

Relationship Between Intermittent Hypoxia, Nocturnal Voiding and Sleep Related Breathing Disorders

MARINA RUXANDRA OTELEA¹, MIHAELA TRENCHEA^{2*}, CORINA ZUGRAVU^{1,3}, RAZVAN HAINAROSIE¹, ALEXANDRU STEFAN RASCU^{1,4}, CRISTIAN DRAGOS STEFANESCU^{1,5*}

¹ University of Medicine and Pharmacy Carol Davila, 37, Dionisie Lupu Str., 020021, Bucharest, Romania

² Ovidius University of Constanta, Medicine Faculty, 124 Mamaia Blvd, 900527, Constanta, Romania

³ National Institute of Public Health, 1-3 Doctor Leonte Anastasievici, 050463, Bucharest, Romania

⁴ Clinical Hospital Prof. Dr. Th. Burghel, 20, Panduri Road, 050653, Bucharest, Romania

⁵ Gen. Dr. Aviator Victor Anastasiu National Institute of Aeronautical and Spatial Medicine, 88th Mircea Vulcanescu Str., 010825, Bucharest, Romania

Nocturia, cardio-vascular diseases and diabetes are frequent in patients with sleep related breathing disorders. In this study, we had analyzed the influence of the intermittent hypoxia on nocturia prevalence and found that cardio-vascular diseases, obesity, age and apnea hypopnea index predict 27.1% of nocturia's variance (Nagelkerke R square = .271, $\chi^2 = 68.35$). In $AHI < 28$, the chance of nocturia is 50% and the difference depends on the presence or absence of the cardio-vascular diseases. For values of $AHI > 28$, the risk of nocturia becomes independent of the presence of the cardio-vascular disease.

Keywords: apnea-hypopnea index, nocturia, sleep related breathing disorders, cardio-vascular disease, ENT

Nocturia is defined as *the complaint that the individual has to wake at night one or more times for voiding (i.e. to urinate)* [1]; depending on the clinical threshold included in the definition (at least 1 or 2 voiding by night), the incidence varies around 50, or 20%, respectively, in both sexes [2]. The pathogenesis of nocturia is very complex, involving multiple neurohormonal loops and local dysfunctions. Regardless the etiology, a common consequence of nocturia is sleep interruption and the circadian dysregulation. In the kidney, the circadian clock regulates endothelin, aquaporin and the expression of Na-epithelial channels [3]. The bladder cells are also subject of the circadian genes influence in the lumbar spinal cord, detrusor, sphincter and urothelium [4]. Based on these research findings, nocturia has been considered a disease of circadian dysfunction.

Sleep related breathing disorders (SRBD) refers to a spectrum of breathing abnormalities occurring during sleep; beside obstructive sleep apnea (OSA), that is the most frequently diagnosed SRBD, upper airway resistance syndrome (UARS), central sleep apnea (CSA) and obesity hypoventilation syndrome (OHS) are included. Arousals, various levels of desaturations and sleep fragmentations are the common findings of these disorders. From the perspective of sleep interruption, nocturia and SRBD might share some pathophysiological mechanisms. Studies have shown that interrupted sleep itself is a potentially harmful and debilitating factor [5], that increases the risk of hypertension, diabetes, mental diseases, malignancies and accidents [6], all having a possible influence on the prevalence of the nocturia. In this regard, we conducted a cross sectional study in patients, when first diagnosed with SRBD, to identify the factors that relates to the prevalence of nocturia.

Experimental part

This study presents the analysis of 326 patients with SRBD, referred, during 2012-2016, to the Somnology

Laboratory of Constanta Clinical Pneumophthisiology Hospital. The research comprised a standard questionnaire, clinical examination, ENT examination and polygraphy test. Before entering into the study, the patients signed an informed consent form. Diurnal sleepiness was evaluated by Epworth score, considering excessive daytime sleepiness (EDS) if Epworth score was ≥ 18 points. The body mass index (BMI) was calculated as weight (kg)/height (m)². International Diabetes Federation (IDF) criteria were used to define the normal values for WC [7]. The neck circumference (NC) was measured in a horizontal plan, below the laryngeal prominence. Abnormal values were considered if NC was >43 cm in women and >45 cm in men. A polygraphy testing was conducted with a STARDUST II RESPIRONICS polygraph and the apnea-hypopnea index (AHI) and the desaturation parameters were extracted from the polygraph datasheets. Apnea was counted if a cessation of flow of ≥ 10 s was noticed, while hypopnea was considered if airflow was reduced by $\geq 30\%$ with a desaturation $\geq 3\%$ from baseline. The BRSD were divided following the current recommendations of the American Academy of Sleep Medicine: OSA, if $AHI > 5/h$, UARS if $AHI < 5/h$ and the minimal peripheral O₂ saturation (minSpO_2) $\geq 92\%$, CSA if $AHI \geq 5$ without respiratory effort, and OHS if BMI was ≥ 30 kg/m² and the average peripheral O₂ saturation (avSpO_2) was less than 90% for longer than 30% of the sleep duration [8]. The severity of AHI was classified as mild if $AHI = 5-14$, moderate if $AHI = 15-29$ and severe if $AHI > 30$. Parameters of the peripheral O₂ saturation (avSpO_2 , minSpO_2 , and time spent below 90% of the oxygen saturation level during sleep, $\text{TS}_{\text{SpO}_2,90\%}$) were measured by pulse oximetry and automatically computed by the polygraph software for the total night sleep duration.

The statistical analysis was performed by SSPS software (Stat Plus for Mac, Analyst Soft Inc. Version V6, 2016). The threshold for the statistical significance was set at 95%. Categorical variables were compared using χ^2 test, and

* email: mtrenchea79@yahoo.com, Phone: 0721979880; cristiandragos@hotmail.com, Phone: 0730047455

numerical variables with Anova or Mann Whitney test, according to the type of distribution. Lastly, a binary logic regression (enter method) was computed, with nocturia as a dependent variable, and age, BMI categories, parameters of the peripheral O₂ saturation and comorbidities as independent ones.

Results and discussions

From the initial 326 patients, a diagnosis of SRBD was assessed among 306 subjects, of which the majority (72.5 %) were men. None of these patients had a previous documented renal failure. Nocturia was mentioned by a great majority (n=184/306). The prevalence of nocturia increased with aging (fig.1), (F=32416.1078, p<0.001) both for men and women ($\chi^2=1.3800$, p=0.2401). Nocturnal respiratory symptoms were present in all patients, but only the reported nocturnal apnea and awakenings were associated to nocturia ($\chi^2=6.4809$, p=0.0391 for apnea, and $\chi^2=8.0945$, p=0.0004 for awakenings). Reported nocturnal apnea was not correlated with age (F= 0.2205, p=0.6392) or gender ($\chi^2=2.2038$, p=0.3492). Awakenings were directly related to age (F=7.531, p=0.0064) and influenced by gender, being more frequent in women (66.67%) than in men (47.75%) ($\chi^2=8.095$, p=0.0044). The relation between awakenings and nocturia was maintained after age adjustment.

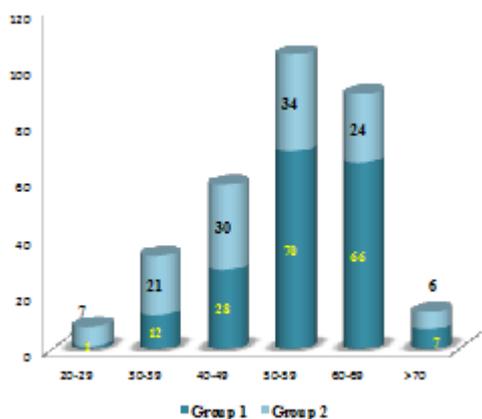


Fig 1. Age distribution in the study groups

The average BMI, WC and NC in men were significantly higher than in women (p < 0.001). A direct relation between each of the anthropometric measures (BMI, WC, NC) and nocturia was noticed (p<0.001), independent to age, but influenced by gender.

The nocturia prevalence according to BRSD by decades of age is represented in figure 2. There was no significant difference in the prevalence of BRSD by gender ($\chi^2=1.38001$, p=0.2401).

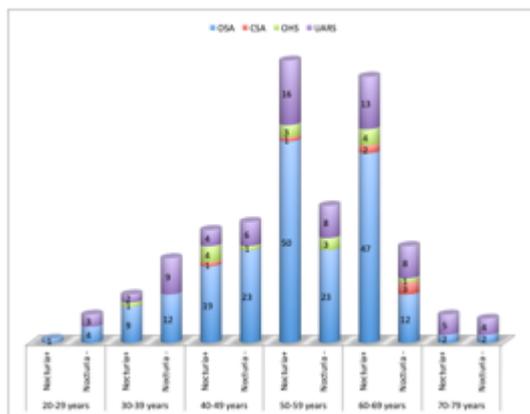


Fig 2. Nocturia by type of BRSD and decades of age

The prevalence of the cardio-vascular diseases in this population was high (65.34%) and, after age adjustment, a significant association with nocturia ($\chi^2=43.0454$, p=0.534839E-11) was found. There was also a significant difference in the number of patients with T2D that reported nocturia ($\chi^2=9.15284$, p=0.00248) as the majority (69.56%) had this symptom; no influence by age was noticed. All parameters reflecting the low levels of peripheral oxygen saturation were significantly associated to nocturia (table 1) and age (U= 7649, p=0.000).

Table 1
THE OXYGEN DESATURATION PARAMETERS RELATION WITH NOCTURIA

Desaturation parameter	Mann Whitney U	P
AHI	8761	0.001
ODI	8877	0.002
Av SpO ₂	9108	0.005
Min SpO ₂	9526	0.024
TS_Sp O ₂	8698	0.001

AHI= apnea- hypopnea index; ODI= oxygen desaturation index; Av SpO₂ = average peripheral saturation of oxygen; Min SpO₂ = minimal peripheral saturation in O₂; TS Sp O₂ = time spent below 90% of the oxygen saturation level during sleep

Although there was no difference by gender or smoking status, mostly patients in group 1 were older than 50 years (74%), with an almost equal distribution in both groups between the fifth, sixth and seventh decade of age (table 2). The anamnesis revealed differences in the nocturnal symptoms such as more frequent nocturnal awakenings ($\chi^2=30.033$, p=4.24677E-8) and reported apneas ($\chi^2=6.4809$, p=0.0391), concordant with a higher average of the Epworth's score. Excessive diurnal sleepiness was present in 20%, significantly more prevalent in group 1 as compared to the group 2 (34.31% vs. 29.09%) ($\chi^2=7.9778$, p=0.0047). All of the measured anthropometric characteristics were higher in the nocturia group. The distribution according to AHI, was different between the 2 groups ($\chi^2=18.1377$ p=0.0004). Patients in group 1 were more frequently in the lowest 25% percentile of the avSpO₂, and above the 75% percentile of the TS_SpO₂90% (fig 3). These distributions were statistically significant ($\chi^2 = 10.1154$, p =0.0064 for the avSpO₂ and $\chi^2 = 10.2593$ p =0.0059 for the duration of TS_SpO₂90%). Results of the regression model of nocturia in SRBD are presented in table 3. Among these statistically significant variables, the greatest influence came from cardio-vascular diseases, followed by obesity (versus normal weight), age and AHI. The final model predicted 27.1% of nocturia's variance (Nagelkerke R square= .271); model χ^2 is 68.35. The greater the value of AHI is, the greater the chance of the intermittent hypoxia can be and the less is the cardio-vascular disease influence on nocturia. In AHI less than 28, the chance of nocturia is 50% and the difference depends on the presence or absence of the cardio-vascular diseases. For values of AHI above 28, the risk of nocturia is significantly higher and becomes independent of the presence of the cardio-vascular diseases.

As confirmed by us, nocturia is a frequent symptom in SRBD patients, with a very important impact on the quality of life. There is a bilateral relation between nocturia and SRBD: awakenings for voiding lead to sleep fragmentation,

Table 2
COMPARISON BETWEEN PATIENTS WITH NOCTURIA AND PATIENTS WITHOUT NOCTURIA

	Nocturia (+)	Nocturia (-)	Total	p
Age (average ± SD)	55.95 ± 9.58	49.43 ± 12.41	53.35 ± 11.24	< 0.0001
Gender (M/F)	129/55	93/29	222/84	0.2401
Smokers (active/exsmokers/never smokers)	64/63/57	51/39/32	115/102/89	0.4394
Epworth score (average + SD)	9.27 ± 5.39	7.24 ± 4.62	8.46 ± 5.19	0.0011
Antropometric measures				
BMI (average + SD)	34.99 ± 6.68	32.54 ± 6.06	34.01 ± 6.54	0.0003
WC (average + SD)	110.52 ± 10.91	106.58 ± 9.26	108.95 ± 10.45	0.0026
NC (average + SD)	43.77 ± 3.63	42.39 ± 3.20	43.22 ± 3.52	0.0013
Type of SRBD				
OSA	128	76	204	
UARS	40	38	78	
CSA	4	6	10	
OHS	12	2	14	
Comorbidities				
Chronic lung disease (Yes/No)	64/120	38/84	102/204	0.5089
Cardio-vascular diseases (Yes/No)	147/37	53/69	200/106	< 0.0001
T2DM (Yes/No)	41/143	11/111	52/254	0.0025
Psychiatric disease (Yes/No)	5/179	4/118	9/297	0.7760
ENT disorders (Yes/No)	47/137	39/83	86/220	0.2209
Severity of SRBD and O ₂ saturation indexes				
AHI (average + SD)	39.20 ± 27.56	28.58 ± 24.43	34.96 ± 26.82	0.0011
Av SpO ₂ (average + SD)	91.54 ± 4.19	92.66 ± 3.44	91.99 ± 3.94	0.0005
Min SpO ₂ (average + SD)	76.81 ± 10.54	79.59 ± 10.63	77.92 ± 10.65	0.0258
TS_SpO ₂ 90% (average + SD)	13.61 ± 14.17	8.94 ± 10.60	11.75% ± 13.05	0.0008

BMI = body mass index; WC = waist circumference; NC = neck circumference; SRBD = sleep related breath disorders; OSA = obstructive sleep apnea; UARS = upper airways resistance syndrome; CSA = central sleep apnea; OHS = obesity hypoventilation syndrome; T2DM= type 2 diabetes; ENT= ear nose and throat; AHI= apnea- hypopnea index; ODI= oxygen desaturation index; Av SpO₂ = average peripheral saturation of oxygen; Min SpO₂ = minimal peripheral saturation in O₂; TS_Sp O₂ = time spent below 90% of the oxygen saturation level during sleep

Table 3
REGRESSION MODEL OF NOCTURIA
IN SRBD

	B (SE)	95% CI for odds ratio		
		Lower	Odds ratio	upper
Age*	-0.40 (0.015)	0.961	0.934	0.989
AHI *	-0.015 (0.007)	0.986	0.972	0.999
Cardio-vascular diseases* (present vs absent)	-1.038 (0.331)	0.354	0.185	0.677
T2D (present vs absent)	-0.428 (0.405)	0.652	0.295	1.440
Obese vs overweight	0.304 (0.662)	1.355	0.371	4.958
Obese vs normal wight *	0.840 (0.328)	2.316	1.217	4.409
avSpO ₂	-0.52 (0.051)	0.949	0.858	1.050
TS_SpO ₂ 90%	-0.13 (0.015)	0.987	0.958	1.017
constant	7.91(4.99)			

AHI = apnea-hypopnea index; T2D = type 2 diabetes; avSpO₂ = average peripheral saturation in O₂; TS_SpO₂90% = time spent below 90% of the oxygen saturation level during sleep

*p<0.01

impairing the overall quality of sleep, already affected by the SRBD. There is also evidence that control of desaturation in OSA reduces the number of nocturnal voiding and the night time urine volume [9].

The high prevalence of nocturia (60.01%) was confirmed in this study, in accordance to previous reports [10-12]. Nocturia showed a positive association with other nocturnal awakenings, self reported apnea episodes and diurnal somnolence, all having an impact on the quality of life. Intermittent hypoxia, hypercapnia and acidosis during the upper airways collapse trigger the pulmonary vasoconstriction, the chemoreceptors and the sympathetic stimulation, particularly in the late expiration phase[13]. The coexistent hypoxia and hypercapnia maintain the high blood pressure and the heart rate increase for more than 15 min even in healthy volunteers [14]. The extreme negative thoracic pressure raises the venous return, while the transmural pressure resulting from the inefficient

diaphragmatic contractions, affects the left ventricular afterload. Ventricular stretch and acidosis stimulates the atrial natriuretic peptide (ANP) release that promotes diuresis. The false hypovolemic signal increases the AVP and aldosteron levels and accumulate water and sodium. A putative model of these complex pathophysiological loops, integrating the main triggers (hypoxemia, hypercapnia and acidosis) to the neuro-hormonal factors is presented in figure 4.

In normal individuals, arginine vasopressin (AVP) has a circadian rhythm of secretion and release; the release fluctuates during the day time, decreases in the evening and reaches the peak between 2-4 a.m.; this circadian rhythm seems to disappear after 50 years of old [15]. The lack of nocturnal overproduction of AVP explains, in part, the increase of the nocturia prevalence with age, but age must not be seen as the only influencing factor of the AVP secretion. Chronic changes in hypothalamic supra-

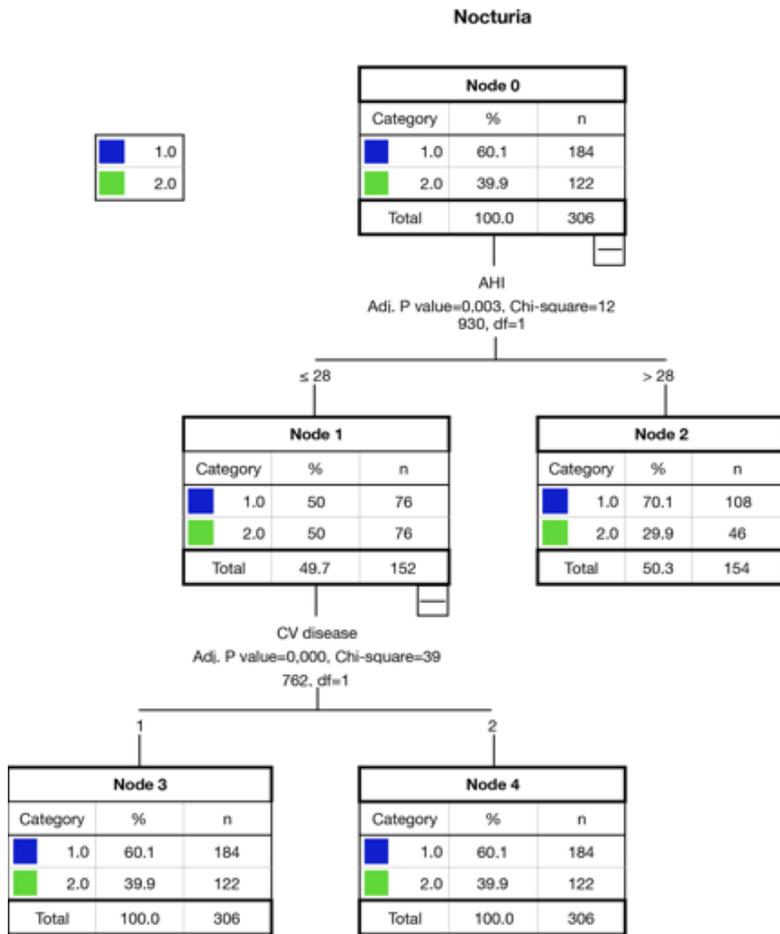


Fig 3. The predictors of nocturia.
Nocturia variable was coded with 1 for presence of the nocturia and 2 for absence of the nocturia.
AHI = apnea hypopnea index; CV disease = cardiovascular disease

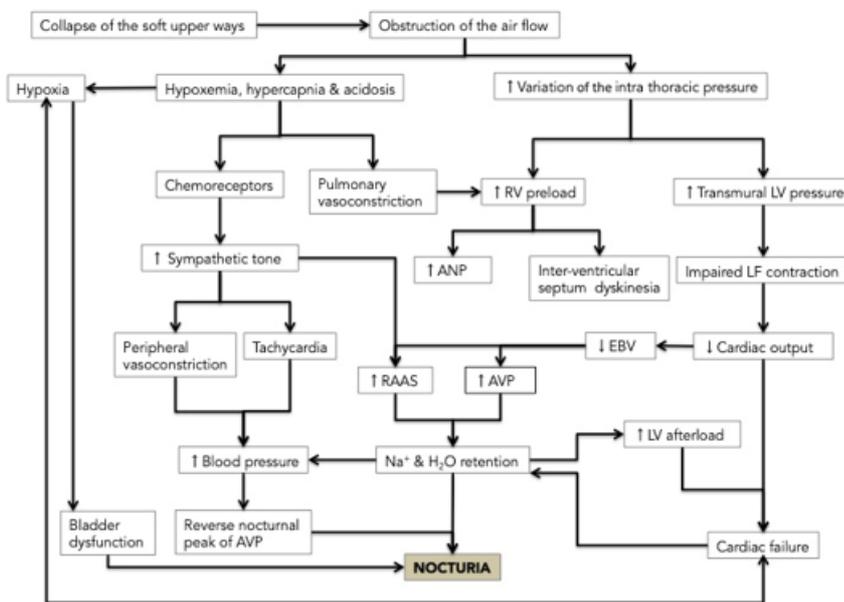


Fig 4. Pathophysiological mechanisms of nocturia in breath related sleep disorders.
ANP = atrial natriuretic peptide; AVP = arginine vasopressin; RAAS = renin angiotensin system; EBV = effective blood volume; RV = right ventricle; LF left ventricle

chiasmatic nuclei (SCN) have been observed in hypertension, with a significant reduction of the content in AVP [16]. In cardiac failure, the reduction in effective circulating blood volume raises the plasma level of AVP [17]. AVP aggravates both systolic (by vasoconstriction) and diastolic (by preload) stress and contributes to natriuretic peptides release. High plasma co-peptin, released together with the AVP, significantly associates to microalbuminuria, independent of age and with decreased renal filtration rate [18]. In fact, the AVP increases during night time only in severe sleep apnea, if AHI is >15 [19], showing that these pathophysiological mechanisms become prominent in repeated intermittent

obstruction of the airflow. These neuro-hormonal modifications are just amplified by the intermittent desaturation, as confirmed by others [10-12]. The regression model derived from our results is underlying the importance of the co-existent cardio-vascular disease in patients presenting with nocturia.

In a previous communication, based on smaller group in which more blood tests were performed, we have reported that the desaturation level and the HbA1C are related [20]. Medical literature provides contradictory results on the relation between diabetes and nocturia, although some direct pathogenic mechanisms were demonstrated [21-23]. In SRBD studies an association was

not found [11] unless a certain degree of severity of the intermittent obstruction and/or of the desaturation were considered [24]. In our final regression model the influence was no more significant. We do not have a conclusive explanation of this finding, but it might be related to factors that we have not assessed, such as the duration and the control of the T2D.

Our results emphasize that the severity of desaturation is a key factor for nocturia, as it is shown in other pulmonary disorders [25,26]. The model derived from our data is consistent with previously found predictors of nocturia in SRBD (age, BMI, hypertension and diabetes) [10,27] but the influence of the other predictors lost their significance, if AHI became higher than 28. This AHI value is at the borderline between the classic 3 degrees of severity of SRBD. In this context, it is of interest to notice that when not associated with intermittent desaturation, high blood pressure or diabetes were not significantly related to the nocturnal polyuria severity and to the number of nocturnal voidings, recorded by the 24h frequency and volume chart monitoring [24]. Lung function reduction associated with the abdominal type of the fat distribution might also contribute to worsening desaturation levels. Lung function was shown to relate to work disability [28] and, as in other lung disorders, to the quality of life [29] and should be considered in patients with high AHI.

Conclusions

The severity of SRBD influences nocturia and nocturia induces awakenings, which affect the duration and sleep architecture. Age, high desaturation, obesity and cardiovascular disease explain almost a third of the nocturia's variance. Intermittent hypoxemia is an important factor of influence of the nocturia prevalence. Particularly if the frequency, as assessed by the apnea-hypopnea episodes, is higher than 28/h, the desaturation is a significant contributor of the SRBD - nocturic phenotype.

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