Clinical Neurophysiology 128 (2017) 1583–1589

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

We could predict good responders to vagus nerve stimulation: A surrogate marker by slow cortical potential shift

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ARTICLE INFO

Article history:
Accepted 31 May 2017
Available online 15 June 2017

Keywords:
EEG
Vagus nerve stimulation (VNS)
Slow cortical potentials (SCPs)
Surrogate marker
Long time constant (TC)

HIGHLIGHTS

- Positive shifts of slow cortical potentials (SCPs) during the VNS period were observed in responders.
- SCP shifts modulated by VNS were more effectively detected by EEGs with long enough time constant.
- Positive polarity of SCP shift on scalp EEG could be an effective marker for response to VNS.

ABSTRACT

Objective: We investigated whether vagus nerve stimulation (VNS) induces a positive shift of slow cortical potentials (SCPs) in patients with >50% seizure reduction (responders) but not in non-responders.
Methods: We analyzed routine clinical electroencephalograms (EEGs) from 24 patients who were undergoing seizure treatment by VNS. The patients were divided into 2 groups by hardware time constant (TC) of EEG: the TC 10-s group (10 patients) and TC 2-s group (14 patients). We compared SCPs at 5 electrodes (Cz and adjacent ones) between the 2 states of VNS: during stimulation and between stimulations. Seizure reduction was independently judged. Correlation between SCP (positivity or not) and seizure reduction (>50% or not) was estimated.
Results: In the TC 10-s group, the correlation between SCP and seizure reduction was significant ($p < 0.05$) (i.e., both good results in 4 and both negative results in 5). In TC 2-s group, the correlation between SCP and seizure reduction was not significant ($p = 0.209$).
Conclusions: A positive shift of SCP recorded by using a TC of 10 s could be a surrogate marker for VNS response.
Significance: SCP could be a biomarker of good responders to VNS.

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http://dx.doi.org/10.1016/j.clinph.2017.05.019
1388-2457/

1. Introduction

Vagus nerve stimulation (VNS) is a palliative treatment option for patients with intractable epilepsy who are not good candidates for surgical resection (Connor et al., 2012). VNS uses an electrical stimulator, like those in cardiac pacemakers, which is implanted in the subclavicular area and delivers trains of electrical pulses to the left vagus nerve via bipolar stimulating electrodes (Terry et al., 1990). The stimulation of the vagus nerve is intermittent, and the usual stimulation condition is set to a signal on-time (VNS ON) of 30 s followed by an off-time (VNS OFF) of 3–5 min (Heck et al., 2002) repeatedly. Positive responses can be obtained within the first 3 months of treatment (Salinsky et al., 1996), and the response has a tendency to increase up to 18 months after surgery (De Taeye et al., 2014). It has been reported that one third of patients have a >50% reduction in seizure frequency, another one third show a 30%–50% seizure reduction, and the remaining one third show no response (Boon et al., 2001).

Neuronal mechanisms of VNS for seizure suppression are not clearly understood yet (Loddenkemper and Alexopoulos, 2008; Fanselow, 2012). In experimental models of epilepsy, it has been reported that VNS produced desynchronization of electroencephalography (EEG) and blocking of spike waves (Zanchetti et al., 1952) as well as an increased seizure threshold (De Herdt et al., 2010). Krahl et al. (1998) demonstrated that the antiepileptic effect of VNS was mediated by locus coeruleus. Chemical activation of parafascicular nuclei, a part of the non-specific thalamocortical projection system, inhibited epileptiform activity (Nail-Boucherie et al., 2005). The thalamocortical projection system has a major role in certain phenomena, such as consciousness, sleep, attention, and idiopathic epilepsy (Hanbery and Jasper, 1954). In humans, a positron-emission tomography (PET) study of VNS response showed activation of the thalamus in patients with seizure reduction (Henry et al., 2004).

Zagon and Kemeny (2000) suggested slow hyperpolarization of cortical pyramidal neurons of the parietal association cortex in anesthetized rats as an underlying mechanism of action of VNS in suppressing seizures. It is clinically useful to extract or record the hyperpolarized state of the cortices in association with VNS in humans by means of scalp EEG. Clinical EEG recorded by using an alternate current (AC) amplifier with very long time constant (TC) can detect slow cortical potential (SCP) or the direct-current (DC) shifts that are generated by either cortical neurons, glias, or their combination, depending on the type of SCP (Ikeda et al., 1996).

Based on previous research on animal studies and the following observations in humans, it can be inferred that depolarization of neurons, seen on EEG as negative SCP shifts, represents activation of excitatory postsynaptic potentials and neuronal excitation. Hyperpolarization of neurons, seen on EEG as positive SCP shifts, represents activation of inhibitory postsynaptic potentials and inhibition of neuronal activity (Prince, 1968; Ayala et al., 1973; Ikeda et al., 1996). Production of scalp-recorded positive SCP by a self-regulation training has been used for suppressing seizures, and some patients have even become seizure free (Kotchoubey et al., 2001; Strehl et al., 2005). On the basis of the above backgrounds, we hypothesized that a positive SCP shift could appear during VNS stimulation in patients with good response to treatment and there could be an absence of positive SCP shift in patients with poor response. Attempts to predict suitable candidates for VNS were reported (De Taeye et al., 2014; Arcos et al., 2014), and showed potential usefulness.

The goal of this retrospective study on data from three different centers was to investigate whether scalp-recorded positive polarity of the SCP shift could be used as a surrogate marker for treatment response to VNS.

2. Methods

2.1. Patient profile

The study was approved by the ethics committees of the Kyoto University Hospital, Kindai University Hospital and Hiroshima University Hospital (IRB#E1736, #25-036 and #Epi1158 respectively). A total of 24 patients (13 women) with intractable epilepsy aged 28.8 ± 17.2 (mean ± standard deviation) years; ranging from 6 to 66 years, at the time of EEG, who have undergone VNS implantation between November 2010 and August 2014 were studied. 10 patients were diagnosed as having symptomatic generalized epilepsy and 14 as having symptomatic partial epilepsy. Their clinical features and related conditions (VNS stimulation interval, time constant of EEG recording and kind of metal for scalp electrodes) are summarized in Supplementary Table S1.

The mean period between VNS implantation and the latest available EEG recording was 12.2 (range, 4.2–36.7) months. The mean follow-up period or post-implantation seizure assessment at the last visit was 24.1 (range, 11.7–43.0) months, the mean time interval between the EEG and last assessment was 11.9 (range, 0.0–28.8) months (Supplementary Table S2).

2.2. VNS stimulation and seizure frequency assessment

All patients underwent VNS device implantation (Cyberonics, Houston, TX, USA), and the stimulation started within 1–2 weeks after the operation. The stimulation time was from the programmed plateau VNS ON time plus 2 s of ramp-up time and 2 s of ramp-down time (Fig. 1). The output parameters of the pulse generator were individually adjusted, and the adjustment methods were similar to those of other institutions (Labiner and Ahern, 2007). The cycles of stimulation were programmed to use a VNS ON time of 30 s, except in Patient 16 (21 s), and a VNS OFF time of 5, 3, or 1.8 min (Supplementary Table S1).

Seizure frequency was calculated on the basis of the patient's seizure diary when available or the records by the physicians-in-charge at the time of the patient's visit, if available. All types of partial and generalized seizures were singularly counted. Baseline monthly seizure frequency before VNS was calculated on the last visit before VNS implantation, or for the patients with more than one visit, the average of up to 3 monthly visits immediately before the implantation was used.

The monthly seizure frequency was obtained by following 2 methods: (1) if the patient's seizure diary was available, the monthly average of all seizures during the 3 months preceding the EEG recording was assessed; (2) if the seizure number was obtained from the physician's records, the monthly seizure frequency was first calculated, and then the average number of seizures in the 2 consecutive months before and in the month of EEG recording was calculated. When the period between the 2 follow-up visits was >3 months, the average number of seizures at the last 2 clinic visits was used as the number of seizures after the VNS.

If epilepsy surgery, such as corpus callosotomy, was performed after VNS, the seizure frequency after the operation was excluded from the analysis. In 4 patients with multiple types of seizures, an accurate counting of atypical absence seizures was not available: in 3 patients, the frequency of atypical absence seizures only was not calculated, and in the remaining 1 patient (Patient 8), the seizure frequencies for each seizure type were not available. Seizure frequency evaluation after VNS was calculated using the following formula (Labar et al., 1998; Fraschini et al., 2013):