Seizure 33 (2015) 24–28

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

The effect of vagus nerve stimulation on cardiorespiratory parameters during rest and exercise

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ARTICLE INFO

Article history:
Received 17 July 2015
Received in revised form 28 September 2015
Accepted 8 October 2015

Keywords:
Vagus nerve stimulation (VNS)
Side effects
Bradycardia, Tidal volume, Breathing frequency

ABSTRACT

Purpose: Vagus nerve stimulation (VNS) has been successfully applied to reduce seizure frequency in numerous patients with epilepsy. However, various side effects, including dyspnea and bradycardia have been reported, that appear exercise related in some patients. This pilot study aims to obtain insight in the cardiorespiratory effects of VNS during both rest and exercise.
Methods: Patients with a VNS device who experience side effects during exercise are compared with patients without side effects. Respiratory and cardiac parameters measured during rest and exercise include heart rate, breathing frequency and tidal volume.
Results: Sixty-two episodes of VNS in five patients with and five patients without side effects were recorded. In addition, five control subjects have been measured. During rest, all subjects showed stable values for the cardiorespiratory parameters. During the first minutes of exercise, heart rate, breathing frequency and tidal volume increased. Thereafter, a steady state was reached again for all subjects. During VNS episodes, eight out of 10 patients showed a small but consistent decrease in heart rate, along with an increase in breathing frequency in eight out of nine patients. Tidal volumes decreased during VNS episodes. These effects, induced by VNS, occurred during both rest and exercise. Magnitude of these effects varied between patients, but was not necessarily related to the intensity of the experienced side effects.
Conclusion: This pilot study shows that VNS causes an increase in breathing frequency and a decrease in tidal volume and heart rate in the majority of patients, during both rest and exercise.

1. Introduction

Vagus nerve stimulation (VNS) was first introduced in 1988, and is now an accepted treatment option for patients with refractory epilepsy, who are not suitable candidates for resective brain surgery or for whom surgery has failed. VNS consists of intermittent electrical stimulation of the left cervical vagus nerve, provided by an implanted pulse generator and a stimulation electrode. The main purpose of VNS is to reduce seizure frequency, which would ideally result in a total termination of seizure occurrence. Long term studies that assessed the efficacy of VNS, concluded that over 50% seizure reduction was accomplished in 20–63% of the patients after treatment for 6 months to 6 years [1–3].

Beside seizure frequency reduction and other positive effects of VNS [4], several side effects have been reported. The most commonly reported side-effects are hoarseness, coughing and dyspnea, with an incidence reported as high as 66% of patients [5]. Most laryngeal symptoms have been contributed to vocal cord adduction, caused by stimulation of the laryngeal branches of the vagus nerve [6]. Respiratory complications by VNS during wake are rarely reported, while alterations of respiratory patterns during sleep appear to be more common in both adults [7,8] and children [9,10]. During sleep, these patients show an increased breathing frequency (BF) and a decreased tidal volume (TV), as a direct effect of VNS. The exact mechanism of this effect is not known, but several mechanisms have been proposed, such as peripheral effects on upper airway musculature innervated by the vagus nerve or more central mechanisms influencing upper airway patency and respiratory effort [7].

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http://dx.doi.org/10.1016/j.seizure.2015.10.004
1059-1311/

Cardiac symptoms, such as bradycardia and even asystole have also been reported, during the intra-operative device testing [11], but there are also reports that mention bradyarrhythmias during regular treatment, even years after implantation [12,13]. Furthermore, changes in heart rhythm variability have been observed, although the direction of the variability changes showed inter-individual differences [13,14]. Cardiac effects of VNS have been attributed to an ineffective anodal block of the lower VNS electrode, causing efferent stimulation of the vagus nerve, which may lead to inhibition of AV conduction tissue, causing various degrees of AV block, or may slow SA nodal firing, or even stop it.

In addition, several patients experience hardly any side effects from VNS during rest, but mention a decrease in physical condition only during exercise, often reported as breathlessness at those moments the stimulator is active [4,8]. The cause of this phenomenon remains unclear; therefore, the aim of this pilot study is to evaluate the effect of VNS on cardiac and respiratory functions during rest and exercise, by recording ECG, pulse oximetry and respiratory parameters (e.g. breathing frequency and tidal volume).

2. Methods

2.1. Subjects

Patients with a VNS were recruited via the epilepsy center SEIN and the neurology department of Medisch Spectrum Twente, The Netherlands. We included five epilepsy patients with VNS who reported shortness of breath and intensified side effects of the stimulation during exercise to their treating physician, five epilepsy patients with VNS without reported side effects specifically during exercise, and five healthy control subjects, all of whom had no cardiorespiratory diseases, diabetes or other disorders affecting the autonomic nerve system. The study conformed to the Declaration of Helsinki and was approved by the institutional review board Twente. All subjects gave written informed consent.

2.2. Measurements

Measurements were performed at the Experimental Center for Technical Medicine at the University of Twente. Before the start of the test, patients were asked to fill in a questionnaire regarding their epilepsy, the VNS induced side effects they experienced and their exercise habits. The settings of the VNS were read via a handheld device. A pulse oximeter was placed on the right middle finger (Avant 9600, Nonin Medical Inc., MN, USA). Cardiorespiratory parameters were acquired synchronously. ECG recordings were performed with a Viasys ECG monitor and respiratory parameters were obtained using a Jaeger Oxycon Pro (a mask with a flow sensor) (both CareFusion, CA, USA). Two bipolar surface electrodes were placed over the VNS electrode on the left side of the neck to record episodes of stimulation and on the chest to record ECG to facilitate heart rate analysis (sample frequency: 2048 Hz).

For the first stage of the measurement, the subjects were seated in a chair for 20 min, reading a magazine. During the second stage of the measurement, the subjects exercised for 20 min on the Ergoselect 100 cycle ergometer (ergoline GmbH, Germany), at a constant level that could be maintained comfortably for the duration of the test. The subjects with VNS had their standard VNS settings programmed and had at least three epochs of stimulation during both the rest and the exercise stage, so that in total at least 60 VNS episodes could be recorded.

2.3. Analysis

For every subject with VNS, epochs of 50 s just prior, during and directly after stimulation were selected, during both rest and exercise. Respiratory parameters of interest were tidal volume (TV), breathing frequency (BF) and saturation, and these values were averaged for each epoch. Obtained ECG data was filtered with a bandpass Butterworth filter from 0.5 to 45 Hz (MATLAB, 2011a, the MathWorks, Inc.). Peak detection was done using the MATLAB function *findpks*. Detected peaks were checked visually and missed peaks were added or erroneous peaks were deleted manually. Heart rate, as measured by beats per minute, was calculated and values were averaged for each epoch. From the same ECG signal, heart rate variability (HRV) was determined in the time domain, as the standard deviation of the heart rate in one epoch.

First, the values of patients with VNS were compared to healthy subjects, to analyze whether the parameters were within the normal range during rest and exercise. Second, in order to avoid differences in weighting, average parameters were calculated for each individual patient before averaging. Third, the average effect of VNS on the cardiorespiratory parameters for all patients was analyzed, disregarding subgroup or phase of the test (rest or exercise), to study the global effect of VNS. Then the specific test phase was taken into account, to investigate whether there were differences between the effect of VNS during rest and exercise. Last, the subgroups were separated, to investigate whether there were differences between patients who did and did not report the side effects during exercise. During both rest and exercise, the average value of the parameters of the epochs during VNS was compared with the average value of the parameters during either the epoch pre or post VNS.

Even though we have a decent number of VNS episodes, the number of subjects in this pilot study was small. Therefore we did not test for statistical significance, but identified whether cardiorespiratory responses to VNS were consistent and reproducible in patients with and without side effects, and during rest and exercise.

3. Results

Ten patients with a vagus nerve stimulator and five healthy subjects were included. The patients with a VNS were all good responders to VNS therapy, and were divided in two groups: group 1 consisted of patients who reported side effects during exercise and group 2 consisted of patients who reported no side effects during exercise. Average age of all subjects (epilepsy patients and healthy subjects) was 44 (20–78) years and for the epilepsy patients the mean time since VNS implantation was 45 (8–132) months.

An overview of subject characteristics can be found in Table 1. Subject 1 (group 1) was measured without the mask, so no respiratory parameters are available. Subject 6 (group 2) terminated the exercise prematurely, so only one VNS episode during exercise is available for analysis. Furthermore, epochs that contained large artifacts hindering proper analysis were excluded.

3.1. Global effect of exercise

Analysis in both healthy subjects and patients shows constant values for tidal volume (TV), breathing frequency (BF), heart rate (HR) and saturation during the 20 min rest period. When exercise is initiated, TV, BF and HR values increase, until they reach a new stable value, which is maintained for the remainder of the 20-min exercise. All values are within normal range and as expected during low impact exercise, healthy subjects and patients alike.

Table 1
Subject characteristics and stimulator settings. Epilepsy is years of epilepsy and VNS represents months since implantation. VNS settings during the measurement: output current/frequency/pulse duration/on-time/off-time.

Subject	Sex	Age [y]	Epilepsy [y]	VNS [months]	Settings of VNS: [mA/Hz/μs/s/min]	Stimulation episodes	
						Rest	Exercise
Group 1: with side-effects							
1	F	34	23	8	2.00/30/500/60/3	3	2
2	F	41	27	120	2.25/30/250/30/3	6	5
3	F	63	61	9	1.00/20/500/60/5	3	3
4	F	21	21	24	1.75/30/500/60/5	3	2
5	M	67	23	24	1.75/20/250/60/5	3	3
Group 2: without side-effects							
6	F	78	72	29	2.00/30/250/60/5	3	1
7	F	52	26	132	1.25/20/130/30/3	4	5
8	M	52	25	10	2.25/30/500/60/5	3	3
9	M	20	8	78	1.75/30/500/60/5	2	3
10	M	44	30	11	2.00/20/500/60/3	3	2
Group 3: controls							
11	F	27	n/a				
12	M	24					
13	M	27					
14	F	52					
15	F	72					

The first VNS episode during exercise was initiated 5 min after the start of the exercise phase, when the new plateau had been reached.

3.2. Respiratory parameters

Eight out of 10 patients reported hoarseness during VNS, of which the five patients in group 1 reported a form of breathlessness during VNS. No respiratory data is available for subject 1, so respiratory parameters are analyzed for 57 VNS episodes in nine patients. In general, VNS causes a small but reproducible decrease in tidal volume and an increase in breathing frequency (Table 2).

Regarding the saturation, no clinically significant effects of stimulation or exercise are observed.

During rest, eight out of nine patients show an increase in BF during VNS. While exercising, six out of nine patients show an increase in BF during VNS: two patients with and four patients without reported side effects. The three patients who do not show the increase in BF during VNS when exercising, show a decrease in BF, and two of them belong to the group with the reported side effects (group 1).

In both subgroups and both stages, average TV decreases during VNS. In rest, eight out of nine patients show a decrease in TV during VNS, whereas seven out of nine patients show this during exercise. One patient without reported side effects (group 2) shows in both stages a small increase in TV during VNS (1% and 3%).

3.3. Cardiac parameters

With regard to the effects of VNS on cardiac parameters, the heart rate (HR) has been analyzed. The 50 s epochs before, during and after VNS that were used for cardiac analysis were first visually inspected, and epochs containing too much noise or artifacts (e.g. due to movement) to be analyzed were discarded.

For 62 VNS episodes, the HR was calculated. Overall, patients showed a consistent decrease in HR during VNS, compared with epochs prior and after VNS (Fig. 1). During rest, nine out of 10 patients show a small decrease in HR during VNS, as compared to the epoch prior to VNS. Compared to the epoch after VNS, eight out of 10 patients have a subsequent increase in HR after VNS. During exercise, six out of 10 patients have a decreased HR during VNS, compared to the epoch before VNS. These six patients also had a decrease in HR during rest, and they are evenly distributed over the two subgroups. Compared to the epoch after VNS, seven out of 10 patients have a subsequent increase in HR after VNS.

Additionally, to check for consistency in HR in between two VNS episodes, HR values of VNS epochs have also been compared with epochs not directly preceding or succeeding the stimulation epoch. Comparison between the stimulation epochs and epochs randomly in between two subsequent stimulation epochs also shows decreased HR during VNS in all patients.

The analyzed epochs of 50 s are too short to reliably assess the heart rate variability within an epoch, so we cannot report on whether HRV is consistently affected by VNS.

Table 2
Overview of average respiratory values (standard deviation) for each subgroup. Pre, during and post: before, during and after stimulation, respectively. Group 1: with side effects, Group 2: without side effects, Group 3: healthy control subjects. SpO2: oxygen saturation, BF: breathing frequency, TV: tidal volume.

		SpO2 [%] (SD)			BF [/min] (SD)			TV [l] (SD)		
		Pre	During	Post	Pre	During	Post	Pre	During	Post
Rest	Group 1	97.3 (1.2)	97.1 (1.4)	97.4 (0.9)	17.7 (4.0)	19.2 (3.0)	18.7 (3.6)	0.52 (0.25)	0.49 (0.27)	0.48 (0.21)
	Group 2	96.8 (1.0)	96.9 (1.2)	96.8 (1.0)	19.7 (1.2)	22.4 (2.9)	20.7 (1.7)	0.40 (0.15)	0.37 (0.13)	0.40 (0.14)
	Group 3		97.5 (0.6)			18.8 (2.3)			0.51 (0.07)	
Exercise	Group 1	96.5 (1.7)	96.9 (2.2)	96.9 (1.9)	26.5 (4.0)	25.9 (4.3)	24.6 (4.5)	1.19 (0.48)	1.13 (0.54)	1.14 (0.60)
	Group 2	97.0 (0.2)	96.7 (0.6)	96.6 (0.6)	22.8 (3.1)	24.4 (3.2)	22.9 (2.8)	1.16 (0.34)	1.10 (0.32)	1.16 (0.32)
	Group 3		97.4 (1.4)			22.4 (1.6)			1.06 (0.19)	

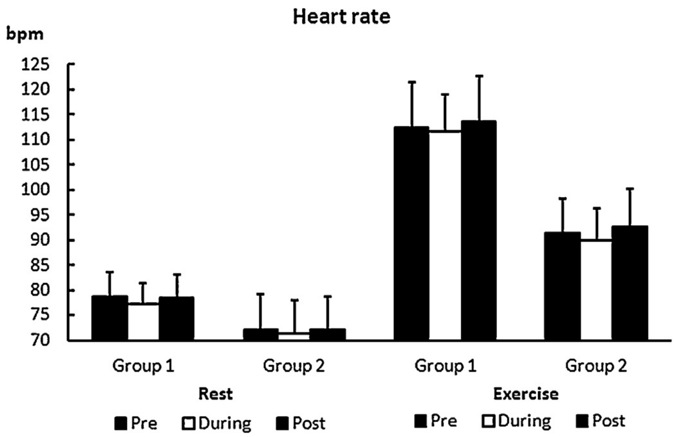

Fig. 1. Average heart rate (HR) in beats per minute (bpm), pre, during and post VNS for both subgroups, during both rest and exercise. Group 1: with side effects, group 2: without side effects. Error bars represent standard deviation.

4. Discussion

The main purpose of this pilot study was to investigate the effect of VNS on cardiac and respiratory functions during rest and exercise, and subsequently, whether there were differences between patients who reported shortness of breath during exercise and those who did not. The main finding of this pilot study is that individual patients generally show reproducible changes in several cardiorespiratory parameters during VNS episodes. Overall, this pilot study shows a decrease in tidal volume and increase in breathing frequency related to VNS in the majority of the patients and a consistent decrease in breathing frequency while exercising in two patients with reported breathlessness during exercising. In all but one patient heart rate decreases during VNS. Although patients show cardiorespiratory changes during exercise, these changes are comparable with or even smaller than the changes during rest. No specific VNS induced differences are found between the two groups, thereby not explaining why some patients with VNS experience breathlessness during exercise, while others do not.

For this pilot study, patients were divided into two subgroups, based on whether or not they reported VNS induced shortness of breath during exercise. However, this separation proved to be challenging, since side effects in general were experienced in a gradual manner, or were not perceived as side effects, or did not counterweight against the benefits of VNS. It is therefore possible that a patient understated the symptoms and ended up in group 2, while he or she should have been in group 1, or vice versa.

We believe that the patients who participated in this pilot study are representative for the (Dutch) healthy VNS patient population and all patients bike in daily life. By letting them bike at the constant speed they would bike normally, we have used an exercise which is perceived equally intensive for all subjects. An interesting difference though, is that the patients who reported no shortness of breath during exercise (group 1) might have been in better physical condition than the patients who did report shortness of breath (group 2), reflected by on average a lower heart rate during rest and while exercising. There is no cardiorespiratory data available from these patients prior to VNS implantation, so it is unknown whether this difference between the two groups was already apparent or perhaps caused by VNS induced side effects. This will be studied in our new prospective study.

4.1. Respiratory parameters

The respiratory side effects of VNS, during both wakefulness and sleep, have been investigated for years. Especially in children, the respiratory pattern is often affected during sleep. Zaaimi et al. showed increased BF and decreased TV during VNS in 10 children, sometimes combined with slightly decreased oxygen saturation [10]. These results are concordant with those of Nagarajan et al. (2003) [18]. In adults, Banzett et al. found no systematic change in TV nor BF during wake, but found an increased end-expiratory volume in patients who received high VNS stimulation intensity [8]. They attributed this effect to A-fiber afferent stimulation. These fibers carry afferent visceral information, as well as laryngeal motor stimuli. Binks et al. (2001) [19] showed that the threshold for A-fiber activation is rather low (0.25–1.5 mA) in their adult subjects. The specific Aδ-fibers carry information from the pulmonary stretch receptors, which play role in the Hering–Breuer reflex. Increased sensory activity of these pulmonary stretch lung-afferents results in inhibition of the central inspiratory drive and thus inhibition of inspiration and initiation of expiration. This reflex is thought to have a small effect on breathing rate and depth during rest, while it may influence rate and depth when TV exceeds 1 l, as during exercising.

The latter might explain why in this pilot study the majority of patients showed an increase in BF during VNS, while patient 3 (group 1) and patient 6 (group 2) showed a decrease in BF during exercise during VNS, as their TV was below 1 l. However, patient 2 also showed a decrease in BF, while her TV exceeded 1 l. Since eight out of 10 patients reported hoarseness as a side effect of their VNS, it is likely that their stimulation parameters are high enough to elicit afferent A-fiber activation. That would also explain the decrease in TV and increase in BF. However, the two patients who did not explicitly report hoarseness also show the decrease in TV and increase in BF. They did not experience hoarseness as a problem.

Furthermore, although there are consistent and reproducible effects of VNS on respiratory parameters, it is not certain whether they are clinically relevant and doubtful they could lead to the feeling of breathlessness during exercise, as there appears to be no difference in VNS induced respiratory effects between groups 1 and 2.

In this study, respiratory values were obtained every 5 s via a mask, which is a relatively low sampling rate to study respiratory differences between stimulation ON and OFF. A more continuous signal would be preferable, to allow breath-for-breath analysis. Furthermore, the mask was perceived as uncomfortable by some subjects, even though it did not impede respiration. It is also possible that the use of the mask made the subjects more conscious of their breathing, resulting in more controlled breathing and thereby influencing the parameters we studied. Alternatively, a chest band, capable of measuring variables such as tidal volume and breathing frequency could be used [8,10].

4.2. Cardiac parameters

Vagal influence on cardiac function can be an undesirable side effect in epilepsy patients, but is also explored as a treatment option for patients with heart failure [15]. Even though stimulation is applied to the left vagus nerve in epilepsy patients, in order to diminish the cardiac interference, (intra-operative) bradycardias and ventricular asystole have been reported [1,11–13,16]. The majority of patients in the current study showed that VNS resulted in a small but reproducible decrease in HR. However, not every patient showed this same response, as one patient in group 1 showed a small but reproducible increase in HR. Furthermore, there are two patients who showed both decreases and some increases in HR during VNS. A previous study by Frei and Osorio also demonstrated the occurrence of bradycardia as well as a combination of bradycardia and tachycardia during stimulation [14].

Even though the decrease in HR we found is small, it is reproducible in majority of the patients and clearly related to VNS. It is however probably too small to play an apparent role in the side effects experienced during exercise. Nonetheless, the effect could be of importance, especially as it appears to be present in both subgroups during both rest and exercise. This effect on heart rate indicates that most likely not all efferent stimulation of the vagus nerve is blocked by the VNS anodal block: one of the VNS electrodes is designed to block efferent stimulation of the vagus nerve. Failure of this anodal block could result in a decrease in heart rate [17] and could also be responsible for the hoarseness many patients report.

Although we found a decrease in TV and an increase in BF and HR in patients who experienced side effects during exercise, the same effects on TV and BF were also present in the group who did not report side effects during exercise. Besides, it turned out that the effect of VNS on TV and BF was present during both rest and exercise, and differences were primarily gradual. It is unlikely that the VNS induced changes in TV, BF and HR during exercise are exclusively responsible for the feeling of breathlessness in some patients.

None of the subjects had a history of cardiorespiratory diseases, diabetes or other disorders that affect the autonomic nerve system that could have influenced the results. However, all patients in this pilot study used medication and although unlikely, it cannot be ruled out that some of the anticonvulsants or other drugs have been of influence on the measured parameters, e.g. heart rate. The cardiorespiratory parameters obtained in patients were comparable to the parameters that were measured in healthy control subjects.

Although we analyzed over 60 VNS episodes, only a limited number of patients participated in this pilot. Several reproducible cardiorespiratory effects of VNS have been found in all patients, but the number of patients is too small to differentiate between patients who report breathlessness during exercise and those who do not, especially since there seems mainly a gradual difference in the experienced side effects.

5. Conclusion

We have investigated the effects of VNS on cardiorespiratory parameters, during both rest and exercise. The breathing frequency increased, tidal volumes decreased and the heart rate decreased consistently during VNS episodes in about 80% of our patients. These effects were present during both rest and exercise, and there was no clear distinction between the patients who reported VNS induced side effects during exercise and those who did not.

Disclosure

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflicts of interest

None of the authors has any conflict of interest to disclose.

Acknowledgments

We would like to thank M.J. Driesse MD, who implanted the VNS devices, for his continuous support and time.

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