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RESEARCH LETTER

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Cardiac vagal tests and vagus nerve stimulation in epilepsy

Introduction

Vagus nerve stimulation (VNS) is currently widely used for the treatment of intractable epilepsy. The device is implanted to stimulate the left vagal nerve, since stimulation on this side is less likely to cause cardiac effects. Severe adverse reactions associated with VNS appear to be rare [11]. Aspiration [2], worsened sleep apnea syndrome [7], psychotic reaction with a forced normalization [5] and cardiac standstill [12] have been reported. The mortality and sudden unexplained death in the cohort of patients under VNS are similar to those suffering from severe epilepsy [1]. Clinical relevant cardiac effects were not observed throughout the study of RR variability in patients treated with VNS [4]. However, some authors suggest that VNS has complex effects on instantaneous heart rate and heart variability and point to the need for more comprehensive studies [3]. In this paper, the direct and the long-term effect of the VNS on cardiac function were studied by using cardiac parasympathetic tests.

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Material and methods

Five patients with resistant epilepsy were studied (Table 1). The cardiac vagal function was studied by evaluation of the heart rate (HR) responses to the Valsalva maneuver, deep breathing and standing.

Valsalva maneuver. While in supine position, the patient blew into a syringe and maintained the pressure in an anaeroid manometer at about 40 mmHg for 10 seconds while the HR was recorded. The Valsalva ratio was calculated as the ratio of the longest R-R interval after the maneuver to the shortest R-R interval during the maneuver. A value of 1.10 or less is defined as an abnormal response, values 1.11–1.20 as borderline and 1.21 or more as a normal response.

Deep breathing. Subjects were trained to breathe deeply at a rate of 6 breaths/min in the supine position. The HR was then monitored continuously on the EMG screen and printed at a paper speed of 25 mm/s for 1 min. The mean ratio of the longest (expiration) to the shortest (inspiration) R-R interval of five breathing cycles was calculated. A value of 1 or less is defined as an abnormal response, values 1.01–1.19 as borderline and values 1.2 or more as a normal response.

Standing. After lying in supine position for 15 min, the patient was asked to get up quickly from the supine to an upright standing position without any help. The HR was continuously monitored during and after standing. The 30/15 ratio was calculated as the ratio of the R-R interval at 30 beats after standing to the R-R interval at 15 beats. A value of 1 or less is defined as an abnormal response, 1.01–1.03 as borderline and 1.04 or more as a normal response.

All tests were performed according to standard conditions of autonomic examination. The tests were carried out prior to implantation of the device and after six months. The VNS device was programmed to work for just 30 seconds. During re-examination of the Valsalva maneuver, each patient was examined three times. During the first trial, the device was off. During the second trial, the device was on at the beginning (total duration of the maneuver was 60 seconds), which means that the device was on during the first 30 seconds of the maneuver. During the third trial, the device was turned on just at the end of the 10th second of expiration. (The device was on from the 10th second to the 40th second of the maneuver).

Each patient was examined twice concerning the deep breathing test. During the first trial, the device was off. In the second trial, the device was turned on at the beginning of the trial and for 30 seconds.

The standing test was performed twice. Once with the device off and the second one with nerve stimulation while the patient was standing.

The VNS parameters are shown in Table 2.

Table 1

Patient	Sex	Age	Epileptic syndrome	antiE treatment	VNS constant parameters
V. P.	F	34	Lennox-Gastaut	Valproic 2000 mg/d Lamotrigine 200 mg/d Phenobarbital 200 mg/d	2.25 mA 500 ms PW slow rate
A. V.	M	27	CPS from frontal lobe	Carbamazepine1600 mg/d Phenobarbital 100 mg/d Clonazepam 6 mg/d	2.75 mA 500 ms PW slow rate
L. K.	M	30	CPS from left frontal lobe with generalization	Oxcarbazepine 1600 mg/d Valproic 1000 mg/d Lamotrigine 387.5 mg/d	1.50 mA 500 ms PW slow rate
M. S.	M	22	Symptomatic (ischemic inj) motor partial seizures with secondary generalization	Carbamazepine1600 mg/d Topiramate 400 mg/d	2.75 mA 500 ms PW slow rate
K. T.	M	25	SPS and CPS (from left frontal lobe)	Topiramate 500 mg/d Lamotrigine 500 mg/d	3.00 mA 750 ms PW slow rate

CPS complex partial seizures; *SPS* simple partial seizures; *PW* pulse width in microseconds

Table 2 VNS parameters

Slow rate stimulation	Parameters	Fast rate stimulation
0–3.5	Output current (in milliampers)	0–3.5
30	Signal frequency (in Hertz)	30
30 s	Signal on time	7 s
5 min	Signal off time	14 s

Results

All of the pre- and post-implantation tests, in all patients, were within normal limits of those specified in our laboratory. The statistical analysis of the results did not show any statistically significant differences, in applying the paired T-test (Table 3).

Discussion

Vagus nerve stimulation is likely to cause increased transynaptic neurotransmission at the sites of vagus nerve terminals in the medulla and sites receiving projections from these areas [2].

Besides the orthodromic conductivity of the stimuli, however, antidromic conductivity during VNS is also produced towards the periphery.

Motor fibers arise from the dorsal motor nucleus to supply autonomic innervations to the heart. As far as the literature is concerned, when the VNS influence on the cardiac function was studied by ECGs and Holter monitoring, data similar to our study were reported [10]. It has also been found that the cardiac rhythm does not change with the stimulation of the vagal nerve during sleep [8].

However, it has been reported that stimulation of the

Table 3 Heart rate ratio

Patient	Valsalva test				Deep breathing			Ratio 30/15		
	After 6 months				After 6 months			After 6 months		
	Baseline	Stimulation off	Stimulation a	Stimulation b	Baseline	Stimulation off	Stimulation on	Baseline	Stimulation off	Stimulation on
1	2.30	2.34	2.08	2.13	1.33	1.3	1.34	1.51	1.43	1.40
2	1.50	1.48	1.65	1.50	1.50	1.66	1.4	1.48	1.50	1.25
3	1.48	1.40	1.57	1.57	1.41	1.58	1.44	1.30	1.20	1.27
4	2.20	2.14	2.22	2.10	1.57	1.44	1.60	1.22	1.11	1.29
5	1.59	1.56	1.66	1.41	1.29	1.24	1.27	1.11	1.14	1.09
		t = 1.33	t = 0.34	t = 0.12	t = 0.77		t = 0.33	t = 1.58		t = 1.27

stimulation a device on at first 30 s of the maneuver; *stimulation b* device on from 10th to 40th second of the maneuver

vagus in animals may cause bradycardia [9], although this has not been reported in patients with VNS. This bradycardia may be due either to the high frequencies which were used for the stimulation of the vagus nerve, or because the stimulation was performed on the right vagus nerve [2].

As far as the sensitivity of the used method is concerned, as well as the small number of patients involved, it is suggested that a more comprehensive study should be performed. Hence, we conclude that the chronic and immediate VNS does not appear to have an effect on the cardiac function, as this has been shown through the cardiac tests of the vagus nerve. These results could emphasize the safety of VNS with regard to cardiac function on epileptic patients.

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