from 38.5 to 12.0, despite marked retrognathia represented for the variable $\text{pog/N-perp} = -15.0$ mm. After 6 months and after 3 years of MRA usage, another polysomnogram (PSG) was carried out. The results showed an AHI=12.0 and 13.0, respectively, besides improvements in other physiologic variables. We concluded that MRA was effective in the treatment of severe OSA with a marked retrognathia. Sleep physicians should consider this therapy option when patients refuse CPAP and surgery approaches.

Keywords: Sleep apnea, obstructive/therapy; Orthodontic appliance design; Orthodontic appliances, functional; Mandibular advancement/instrumentation; Retrognathism

RESUMO

O objetivo deste estudo foi demonstrar a eficácia do uso do aparelho reposicionador mandibular (ARM) para o tratamento da apnéia obstrutiva do sono (AOS) grave em um paciente com severa alteração craniofacial e que recusou a terapia com pressão positiva contínua nas vias aéreas (CPAP). O índice de apnéia e hipopnéia (IAH) reduziu de 38,5 para 12,0, apesar de a alteração craniofacial representada para a variável $\text{pog/N-Perp} = 15,0$ mm. O exame de polissonografia (PSG) foi realizado com o aparelho *in situ* após 6 meses de uso e após 3 anos. Os resultados mostraram IAH=12,0 e 13,0, respectivamente, além de melhoras em outras variáveis fisiológicas. Concluímos que o ARM foi efetivo no tratamento da AOS grave acompanhada de uma severa alteração craniofacial. Médicos do sono devem considerar essa opção terapêutica quando pacientes portadores de SAOS grave recusarem o uso de CPAP e técnicas cirúrgicas.

Descritores: Apnéia do sono tipo obstrutiva/terapia; Desenho de aparelho ortodôntico; Aparelhos ortodônticos funcionais; Avanço mandibular/instrumentação; Retrognatismo

INTRODUCTION

According to the recent practice guidelines about the treatment of obstructive sleep apnea (OSA) with an mandibular repositioning appliance (MRA), the continuous positive airway pressure (CPAP) is considered to be a gold standard treatment for moderate and severe OSA, and it is indicated whenever possible before considering oral appliance⁽¹⁾. Because OSA is a multifactor disease, its treatment demands a multiprofessional approach. Generally, for the moderate and severe OSA patients, the physicians consider the advantages of CPAP therapy, upper airway surgery, or a combination of both treatments and, in specific cases, a maxillo-mandibular advancement surgery is suggested. Nevertheless, most patients decline surgery options and refuse or discontinue the CPAP therapy even knowing that this one allows the best results for this pathology. In the daily clinic, even severe OSA individuals who also show cranioskeletal abnormalities, such as marked maxillary and/or mandible retraction, microgenia, maxillary atresia, and marked upper airway constriction, generally prefer using OA instead of orthognathic surgery. Among the best-studied alternative treatments for OSA there is the MRA, designed to hold the mandible forward during sleep, increasing upper airway dimension and preventing the narrowing/collapse of the pharynx^(2,3). Actually, there are several studies proving the efficacy and the safety of OA therapy^(3,4). Follow-up studies have identified some drawbacks of these appliances, such as excessive salivation, occlusive changes, and temporomandibular joint or dental pain, though these last mentioned effects appear to be rare and tolerated by the majority of the patients in cases series^(5,6). There is little literature focusing the efficacy of MRA treatment in severe OSA patients and also in severe

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OSA patients with severe craniofacial alterations^(7,8). The aim of this case report was to share the results obtained with an MRA used in the treatment of severe OSA, over three years follow-up, in a patient with a severe retrognathia and micrognathia and refused CPAP usage.

CASE REPORT

A 32-year-old man with a body mass index (BMI) of 25.85 kg/m² and neck size of 42.0 cm was referred to us from a private sleep Medicine clinic to evaluate the possibility about the treatment of a severe OSA with a MRA. He underwent two polysomnograms (PSG), one basal PSG and one continuous positive airway pressure (CPAP) titration PSG. As indicated in Table 1, the apnea/hypopnea index (AHI) was 38.5, the minimum oxygen saturation (SaO₂ nadir) was 67.0%, the arousals index was 35.0/h and sleep efficiency (SE) was 94.7%. At the first appointment in the dentist office, he complained of snoring, nocturnal breathing arrests, tiredness upon awakening, and difficulty in concentrating. The score for Epworth Somnolence Scale (ESS) was 9.0 and, curiously, he related no excessive sleepiness. He related a vasomotor rhinitis, and from time to time he had to use a specific medication. When asked about CPAP treatment he said that during the sleep night titration he had difficulties to adapting to CPAP (11 cmH₂O) and refused to use it as a life therapy, since the AHI and arousals did not reduced, according to his expectation (Table 1). After this, he rented a CPAP for a month, to try once again this therapy, and related difficulties in adapting, probably due to his frequent nasal obstruction. Finally, he asked his sleep doctor for another treatment alternative, which was an oral appliance. The oral and facial evaluation revealed an ogival palate, a transversal atresic maxillary, the absence of the tonsils, an open mouth on rest, dental malocclusion class II, open bite, narrow face with vertical growth predominance, jaw on lower position, retrognathia and micrognathia (Figure 1). Patient's upper and lower arches presented all dental elements and temporomandibular joint (TMJ) palpation, and auscultation revealed no signs of dysfunction. A lateral cephalometric radiograph and upper and lower cast models were requested to evaluate the upper airway dimensions and dentoskeletal pattern. Cephalogram findings showed a marked maxillomandibular deficiency and a marked anteroposterior reduction of upper airways, severe retrognathia and the craniovertebral angulation was reduced (Table 2). Considering the degree of craniomaxillofacial abnormalities, the presence of severe OSA and the limited results with CPAP, a simultaneous maxillary and mandibular advancement (MMA) was suggested. It was explained that MMA is a surgery that has been shown

to be a highly effective treatment for apneic individuals with a maxillomandibular deficiency⁽⁹⁾, and after MMA an enlargement of upper airways occurs, and the collapsibility of the airway is decreased due to increased tension of the velopharyngeal and suprahyoid musculatures⁽¹⁰⁾. Despite all information given to the patient, he declined MMA option and preferred trying MRA as treatment for OSA before an invasive approach. The appliance chosen was the adjustable PM Positioner™, fabricated in two parts, joined together by two expanders on each side, which allow for titration according to each individual need. A constructive wax bite was approximately 60.0% of maximum protrusion, which was sent along with the cast models to the specialized laboratory for the OA manufacture. The increase in the vertical dimension did not exceed 7.0 mm, providing good appliance adaptation and effectiveness allied with comfort. The placement of the MRA proceeded (Figure 2) with advice given about the care and hygiene of the appliance. Similarly, the information about the follow-up visit twice a year and the need of a PSG once each two years was given. The initial titration was 1 mm and the subsequent titrations, 0.50 mm, were performed weekly to prevent TMJ symptoms. The total advancement reached about 9.0 mm and took about 2 months to complete. Side-effect related by the patient was only a dry mouth sensation lasted for the two first months. After six months and three years, a PSG was carried out to evaluate the efficacy of MRA over time.

Table 1: Polysomnogram findings from prior treatment to three year follow-up

PSG variables	Basal PSG	CPAP PSG	PSG after 6 months	PSG after 3 years
AHI	38.5	25.0	12.0	13.0
SaO ₂ min (%)	64.0	79.0	80.0	81.0
Arousal index	34.0	21.0	2.2	4.0
REM (%)	23.0	24.0	21.2	20.0
Sleep efficiency (%)	94.7	90.5	95.0	94.0

PSG: polysomnogram; CPAP: continuous positive airway pressure; AHI: apnea/hypopnea index; REM: rapid eye movement; SaO₂: minimum oxygen saturation.

Table 2: Cephalometric findings

Cephalometric values	Patient value	Normal value
SNB	74.0°	80.0°
ANB	5.5°	2.0°
PAS	8.8 mm	15.5 mm
CVA	86.0°	101.0 mm
Pog/N-Perp	-15.0 mm	0-1.0 mm

SNB: relationship of the mandible to the cranial base; ANB: relationship between upper and lower jaws; PAS: posterior airway space; CVA: angle between cranial and cervical spine; Pog/N-Perp: Pogonion to nasion perpendicular.

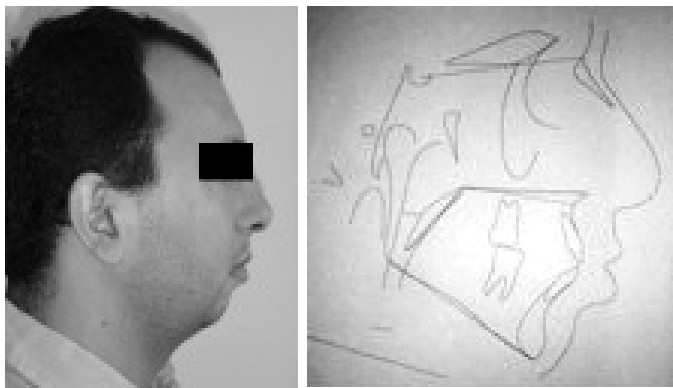


Figure 1: Patient facial pattern – severe retrognathia

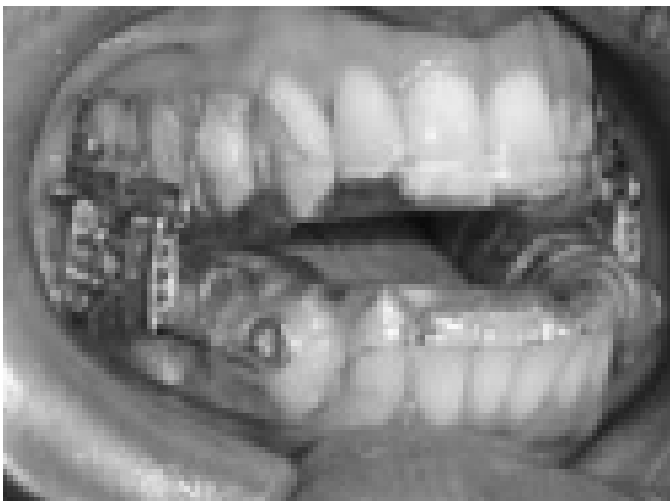


Figure 2: Lateral view of mandibular repositioning appliance (MRA) *in situ*

RESULTS

A comparison of the initial PSG and the PSG taken with the MRA *in situ* after six months (Table 1) revealed that snoring had significantly reduced, according to his spouse report, and the AIH has reduced from 38.5 to 12.0, the SaO₂ nadir rose from 67.0% to 80.0%, the arousals index decreased from 34.0 to 2.2, and there were improvement in other physiologic variables (Table 1). The results after three years of OA usage showed that MRA was still effective, with an AHI=13.0, and his wife stated that snoring was still reduced, but not totally eliminated. The patient related that subjective symptoms have improved, such as snoring, nocturnal breathing arrests, tiredness upon awakening, and difficulty in concentrating. ESS values remained the same, since the patient did not complain of excessive sleepiness before treatment.

DISCUSSION

The use of an MRA to treat a severe OSA with an AHI over 38.0 was efficient. Even the patient skeletal pattern presented unfavorable measures. It must be noted that, in

this case, the low BMI could have been an important factor to achieve the significant decrease of AHI⁽¹¹⁾. Another factor that must have contributed to this result was the presence of a marked retrognathia, with an angle between mandible and cranial base (SNB=74°), an angle between upper and lower jaw (ANB=5.8°)⁽¹²⁾ and the relationship of mandible to cranial base Pog/N-Perp= -15.0 mm⁽¹³⁾. A cephalometric study comparing 30 OSA patients to 30 normal ones showed that OA was more effective when SNB angle and posterior airway space (PAS) presented narrow values⁽¹⁴⁾. In our study, patient's PAS was 8 mm (Table 2) before treatment, which also converge to Otsuka et al.⁽¹⁵⁾ study, in which they stated that smaller dimensions of PAS are predictive success factor in responder patients, otherwise, the small values of SNB were not significant factor in the responder group, which was composed of mixed OSA severity. In a previous study⁽⁷⁾, the authors showed a favorable result using MRA to treat a severe OSA in two patients with craniofacial alterations. In our work, OA usage reduced the AHI from 38.5 to 12.0 events per hour after 6 months, and to 13.0 after 3 years. Barthlen et al.⁽¹⁶⁾ compared the efficacy of three types of oral device to treat severe patients and found that mandibular positioning appliance, as used in our study, was most effective to treat OSA in a group with severe patients only. In a recent study, a severe OSA was successfully treated with an OA⁽¹⁷⁾. We can find in the literature several articles showing the use of OA to treat OSA in a group that also have severe OSA patients^(2,3,14,15), but there are little articles using a group of severe OSA only^(7,16,17). Despite CPAP can reach better results, studies have shown that patients prefer MRA treatment⁽¹⁸⁾. The American Academy of Sleep Medicine (AASM)⁽¹⁾ states that MRA therapy should be used as first option on snoring and mild SAOS patients. Our patient's characteristics are not uncommon amongst successful OA therapy, and literature shows that most OSA patients are CI II malocclusion⁽⁹⁾, but to our knowledge, there are no studies showing an OA treatment efficacy with three year follow-up in a severe OSA patient, independently of cephalometric characteristics. This result can bring more confidence to dentists to treat severe patients who cannot accept or adapt to CPAP treatment. We believe that other physiologic variables might be evaluated in further studies (e.g. blood pressure). Our study objectively showed that it is important to understand that, in specific cases, it is better to carry out a MRA treatment than leave the patient remains without any SAOS treatment.

CONCLUSION

The results after six months and three years of MRA use showed that the device was efficient to treat severe OSA;

its efficacy remained at an optimum level after three years, despite the craniofacial status presenting unfavorable values. Further studies focusing the evaluation of blood pressure in these cases are necessary, since the OA may be used for a long time to treat OSA.

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The influence of intensity of exercise over periodical leg movement and obstructive sleep apnea syndrome: a case report

A influência da intensidade do exercício físico nos movimentos periódicos das pernas e na síndrome da apnéia obstrutiva do sono: um relato de caso

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ABSTRACT

There is evidence that regular exercises promote a number of changes and physiological benefits, and can be considered a non-pharmacological intervention, which improves the sleep quality of people who really do not have any sleep disorders. Yet, few studies have assessed how exercise can benefit a specific population with sleep disturbance. The aim of this study was to examine the influence of an aerobic training (AT) program of variable intensity in a sample of volunteers who had periodic leg movement (PLM) and obstructive sleep apnea syndrome (OSAS). The 51 year-old volunteer, body mass index (BMI) 28.67 kg/m², sedentary, presenting PLM (rate >53.5/hour) and OSAS (AHI index >12.8/hour) was submitted to aerobic training on a treadmill in the mornings 3 times a week, each session lasting 40 minutes, thus totaling 72 sessions. Prior to aerobic training, the volunteer took a maximum effort test (MET) so that prescription of safe aerobic training could be made. The first aerobic training was done at 60% of the VO₂peak so that acute effects of exercise could be assessed. Sessions 2 up to 24 were performed at ventilation threshold 1 (VT1) and sessions 25 to 48 were performed between ventilation threshold 1 and ventilation threshold 2 while sessions 49 to 72 were done between VT1 and VT2, with predominance at VT2. Polysomnographic and maximum effort test tests were carried out every 6 months throughout the aerobic training period and one month after the 72 sessions (suspension of training). We demonstrate that aerobic training at the intensity of VT1 promoted a reduction in the rate of periodic leg movement in relation to baseline values (53.5/h to 38.6/h). After the increase in intensity of aerobic training and a shift to the VT1 and VT2 range with predominance in VT2, the rate of periodic leg movement rose (63.8/h), and after one month of training suspension this rate was still higher than that of its corresponding moment baseline value (72.8/h). The AHI also increased during heightened AT when AT was performed at the intensity of VT1 27.8/h during AT compared to baseline 12.8. Such rates approached baseline values at VT1 and VT2 with predominance at VT2 (13.0/h) only to increase once again after one

month suspension of training. AT at loads compatible with VT1 promoted enough improvement in the rate of periodic leg movement to down-grade the condition from severe to moderate, but sleep apnea syndrome increased at that intensity of exercise climbing from mild to moderate. Such results suggest that the benefits credited to AT have distinct mechanisms of action in periodic leg movement and sleep apnea syndrome

Keywords: Sleep; Leg/physiopathology; Restless legs syndrome; Sleep disorders; Electromyography; Polysomnography; Sleep apnea, obstructive; Exercise therapy

RESUMO

Há evidências de que o exercício físico regular promove uma variedade de adaptações e benefícios fisiológicos. O exercício físico pode ser considerado uma intervenção não-farmacológica para a melhora da qualidade do sono em pessoas que apresentam algum distúrbio do sono. No entanto, poucos são os estudos que avaliam os benefícios de-correntes do exercício físico para essa população específica. O presente estudo teve por objetivo avaliar a influência de um programa de treinamento físico aeróbio (TFA) realizado em diferentes intensidades em um voluntário que apresentou, no exame polissonográfico, movimento periódico das pernas (MPP) e síndrome da apnéia obstrutiva do sono (SAOS). O voluntário, com 51 anos, 91 kg, 178 cm, índice de massa corpórea (IMC) de 28,67, sedentário, apresentando MPP (>5/hora) e SAOS (índice >5 hora) foi submetido a um programa de TFA (esteira) pela manhã 3 vezes por semana, com duração de 40 minutos cada sessão, totalizando 72 sessões. Inicialmente, foi realizado um teste de esforço máximo (TEM) para a prescrição do treinamento físico aeróbio. A primeira sessão de treinamento físico aeróbio foi realizada a 60% do VO₂pico para análise do efeito agudo do exercício físico, as sessões 2 a 24 foram realizadas no limiar ventilatório 1 (LV1), as sessões 25 a 48 foram intervaladas entre o LV1 e LV2, e as sessões 49 a 72 foram

Study carried out at Hospital São Paulo, Universidade Federal de São Paulo – UNIFESP, São Paulo (SP), Brazil.

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intervaladas entre o LV1 e LV2 com predomínio no LV2. Foram realizados exames polissonográficos e TEM durante os 6 meses do treinamento físico aeróbio e após 1 mês do término das 72 sessões de TFA (destreino). Foi demonstrado que o treinamento físico aeróbio realizado na intensidade do LV1 promoveu uma redução no índice de movimento periódico das pernas em relação aos valores basais (53.5/h a 38.6/h). Após o aumento da intensidade do treinamento físico aeróbio para intervalado entre o LV1 e LV2 com predominância em LV2, o índice do movimento periódico das pernas se elevou (63.8/h), visto que após um mês de destreino esse índice se apresentou mais alto do que o encontrado no momento basal (72.8/h). O índice da síndrome da apneia obstrutiva do sono apresentou aumento durante o treinamento físico aeróbio realizado na intensidade do LV1 em relação ao seu valor basal (12.8/h a 17.7/h), retornando próximo aos valores basais na intensidade de LV1 e LV2 com predominância em LV2 (13.0/h) e aumentando novamente após um mês de destreino (16.0/h). O exercício físico aeróbio com carga equivalente ao LV1 promoveu uma melhora no índice do movimento periódico das pernas, demonstrando mudanças na classificação de grave para moderado. No entanto, síndrome da apneia obstrutiva do sono demonstrou um aumento no seu índice com essa intensidade de treinamento, passando de leve para moderado. Esses resultados sugerem que o mecanismo de ação do exercício físico para esses dois distúrbios do sono age de maneira distinta em relação aos benefícios propostos pelo treinamento físico aeróbio.

Descritores: Sono; Perna/fisiopatologia; Síndrome das pernas inquietas; Transtornos do sono; Eletromiografia; Polissonografia, apnéia do sono tipo obstrutiva; Terapia por exercício

INTRODUCTION

It is widely assumed that many factors bear influence upon the architecture of sleep. Periodic leg movements disturbance (PLMD), the restless leg syndrome (RLS) and obstructive sleep apnea syndrome (OSAS) are sleep disturbances that interfere in sleep architecture. The first two, PLMD and RLS, are characterized as movement disorders related to sleep, and their most impacting consequence upon the quality of life of the patient is the reduction of the quality and efficiency of sleep, a condition that is accompanied by daytime somnolence. OSAS, in turn, is mainly characterized by repetitive events of either partial (hypopnea) or total (apnea) obstruction of the upper airway causing hypoxemia, and in prolonged cases, hypercapnia that is often reverted by arousals causing sleep fragmentation⁽¹⁾. Because of its ubiquity, the approach taken to deal with OSAS should be that of a public health issue⁽²⁾. The association of these disturbances is common. In a study conducted by Al-Alawi et al.⁽³⁾, it was demonstrated that the combination of OSAS and PLM resulted in increased daytime somnolence, and that PLM associated with OSAS proved to be more prevalent than in PLM in relation to RLS.

There is evidence that regular exercise produces a number of physiological benefits. Adaptation to exercise may be observed in the young, adult and aging populations as well as in those who suffer from some diseases. Factors such as the level of physical fitness, time and design of exercise, genetic factors, age and gender may bear influence in the extensive repertoire of adaptation strategies the body deploys in order to have a better quality of life⁽⁴⁾.

Systemized exercise is considered a non-pharmacological intervention that improves the quality of sleep and its disturbances⁽⁵⁾. Epidemiological studies have demonstrated that exercise causes improvement of the quality of sleep and reduces daytime somnolence^(6,7). There are few studies that have examined the influence of exercise upon sleep disturbances alone. Recently, Aukermam⁽⁸⁾ carried out a study that involved a program of combined exercises (aerobic and resisted exercise) with the purpose of analyzing its effectiveness in symptoms of RLS. Twenty-three volunteers (11 belonging to the experimental group and 12 to the control group) were submitted to aerobic and resisted exercise, 3 times a week for 12 weeks. In order to analyze the RLS variable, the questionnaire International RLS Study Group Scale (IRLSSG)⁽⁹⁾ was applied, which assesses the symptoms of gravity, frequency, and impact of RLS upon the quality of life. Results demonstrated that from the 6th week on, symptoms of RLS presented a statistical reduction in relation to the Control Group. There was no significant difference between the 6th and the 12th week. The authors concluded that the program of combined exercises was effective in the improvement of symptoms of RLS, but further studies are required to demonstrate how different modes of exercise influence each symptom.

Giebelhaus et al.⁽¹⁰⁾ carried out a study on sedentary individuals with moderate and severe OSAS wherein an aerobic and resisted exercise program was deployed, under supervision, 2 hours a day, twice a week, for 6 months. No significant differences were encountered in cardiorespiratory parameters and body mass throughout training, but there was a significant reduction in the rate of apnea events per hour, from 32.8 to 23.6, which did not result in alteration of body mass or in sleep architecture.

However, the effect of exercise in patients who present a combination of two or more sleep disturbances, particularly of PLM and OSAS, was not found in the literature. Thus, which prompted us to examine the isolated case of a patient who had that combination (PLM and OSAS), the objective of the present study, was to evaluate the influence of an Aerobic Training (AT) program with variable intensity.

THE CASE

The study had the approval of the ethical board for research of the Hospital São Paulo, Universidade Federal de São Paulo (Protocol - 0948/05). Once the required clarifications were given and prior to the commencement of the protocol, the patient signed an informed consent form agreeing to partake in the study.

A white male, 51 years old, weighing 91 kg and measuring of 1.78 m in height who, for 8 years, has complained of sudden kicks during sleep that awaken him. The patient looked for a sleep specialist and was referred to polysomnography (PSG). The PSG revealed he had PLM and OSAS. To treat his sleep disturbances, the patient was offered the alternative of partaking in an aerobic exercise program for six months. Upon his engagement in the program, the patient was physically evaluated by means of electrocardiograms taken at rest and effort and by laboratory exams to determine whether or not he would be apt to participate in the study as well as to establish the dosages of iron (ferritin), so that its relation with PLM could be verified.

The experimental design

The patient took a 6-month aerobic training program wherein exercise was performed in the morning (7:00) 3 times a week, totaling 72 exercise sessions. After adapting to the exercise apparatus by exercising every other day for 3 days on the treadmill (Life Fitness® 9700 HR), the patient underwent a maximum effort test (MET) so that the adequate prescription of exercise intensity could be established. On the 1st session of exercise, at 7:00, a PSG was taken in order to assess the acute effect of exercise. The patient then took to his daily affairs as he normally would only to return to the lab again at 21:00 for PSG arrangements. To assess the effects of chronic exercise, PSG was taken on the day subsequent to the sessions 2 and 6 months into the training program. After 6 months, another MET was taken at 60% of maximum oxygen consumption, and on that same day a PSG recording was collected so that the acute effect of the training could be appreciated. After the last training day, the volunteer took a PSG and remained a month without doing any kind of exercise. A last PSG was taken at the end of the idle month to collect data on the period relative to loss of fitness.

The experimental protocol

Polysomnographic exam

The sleep parameters were recorded by means of PSG using the device EMBLA S7000® at epochs with 30-second intervals classified as awake, stages 1, 2, 3 and 4 of NREM

and REM, according to the standardized protocol by Rechtschaffen and Kales⁽¹¹⁾.

The electroencephalographic recording was obtained by means of fixated electrodes according to the directives of the International System 10-20⁽¹²⁾. Four electroencephalographic derivations were used, two electrooculogram channels, two electromiogram channels (submentonian and legs) and an ECG derivation. Termistor and nasal canula were used to monitor airflow, and belts to monitor thoracic and abdominal effort, transcutaneous oximetrics to record oxygen saturation, and a sensor to verify the position of the trunk during sleep.

The recording of muscular tonus by electromiography was done by placing two electrodes in the mentonian/submentonian regions. These were placed on both legs over the anterior tibial muscle. PLM was gauged visually scored by a trained sleep in accordance with the criteria established by the ASDA Task Force⁽¹³⁾.

The maximum effort test (MET)

Aerobic exercise and the maximum effort test (MET) were performed on a treadmill (Life Fitness® 9700 HR). Initial speed was set at 4 km/h, increasing 1 km/h every minute until the volunteer reached either exhaustion or maximum heart rate. The surface of the treadmill was set at an inclination of 1% to simulate open terrain⁽¹⁴⁾. VO_{2peak} was obtained by means of analysis of ventilation alterations during the MET after incremental loads. Recording of the data was done using the metabolic analyzer Quark PFT Ergo 4 (Cosmed®).

Aerobic exercise was done at ventilation thresholds VT1 and VT2. The term VT refers to the point in which pulmonary ventilation increases out of proportion in relation to oxygen consumption during exercise with incremental loads⁽¹⁵⁾. It is assumed that H⁺ ions from lactic acid are tamponated by blood bicarbonate, thereby producing excess of CO₂ which, in part, increases ventilation (VE). The theory holds that the initial concentration of lactic acid coincides with the hyperventilation induced by exercise when it is done with incremental loads⁽¹⁶⁾. At VT1 (moderate exercise), exercise with load increment is related to the moment in which there is an equivalent increase of oxygen ventilation (VE/VO₂) as well as oxygen pressure (PETO₂), but without an equivalent change in CO₂ ventilation (VE/VCO₂) or in CO₂ pressure (PETCO₂). As intensity of exercise exceeds this threshold, metabolic acidosis causes a plunge in pH followed by an increase of VE/VCO₂ and reduction of PETCO₂, reaching the “point of respiratory compensation” of metabolic acidosis or VT2 (intense exercise)⁽¹⁷⁾.

The use of VT in the determination of the capacity to execute prolonged exercise and limitation of performance

has grown in the past years as it is an objective parameter collected in a noninvasive manner⁽¹⁸⁾, and one that can be used as a variable or parameter for the prescription of exercise.

Training prescription

The 72 training sessions were distributed into 4 periods, 40 minutes each:

- period I (3 sessions): Volunteers adapted to the exercise and equipment;
- period II (11st – 24th session): training at VT1 intensity, the 1st session being at 60% of VO₂peak for 30 minutes for the determination of acute effects of exercise;
- period III (25th - 48th session): training at intensities between VT1 and VT2;

Table 1: Results obtained in the assessments of cardiorespiratory capacity along the six months of exercise

Assessment of the cardiorespiratory capacity	Basal	6 Months	After idle period
VO ₂ max (L/min)	3.3	3.72	3.23
VO ₂ max (mL/kg/min)	38.07	42.83	36.76
VE max (L/min)	121.6	131.7	111.1
HR max (bpm)	162	168	176
HR prev (bpm)	170	169	169
Oxygen consumption (VT1) l/min	1.72	2.34	1.94
Oxygen consumption (VT2) mL/kg/min	19.36	26.3	22.1
HR (VT1)	120	128	141
Speed (VT1) Km/h	7	9	8
Oxygen consumption (VT2) L/min	2.39	3.03	2.47
Oxygen consumption (VT2) mL/kg/min	26.36	34.05	28.12
HR (VT2)	148	151	157
Speed (VT2) km/h	9	11	9

Descriptive data of the sample.

VO₂: oxygen consumption; VE: ventilation maximum; HR: heart rate; VT: ventilation thresholds.

Table 2: Results obtained from polysomnographic exams along the six-month exercise period

Polysomnographic data	Basal	Acute	2 Months	6 Months	Acute	After idle period
Total sleep time (minutes)	427.5	368	374.5	351.5	398.5	419
Sleep efficiency (%)	91.3	89.9	80.2	89.5	92.4	87.2
Sleep latency (minutes)	6.4	0.6	3.2	4.7	7.3	4.2
REM sleep latency (minutes)	87	56	73.5	71	49	70
Time awake after sleep onset (minutes)	34.5	40.7	89.1	36.8	25.5	57.1
Stage 1 (%)	3.9	4.2	4.1	2.7	3.1	4.5
Stage 2 (%)	56.3	54.1	56.7	60.3	55	62.3
Slow wave sleep (%)	16.7	17.6	16.7	12.3	14	9.8
REM (%)	23.2	24	22.4	24.8	28	23.4
Microarousals rate (/h)	19.7	20.3	31.6	36.6	27.3	29.3
PLM Rate (/h)	53.5	68.9	38.6	63.8	81.5	72.8
Apnea-Hypopnea Index (h)	12.8	11.1	27.8	16	13	16

Descriptive data of the sample.

REM: rapid eye movement; PLM: periodical leg movement.

- period IV (49th - 72nd session): training with emphasis on VT2 intensity and recovery at VT1.

All tests were carried out within the laboratory at controlled temperature (22°C and 24°C) and relative air humidity between 40 and 60%.

RESULTS

Analyses of blood iron (170 ug/dl) and ferritin (411,1ng/ml) were within normality for the population.

Table 1 depicts the values of the ergospirometrical variables that were found after the MET. Results that refer to the sleep pattern after exercise are depicted in Table 2. It was observed that PLM decreased in the two-month training period and returned to values classified as severe after six months' training. The classification of OSAS, in turn, shifted to moderate after the first two months of training only to resume baseline values six months after training.

DISCUSSION

After a six-month, three-time-a-week aerobic training program, it was demonstrated that a patient who had PLM and OSAS presented different responses in the rate of these disturbances in relation to the intensity of exercise.

When the exercise was moderate, the rate of PLM reduced after two month's exercise, but resumed baseline values after six months of intense exercise. A partially inverted scenario occurred with OSAS, which is to say that AHI increased in the two months of moderate exercise (VT1) and resumed baseline values after six months of intense (VT2) exercise.

PSG recordings taken on the day of acute exercise and at the end of the day of aerobic exercise (for chronic effects) did not reveal significant differences in the variables of the sleep pattern. Physical exercise itself does influence

the sleep architecture, as Hague et al.⁽¹⁹⁾ verified that systemized training promotes an increase in slow wave sleep, in total sleep time, in stage 2 of NREM sleep, and also in latency for the onset of REM sleep, and may still reduce the total sleep time of REM and latency for the onset of sleep in athletes. This corroborates the view held by most researchers examining the influence of exercise upon sleep who promptly verify that exercise causes an increase in slow wave sleep and increase of latency for REM sleep, as well as a reduction of REM sleep^(20,21). Notwithstanding, the current investigation did not verify any marked alteration in the sleep stages of the volunteer, only a reduction of latency for REM sleep, but no reduction of slow wave sleep in the first half of the night and/or increase of REM sleep when PSG was recorded on the exercise day to assess acute and chronic effects of the training. It should be said at this point that there is evidence that the volume of exercise should be higher before significant sleep alterations can be expected^(22,23). In the current study, the intensity and duration of exercise show that moderate exercise reduced the intensity of PLM but increased the number of microarousals and AHI enough to re-classify it from mild to moderate. Increased intensity exercise led rates of PLM to exceed baseline values while those of AHI reduced approaching baseline values.

According to Rodrigues et al.⁽²⁴⁾, the association of OSAS and RLS are responsible for complaints of daytime somnolence. This investigation attempted to verify whether fatigue symptoms and excessive daytime somnolence prior to and after Continuous Positive Airway Pressure (CPAP) treatment in patients with OSAS and RLS. At the beginning of the study, no significant differences were found between groups, but after the CPAP treatment those patients who presented an association with disturbances presented higher scores in the Epworth Sleepiness Scale and in the Pichot fatigue/depression questionnaire. This leads to the conclusion that CPAP was more effective in the treatment of OSA, the symptoms remained more due to PLM.

Norman et al.⁽²⁵⁾ carried out a study about the effects of exercise over OSAS in patients who had moderate to mild cases and who were requested to participate in an aerobic training program that would last six months. The following pre and post-training exams were: PSG, treadmill effort test, and anthropometric measurements. In addition, a questionnaire was given on quality of life. At the 4th month, a new effort test was done on the treadmill in order to adjust the training load if necessary. The results showed that there was a significant reduction in the AHI, with improved total sleep time, sleep efficiency, number of arousals per hour, and body mass. Thus, it can be inferred that physical training had a positive impact upon not only

OSAS but also the conditioning of aerobic capacity as well as quality of life. This comes to show that exercise can indeed be adopted as a non-pharmacological means of dealing with OSAS.

Herein, the volunteer presented improvement in the cardiorespiratory capacity, reduced fat percentage with no alteration in body mass, and, even suffering of OSAS, there was good quality and efficiency of sleep, and no alteration in sleep architecture was verified.

De Mello et al.⁽²⁶⁾ observed, by means of PSG, that exercise in athletes who suffered medullar lesion significantly reduced PLM during sleep. One hypothesis for the relation between exercise and reduction of PLM is the release of β -endorphin that occurs with exercise. It is known that blood concentration of β -endorphin increases with exercise, depending on the intensity, duration and volume of training, and that the substance acts in very much the same way that the exogenous opioids that are used in the treatment of PLM⁽²⁷⁾.

Although there is no consensus in the literature as to the best type, time, intensity or duration of exercise, physical training is definitely recommended in the promotion of quality of life. And we may suggest that the results collected herein reflect mechanisms distinctly dependent upon either PLM or OSAS, which means that exercise presents diverse effects on each of these two disturbances that are verifiable in the relevant association between the modulation of PLM and OSAS symptoms and intensity and volume of exercise.

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Influence of social factors on the sleep-wake cycle in children

Influência de fatores sociais sobre o ciclo sono-vigília de crianças

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ABSTRACT

In children, the sleep-wake cycle (SWC) is influenced by both social and biological factors. Recently, lifestyle changes have introduced a number of social factors that negatively impact sleeping patterns. This review characterizes the sleep-wake cycle and describes how social factors influence this cycle in children. Social factors such as bed-sharing and room-sharing, as well as media use, the family environment, and the school schedule, all impact a child's routine and affect health and well-being. While a routine can benefit a child's health, in some situations these factors can delay the beginning of sleep and negatively impact the sleep-wake cycle. When coupled with a school schedule that begins early in the morning, these factors can result in partial sleep deprivation, sleep disturbances, and irregular sleeping and waking times. These sleeping problems can result in low school performance, obesity, attention-deficit/hyperactivity disorder, and to be a predictor of insomnia in adolescents.

Keywords: Sleep-wake transition disorders; Socioeconomic factors; Child; Sleep deprivation; Sleep disorders

RESUMO

O ciclo sono e vigília (CSV) de crianças é influenciado por fatores biológicos e sociais. Entretanto, devido ao estilo de vida atual, as mudanças sociais aumentam e apresentam um impacto negativo no padrão de sono. Essa revisão tem como objetivo caracterizar o ciclo sono e vigília e a influência de fatores sociais sobre esse ciclo em crianças. O co-leito, quarto compartilhado, uso da mídia, ambiente familiar e horário escolar são alguns dos fatores sociais que fazem parte da rotina da criança e trazem benefícios para a saúde e o bem-estar. Entretanto, em algumas situações podem retardar o início do sono interferindo de forma negativa no ciclo sono e vigília de crianças, na medida em que associados ao horário escolar matutino, provocam irregularidade nos horários de dormir e acordar, privação parcial de sono e distúrbios de sono. Essas alterações podem ter como conseqüências um baixo desempenho escolar, obesidade, transtorno de déficit de atenção e hiperatividade e o aparecimento da insônia na adolescência.

Descritores: Distúrbios da transição sono-vigília; Fatores socioeconômicos; Criança; Privação do sono; Distúrbios de sono

INTRODUCTION

The sleep-wake cycle (SWC) is one of the most extensively studied biological rhythms in humans. Previous research

has shown that sleep plays an important role in restoring physiological and biochemical processes^(1,2), consolidating memory^(3,4), and maintaining energetic balance^(5,6).

The SWC is regulated throughout the day via two processes: the circadian and the homeostatic process⁽⁷⁾.

The circadian process regulates the alternation between sleeping and waking states by initiating or preventing sleep at specific times throughout the day^(7,8). While this process regulates sleep based on time, the homeostatic process controls sleeping patterns based on the duration of previous waking and sleeping states. Upon waking, there is little desire to sleep, but it increases as the waking state progresses – ultimately resulting in sleep. During sleeping states, the homeostatic process gradually decreases the desire to sleep until waking is initiated^(7,8). Thus, the interaction between the homeostatic and the circadian processes regulates the initiation and the cessation of sleep, and the maintenance of the states of sleep and wake^(7,8).

The SWC is also influenced by cultural factors and lifestyle habits that can deprive people of sleep benefits. Because we are now a “twenty-hour society”, nighttime activity has been dramatically increased, impacting the SWC of both adults and children⁽⁹⁾.

Children need an adequate night of sleep to maintain alertness and responsiveness in social interactions⁽¹⁰⁾. While recent lifestyle changes have caused children to go to bed later during weekdays (because of distractions such as television, the internet, and video games), children must still wake up early for school, resulting in partial sleep deprivation and an irregular sleep schedule. Several studies have associated partial sleep deprivation and health impairments with obesity^(5,6,11), reduced cognitive performance^(12,13), and attention-deficit/hyperactivity disorder^(13,14). Moreover, these alterations in the SWC can influence a child's physiological, psychological, emotional, behavioral, and cognitive development⁽¹⁵⁾. Therefore, this review aimed to characterize the SWC and describe how social factors influence this cycle in children between one month and ten years of age.

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SLEEP-WAKE CYCLE

During infancy, newborn children display a polyphasic sleep pattern that is characterized by several episodes of sleep throughout the day⁽¹⁶⁻¹⁸⁾. Throughout the first year of life, the SWC begins to synchronize with the environmental light-dark cycle as the neural pathways responsible for synchronizing biological and environmental factors mature^(16,17,19). As they grow older, children go to bed and wake up earlier, increasing their nighttime sleep while the number of daytime sleep episodes (naps) decreases^(16,20). This reduction in daytime sleep results in an overall sleep reduction; the average daily duration of sleep decreases from 14 hours, in the first year of life, to 10 hours after 7 years of age (Table 1)^(16,19,21-23). However, the daily duration of sleep varies between weekdays and weekends⁽²²⁾.

However, in view of biological variations in preference with regard to the times of sleeping and waking (diurnal preference) and cultural aspects, there is not a specific age at which a child stops napping⁽²⁴⁾ or a specific pattern of sleep initiation, cessation, or duration at each age⁽²⁵⁻²⁸⁾. Even children of the same age display different sleep times⁽¹⁸⁾. Thus, the daily duration of sleep at each age is only a parameter because each individual's need for sleep varies (Table 1).

In addition to developmental, individual, and cultural changes that affect the SWC, infancy is marked by changes in the social environment, such as beginning school and sleeping alone. Habitual bedtime behaviors (bedtime rituals) and sleep location (bed-sharing or room-sharing with parents) can compensate for these changes by calming the child during the transition between waking and sleeping states.

BED- AND ROOM-SHARING

Some infants share a bed (bed-sharing) or a bedroom (room-sharing) with their parents. These behaviors are a function of culture^(29,30) and the socio-economic level of the family⁽³¹⁾.

Several studies have observed that children who share a bed or a bedroom with their parents have higher self-esteem, less anxiety⁽³²⁾, greater comfort when feeding⁽³³⁾, and more maternal interaction⁽³⁴⁾. However, there is also evidence that these behaviors can have negative effects, such as resistance at bedtime, which delays both sleep and waking and reduces nighttime sleep duration⁽³¹⁾. In addition, these behaviors are associated with the frequency of nighttime waking and sudden infant death syndrome^(31,35-37).

Bed-sharing is common during the first years of life, reaching its maximum occurrence between three and five years of

age and then decreasing as the child begins to sleep in its own room^(31,36). The increased incidence of co-sleeping between three and five years of age is probably caused by increasing locomotor independence⁽³⁶⁾ and the beginning of school, both of which have a strong impact on the SWC of children. A study by Silva et al.⁽³⁸⁾ found that only 7% of school children between seven and ten years of age sleep by themselves.

BEDTIME RITUALS

The most common bedtime rituals are sleeping with a favorite object (transitional object), sleeping with the lights on, drinking milk^(10,38), calling for a parent at night, and requiring the mother's presence in the bedroom⁽¹⁰⁾.

Children use transitional objects such as blankets, body parts (thumb sucking), toys, or other objects (a pillow, a pacifier, a parent's clothing, or a stuffed animal) to provide security in the mother's absence and facilitate the transition between waking and sleeping states^(18,39-40). When the transitional object is part of the bedtime routine, blankets, toys, and pacifiers are used most often. Girls and younger children prefer to sleep with a blanket or toy, but this behavior decreases at approximately five years of age^(10,38).

No study has yet evaluated the influence of transitional objects on the SWC because previous studies have largely investigated the soothing effects of transitional objects^(10,38-41).

In addition to transitional objects, other behaviors, such as sleeping with the lights on^(10,38), drinking milk or other beverages before bedtime⁽³⁸⁾, or calling for a parent at night⁽¹⁰⁾, can minimize sleep-related fear and anxiety in children in the first ten years of life.

However, Beltramini and Hertzog⁽¹⁰⁾ argue that the bedtime ritual involves several distinct behaviors: 1) putting on pajamas or changing a diaper, 2) drinking a beverage such as milk, 3) listening to a story or song, and 4) a kiss good night. More than 30 minutes a day are necessary to execute this routine, and longer times are required for the execution of these rituals as the child grows older⁽¹⁰⁾.

The influence of these additional rituals (sleeping with the lights on, drinking milk and calling for a parent at night) on the SWC is unknown. It should be noted, however, that sleeping with the lights on can suppress the release of melatonin, which is secreted by the pineal gland when there is no light on the retina. Light thus inhibits the release of melatonin, favoring the waking state, whereas the absence of light induces melatonin release and induces the sleep state⁽⁴²⁾. The cyclic variation of

Table 1: Average and standard deviation of total sleep duration from different questionnaire-based studies

Age (years)	Total sleep duration (hour)			
	Switzerland – Iglowstein et al. ⁽¹⁹⁾	Switzerland – Jenni et al. ⁽²¹⁾	Saudi Arabia – BaHammam et al. ⁽²²⁾	Egypt – Abou-Khadra ⁽²³⁾
1	13.9±1.2	14.6±1.4	-	-
4	11.8±1.0	12.1±1.2	-	-
7	10.6±0.7	11.1±0.7	9.4±1.3	9.06±1.29
10	9.9±0.6	10.1±0.6	9.2±1.3	9.06±1.07

light and dark of environment is the main synchronizer of the SWC; therefore, light can both stimulate the release of melatonin and delay the beginning of sleep depending on when the individual is exposed to the stimulus. According to Khalsa et al.⁽⁴³⁾, a light pulse between the end of the waking state and the beginning of the sleeping state delays sleeping and waking times, whereas a pulse between the end of the sleeping state and the beginning of the waking state advances these times.

Several studies have shown that adolescents who live in urban areas, which are exposed to artificial light at night, display later sleep times relative to students in rural areas. This difference is caused by artificial light, which delays melatonin release and, consequently, sleep time^(44,45). Nevertheless, further studies are necessary to determine whether sleeping with the lights on affects the SWC of children, and whether this stimulus can delay sleep times in the same way that it affects adolescents in urban areas.

MEDIA USE

Some parents incorporate television into their child's bedtime routine or associate television with their child falling asleep^(46,47). Watching television before bedtime or having a television in the bedroom apparently minimizes difficulties at bedtime. Nevertheless, television can delay the beginning of sleep⁽⁴⁶⁾ and, in the long term, may result in the child requiring television to fall asleep. This dependency results in a vicious cycle in which the television becomes a transitional object.

Using the television as a transitional object not only delays the beginning of sleep, but also leads to irregular sleep times, shorter sleep duration, bedtime resistance, sleep disturbances, and daytime sleepiness⁽⁴⁶⁻⁴⁹⁾.

When compared with the television, the computer can have a similar – or even a stronger influence – on the SWC. However, the effects of computers on children's sleep have only been observed in one Chinese study by Li et al.⁽¹⁵⁾, who demonstrated that children with computers in their bedrooms not only fall asleep and wake up at later times during weekdays and weekends, but also have shorter sleep durations during weekdays. This study provides evidence that computers have a negative impact on sleep that is similar to the effects of television. However, further studies are required to confirm this effect in children.

Therefore, parents should limit the use of media – particularly in the bedroom – to promote good sleep habits and improve the quantity and quality of the child's sleep^(15,49).

FAMILY ENVIRONMENT

Although parents try to minimize social changes by manipulating bedtime behaviors, there are other factors that can affect sleep quality and a child's well-being. These factors include family conflicts, marital *status*, education level, and socioeconomic level^(22,31,49-55).

Nevertheless, parents often fail to recognize that both a child's well-being and sleeping habits can be negatively

affected by a family environment that is not conducive to good sleep habits⁽²²⁾.

A high level of conflict between parents or other family members can reduce sleep quality in children. Family conflicts reduce the quantity of sleep and increase nighttime sleep fragmentation, both of which result in daytime sleepiness^(50,51). In addition, children in chaotic family environments can develop adolescent insomnia because a family with frequent conflicts often has poor sleep habits. These environments are noisy and lack a routine that supports good quality sleep⁽⁵²⁾.

In addition to family conflicts, Phillips⁽⁵³⁾ observed that the marital state of parents influences the well-being of children. Children of married parents have higher well-being because they tend to go for walks and are told stories more often than children of single parents. These behaviors may result from the mother or father's attempt to compensate for the other parent's absence, according to their work schedule. However, this study did not investigate the relationship between marital *status* and a child's sleep patterns.

Parental education level is also related to a child's sleep. A higher educational level may be associated with a higher quality of sleep because children of illiterate or minimally educated mothers sleep later and display a reduction in total sleep duration (daytime and nighttime sleep)^(22,51).

In addition, children from low socio-economic levels often have more sleep problems because they wake up late, stay in bed for longer periods, and have an increased frequency of nighttime waking. These children may also sleep less efficiently because they have to share their bedroom and the house with more people. These factors, in addition to the low educational level of the parents, often prevent an adequate bedtime routine from being instituted^(54,55).

An adequate family environment is thus critical in maintaining regular sleep schedules, providing better sleep quality⁽¹⁹⁾ and instilling good sleep habits, behaviors that, over time, can have a positive effect on a child's well-being. Recently, children have been going to bed increasingly late and spending less time sleeping, a trend likely caused by social pressures and the relaxation of parental restrictions^(9,19,56).

SCHOOL SCHEDULE

School is one of the most important components of a child's psychosocial environment, and have a direct impact on sleep schedules. Because of the school start times, children wake up and go to bed earlier during the weekday, and have shorter sleep durations on weekdays than weekends^(16,38,49,50). Children between seven and ten years of age who go to school in the morning display a higher frequency of naps; these children also go to bed approximately one hour earlier than children who go to school in the afternoon⁽³⁸⁾.

These behaviors indicate partial sleep deprivation during the week that is usually accompanied by sleep "com-

pensation” on the weekends, a pattern often observed in adolescents⁽⁵⁷⁻⁵⁹⁾. However, the difference between weekend and weekday sleep schedules⁽²²⁾ is less dramatic in children because of a natural predisposition to begin and end sleep earlier. In addition, parents have more influence on sleeping and waking times in young children^(19,56).

The partial sleep deprivation and the sleep schedule irregularities that are related to a morning school schedule should not be found in children who naturally wake up early. However, bed-sharing, room-sharing, media use, and the family environment can all contribute to these alterations in sleep patterns. Some of these factors can have a positive effect on sleep habits; however, if used incorrectly or, in the case of media, used in excess or too close to bedtime, these factors can impair sleep because they prolong the waking state. In addition, these factors can increase nighttime exposure to light, acting on regulatory homeostatic and circadian sleep processes and leading to partial sleep deprivation and irregular waking and sleeping times.

If these social factors are minimized or used to positively influence sleeping habits, it may be possible to improve school performance by maintaining regular sleep schedules and decreasing or even avoiding partial sleep deprivation. Touchette et al.⁽¹³⁾ emphasize the importance of having children go to bed early and maintaining regular sleep schedules during both the weekdays and weekends, thus increasing sleep duration and maximizing development.

CONCLUSION

From the characterization of the SWC is observed that sleep patterns change during infancy such that children increase the duration of nighttime sleep and decrease the frequency of naps during the daytime. In addition, they tend to go to bed and wake up earlier.

The SWC of children can be influenced by social factors, such as bed-sharing, room-sharing, bedtime rituals, media use, as well as family and school environments, all of which contribute to a child’s routine and improve health and well-being. In some situations, however, these factors can delay the beginning of sleep and thus negatively interfere with the SWC of children. These factors are especially problematic when they are combined with a morning school schedule, resulting in partial sleep deprivation, sleep disturbances, and irregular bedtimes and waking times. These alterations in sleep habits can cause low school performance, obesity, attention-deficit/hyperactivity disorder, and are a predictor of insomnia in adolescence.

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Sleep and behavioral research: overview on global trends and Brazilian contributions to this field

Sono e pesquisa comportamental: panorama sobre tendências mundiais e contribuição brasileira neste campo

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ABSTRACT

The relationship between sleep and behavioral changes is quite clear. There are many neuro-behavioral co-morbidities that are related to sleep. In line with the aims of translational science, pre-clinical research has been shown to have great value for psychiatric research in Brazil and worldwide, and this importance can be extended to sleep studies. Thus, the present article aimed to present a broad view of basic behavioral science, especially the research using animal models, and focused on the global research output on the subject of “sleep”, study trends and the Brazilian contribution to the field. The presented data demonstrate the increasing importance of Brazilian research to the field of sleep research, the Brazilian contribution to the worldwide knowledge of this subject and the adequacy of this theme to knowledge formation in the country, which is growing both in volume and publication relevance.

Keywords: Sleep; Behavioral research; Brazil

RESUMO

A relação entre sono e alterações comportamentais é bastante clara. Diversas são as comorbidades neuro-comportamentais relacionadas ao sono. Do ponto de vista da ciência translacional, a pesquisa pré-clínica tem se mostrado de grande valia à pesquisa psiquiátrica, tanto brasileira como mundial, e essa importância é extensível a estudos sobre sono. Desse modo, o presente artigo visou apresentar um panorama sobre a ciência básica comportamental, especialmente a conduzida com animais de experimentação, sendo enfocadas a produção global sobre o tema “sono”, as tendências de estudo e a participação brasileira nesse cenário. Os dados apresentados demonstram a crescente importância da pesquisa brasileira às pesquisas do sono, a participação do Brasil na produção mundial sobre o tema e a adequação desse campo de pesquisa à realidade de formação de conhecimento do país, que é ascendente tanto em volume quanto em relevância de publicações.

Descritores: Sono; Pesquisa comportamental; Brasil

INTRODUCTION

The relationship between sleep and behavioral disturbances is quite clear^(1,2). There are many neuro-behavioral co-morbidities related to sleep and associated factors such

as sleep restriction and sleep-disordered breathing^(3,4). Thus, the importance of this subject to psychiatric research is evident⁽⁵⁾ and demonstrated by many recent reviews that discuss the relationship between sleep and psychiatric disorders, such as depression⁽⁶⁾, anxiety⁽⁷⁾ and mood disturbance⁽⁸⁾.

Basic science and translational research, defined as the process by which ideas and discoveries derived from basic science research, become applicable to the treatment and prevention of human diseases⁽⁹⁾, and have greatly contributed to psychiatric research in general⁽¹⁰⁾, especially to Brazilian psychiatric research⁽¹¹⁾. This contribution reflects the specific study relevance to the accumulation of knowledge about various specific disorders and psychiatric conditions and tends to extend to basic behavioral research and its relationship with sleep.

Knowing the importance of researches regarding the relationship between psychiatric disorders and sleep and considering the efficient way in which basic research approaches this association, the present article aimed to present a general overview of the relationship between basic and behavioral research, in particular the research that uses animal models to study sleep. The focus is on the global production of research on this subject, study trends and the Brazilian contribution to the field.

RESEARCH METHODOLOGY

From information obtained through the Web of Knowledge database, an estimate of the worldwide production on sleep and various relevant behaviors to translational science was made. The following descriptors were used in this estimation: “sleep”, “behavior”, “animals”, “rat”, “rats”, “mouse”, “mice”, “anxiety”, “depression”, “mood”, “stress”, “sexual behavior”, “aggression”, “aggressive behavior”, “feeding behavior” and “maternal behavior”, combined using the boolean operators “AND” and “OR”. In addition, “country/territory” and “publication year” filters were employed for further analysis.

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The evolution of the literature on sleep in general was analyzed in a descriptive manner, with a focus on basic science research and the behaviors listed above. For this analysis, the period between 1945 and 2010 was considered, since it corresponds to the years catalogued in the employed database. Independent analyses were then performed for each considered behavior.

RESEARCH ABOUT SLEEP: A GENERAL ANALYSIS

Descriptor: "Sleep"

In the used database, a search for "sleep" found 89,194 publications. This list of publications exhibits a clear temporal influence, with an obvious increase in the number of publications year by year. As an example of this trend, the number of indexed publications from 1950 (18 publications), 1970 (416), 1990 (903) and 2009 (6,929) can be analyzed. In fact, during the 1990s, there was a large increase in the annual number of publications about sleep, a trend that has been maintained ever since. For example, the number of publications in 2009 represents a 113% increase compared to the number in 2000 and a 667% increase when compared to 1990.

The Brazilian production of sleep research publications follows the global trend toward increased productivity. Although it only entered the international publishing scene for this field in the 1980s (when it occupied the 20th position in publication numbers), Brazil currently offers unique contributions to worldwide publication on the subject; it is the 13th most prolific country in terms of sleep publications, with a total of 1,405 publications, corresponding to 1.57% of the total worldwide production. The last decade has shown an intense growth for Brazilian sleep research, as evidenced by the 567% increase in publication numbers between 2000 and 2009. When only 2009 is considered, Brazil ranks 9th in sleep publication and is responsible for 3.28% of the worldwide production. The Brazilian productivity in this field can also be seen when examining the institutions that produce the most publications on this subject. In 2009, Universidade Federal de São Paulo ranked 4th in the number of worldwide sleep publications, having published 98 articles. The top spots in this ranking were Harvard University (211 articles), The University of Pennsylvania (137 articles) and The University of Pittsburgh (104 articles).

SLEEP AND BASIC RESEARCH: GENERAL ANALYSIS

Descriptors: "Sleep" AND ("animals" OR "rat" OR "rats" OR "mice" OR "mouse")

Similarly to general sleep research, the production of basic science papers on the subject also shows increases over time, although in a smaller proportion. Among the 89,194 studies on sleep that are indexed in the employed database, 11,521 were basic science papers (specifically, research with rodents, based on the used descriptors), which amounts to 12.9% of the total. In 2009, 798 works were completed in

basic sleep research, representing a 78% increase compared to 2000 and a 706% increase compared to 1990.

Although the worldwide growth in basic sleep research has been inferior to the overall growth in research on the subject, prominence of in the worldwide sleep research scene is greater within the basic science realm. The Brazilian body of basic science sleep research is responsible for 3.61% (416 publications) of the worldwide production, ranking 8th in terms of publication numbers. If considering only 2009, Brazil takes the 5th place, as it is responsible for 6.14% of the worldwide production.

SLEEP AND BASIC SCIENCE BEHAVIORAL RESEARCH

Descriptors: "Sleep" AND ("animals" OR "rat" OR "rats" OR "mice" OR "mouse") AND "behavior"

The sleep-related body of basic science research, when restricted to studies that focus on behavior, contains 1,557 indexed publications, with an accentuated productivity increase beginning in the 1990s. This increase continues today, with a worldwide production of 115 publications in 2009, a 51.3% increase over the year 2000.

In the 1990s, when worldwide animal behavior research on sleep exhibited the above-mentioned increase, the Brazilian research program was just beginning and was still internationally insignificant. However, the Brazilian research in this field is currently highly relevant, and Brazil is the 3rd most productive country, responsible for 7.25% of the total worldwide production and for 6.95% of the 2009 worldwide production. This great Brazilian presence in the international arena tends to persist when individual behaviors are analyzed, as will be noted below.

SLEEP AND BASIC RESEARCH ON STRESS

Descriptors: "Sleep" AND ("animals" OR "rat" OR "rats" OR "mice" OR "mouse") AND "stress"

The worldwide production of basic sleep research related to stress is consistent with the trends described above. A considerable increase in the publication number is noted from 1990 to the present. In total, 1,123 works on the subject are indexed, with 146 published in 2009.

Brazil has the 4th greatest publication number in this field, tallying 87 papers, which corresponds to 7.75% of the total. The Brazilian publication trend follows that of the worldwide increase, but on a smaller scale, with 12 publications each in 2008 and 2009, when it ranked 2nd in terms of publication numbers.

SLEEP AND BASIC RESEARCH ON DEPRESSION

Descriptors: "Sleep" AND ("animals" OR "rat" OR "rats" OR "mice" OR "mouse") AND "depression"

The worldwide body of researchers has been extremely productive in the study of sleep and depression since the be-

ginning of the 1990s, with 50 indexed publications in 2009 and an observed peak of 71 publications in 2007. Although the worldwide publication is extensive, the Brazilian participation is not as prominent as it is with other analyzed behaviors. Brazil occupies the 10th position for publication numbers in this field, being responsible for 3.15% of the total.

SLEEP AND BASIC RESEARCH ON ANXIETY

Descriptors: “Sleep” AND (“animals” OR “rat” OR “rats” OR “mice” OR “mouse”) AND “anxiety”

The worldwide research body on sleep and anxiety in animals laboratory was largely established the mid-1990s, after which a rapid increase in publication numbers occurred. While in 2000 there were only 11 studies on the subject, in 2008 there were 40 and in 2009 there were 30 articles published.

Brazil, as with basic science behavior and sleep studies in general, plays a significant role in the basic research that is related to sleep and anxiety behavior. The Brazilian production is equivalent to 7.8% of the worldwide production, ranking 3rd in the number of publications on the subject.

SLEEP AND BASIC RESEARCH ON SEXUAL BEHAVIOR

Descriptors: “Sleep” AND (“animals” OR “rat” OR “rats” OR “mice” OR “mouse”) AND “sexual” AND “behavior”

Worldwide, basic research on sleep and sexual behavior has shown little growth over two decades. Although it began to gain momentum as a research field in the 1990s, it never passed the mark of 15 annual publications, having indexed a total of only 130 works. However, although the volume of publications concerning this specific behavior is not large, the representation of Brazil is notable, as it is the 2nd biggest contributor in terms of publications on the subject. The Brazilian production accounts for 30.77% of the overall publications on sexual behavior and sleep. The year 2007 is particularly notable, as Brazil was the country with the greatest contribution in this year, with 69.23% of publications, a feat that was repeated in 2009.

SLEEP AND BASIC RESEARCH ON FEEDING BEHAVIOR

Descriptors: “Sleep” AND (“animals” OR “rat” OR “rats” OR “mice” OR “mouse”) AND “feeding behavior”

There are 112 publications on sleep and feeding behavior that are indexed in the consulted database. These publications follow an erratic temporal pattern, with unstable worldwide production, varying between 6 and 16 works per year in the last decade, with successive increases and decreases in publication numbers during these years. Amongst these papers, 16 are Brazilian, which accounts for 14.29% of the total. Although Brazilian participation is expansive in this field, there is no observed increase in

publication numbers over time, with a maximum number of publications of three per year in both 2006 and 2008. Nevertheless, Brazilian research on sleep and feeding behavior ranks 3rd worldwide.

SLEEP AND BASIC RESEARCH ON AGGRESSIVE BEHAVIOR

Descriptors: “Sleep” AND (“animals” OR “rat” OR “rats” OR “mice” OR “mouse”) AND (“behavior aggression” OR “aggressive”)

Worldwide, the basic science research on the relationship between aggressive behavior and sleep is limited, but it has been consistent since research began on this topic in the middle of the 1980s. In total, only 69 studies are indexed. Among this small publication number, the Brazilian participation is notable, with 9 publications, accounting for 13.04% of the total. In this field, Brazil is the 2nd most productive country in terms of publication numbers.

SLEEP AND BASIC RESEARCH ON MATERNAL BEHAVIOR

Descriptors: “Sleep” AND (“animals” OR “rat” OR “rats” OR “mice” OR “mouse”) AND “maternal” AND “behavior”

Among all analyzed behaviors, basic science research on the relationship between sleep and maternal behavior was the most limited. Only nine works are indexed in the database, and none have come from Brazilian researchers.

The global and Brazilian evolution of sleep publications in general and in basic science research is presented in Figure 1. Figure 2 presents the global and Brazilian evolution of research on sleep broken down by the described behaviors. Table 1 presents descriptive statistics pertaining

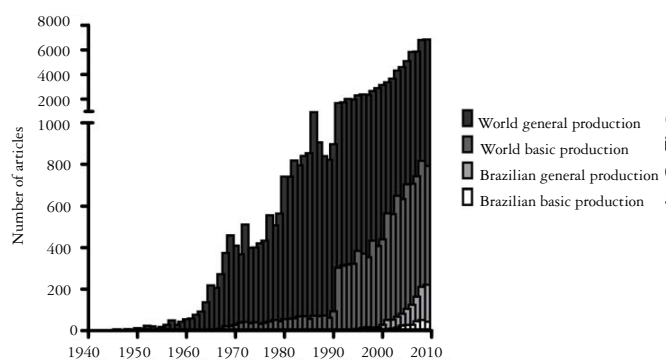


Figure 1: General and basic science production about sleep from 1940 to 2010, both in worldwide and Brazil. The vertical axis was broken into two disproportionate segments to better data visualization. General production refers to the total publication production pertaining to sleep in the considered period, encompassing both clinical and basic research. Basic research refers to animal research on sleep, with the research being completed with rodents as animal models.

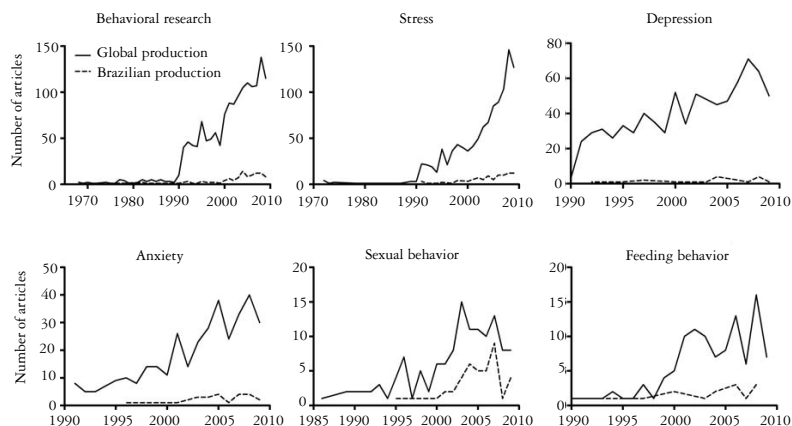


Figure 2: Temporal evolution of worldwide and Brazilian productivity in basic science research on sleep. The data refer to general behavioral research and research specifically on stress, depression, anxiety, sexual behavior and feeding behavior. Data on aggressive and maternal behavior are not presented due to low publication numbers. In all representations, the size of both axes was adjusted to the publication volume. It is notable that in all of the cases, there is a global trend of increased productivity; however, this finding becomes less evident when only Brazilian research is considered, as the production growth amplitude is decreased.

Table 1: Brazilian and world production between the years 2000 and 2009, regarding the addressed behaviors. The Brazilian participation in relation to world production is presented in percentages

	World			Brazil		
	Total production	Production in 2000	Production in 2009	Total production	Production in 2000	Production in 2009
Sleep (general analysis)	89,202	3,242	6,929	1,405 (1.58%)	34 (1.05%)	227 (3.28%)
Sleep and basic research	11,52	446	798	416 (3.61%)	9 (2.02%)	49 (6.14%)
Sleep and behavior research	1,157	76	115	113 (9.77%)	4 (5.26%)	8 (6.96%)
Sleep and stress	1,123	36	127	87 (7.75%)	3 (8.33%)	12 (9.45%)
Sleep and depression	824	52	50	26 (3.16%)	1 (1.92%)	1 (2%)
Sleep and anxiety	359	11	30	28 (7.80%)	1 (9.09%)	2 (6.67%)
Sleep and sexual behavior	130	6	8	40 (30.77%)	1 (16.67%)	4 (50%)
Sleep and feeding behavior	112	5	7	16 (14.29%)	2 (40%)	0
Sleep and aggressive behavior	69	2	2	9 (13.04%)	0	0
Sleep and maternal behavior	9	1	0	2 (22.22%)	0	0

to publications on sleep and the described behaviors, and Table 2 presents the ranking of the most productive countries in terms of basic science research on sleep and the listed behaviors.

DISCUSSION

The present study aimed to propose an overview and to demonstrate, in a synthetic manner, the current evolution of the Brazilian and worldwide basic behavioral sleep research. However, for an appropriate discussion of the presented data, some considerations must be raised. It is noted that the results do not necessarily reflect all of the publications on the examined subjects, but rather the total indexed publications in the analyzed database (Web of Knowledge). Although the information was obtained from a database with international prestige and broad coverage, it is not possible to guarantee that all publications on the subject are accessible in

this manner. Moreover, it is emphasized that the presented data pertain only to studies that were found in searches that used the terms noted above. Changes in the search terms can result in substantial changes in the publications that are found. However, even with the cited caveats, the search results seem to satisfactorily reflect the actual situation surrounding the researched topics. Finally, one must remember the focus of this article: basic science research in the field of sleep and behavior using animal models, specifically rodents.

A clear increase, beginning in the early 1990s, is noted herein with regard to the worldwide scientific production of both basic science and overall research on sleep. A similar increase is also noted when just Brazilian research is examined; however, the Brazilian increase is delayed slightly, between the end of the 1990s and the beginning of the 2000s. An increase in the Brazilian participation relative to the

Table 2: Ranking of the countries with the greatest total scientific productivity in 2009, regarding sleep broken down by the assessed behaviors. The hyphens indicate that there was no corresponding production in the category in question. For example, in 2009 there were no publications about sleep and maternal behavior, and all publications on sleep and sexual behavior in 2009 were produced by only the four countries listed

	Scientific production									
Sleep (general analysis)										
Total	1)	U.S.A.	2)	Canada	3)	England	4)	Germany	13)	Brazil
2009	1)	U.S.A.	2)	England	3)	Canada	4)	Germany	9)	Brazil
Sleep and basic research										
Total	1)	U.S.A.	2)	Japan	3)	France	4)	Canada	8)	Brazil
2009	1)	U.S.A.	2)	Japan	3)	Canada	4)	France	5)	Brazil
Sleep and behavioral research										
Total	1)	U.S.A.	2)	Japan	3)	Brazil	4)	Canada	5)	France
2009	1)	U.S.A.	2)	Mexico	3)	Japan	4)	Brazil	5)	France
Sleep and stress										
Total	1)	U.S.A.	2)	France	3)	Japan	4)	Brazil	5)	Germany
2009	1)	U.S.A.	2)	Brazil	3)	France	4)	Japan	5)	Canada
Sleep and depression										
Total	1)	U.S.A.	2)	Germany	3)	Canada	4)	France	7)	Brazil
2009	1)	U.S.A.	2)	Germany	3)	Canada	4)	England	15)	Brazil
Sleep and anxiety										
Total	1)	U.S.A.	2)	France	3)	Brazil	4)	Germany	5)	Italy
2009	1)	U.S.A.	2)	France	3)	Brazil	4)	Germany	5)	Italy
Sleep and sexual behavior										
Total	1)	U.S.A.	2)	Brazil	3)	Mexico	4)	India	5)	Canada
2009	1)	Brazil	2)	U.S.A.	3)	Mexico	4)	Japan	-	-
Sleep and feeding behavior										
Total	1)	U.S.A.	2)	Japan	3)	Brazil	4)	England	5)	France
2009	1)	U.S.A.	2)	Japan	3)	Canada	4)	Mexico	5)	South Korea
Sleep and aggressive behavior										
Total	1)	U.S.A.	2)	Brazil	3)	Japan	4)	Holland	5)	England
2009	1)	U.S.A.	-	-	-	-	-	-	-	-
Sleep and maternal behavior										
Total	1)	U.S.A.	2)	France	3)	Italy	4)	Belgium	5)	Canada
2009	-	-	-	-	-	-	-	-	-	-

overall production can also be seen over time, with the Brazilian contribution achieving great relevance in recent years. When considering basic behavioral sleep research, this same trend is maintained, with increased worldwide production beginning in the 1990s, and increased Brazilian contribution commencing in the following decade.

It is possible to clearly identify a similar increase in the number of worldwide publications in some of the analyzed behaviors, but not in all. Specifically, sleep relationship with stress, depression and anxiety behaviors presents evident growth in publication numbers with time, whereas its relationship with feeding and sexual behaviors showed less evident growth in the published article numbers. Finally, articles on sleep and aggressive and maternal behaviors did not show any increase in publication number over the years and never exceeded ten annual publications. These data evidence a possible lack of interest by the international scientific community in the relationship between sleep and these two underestimated behaviors.

When analyzing Brazilian production in the behaviors examined separately, different results are obtained from those acquired in basic and overall research on sleep, in which Brazilian research followed the worldwide trends, although in a smaller degree and with a slight delay. In general, for the majority of the studied behaviors, the number of indexed publications did not exceed ten per year and did not demonstrate a clear increase with time, instead maintaining an erratic and irregular pattern in the annual publication number. This may be due to the recent increased Brazilian production on sleep in relation to worldwide production. Nonetheless, two of the analyzed behaviors differed from this pattern. The publications on stress and sleep seem to follow a trend of increased publication numbers, having maintained a stable average of more than 10 annual publications since 2006, and publications about sleep and sexual behavior stand out not for the volume of publications, but for the Brazilian representation within the worldwide production.

Nevertheless, even though the volume of Brazilian publications referring to the analyzed behaviors seems not to have increased in recent years, the proportion of the Brazilian contribution is extremely important in the global context. For all of the analyzed behaviors, Brazil was ranked between 2nd and 10th; it is among the most productive nations and is becoming, in some specific cases (for example, the publications on “sleep and sexual behavior” in the years from 2007 to 2009), the most productive. In this context, Brazil often ranks ahead of countries that are well-known for scientific production, such as Germany, France, England and Japan, as noted in Table 2.

The data on Brazilian research, specifically for general, basic science and basic behavioral sleep research, are in accord with the observed increase in the Brazilian contribution to the fields of Psychiatry, Psychobiology and mental health⁽¹²⁾. Moreover, the importance of Brazilian basic research, especially research with experimental animals, has become increasingly evident⁽¹³⁾.

This increased importance of Brazilian sleep research on the global scale demonstrates the competence of the country in the dynamics of the acquisition and presentation of scientific data on the subject. One can see that there has been a large increase in the global understanding of various sleep-related factors over the last few decades, including genetics, neurophysiology, psychobiology and cellular biology⁽¹⁴⁾. As evidence of this worldwide trend beyond the data presented in this article, the increased number of global sleep-specialized journals about sleep can be cited. While in the beginning of the 1990s there was only 1 journal specifically dedicated to sleep research (*Sleep*), in 2004 there were already at least 16 specific journals on the subject^(15,16). Since then, the number of periodicals has grown even more, with other sleep journals having appeared, such as *The Journal of Clinical Sleep Medicine*, *Sleep Medicine Clinics* and *Sleep Science*.

Obviously, the emphasis of this article on Brazilian basic sleep research does not aim to detract from the importance of clinical sleep research and the other Brazilian research fields. Considering animal research as an important tool for the study of human sleep⁽¹⁷⁾ and considering the definition and importance of translational science⁽⁹⁾, both branches of sleep science – basic and clinical – interact and cooperate toward achieving the same goals.

In short, the present article aimed to propound a broad view on the importance and relevance of the Brazilian contribution to the published literature on sleep, specifically to the scientific production of basic sleep behavior research.

The presented data demonstrate the importance of Brazilian basic science research in the field of sleep research, the participation of the country in the worldwide production on this subject and the adequacy of the outputs of this research field, which are increasing both in volume and publication relevance.

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Authors instructions

SCOPE AND POLICY

The SLEEP SCIENCE journal (ISSN 1984-0659 print version) published every three months, is the official organization of Associação Brasileira de Sono (ABS) and Federação Latino-Americana de Sociedades de Sono (FLASS) for publication of scientific papers concerning sleep, chronobiology, and related topics.

After being approved by the Editorial Board, all articles will be evaluated by two or three qualified reviewers, and confidentiality will be preserved throughout the review process. Articles that fail to present merit, have significant errors in methodology or are not in accordance with the editorial policy of the journal will be directly rejected by the Editorial Board, with no recourse. Original manuscripts, those that have not been published elsewhere except in abstract form, on any aspect of sleep will be considered. The accuracy of all concepts presented in the manuscript is the exclusive responsibility of the authors. The journal reserves the right to make stylistic, grammatical and other alterations to the manuscript. Manuscripts must not be concurrently submitted to any other publication, print or electronic. Articles may be written in Portuguese, Spanish or English.

Papers should state that the protocol has been approved by the Ethics Committee of the Institution where the research was carried out. All studies involving human subjects should inform that written consent has been obtained from all subjects (individually).

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It is requested that the authors strictly follow the editorial guidelines of the journal, particularly those regarding the maximum number of words, tables and figures permitted, as well as the rules for producing the bibliography. Failure to comply with the author instructions will result in the manuscript being returned to the authors so that the pertinent corrections can be made before it is submitted to the reviewers. Special instructions apply to the preparation of Special Supplements and Guidelines, and authors should consult the instructions in advance by visiting the homepage of the journal.

Abbreviations should be used sparingly and should be limited only to those that are widely accepted. All abbreviations should be defined at first use.

The following rules were based on the standard proposed by the International Committee of Medical Journal Editors (ICMJE) and published in the article Uniform Requirements for Manuscripts Submitted to Biomedical Journals, updated in October 2009, and available from: <http://www.icmje.org/>

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Authors should state in the cover letter that the manuscript is intended to be a full-length paper.

Short Communication: a short communication is a report on a single subject which should be concise but definitive. This scope of this section is intended to be wide and to encompass methodology and experimental data on subjects of interest to the readers of the journal. The text should not exceed 12 pages double-spaced, typed in 23 line each, have a maximum of two figures or tables (or one of each) and 20 references. Authors should state in the cover letter that the manuscript is intended to be a Short-Communication.

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Overview: an Overview does not contain unpublished data. It presents the point of view of the author(s) in a less rigorous form than in a regular review or mini-review and is of interest to the general reader. The text should not exceed 5,000 words, excluding references and illustrations (figures or tables). The number of illustrations should not exceed 8 and 60 references.

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The title page should include the title in English and in Portuguese; a running title to be used as a page heading, which should not exceed 60 letters and spaces; the full names and institutional affiliations of all authors; complete address, including telephone number, fax number and e-mail address, of the principal author; and a declaration of any and all sources of funding.

Abstract: The abstract should present the information in such a way that the reader can easily understand without referring to the main text. Abstracts should not exceed 250 words. Abstracts should be structured as follows: Objective, Methods, Results and Conclusion. Abstracts for review articles and case reports may be unstructured.

Abstracts for Short Communications and Case Reports should not exceed 100 words and should not be structured.

Keywords: Three to six keywords in English defining the subject of the study should be included.

Tables and Figures: All tables and figures should be in black and white, on separate pages, with legends and captions appearing at the foot of each. All tables and figures should be submitted as files in their original format. Tables should be submitted as Microsoft Word files, whereas figures should be submitted as Microsoft Excel, .tiff or .jpg files. Photographs depicting surgical procedures, as well as those showing the results of exams or biopsies, in which dying and special techniques were used will be considered for publication in color, at no additional cost to the authors. Dimensions, units and symbols should be based on the corresponding guidelines set forth by the Associação Brasileira de Normas Técnicas (ABNT, Brazilian Association for the Establishment of Technical Norms), available from: <http://www.abnt.org.br>.

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References: References should be listed in order of their appearance in the text and should be numbered consecutively with Arabic numerals. The presentation should follow the Vancouver Style, updated in October of 2004, according to the examples below. The titles of the journals listed should be abbreviated according to the style presented by the List of Journals Indexed in the Index Medicus of the National Library of Medicine, available at: <http://www.ncbi.nlm.nih.gov/entrez/journals/loftext.noprov.html>.

A total of six authors may be listed. For works with more than six authors, list the first six, followed by 'et al.'.

Examples:

Journal articles

1. Tufik S, Lindsey CJ, Carlini EA. Does REM sleep deprivation induce a supersensitivity of dopaminergic receptors in the rat brain? *Pharmacology*. 1978;16(2):98-105.
2. Andersen ML, Poyares D, Alves RS, Skomro R, Tufik S. Sexsomnia: abnormal sexual behavior during sleep. *Brain Res Rev*. 2007;56:271-82.

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Chapter in a book

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Others situations

In other situations not mentioned in these author instructions, the recommendations given by the ICMJE should be followed, specifically those in the article Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication (Updated October 2009), available from: <http://www.icmje.org/>. Additional examples for special situations involving references can be obtained at: www.nlm.nih.gov/bsd/uniform_requirements.html

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The manuscript must be accompanied by a letter signed by all authors, with permission for publication and a statement that is unprecedented and has not been submitted for publication in another journal or book. That letter must include: a) conflicts of interest; b) certificate of approval by the ethics committee of the institution where the research was carried out when the investigation involves experiments on humans or animals; c) documentation of the possible sources of funding work; d) a statement that participants provided signed consent forms, in the case of medical research on humans; e) letter of transfer of copyright to the Journal Sleep Science.

Important note: the journal Sleep Science in support of policies for the registration of clinical trials of the World Health Organization (WHO) and the ICMJE, recognizing the importance of such initiatives for recording and promoting international information on clinical studies, open access, will only accept for publication from August 2009 articles of clinical research that have received an identification number to one of the Clinical Trial Registry validated by the criteria established by WHO and ICMJE, available from: <http://clinicaltrials.gov> or the Pubmed website.

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