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Effect of chronic vagal nerve stimulation on interictal epileptiform discharges

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ABSTRACT

We evaluated the effect of vagus nerve stimulation (VNS) on interictal epileptiform discharges (IEDs) in 32 epileptic patients (18 females; 14 males) with an average age of 42.2 ± 11.4 years, all of whom had been suffering from epilepsy for an average of 29.2 ± 14.5 years. All of the patients had received VNS for 5 years. The first EEG was performed prior to the initiation of stimulation; the second EEG was performed at the 5-year follow-up visit. The duration of each EEG was 30 min. We compared these two EEGs in terms of the number of IEDs present in each patient and correlated them to other variables.

The average total number of IEDs during EEG and the total number of seconds in which IEDs were present decreased significantly after 5 years of stimulation from 97.3 ± 106.9 resp. 80.6 ± 86.1 to 49.4 ± 94.0 resp. 37.8 ± 65.0. Although there was no positive correlation between the reduction of IEDs and the percent of seizure reduction, we found a greater decrease of IEDs in patients who responded to VNS in comparison to those who did not. The decrease of IEDs was more pronounced in patients suffering from temporal lobe epilepsy than in patients suffering from extratemporal epilepsy. No other significant correlations were found.

VNS reduced IEDs in patients chronically simulated for epilepsy. The reduction of IEDs was greater in patients who responded to VNS and in patients suffering from temporal lobe epilepsy.

1. Introduction

Vagus nerve stimulation (VNS) is a non-pharmacological treatment for epilepsy. Literature generated in recent years has shown that VNS is a safe, tolerable, and effective adjunctive therapy for patients with refractory epilepsy. Its effectiveness was demonstrated both in controlled and in open-label trials.[1–5]

Pilot experimental data on animal models showed that VNS may have different effects on EEG and interictal epileptiform discharges (IEDs).[6–9] High-intensity and high-frequency vagal stimulation produces desynchronization in cortical EEG in animal models, and lower intensity stimulation at the same rate causes synchronization.[6,7]

Human data showed different effects of IEDs during both acute and chronic VNS. The initial data obtained from adult patients with refractory epilepsy did not reveal any significant changes of IEDs or any changes in the frequency power spectrum.[10,11]

Koo demonstrated the reduction of IEDs and improvement of interictal EEG in adult patients suffering from both focal and generalized seizures.[12] Other studies confirmed this data in both adults and children with various types of epilepsies and seizures including epileptic encephalopathies.[13–15] Two of these studies demonstrated a significant correlation between the percent of seizure reduction and the reduction of IEDs.[13,15]

We conducted our study on 32 patients suffering from refractory epilepsy. All of them were treated with VNS for 5 years to determine whether chronic VNS influences IEDs and whether there are potential correlations between this effect and other clinical variables (etiology, age of seizure onset, duration of epilepsy, percent of seizure reduction after 5 years of VNS, responder rate, and effect of on-demand magnetic extrastimulation).

2. Methods

We performed a retrospective, explorative, monocentric trial to explore the effect of chronic VNS on IEDs. We included all of the patients in our clinic who had completed 5 years of VNS between April 2004 and April 2008.

Thirty-two epileptic patients (18 females, 14 males) with an average age of 42.2 ± 11.4 years, all of whom had been suffering from epilepsy for an average of 29.2 ± 14.5 years, participated in the study. VNS therapy had been recommended by a special committee of the Brno Epilepsy Center. None of the patients who received VNS were considered to be a suitable candidate for resective surgery. All of the

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patients underwent a complete presurgical evaluation (long-term video-EEG monitoring, magnetic resonance imaging, neuropsychological assessment, interictal FDG positron emission tomography in all patients; interictal and/or ictal HMPAO single photon emission tomography, and Wada tests in patients where applicable). A VNS device (Cyberonics Inc., models 100 and 101 NCP, Houston, TX, USA) was implanted. A standard surgical technique was used to implant the VNS device.[14,15] All of the patients were implanted with the VNS device 5 years prior to the beginning of this study, and intermittent stimulation of the vagal nerve started on the day of implantation. Informed consent was obtained from each patient prior to the study, and the study received the approval of the St. Anne's Hospital Ethics Committee.

2.1. Stimulation characteristics

The following stimulation parameters of chronic VNS were applied at the time of the study: a 20 Hz frequency in 30 patients, 30 Hz in 2 patients; a pulse width of 250 μs in all patients; a 30 s/5 min on/off cycle was used in 5 patients, 21 s/3 min in 9 patients, 21 s/1.8 min in 6 patients, 30 s/1.8 min in 8 patients, 30 s/3 min in 2 patients, and 30 s/1.8 min in 2 patients. The output current ranged from 1.00 to 2.00 mA, with an average of 1.56 ± 0.29 mA. The magnetic parameters were adjusted in all subjects for extrastimulation. The values of this output current were 0.25 mA higher that of the intermittent stimulation in each subject; the other parameters for the extrastimulation were identical to those mentioned above.

2.2. Clinical characteristics

We collected data from each patient concerning the etiology of epilepsy, seizure type, localization of epilepsy, and any previous epilepsy surgery procedures.

2.3. EEG analysis

The 32-channel Brain Quick system (Micromed), using a 10-20 system, was used for scalp recording. EEG was amplified with a bandwidth of 0.4–100 Hz, at a sampling rate of 128 Hz. No seizures were noted (neither by the patients themselves nor by their caregivers) for at least 24 h prior to the EEG analysis or during the entire EEG procedure in any of the subjects. We performed two EEGs without either photic stimulation or hyperventilation, both at the same approximate time of day (between 10 a.m. and 1 p.m.). Each EEG lasted at least 30 min for each patient, during which the patient lay in a supine position, with closed eyes. Vigilance was evaluated continuously by experienced nursing staff on the basis of the character of the EEG curve. The EEG recording lasted usually more than 30 min; we excluded any periods with significant artifacts and included only 30 min of recording free of artifacts. The first EEG was administered 1–3 months prior to the implantation of the VNS device, and the second EEG after 5 years of stimulation.

The EEG for all of the patients was visually analyzed. Only definite spikes, sharp waves, and spike-wave complexes were considered epileptiform abnormalities; their shapes were distinguished by morphology and/or amplitude from the background activity. Nonepileptogenic or uncertain sharp discharges were not considered significant. Both focal and generalized IEDs were always included in the analysis. Two people analyzed the EEG. We did not assess inter-observer reliability. Only the epileptic graphoelements that both observers agreed on were included in the analysis. Both authors who analyzed the EEGs were aware of each patient's outcome, but were blinded at the time of their review to which patient's EEG they were reviewing.

We visually analyzed two different paradigms: the absolute number of IEDs in each 30-min EEG and the number of seconds in which IEDs were present. Both analyses were included in the statistical analysis.

For each patient, we counted the ratio R_{IED}—the ratio of the number of IEDs in the preoperative EEG and in the EEG at the 5-year follow-up ($R_{IED} = IED_{preop}/IED_{5\ year}$). We also counted the ratio R_{SEC}—the ratio of the number of seconds in which IEDs were present in the preoperative EEG and in the EEG at the 5-year follow-up visit ($R_{SEC} = SEC_{preop}/SEC_{5\ year}$). This ratio was then calculated as a percentage, treating the baseline IED_{preop} as 100%.

R_{IED} and R_{SEC} were compared and correlated with other variables (etiology, age of seizure onset, duration of epilepsy, percent of seizure reduction after 5 years of VNS, responder rate, and effect of on-demand magnetic extrastimulation). The data collected for this study were based on the patients' files and seizure diaries. The monthly seizure frequency was evaluated from patients' seizure diaries at the preoperative visit and at the 5-year follow-up visit (the day of second EEG). The mean monthly seizure frequency at baseline and at the last follow-up visit was the mean seizure frequency of the previous 6 months.

2.4. Statistical analysis

The Wilcoxon rank test was used to compare the absolute number of IEDs and the number of seconds in which IEDs were present, preoperatively and after 5 years of stimulation. The Mann–Whitney U test was used to compare R_{IED} and R_{SEC} in the groups of patients with different etiology, localization of epilepsy, effect of magnetic extrastimulation, and responder rate. The Spearman rank correlation test was used to calculate the correlation between R_{IED} and R_{SEC} and the ages of the patients, duration of epilepsy, age of epilepsy onset, and the percent of seizure reduction. SPSS 13.0 was used to perform the statistical analysis. $p < 0.05$ was considered to be statistically significant.

3. Results

3.1. Clinical characteristics

Symptomatic etiology was revealed in 23 patients; cryptogenic etiology was revealed in 9 patients. No patient suffered from idiopathic generalized epilepsy. The cause of the epilepsy was established as mesiotemporal sclerosis in 6 patients, and as some type of malformation of cortical development in 5 patients. Perinatal lesions were found in 4 patients, postencephalitic lesions in 3 patients, glioma and angioma occurred in 2 patients each, and diffuse posttraumatic lesions in both hemispheres occurred in 1 patient.

Sixteen patients suffered from temporal lobe epilepsy (TLE) and 16 patients from extratemporal epilepsy (exTLE) (5 patients—frontal lobe epilepsy, 1 patient—parietal lobe epilepsy, 7 patients—probable multilobar ictal onset, 3 patients—undetermined ictal onset). Focal seizures with or without secondary generalization occurred in 28 patients; generalized tonic–clonic seizures without any clear focal onset occurred in 4 patients. Previous unsuccessful resection surgery to treat the epilepsy had been performed in 4 patients (tailored lesionectomy in 3 patients; antero-medial temporal lobe resection in 1 patient). Partial anterior callosotomy had been performed in 3 patients.

3.2. Efficacy of VNS

The average number of all seizures at the baseline, i.e. prior to the implantation of VNS; in all patients was 34.5 ± 40.2 seizures per month. At the 5-year follow-up, the average number of all seizures, regardless of seizure type, dropped to 6.8 ± 8.9 seizures per month. The average percent seizure reduction after 5 years of VNS in all 32

Table 1
Average R_{IED} and R_{SEC} in responders and nonresponders to chronic VNS. Statistically significant differences are indicated by *.

	Responders	Nonresponders	Statistics
Average R_{IED}	0.59 ± 0.61	0.97 ± 0.99	$Z = 1.99$; $p = 0.039$*
Average R_{SEC}	0.54 ± 0.46	0.95 ± 0.82	$Z = 1.92$; $p = 0.042$*

patients reached 69.4%. At the 5-year follow-up, 3 patients (9.4%) were seizure-free, 7 patients (21.8%) had ≥90% seizure reduction, and the other 12 responding patients (37.5%) had ≥50% seizure reduction. In total, 22 patients (68.7%) reached ≥50% seizure reduction and were classified as responders, and 10 patients (31.3%) were classified as nonresponders.

We noted the positive effect of magnetic extrastimulation when used (either by the patients themselves or by a caregiver) in abolishing >50% seizures in 11 out of 32 patients (34.4%).

3.3. EEG analysis; IEDs

The total number of IEDs during EEG prior to the implantation ranged from 0 to 330 IEDs (average of 97.3 ± 106.9; median of 49). The number of seconds in which IEDs were present, at that time, ranged from 0 to 315 s (average of 80.6 ± 86.1; median of 37) per 30-min EEG procedure. The total number of IEDs during EEG at the 5-year follow-up ranged from 0 to 447 IEDs (average of 49.4 ± 94.0; median of 19.5). The number of seconds in which IEDs were present, at the 5-year follow-up, ranged from 0 to 294 s (average of 37.8 ± 65.0; median of 16.5) per 30-min EEG procedure. The decrease in the total number of IEDs and the number of seconds in which IEDs were present at the 5-year follow-up visit in comparison to pre-implantation was statistically significant according to the results of the Wilcoxon rank test.

$R_{IED} \leq 0.5$ (i.e. at least 50% reduction of the number of IEDs) was present in 13 out of 32 patients (40.6%); similarly, $R_{SEC} \leq 0.5$ (i.e. at least 50% reduction of seconds in which IEDs were present) was noted in the same 13 patients.

There were significant differences between responders and nonresponders in terms of average R_{IED} and R_{SEC}. Average R_{IED} and R_{SEC} were significantly lower in patients who responded to VNS in comparison to patients who did not (0.59 ± 0.61 and 0.54 ± 0.46 in responders); 0.97 ± 0.99 and 0.95 ± 0.82 in nonresponders (Table 1).

Both average R_{IED} and R_{SEC} was significantly lower in patients suffering from TLE in comparison to patients suffering from exTLE (0.56 ± 0.59 and 0.52 ± 0.56 in TLE; 0.85 ± 0.88 and 0.77 ± 0.76 in exTLE). There were no significant differences between these groups in terms of the number of responders and the average seizure reduction. In conclusion, EEG improvement was significantly more pronounced in patients with TLE than in those with exTLE (Table 2).

There were no significant correlations between R_{IED} and R_{SEC} and percent seizure reduction.

Neither R_{IED} nor R_{SEC} significantly correlated with the age of patients, the duration of epilepsy, or the age of epilepsy onset. There were no differences in either the average R_{IED} or the average R_{SEC} between the patients with symptomatic and the patients with cryptogenic etiology of epilepsy, or between the patients who responded positively to magnetic extrastimulation in comparison to patients who did not (Table 2).

4. Discussion

Our study clearly demonstrated that VNS has an effect on the frequency of IEDs in patients chronically treated by VNS. We can conclude that VNS positively affects the interictal EEG regardless of the seizure frequency. However, we should stress that about two-thirds of our patients were responders and that the average percent seizure reduction after 5 years reached 69.4% in our patients. In contrast to the results of our study, early data from human testing did not demonstrate any significant effect of VNS on interictal EEG regardless of seizure outcome. These studies were performed on refractory adult patients. In addition to the lack of effect on EEG, the earlier EEG tests of VNS did not reveal any effect on ictal epileptiform activity and normal EEG rhythms.[10,11] Other studies reported the chronic effect of VNS on EEG. The most cited study by Koo[12] demonstrated the positive effect of chronic VNS on EEG in 21 patients. Koo demonstrated a progressive increase in the duration of spike-free intervals and a progressive decrease in the duration and frequency in IEDs in 5 patients with numerous IEDs on baseline EEG. The other 16 patients also showed a statistically significant progressive decrease in the number of IEDs over time.[12] Our study cannot provide data concerning gradual changes in EEG over time, because we performed only two EEGs in 5 years. However, our analysis has demonstrated the positive effect of VNS in EEG results for twice as many patients and over a longer period of time. More recently published studies performed on children with refractory epilepsy, including severe childhood epilepsies, also reported a significant reduction of spikes over a period of time (up to 2-year follow-up).[13,14] Most recently, Wang et al. reported the positive effect of long-term VNS on IEDs in a small series of 8 patients with refractory epilepsy.[15]

We did not demonstrate a clear correlation between the percent of seizure reduction and the reduction of IEDs after 5 years of VNS, but we observed a significantly greater reduction in IEDs in patients who responded to VNS than in those who did not. Similar results are mentioned relatively rarely in the literature. Ebus et al. reported a significant correlation between spike rate and seizure frequency in 19 children with severe childhood epilepsies, mostly Lennox–Gastaut syndrome.[13] Wang et al. demonstrated a similar correlation in 8 adult patients with refractory epilepsy.[15]

Explanations for the different results concerning the influence of VNS on interictal EEG remain speculative. While the first human data in the early 1990s showed no substantial effect, some studies published in the last 8 years have provided positive results. Two explanations are probable. The earlier studies included a smaller number of patients than the more recent studies, and the duration of stimulation was much longer in the more recent studies. While in the pilot studies, the duration of stimulation did not exceed 1 year,[10,11] the EEG was evaluated after 1 year in other studies,[12,13] and after 5 years of stimulation in our study. Delayed EEG changes in our study and other more recent studies are similar to the results

Table 2
Average R_{IED} and R_{SEC} in patients with different responses to magnetic extrastimulation. Different etiology and localization of epilepsy and statistically significant differences are indicated by *.

	Magnetic extrastimulation		Etiology of epilepsy		Localization of epilepsy	
	Positive effect	Negative Effect	Cryptogenic	Symptomatic	Temporal	Extratemporal
Average R_{IED}	0.57 ± 0.48	0.89 ± 0.92	0.94 ± 0.23	0.72 ± 0.93	0.56 ± 0.59	0.77 ± 0.76
Statistic	$Z = 0.854$, $p = 0.41$		$Z = 1.823$, $p = 0.071$		$Z = 1.912$, $p = 0.043$*	
Average R_{SEC}	0.54 ± 0.44	0.79 ± 0.78	0.84 ± 0.27	0.65 ± 0.79	0.52 ± 0.56	0.85 ± 0.88
Statistic	$Z = 0.71$, $p = 0.47$		$Z = 1.55$, $p = 0.122$		$Z = 1.889$, $p = 0.046$*	

of previously published animal studies.[6,16] VNS probably produced a chronic modulation of brain synaptic activity, although the precise mechanism of action is unknown. Hypothetically, the longer the modulation, the more pronounced the effect, both on the clinical status and on the EEG. A progressive decline in the number of epileptic seizures and an increased number of patients who responded to VNS was repeatedly demonstrated in the literature.[4,5,17–19]

Our study showed that there was a greater reduction of IEDs in both measurements in patients with TLE in comparison to those with exTLE without reference to responder rate. The different effect of VNS on EEG in different epileptogenic zones has not yet been discussed in the literature. The explanation of this result is hypothetical. The number of studies using functional imaging techniques, such as single photon emission tomography (SPECT) and positron emission tomography (PET), have demonstrated widespread changes in blood flow and metabolism in several cortical and subcortical regions during acute VNS.[20–22] The changes were most prominent in the thalamus, postcentral region, and in various parts of limbic system (amygdala, hippocampus, cingulate gyrus). VNS may preferentially influence the limbic system structures including the temporal lobe. Nevertheless, no studies stressed a better effect of VNS in TLE in comparison to exTLE.

Although there are different data concerning the EEG changes in chronic VNS patients, our study, performed on the highest number of patients and with a long-term outcome, clearly demonstrated that there was a significant improvement in the interictal EEG in patients chronically treated with VNS. The effect on EEG is emphasized in those patients who respond to chronic stimulation and in patients suffering from TLE. Further studies analyzing the consecutive EEGs after VNS should be performed to evaluate the changes of EEG caused by VNS over a period of time.

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