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Short communication

Cardiac-based vagus nerve stimulation reduced seizure duration in a patient with refractory epilepsy

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ABSTRACT

Purpose: A novel vagus nerve stimulation (VNS) device was recently approved in Europe which rapidly detects increases in heart rates (HR) and applies an additional stimulus if HR-increases exceed a given threshold. The effects of HR-triggered VNS-pulses on seizures were not reported yet under controlled conditions. Here, we quantified the effects of HR-triggered VNS-pulses on the seizure duration in one patient.
Methods: The novel VNS device was implanted in a 29-year old man with refractory epilepsy. After implantation, the patient underwent video-EEG telemetry for 68 h with no changes in anticonvulsant drugs. On the first day the patient only received sham-stimulation. During the following 46 h HR-related VNS-stimulation was set to 2 mA. Seizure duration was determined based on clinical signs.
Results: Twelve stereotypical seizures were recorded (six during sham- and six during the active stimulation). The VNS device recognised a total of 139 events as a seizure and correctly identified 11 seizures. The HR-triggered VNS-stimulation significantly reduced the total seizure duration from 33.2 ± 4.8 s to 26.5 ± 5 s and the remaining seizure duration after the onset of the extra-stimulation from 27.8 ± 4.3 s to 16.2 ± 3.2 s. With the given configuration in this patient, sensitivity and specificity of HR-based seizure-detection amounted to 92% and 13.5%, respectively.
Conclusions: This case illustrates that VNS-stimulation in response to seizure-related HR-increases is able to significantly reduce seizure duration. Despite the limitations of our case, its promising results should prompt larger studies to confirm the clinical benefit of this novel device.

1. Introduction

Vagus nerve stimulation (VNS) is an established and safe therapy for people with refractory epilepsy leading to a significant improvement of seizure control in a considerable proportion of the implanted patients [1–3]. A novel VNS device was recently approved in Europe, which rapidly detects increases in heart rates (HR) and applies an additional stimulus if the HR-increase exceeds a given threshold (AspireSR™ generator, Cyberonics Inc., Houston, USA). Given that the majority of focal seizures are associated with an increase in HR and only a minority with no apparent change or a decrease in HR [4–6], many patients could potentially benefit from the use of this novel device. Importantly, some patients and relatives have reported an attenuation or shortening of seizures due to additional magnet vagus nerve stimulation [7,8]. To date, however, the effects of such HR-triggered VNS-pulses on the duration and severity of seizures have not been studied under controlled conditions. Here we report on a patient with refractory epilepsy who was recently implanted with such a novel VNS device at our centre.

2. Methods

2.1. Heart rate device setting

Pre-surgical electrocardiogram (ECG; Schiller, Ottobrunn, Germany) was performed 24 h before surgery following the manufacturer's protocol for the AspireSR™ generator (Cyberonics Inc., Houston, USA) in order to determine the patient's heart vector in seven different body positions. To increase the HR-detection sensitivity, at least four representative R-waves were measured from peak to peak in each body position and the R-wave with the

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minimal amplitude was chosen. According to the manufacturer's protocol, a median of 0.8 mV determined of the seven minimum R-waves was used for the HR detection setting and the third sensitivity level was applied when R-wave amplitudes were measured between 0.71 and 0.85 mV. During the entire video-EEG monitoring, the VNS-detection device was switched on and the threshold kept unchanged in all conditions. The heart beat sensitivity threshold of 50% was chosen, because HR increased by at least 57% during five habitual seizures recorded during a diagnostic video-EEG monitoring 2 years prior to VNS-implantation.

2.2. Video-EEG-monitoring and determination of seizure duration

One day after VNS-implantation, the patient underwent video-EEG monitoring (Micromed S.p.A, Mogliano Veneto, Italy) with the help of scalp EEG according to the 10/20 system for 68 h without changes of anticonvulsant drugs (Fig. 1A). The device tablet was synchronised with the time of the video-EEG system. The patient complied with the following procedure: no regular cyclic VNS-stimuli during the first 22 h (control condition). During this period, the VNS-device only detected HR-increases and eventually applied a sham-stimulation (stimulus at 0.125 mA with a pulse width of 500 μs at a frequency of 30 Hz for 60 s). After these 22 h, cyclic regular VNS-stimulation was initiated up to 2 mA (which was very well tolerated) on days 2–4 (Fig. 1A). The cardiac-based and seizure-related extra-stimulus was also set to 2 mA. Finally, the patient underwent another 46 h of video-EEG-monitoring on days 5 and 6 (Fig. 1A). During this phase, the cycle stimulation was set to 0 mA with a stimulus duration of 7 s, a pulse width of 500 μs and off-time of 180 min (thus no regular cyclic VNS stimulation), whereas the HR-triggered VNS-stimulus was set to 2 mA (stimulus duration 60 s, pulse width 250 μs). Seizure duration was determined by two epileptologists (KGH, RS) based on clinical features and blinded to the sham-stimulation period (control) or active HR-triggered VNS stimulation period (the ictal EEG pattern was commonly compromised by movement artefacts and therefore it was less precise to determine seizure duration based on ictal EEG pattern than on clinical features). The remaining seizure duration after the onset of the HR-triggered VNS-stimulation was measured by subtracting the latency between seizure onset and start of the HR-triggered VNS-stimulus from the total seizure duration.

2.3. Statistical measures

The novel VNS-device detects events with HR-increases exceeding a given threshold and stores date, time and whether VNS-stimulation was performed in response to the event. Only those events during which the VNS-device has delivered an extra-stimulus were considered as a seizure detected by the device. According to the manufacturer, the device does not stimulate in the following circumstances: (1) The HR-increase lasts less than 1 s. (2) HR-triggered stimulation was set to 0 mA or seizure detection was switched off. (3) Seizure detection is switched "on", but the stimulation is prevented by an internal algorithm (the so-called "Enforced-Off-Time" which lasts for at least 30 s up to a duration as long as the HR-triggered stimulation).

The sensitivity of the VNS-device was determined by dividing the number of correctly detected seizures (true positives as assessed by video-EEG monitoring) by the sum of the number of correctly detected seizure and the number of non-detected seizures (false negatives). The positive predictive value (PPV) was calculated by dividing the number of true positives by the sum of the number of true positives and the number of events the device wrongly classified as seizures (false positives). The specificity was determined by dividing the number of correctly detected non-seizure events with increased HR (true negatives) by the number of total non-seizure events with increased HR. The negative predictive value (NPV) was calculated by dividing the number of true negatives by the sum of the number of true negatives and the number of false negatives.

The Shapiro–Wilk test and normal probability plot was used to test for normality (Rstudio version 0.98.507, FOAS, Boston, USA). Two-sided unpaired Student's *t*-test was performed to compare seizure duration during sham-stimulation (control condition) and HR-triggered VNS-stimulation (test condition) (GraphPad Prism 6, GraphPad Software, San Diego, USA).

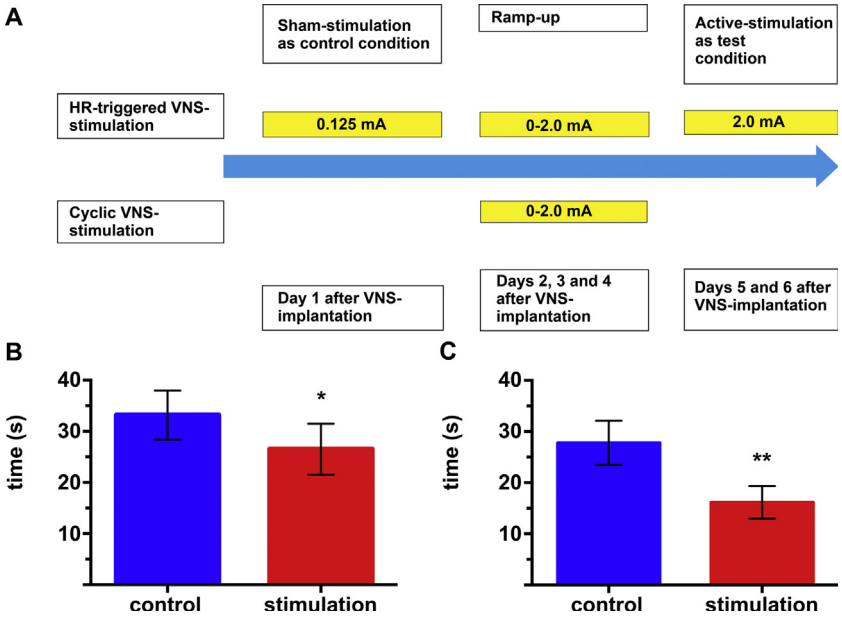

Fig. 1. (A) Flow chart of the VNS-settings at different time points in our patient. (B) The total seizure duration in the period with or without sham-stimulation (control condition, $n = 6$) was compared to the period in which the active HR-related VNS-stimulation was switched on (test condition, $n = 6$). (C) Comparison of the remaining seizure duration (after the onset of the VNS-pulse) between the period with sham-stimulation ($n = 5$) and active HR-related VNS-stimulation ($n = 6$). Bar charts represent mean ± SD.