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Impact of vagus nerve stimulation on sleep-related breathing disorders in adults with epilepsy

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Highlights:

- VNS induced SAS was observed in 28% of patients
- Few patients had related clinical symptoms, are could be treated
- Routine screening for SAS might represent a reasonable approach

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Abstract

Background: Vagus nerve stimulation (VNS) can induce a sleep apnea syndrome (SAS), which in turn can worsen seizure control and represents a cardiovascular risk factor. Epidemiology of VNS-induced SAS has received little attention to date. The purpose of this study is to estimate the VNS-induced SAS prevalence and to explore clinical variables potentially correlating with its development.

Methods: We analyzed the computerized medical records of 18 consecutive adults treated for refractory epilepsy with VNS, implanted between May 2008 and October 2015. Patients underwent polygraphy or polysomnography before and after VNS implantation. Between patients with and without SAS, we compared variables related to epilepsy type and device parameters.

Results: Two patients had SAS and were treated before implantation; one improved after VNS, the other worsened. Four other patients developed SAS after VNS: induced/aggravated SAS occurred in 5/18 patients (prevalence: 27.8%). Only 2 of them had symptoms: one complained of important snoring, the other reported seizure worsening. All 5 patients were successfully treated by combinations of cPAP, positional therapy, or VNS parameters modification. There was no statistically significant difference between potential predictors.

Conclusion: Despite the relatively modest clinical impact on epilepsy, in view of the associated cardiovascular risk factor development, easy treatment, and the relatively high SAS prevalence, routine screening for SAS before and after VNS implantation may represent a reasonable practice.

1.Introduction

Vagus nerve stimulation (VNS) is a palliative therapy for refractory epilepsy; it is used since more than 20 years and is regarded as safe, well tolerated and effective [1-5]. A seminal study about the effect of VNS on sleep [6] analyzed polysomnographies (PSG) of four patients with VNS before and after treatment, showing that the apnea-hypopnea index (AHI) was significantly higher with activated VNS; several subsequent observations found comparable results [7-10]. VNS seem to increase both respiratory effort and airways obstruction during its activation [6,7,9-13]. Both peripheral and central mechanisms represent possible explanations for changes in respiratory patterns. The former would be triggered by stimulation and subsequent narrowing of the upper airways musculature [6,7,12,14]. Since the vagus nerve has projections to the brainstem respiratory control centers [6,7,12,14], a central inhibition of respiratory drive could also be observed.

Even if changes in respiratory patterns are found in many patients, they do not seem clinically relevant in most. While the majority of studied patients shows changes in respiratory patterns (34-100%), only 0-33% develop SAS [7,12,13,15]. To date, however, the prevalence of SAS in patients with VNS remains largely unknown, due to the fact that the aforementioned studies included relatively small groups of patients selected from a sleep medicine angle, who are not necessarily representative of the whole population of patients with epilepsy implanted with VNS. Nevertheless, VNS related SAS seems to be frequent enough that sleep study screening before implantation is considered [8,9,12,13,16,17]. Screening after the implantation could be also important, in as much as VNS increases wakefulness [18], which could mask one of the cardinal symptoms of SAS, daytime somnolence [6,19,20].

While lacking an evidence-based approach, many treatment options have been described for patients with VNS related SAS: continuous positive airway pressure (cPAP) [8,9,13,14,16,17,21]; positional therapy [8,9]; changes in stimulator settings (especially increasing OFF time or decreasing stimulation frequency) [6,8,16,17,22]. It has been suggested that VNS parameters modifications might further enhance the cPAP impact [14]. In severe cases, VNS deactivation at night has been mentioned [8,16,17]. Treating SAS seems important not only for the quality of life, but also because sleep disruption can increase seizure frequency [6,8,17], on top of representing an independent cardiovascular risk factor [19,23].

To summarize, a link between the VNS and sleep respiratory disorders is described but the prevalence of this side effect is unknown. Clinical variables potentially associated with it have not been clearly elucidated to this day, with only one recent study postulating left vocal cord abduction as a predisposing factor [17].

2.Methods

This is a retrospective cohort study assessing the prevalence of VNS-induced SAS, and exploring potential clinical variables correlating with its development. The study was

approved by our ethics committee.

We analyzed the computerized medical records of consecutive adults (>18 years old) implanted with VNS for refractory epilepsy at our center between May 2008 and October 2015; follow-up extended until May 2017. Sleep recordings took place in our sleep center (PSG) or at home (PG), in accordance with the American Academy of Sleep Medicine's 2007 recommendations [24]. Apnea was defined as a decrease of at least 90% of airflow from baseline, lasting 10 s or longer, while hypopnoeas were scored according to the 2012 American Academy of Sleep Medicine criteria (≥30% decrease of airflow lasting at least 10 s, associated with either arousal or a ≥3% O_2 saturation decrease) [25]. All studies but one were conducted at the sleep center of the CHUV and interpreted by AOR, a sleep certified neurologist. Most studies were ambulatory polygraphies, chosen as they are more convenient than polysomnographies both for patients and reimbursement, while retaining comparable sensitivity in SAS diagnosis [26,27]. All patients underwent a sleep study before implantation to screen for SAS, as this would have needed specific treatment. They also underwent a control sleep study after implantation. The mean number of apnoeas and hypopnoeas per hour of sleep (apnoea-hypopnoea index [AHI]) was calculated. SAS was defined after [16] (mild: AHI=5-10/h, moderated: AHI=10-15/h; severe if AHI≥15). We stratified the cohort in two groups: patients who worsened already existing SAS or developed it after implantation, patients without SAS worsening or development.

We compared several potential explanatory variables related to SAS development between the two groups: demographics, being overweight (defined as a BMI>25), history of arterial hypertension or diabetes, variables related to epilepsy diagnosis (main seizures type -focal or generalized-, percentage of VNS related decrease in seizures frequency, medication -presence of valproate, VPA), VNS parameters (current intensity, pulse frequency, duration, and ON and OFF times). We also compared the reported magnet efficacy (defined as an effect in at least 30% of seizures in terms of shortening of the episode or of the postictal state) and a subjective significant increase in vigilance (reported by the patient or relatives/caregivers).

Given the small groups of patients, Fisher's exact tests were used to analyze dichotomous variables, and Mann-Whitney U-tests for continuous variables, using two-tailed approaches. We used the online application *Socscistatistics* [28] to perform the tests, and considered p-values <0.05 to be statistically significant. Correction for multiple comparisons was not performed in view of the exploratory character of the study.

3.Results

In the study period, 19 adult patients received VNS at CHUV, of whom one died of a probable SUDEP after eight months; due to lack of information regarding sleep quality, we excluded him from the study. We therefore analyzed 18 patients. The main clinical variables for each patient are summarized in **Table 1**, types of sleep studies performed and the observed AHI are summarized in **Table 2**. All patients had a sleep study before implantation: two showed SAS (patient 6 was treated with positional therapy, patient 9 with cPAP); a follow-up sleep study occurred after a median latency of 36 months (range: 6 months to 7 years) in 16

patients; in two subjects with severe cognitive impairment relatives refused to perform a follow-up study. These two patients showed no symptom suggesting SAS (increased somnolence, snoring, xerostomia), nor seizure worsening and were attributed to the group with no SAS. Four subjects (patients 1,4,13 and 15) developed SAS *de novo* and patient 9 with cPAP showed worsened AHI. The rate of VNS-induced or aggravated SAS was thus 27.8%. The majority of respiratory events were hypopneas, mostly of obstructive nature, although a central component was observed in up to 25% of them (details not shown).

The SAS of patient 1, whose husband complained about new-onset snoring and apneas, resolved by changing the device parameters: intensity and pulse frequency were reduced and a high duty cycle mode was activated. She underwent two follow-up sleep studies: the first with parameters unchanged showed an AHI at 12.7/h, the second one, with modified parameters, an AHI at 0/h. Patient 4 was not treated for SAS since the latter had no clinical impact. Patient 9 had already cPAP before implantation and continued it, he remained asymptomatic. Patient 13 had an increased daytime seizure frequency after VNS, possibly promoted by SAS; she improved regarding both seizures and SAS by decreasing current intensity from 1.75 mA to 1.25 mA. Patient 15 had no complaint related to SAS, nevertheless OFF-time was increased from 3 to 5 minutes.

As exposed in **Table 3**, there was no significant difference between patients with and without VNS induced/aggravated SAS on any collected variable, except a trend for greater VNS intensity in the SAS group.

4.Discussion

To the best of our knowledge, our study is the first to estimate the rate of VNS-induced SAS in a non-selected adult population, and to explore clinical variables potentially correlated to the development of a SAS after VNS implantation. The main findings were that VNS induced or aggravated SAS in 27.8% of patients; we did not find any variable significantly predicting the risk of VNS-induced SAS.

Our results confirm the link between VNS and SAS, and therefore seem to justify a routine post-implant screening. The prevalence of SAS before VNS implantation in our cohort (2/18 patients, 11%) admittedly appears somewhat lower than that reported in a recent population-based study conducted with home polysomnography in our geographic area [29]. This may be related to a younger age of our patients and lower prevalence of SAS risk factors, such as high blood pressure, diabetes, and obesity, as compared to the aforementioned cohort. It seems unlikely that the methods used to detect SAS in our cohort underestimated its prevalence [26]. This might thus suggest that established risk factors for sleep apnea outside a VNS context, such as male gender, age, or metabolic syndrome [29-32] may not directly apply for VNS-induced SAS. These observations support the idea that the still unclear pathophysiologic mechanisms of VNS-induced SAS are somewhat different from those causing SAS in subjects with no VNS or epilepsy.

We noticed that only one out of the five patients who developed SAS had concomitant increased seizures frequency. Nevertheless, we feel that screening for SAS in this particular population remains warranted, in as much as SAS is unlikely to remit spontaneously over time if VNS is pursued, and it represents an important cardiovascular risk factor [19,23]; for example, SAS treatment in an acute stroke setting may enhance functional recovery [33, 34]. Furthermore, the potential beneficial role of modifying SAS beyond vascular pathologies has been recently suggested , as it appears to be related to cognitive impairment [35].

Only higher stimulation intensity might possibly have an impact on SAS development, but requires confirmation in larger studies. This observation appears logical, since decreasing the intensity of stimulation are known to improve SAS. Concerning treatment, all the three patients whose VNS parameters were changed to treat SAS had their condition improved: increasing OFF time and reducing stimulation intensity seem effective [22].

The present study confirms previously described information: respiratory events were more frequently obstructive than central [6,7,13]; furthermore 4/5 of our patients with VNS-induced SAS reported increased vigilance as a favorable effect [18], underscoring that somnolence may be masked by VNS.

We acknowledge that the study is limited by the small number of patients, which hampers its statistical power. Conversely, the fact that the population was non-selected by sleep criteria represents a strength in our view. Estimations of VNS effect on seizures and vigilance relied on reporting by patients and relatives and not on objective measures. This study was not designed to assess the type of SAS induced by VNS. As previously mentioned, PG and PSG should have comparable sensitivity in SAS diagnosis [26,27]. A further limitation is that two of our patients did not undergo any control sleep study after implantation, which could have led to underestimate the true rate of VNS-induced SAS. Further studies with larger cohorts seem necessary to shed further light on potential risk factors for developing SAS in this clinical setting.

Table 1: Clinical characteristics of all patients							
N°- Age- Gender		**Epilepsy type**	**Etiology**	**% Reduction of seizures with VNS**	**Parameters of VNS device (at time of the sleep study)**	**Medication**	
1.	**50-F**	Focal	Adult Rasmussen Encephalitis	>75%	2.5 mA, 30 Hz, 250 µs, 30 sec on, 05 mn off	LTG, PGB, LEV, CLZ	*
2.	**34-F**	Focal/ generalized	Ring 20 chromosome	0%	0.5 mA, 20 Hz, 250 µs, 30 sec on, 5 mn off	OXC, CLZ	
3.	**27-M**	Generalized	Dravet syndrome	>75%	2.25 mA, 20 Hz, 250 µs, 30 sec on, 5 mn off	PHT, VPA, LEV, CLZ	
4.	**31-F**	Focal	Unknowm	>75%	2 mA, 20 Hz, 250 µs, 21 sec on, 0.8 mn off	LTG, FBM, PGB	*
5.	**39-M**	Generalized	Unknowm	>50%	1.75 mA, 20 Hz, 250 µs, 30 sec on, 5 mn off	VPA, LEV, LTG, CLZ	
6.	**37-M**	Focal	Polymicrogyria	0%, shorter	2.25 mA, 30 Hz, 250 µs, 30 sec on, 1.8 mn off	LTG, VPA, CLBZ	
7.	**52-F**	Focal	Hippocampus sclerosis	0%	2 mA, 20 Hz, 250 µs, 30 sec on, 1.8 mn off	LTG, TPM	
8.	**52-M**	Focal	Perinatal hypoxia	0%, shorter	1.75 mA, 20 Hz, 250 µs, 30 sec on, 5 mn off	LEV, PGB	
9.	**26-M**	Focal	Focal cortical dysplasia	>90%	2 mA, 20 Hz, 250 µs, 7 sec on, 0.3 mn off	PHT, OXC, RTG, CLZ	*
10.	**35-F**	Focal	Hippocampus sclerosis	50%, shorter	1.75 mA, 20 Hz, 250 µs, 30 sec on, 5 mn off	CBZ, TPM, PGB	
11.	**28-F**	Focal	CDKL5	>70%, shorter	1.5 mA, 20 Hz, 250 µs, 30 sec on, 5 mn off	LTG, VPA, CLBZ	
12.	**31-M**	Generalized	Unknown	>90%	1.5 mA, 20 Hz, 250 µs, 30 sec on, 5 mn off	VPA, RUF, ZNS	
13.	**26-F**	Focal	Perinatal hypoxia	50%	1.75 mA, 20 Hz, 250 µs, 30 sec on, 1.8 mn off	OXC, LTG, LEV	*
14.	**25-M**	Focal/ generalized	Unknown	>50%	1.75 mA, 20 Hz, 250 µs, 30 sec on, 1.1 mn off	TPM, OXC, RUF, CLZ	
15.	**34-M**	Generalized	Unknown	>50%	2 mA, 20 Hz, 250 µs, 30 sec on, 3 mn off	PB, RUF, CLBZ	*
16.	**25-M**	Generalized	Unknown	>90%	1.25 mA, 20 Hz, 250 µs, 30 sec on, 5 mn off	LTG, TPM, VPA	
17.	**23-M**	Focal	Focal cortical dysplasia	>75%	1.5 mA, 30 Hz, 250 µs, 30 sec on, 5 mn off	LEV, CBZ, TPM, PER	
18.	**22-M**	Generalized	Unknwon	>90%	1.25 mA, 20 Hz, 250 µs, 30 sec on, 1.1 mn off	VPA, OXC, SUL, CLZ	

***Patients 1, 4, 9, 13 and 15 (highlighted lines) were suffering from SAS induced/aggravated by VNS.**
CLBZ : clobazam, , CLZ : clozapine, LTG : lamotrigine, LEV : levetiracetam, FBM : felbamate OXC : oxcarbazepine, , PER : perampanel PB : phenobarbital, PHT : phenytoin , PGB : pregabaline, RTG : retigabine,, RUF : rufinamide, VPA : valproic acid ,ZNS : zonisamide

Table 2: diagnosis and treatment of Sleep Apnea Syndrome in all patients					
	Sleep study before VNS implantation	**AHI**	**Sleep study after VNS implantation**	**AHI**	**Treatment**
1.	PG	0.4/h	PG (twice)*	**12.7/h – 0/h**	Change of parameters
2.	PG	0.4/h	PSG	0.4/h	
3.	PSG	2/h	-	-	
4.	PG	1.5/h	PG	**13.5/h**	None
5.	PG	1.6/h	PG	3.8/h	
6.	PG	**9.5/h**	PG**	3.6/h	Positional
7.	PG	0.4/h	PSG	0.8/h	
8.	PG	2.9/h	PG	2.9/h	
9.	PG	**17.7/h**	PG	**68/h**	cPAP
10.	PG	0.5/h	PG	0.9/h	
11.	PG	0.1/h	PG	0/h	
12.	PG	3.7/h	PSG	3.4/h	
13.	PSG	1.1/h	PG	**45.5/h**	Change of parameters
14.	PG	0.8/h	-	-	
15.	PG	3.8/h	PG	**11.1/h**	Change of parameters
16.	PG	0.8/h	PG	1.2/h	
17.	PG	0.8/h	PG	0.1/h	
18.	PSG	2.2/h	PG	1.8/h	

Patients 1, 4, 9, 13, 15 were diagnosed and treated for a VNS-induced SAS.
PSG: polysomnography; PG: ambulatory polygraphy; AHI: apnea-hypopnea index
*** Patient 1 underwent 2 PG after the VNS implantation, the first with standard stimulation and the second with low intensity.**
**** Patient 6 underwent the second PG under positional treatment**

Table 3: characteristics of patients stratified for VNS induced/aggravated SAS				
Characteristics		**Patients with SAS (n=5)**	**Patients without SAS (n=13)**	**p-value**
Gender	Female Male	3 2	4 9	0.326 *
Age (median ; range)		31 ; 26-50	31 ; 22-52	1 **
BMI	Overweight	1	2	1*
Diabetes or hypertension		0	0	1*
Epilepsy type	Focal Generalized	4 1	7 6	0.595*
Seizures frequency (median ; range)	Baseline Focal (per month)	100 ; 1-300	13 ; 0-75	0.258 **
	Baseline generalized (per year)	0 ; 0-36	0 ; 0-48	0.960**
	Effect of VNS on seizures	Decrease of >75% ; 50-90%	Decrease of >70% ; 0-90%	0.459 **
VPA medication at implant	VPA	0	7	0.101*
Parameters of VNS device (at time of the sleep study) (median ; range)	Intensity	2.0 mA ; 1.75-2.5 mA	1.75 mA ; 0.5-2.25 mA	0.055 **
	Frequency	20 Hz ; 20-30 Hz	20 Hz ; 20-30 Hz	0.920**
	Pulse duration	250 µs ; 250-250 µs	250 µs ; 250-250 µs	0.960 **
	Time ON	30 s ; 7-30 s	30 s ; 30-30 s	0.219 **
	Time OFF	1.8 mn ; 0-3-5 mn	5 mn ; 0.8-5 mn	0.139 **
Magnet effect	Yes No	3 2	9 4	1*
Vigilance	Better Unchanged	4 1	11 2	1*
SAS : sleep apnea syndrome, VNS : vagus nerve stimulation, VPA : valproic acid, BMI : body mass index ***Fisher's exact test, **Mann-Whitney U-test**				

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