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

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Abstract

Background

Vagus nerve stimulation (VNS) is a palliative treatment for refractory epilepsy that can induce a sleep apnea syndrome (SAS). Until now, prevalence of VNS-induced SAS and risk factors for developing it have barely been studied. The purpose of this study is to estimate the prevalence of a VNS-induced SAS and to identify if any clinical variable correlates with development of SAS after VNS implantation.

Methods

We analyzed the computerized medical records of 18 adults treated for refractory epilepsy who were implanted with a VNS at the University Hospital of Lausanne (CHUV), Switzerland between May 2008 and May 2017. The patients underwent a polygraphy (PG) or a polysomnography (PSG) before and after VNS implantation to screen for SAS. We compared retrospectively demographic variables, variables related to the epilepsy, and to the device's parameters between the patient with and without SAS.

Results

In out cohort the prevalence of VNS-induced SAS was 27.8%. We did not find any statistically significant difference between the variables in the two groups but we found some trends in terms of medication, intensity of the stimulation and OFF time of the device.

Conclusion

The relatively high SAS prevalence that we observed and the lack of identified risk factors for developing SAS suggest that a screening for SAS before and after VNS implantation may represent a reasonable practice for every adult patient.

Key words

Vagus nerve stimulation, refractory epilepsy, sleep-related breathing disorders.

Table of contents

Introduction

The vagus nerve stimulation (VNS) is a palliative therapy for refractory epilepsy and depression. It can be used to decrease seizure frequency in patients not responding to antiepileptic drugs (AED). The VNS sends stimulations produced by a generator usually placed subcutaneously in the left anterior axillary region, in front of the great pectoral muscle, and reaches the left vagus nerve. The mechanism by which the VNS works has not been fully explained; several possibilities have been postulated, among others stimulation of the nucleus of the tractus solitarius [1,2,3,4]. Several variables have to be adjusted, such as ON and OFF times of stimulation, output current, frequency and pulse width. An example of typical target settings would be a pulse of 0.5ms repeated at 20-30Hz for 30s, every 300s, with a current of 1.0-1.5mA [5]. The firsts randomized controlled trials (RCT) were performed in the early 1990s, showing that it was safe, well tolerated and effective as a treatment of refractory epilepsy [6,7,8,9]. It is approved by the Food and Drug Administration (FDA) since 1997, and is reimbursed in Europe and in Switzerland since several years.

A study about the effect of the VNS on sleep published in 2000 [2] analyzed polysomnographies (PSG) of four patients with VNS before and after treatment. This study (and several others since then [3,5,10,14]) revealed an apnea-hypopnea index (AHI), defined as the number of apneas or hypopneas divided by the number of hours asleep, to be significantly higher when the VNS was activated. It also showed that VNS decreased airflow and increased both respiratory effort and airways obstruction during its activation [2,3,10,11,12,13,14]. Both peripheral and central mechanisms would be possible explanations for changes in respiratory patterns. The peripheral mechanism would be explained by stimulation of the upper airway musculature producing a narrowing [2,3,12,15]. The central mechanism is also plausible, since the vagus nerve has projections to the brainstem respiratory control centers [2,3,12,15]. Even if changes in respiratory patterns are found in many patients, they do not seem clinically relevant in most. Only a few patients develop a sleep apnea syndrome (SAS) defined as an AHI ≥5 (SAS is considered mild if AHI=5-10/h, moderated if AHI=10-15/h and severe if AHI≥15) [16]: a seminal study [3] reported changes in respiratory patterns in 14/16 patients; 2 of them developed SAS. Another assessment [12] reported changes in respiratory patterns in 9/26 patients, with 5 developing SAS; in a further study [13] 8/9 patients changed their respiratory patterns and 3 had SAS. In another analysis [17] changes in respiratory patterns were observed in 7/8 patients but none of them developed SAS.

To this day, to the best of our knowledge, prevalence of changes in respiratory patterns and SAS in patients with VNS is basically unknown. This is due to the fact that the aforementioned studies have included relatively little groups of patients selected from a sleep medicine angle, which are not necessarily representative of the general population of patients with epilepsy implanted with VNS. However, this side effect seems to be frequent enough so that many authors recommend a screening by PSG before and after the stimulator's implantation [5,10,12,13,19,20]. Screening after the implantation could

be important, since it is known that VNS increases daily wakefulness [23], which can compensate one of the cardinal symptoms of the SAS, daytime somnolence [2,4,22,24].

There are many treatment options for patients who suffer from SAS due to VNS. The more frequently used are the continuous positive airway pressure (cPAP), efficacious if the compliance is good [5,10,13,15,19,20,25], and/or changes in stimulator settings [2,5,18,19,20]. SAS improvement by increasing OFF time of the VNS or by decreasing stimulation frequency has indeed been reported [18], the objective being to set the stimulator to optimize seizure control while limiting side effects on sleep. A case report has suggested that introducing cPAP and changes in the VNS settings might further enhance the impact of cPAP treatment [15]. In severe cases, some authors even recommend to deactivate the VNS at night [5,19,20], which however practically may not prove very easy. Other modifications might be considered, such as changing the AED if they increase weight [10,19], or positional therapy [5,10]. To date, none of those therapies is considered as evidence-based in this particular patients' setting, and the choice has to be individualized. Treating SAS seems important for the quality of life of the patient but also because it is well known that sleep disruption can increase seizure frequency [2,5,20], besides representing a cardiovascular risk factor [21,22].

To summarize, a link between the VNS and sleep respiratory disorders is described but the prevalence of this side effect is unknown. Risk factors for developing sleep disorders have not been clearly elucidated to this day. Only one recent study [20] postulates left vocal cord abduction as a predisposing factor. Identifying other predictors would be relevant for many reasons: it would help selecting which patients need a sleep screening, and could even prevent the development of SAS if it were possible to eliminate those factors.

Material and methods

The purpose of this retrospective cohort study is to assess the prevalence of a VNS-induced SAS, and to identify if any clinical variable correlates with development of SAS after VNS implantation in adults. The study was approved by our ethics committee (CER-VD).

Patients

In this cohort study, we analyzed the computerized medical records of consecutive adults (>18 years old) treated for refractory epilepsy with AED and who were implanted with a VNS at the University Hospital of Lausanne (CHUV), Switzerland between May 2008 and May 2017.

We divided the cohort in two groups: one of patients who developed SAS after implantation and the other with those who did not. All patients underwent a sleep study before implantation to screen for SAS. This was performed since SAS would have needed treatment before the implantation, or might even have represented a contraindication. Their results, as those of control sleep studies, were retrieved, and the evolution in SAS prevalence assessed. Sleep studies were scored according to existing guidelines [26]. All studies but one were conducted at the sleep center of the CHUV and interpreted by AOR, a sleep certified neurologist.

We compared retrospectively several potentially explanatory variables related to SAS development between the two groups. Firstly, demographic variables such as gender, age, overweight (defined as a BMI>25), and history of arterial hypertension or diabetes. Secondly, variables related to epilepsy diagnosis, such as the main type of seizures (focal or generalized), the effect of VNS on decrease in seizures frequency and medication (presence of valproate, VPA). Thirdly, VNS parameters such as current intensity, pulse frequency, duration, and ON and OFF times. We also compared the efficacy of the magnet (defined as an effect in at least 30% of seizures in term of shortening of the episode or of the postictal state) and the subjective increase in vigilance (reported by the patient or his caregiver).

Statistical analysis

Since we studied two small groups of patients, we used Fisher's exact tests to analyze dichotomous variables, and Mann-Whitney U-tests to search for significant differences between the two groups in continuous variables, using two-tailed analyses. We used the online application « socscistatistics » 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.

Results

Prevalence

In the study period of 9 years, 19 adult patients received VNS in the CHUV, of whom 1 died after 4 years. Due to the lack of information, we excluded him from the study. We therefore analyzed 18 patients; 4 developed a SAS *de novo* and 1 already had it before implantation and worsened. Therefore the prevalence of the VNS-induced SAS was 27.8%.

Characteristics and clinical evolution

The main clinical variables of each patient are summarized in table 1.
Sixteen out of 18 subjects underwent a control sleep study after implantation, after a median latency of 36 months (from 6 months to 7 years). The types of sleep studies performed and the observed AHI are summarized in table 2. Most sleep studies were ambulatory polygraphies, chosen as they are more convenient both for patients and costs than polysomnographies, and they retain comparable sensitivity in SAS diagnosis [27,28].

Patients 1, 4, 9, 13 and 15 suffered from SAS induced by VNS. The majority of respiratory events were hypopneas, mostly of obstructive nature, although a central component was observed in 5-25% of them. Patients 6 and 13 were already suffering from SAS before VNS implantation. The condition of patient 6 remained constant after implantation; therefore we included him in the second group. As the condition of patient 13 worsened, he was included in the first group. Patients 3 and 14 did not undergo a control sleep study after implantation due to the severe cognitive impairment they were suffering and the wish of their families. They were neither snoring nor showing any symptom of SAS and therefore were included in the second group.

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 sleep studies: the first with the parameters unchanged showed an AHI at 12.7/h, the second one with modified parameter showed an AHI at 0/h. Patient 4 was not treated for SAS since this had no clinical impact. Patient 9 was already treated with cPAP before implantation and continued it. Patient 13 had an increased seizure frequency after VNS was started because of the SAS. The situation improved by decreasing the current intensity from 1.75 mA to 1.25 mA. Patient 15 had no complaint related to SAS.. He was treated by changing parameters; he had OFF-time increased from 3 to 5 minutes.

SAS associated factors

As exposed in table 3, there was no statistical difference between the two groups; we only found some trends in terms of medication, intensity of the stimulation and OFF time of the device. Demographic variables, those related to the epilepsy (type, frequency), and the VNS stimulation parameters (frequency, time ON, vigilance, magnet effect) were far from significant.

Discussion

To the best of our knowledge, our study is the first to estimate the prevalence of a VNS-induced SAS in a non-selected adult population, and to investigate if any clinical variable correlates for the development of a SAS after a VNS implantation. Our main findings were that the VNS induced or aggravated SAS in 27.8% of our patients with epilepsy; we did not find any statistically significant variable related to the development of a VNS-induced SAS.

Our results confirm the link between VNS and SAS, and therefore seems to justify a routine post-implant screening in our view. The prevalence of SAS before VNS implantation in our cohort (2/18 patients, 11%) appears somewhat lower than that reported in a recent population based study conducted with polysomnography in our area [29]. This may be related to the younger age of our patients and their low prevalence of specific risk such as arterial hypertension, diabetes, obesity; it is in fact unlikely that the methods used to detect SAS in our cohort underestimated significantly its prevalence [27]. It seems thus that established risk factors for sleep apnea outside a VNS context, such as male gender, age, metabolic syndrome [29,30,31,32] do not apply for a VNS-induced SAS. These observations support the idea that the still unclear pathophysiologic mechanisms causing a 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 a SAS had an increase in seizures frequency. Nevertheless, we feel that despite this relatively uncommon worsening of epilepsy control, screening for SAS in this particular population is warranted, since it also represents an important cardiovascular risk factor [21,22].

None of the potential predictor variables we explored was statistically significant for the development of a SAS. We only found some trends, firstly concerning medication: no patient suffering from VNS-induced SAS was on valproate (VPA) at implant, as opposed to 6/13 patients of the other group. This seems counterintuitive, as VPA is known to increase weight, and requires further exploration in larger cohorts. Concerning variables related to the VNS parameters, our analysis shows that higher intensity and shorter OFF time might possibly have an impact on SAS development. These observations appear logical, since increasing OFF time and decreasing the intensity of stimulation are known to improve SAS.

In addition, our study confirms some previously known information. Firstly, we observed that the respiratory events were more frequently obstructive than central [2,3,13], although the mechanisms have not been fully explained yet. Secondly, concerning treatment, all the 3 patients whose VNS parameters were changed to treat the SAS had their condition improved. This confirms that increasing OFF time and reducing intensity of the stimulation are effective [18]. Thirdly, the VNS is already known to increase vigilance [23], which can be observed despite of the SAS. As

demonstrated in our population, 4/5 of our patients suffering from SAS had such as subjective favorable effect.

The study is limited to a restricted number of patients, which may have limited its statistical power, but the fact that the population was non-selected by sleep criteria represents a strength. This study was not designed to assess the type of SAS induced by VNS. A further limitation is that two of our patients did not undergo any control sleep study after the implantation.

Conclusion

The relatively high SAS prevalence that we observed, the effect on vigilance, which can mask SAS symptoms, and the lack of identified risk factors for developing SAS, suggest that a screening for SAS before and after VNS implantation may represent a reasonable practice for every adult patient, besides from those already suffering from SAS.

Further studies with larger cohorts seem necessary to shed light on the existence of any risk factors for developing a SAS in this clinical setting. It would be especially relevant to investigate the trends we found in terms of VPA co-medication, OFF time and current intensity.

Table 1: characteristics of the 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	>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	>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	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	Cryptogenic	>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	Cortical dysplasia	>75%	1.5 mA, 30 Hz, 250 µs, 30 sec on, 5 mn off	LEV, CBZ, TPM, PER	
18. **22-M**	Generalized	Genetic	>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 by the 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 SAS					
	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: polygraphy; AHI: apnea-hypopnea index
*** Patient 1 underwent two PG after the VNS implantation, the first one with standard stimulation and the second one with low intensity.**
**** Patient 6 underwent the second PG under positional treatment**

Table 3: characteristics of each group and result of the statistical analysis				
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 **The p-values were calculated with *Fisher's exact test and **Mann-Whitney U-test**				

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