Original article

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Early experiences with tachycardia-triggered vagus nerve stimulation using the AspireSR stimulator

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ABSTRACT – Many epilepsy patients treated with vagus nerve stimulation additionally use an "on-demand" function, triggering an extra stimulation to terminate a seizure or diminish its severity. Nevertheless, a substantial number of patients are not able to actively trigger stimulations by use of a magnet, due to the absence of an aura or inability for voluntary actions in the early phase of a seizure. To address this need, a novel implantable pulse generator, the AspireSR VNS system, was developed to provide automated ictal stimulation triggered by a seizure-detecting algorithm. We report our experience with three patients in assessing the functionality of ictal stimulation, illustrating the detection system in practice. Detection of ictal tachycardia and variable additional detections of physiological tachycardia depended on the individual seizure-detecting algorithm settings.

Key words: refractory epilepsy, vagus nerve stimulation, ictal tachycardia, closed-loop stimulation

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The majority of epileptic patients are treated with a continuous intake of antiepileptic drugs. In case of pharmaco-resistance, brain stimulation is used to reduce seizure frequency and severity. Only recently, an implantable closed-loop system, based on the detection of intracranial EEG seizure patterns, has been approved by the Food and Drug Administration, to be used in patients with known seizure onset zone (Morrell, 2011). Not all patients with drug-resistant epilepsy have unifocal epilepsy, moreover, the seizure onset zone is not sufficiently well known to apply this new device in all patients with unifocal seizure onset. Additional developments of closed-loop stimulation devices

using different approaches for seizure detection and for brain stimulation are thus of great interest (Shoeb *et al.*, 2009; Bergey, 2013; Schulze-Bonhage and Coenen, 2013; Fisher and Velasco, 2014). Here, we report early experiences with ictal tachycardia-based automated stimulation of the vagus nerve to treat drug-resistant focal epilepsy.

Ictal tachycardia (IT), a physiological change that the patient may not be aware of, can be the first detectable clinical manifestation or occur later during the course of the seizure (Parisi *et al.*, 2005; Nilsen *et al.*, 2010; Hirsch *et al.*, 2015). The prevalence of ictal tachycardia has been reported to be between 33% and 100% (Garcia *et al.*, 2001; Zijlmans *et al.*, 2002; Işik *et al.*, 2012). It is more frequent in temporal lobe epilepsy and frequently associated with mesial temporal lobe sclerosis, cortical dysplasia, heterotopia, and cortical lesions (Garcia *et al.*, 2001; Opherk *et al.*, 2002; Rugg-Gunn *et al.*, 2004; Britton *et al.*, 2006).

Many patients treated with chronic interval stimulation VNS additionally apply on-demand VNS using a magnet to activate an extra stimulation, which can terminate a seizure or diminish its severity (Boon *et al.*, 2001; Morris, 2003; Wang *et al.*, 2009; Englot *et al.*, 2011; Majkowska-Zwolińska *et al.*, 2012). Nevertheless, a substantial number of patients are not able to use the magnet for various reasons; for example, patients with nocturnal seizures, patients with intellectual disability who are unable to handle the magnet, or patients who do not experience an aura.

The AspireSR™ VNS model was designed to detect IT using a patented cardiac-based seizure-detecting algorithm (SDA). The aim of the device is to detect a potential seizure and deliver an IT-triggered stimulation to the vagus nerve in an automatic magnet mode (AMM). The performance of automated seizure detection was assessed in a prospective observational multi-site study (E-36 study; Boon *et al.*, 2015). The cardiac-based SDA demonstrated high sensitivity and acceptable specificity. With responder rates of 29.6% at 12 months follow-up, the effects on seizure frequency were modest (Boon *et al.*, 2015). Hampel recently reported a sensitivity of 92% and a specificity of 13.5% of the SDA in a single patient and a significant decrease in seizure duration due to closed-loop VNS with the Aspire SR (Hampel *et al.*, 2015). Here, we illustrate functionality, tolerability, and clinical efficacy after two years of treatment in three patients participating in the E-36 study at two European epilepsy centres.

Materials and methods

For the purpose of the E36 study (Boon *et al.*, 2015), ictal tachycardia was defined as an increase in heart rate during a seizure, specifically exceeding 100 bpm and increasing by at least 55% or 35 bpm above baseline. This baseline heart rate is determined by a moving average of the instantaneous heart rate over the previous five minutes; the foreground heart rate is determined by a moving average of the most recent 10 seconds. Heart rate sensing is based on detection of R waves by the implanted pulse generator and the electrode fixed to the vagus nerve. The algorithm implemented in the Aspire stimulator additionally ensures that the stimulation on time due to detections does not exceed the off time, to preclude over-stimulation.

In the E36 study, the patients were randomized into three different SDA settings, corresponding to the different thresholds (SDA settings: 2, 4 and 6) that are required to detect a significant increase in the relative heart rate. SDA setting 2 requires a 60% change in relative heart rate to detect a seizure, compared to SDA setting 4 and 6 which only require a 40% and 20% increase, respectively. According to the study protocol, patients were hospitalized two weeks after implantation for a period of five days to record seizures with only the SDA mode activated during continuous video-EEG recording, with surface EEG, ECG, and assessment of stimulator activations. During this stay, a standardized step exercise test was also performed to check for false positive stimulations. The choice of the patients was based on:

– performance of the device to detect ictal tachycardia;
– quality of EEG and ECG recordings;
– completeness of seizure agendas and scales.

Patient 1 and 3 were implanted in Brussels and were part of a group of six patients included in the E-36 trial. Patient 2 was implanted in Freiburg and was part of a group of three patients from the E36 trial.

Case 1

The first patient was a right-handed, 27-year-old female patient suffering from bitemporal symptomatic epilepsy with frequent focal seizures without aura, that were characterized by a loss of contact, an ictal tachycardia, a tonic contraction of the right side of her face, and right arm and oral automatisms.

Her epilepsy was diagnosed in 2006 after an episode of gastroenteritis, associated with diplopia. Clinical examination at that time showed a horizontal right gaze nystagmus without any oculomotor nerve paresis. Lumbar punction showed 8 lymphocytes/µl. Oligoclonal IgG specific bands were present. Herpes PCR was negative. MRI revealed FLAIR hyperintensities in the basal ganglia and posterior part of optical nerve bundles. With the hypothesis of an acute disseminated encephalomyelitis (ADEM), she was initially treated with corticosteroids. She relapsed three months later,

again in the context of a flu-like syndrome, with a horizonto-rotatory right gaze nystagmus, minor right sensorimotor deficit, and left Babinski. The MRI revealed the same basal ganglia hyperintensities with left predominance. As the working hypothesis at that time was an inflammatory demyelinating disease, she was treated with corticosteroids for a second time. She only partially recovered and developed focal seizures and behavioural and cognitive problems thereafter. Control MRI showed bitemporal damage, which was most likely the cause of her new-onset epilepsy. Retrospectively, the most probable explanation was the occurrence of viral encephalitis of unknown origin that affected first the basal ganglia and in a second phase, the temporal lobes.

Thereafter, she developed refractory epilepsy and was referred in 2010 to the Saint Luc Epilepsy Centre for a pre-surgical evaluation. At that time, her antiepileptic drug regimen consisted of carbamazepine at 600 mg 2x/day and topiramate at 150 mg 2x/day. The seizure frequency lied between 2 to 10 seizures a day. She had tried levetiracetam and phenobarbital before. After a non-invasive evaluation, she was implanted with bilateral mesiotemporal electrodes. Invasive video-EEG recording revealed a bitemporal onset. Moreover, her seizures were characterized by an early onset of ictal tachycardia with an approximately 20% increase in heart rate. After a multidisciplinary discussion, it was decided that she was not a good surgery candidate and a VNS therapy with the new AspireSR VNS system was proposed.

In November 2012, she was implanted with the Aspire VNS system. Preoperatively, peak to peak R wave amplitudes were measured in different positions, which were required to establish the appropriate heart beat sensitivity parameter, allowing the system to sense the heartbeat correctly.

She was randomized to SDA setting 6, triggering stimulation at an increase in heart rate by 20%. The patient was hospitalised two weeks after implantation at the epilepsy monitoring unit (EMU) to titrate the stimulation and to record seizures with the VNS seizure detection and automatic stimulation mode on. During her hospitalisation, we recorded six complex partial seizures. None of these seizures presented with an ictal tachycardia, as defined in the methods, however, on average, an approximate 22% heart rate increase was related to the seizure. Four of the six seizures were successfully detected by the SDA and an acute stimulation was delivered between 6 to 18 seconds after EEG seizure onset. In the non-detected seizures, the tachycardia was not large enough in magnitude, nor sustained enough, and consequently the SDA did not detect it (only a 3.7% or 13.1% increase in heart rate). The SDA was already programmed to the most sensitive parameter, thus changing the SDA sensitivity would not have permitted detection of the seizure. This is why the physician must analyse the seizures before implantation, to carefully look for heart rate changes, as the system ultimately requires the physician to adapt sensitivity individually for each patient. Over the period of 65.7 hours recorded during the video-EEG monitoring, there were 239 false positive stimulations (3.6/hour). The mean seizure duration of the three previously recorded seizures was 39.6 seconds (SD: 20.6 seconds) compared to 25.3 seconds (SD: 3.1 seconds) for seizures that were treated with automatic stimulation during the EMU stay. Moreover, each of the four stimulated seizures terminated during the stimulation. Seizure severity was assessed using the seizure severity questionnaire and did not improve over time. Despite the efficacy of the SDA system, seizure frequency did not decrease over time (*table 1*) and secondary generalized seizures persisted. Nevertheless, the patient did report an improvement in quality of life scores, with a QOLIE31-P exceeding the minimally important change threshold of 5 at 18 and 24 months of follow-up (*table 1*). The stimulation parameters at 24 months were programmed as follows: 25 Hz, pulse width of 250 μseconds, signal ON time of 30 seconds, signal OFF time of 5 minutes, magnet pulse width of 250 μseconds, and magnet ON time of 60 seconds. Intensity of stimulation was gradually up-titrated and at 24 months of follow-up, stimulation parameters were programmed to 1.75 mA normal mode, 1.75 mA magnet mode, and 1.875 mA auto-stimulation mode. Initially, she reported some difficulty in swallowing, but this side effect disappeared over time. She had no complaints of the stimulation while doing minor physical effort.

Case 2

This patient was a 24-year-old male with a bihemispheric epilepsy of unknown aetiology. He suffered from frequent focal seizures characterized by a somatosensory aura of the upper limbs (either right- or left-sided), progressing to tonic-clonic movements of the arm and occasional march to the ipsilateral leg. Prior to participation in the E36 study, seizures usually occurred in series of up to 50 per month with predominance at night, and seizure-free periods lasting up to a maximum of two weeks. The last occurrence of rare bilateral tonic-clonic seizures was two years prior to VNS implantation.

His epilepsy was diagnosed at the age of 16, when three bilateral tonic-clonic seizures occurred. Clinical examination and MR imaging at that time revealed no abnormalities. Under treatment with oxcarbazepine, the patient remained seizure-free for five years. Thereafter, seizures relapsed and persisted under

Table 1. Follow-up of seizure frequency, QOLIE 31-P and SSQ scores after closed and open-loop vagus nerve stimulation.

	Patient 1			**Patient 2**		
	Sz/week	**QOLIE 31-P Total**	**SSQ**	**Sz/week**	**QOLIE 31-P Total**	**SSQ**
Baseline*	6.5	29.03	3.46	1.8	40.72	2.38
3 months	5.5	28.20	no value	7.4	31.11	1.61**
6 months	4.3	23.30	3.61	7.1	28.11	1.88**
12 months	14.4	30.85	3.81	1.8	42.66	no value
18 months	13.5	41.19**	3.35	0	68.31**	no value
24 months	5.4	35.83**	no value	0	51.13**	no value

	Patient 3		
	Sz/week	**QOLIE 31-P Total**	**SSQ**
Baseline*	1.1	31.22	4.03
3 months	1.0	65.61**	2.24**
6 months	0.2	75.61**	2.00**
12 months	0.2	62.74**	1.75**
18 months	0.4	60.82**	no value
24 months	0.1	53.99**	0.50**

*Four-week period with stimulation off (two weeks before and two weeks after implantation).
QOLIE 31**: Meets the Minimal important change criteria for Clinically Significant Improvement (MIC); the optimal MIC value for the total score change is 5.
SSQ**: Meets the Minimal important change criteria for Clinically Significant Improvement (MIC) as defined in the Scoring scheme for SSQv2 Questionnaire.

monotherapy with lamotrigine at dosages of up to 800 mg/d.

He was then referred to the Freiburg Epilepsy Centre for a presurgical evaluation in 2011. Video-EEG monitoring with surface EEG showed focal seizures with clonic movements of the right upper limb and a left central EEG pattern, as well as clonic seizures of the left upper limb with a right central EEG pattern. During his seizures, ictal tachycardia occurred regularly, with a 20% to 100% increase in heart rate. Repeated high resolution 3 Tesla MRI and FDG-PET showed no abnormalities. Despite the addition of levetiracetam at 3,750 mg/d, seizures persisted with unchanged frequency.

Due to the absence of a lesion on MRI, and semiological and EEG evidence for bihemispheric seizure generation, the patient was offered VNS treatment. In December 2012, the patient was implanted with the Aspire VNS system. He was randomized to an SDA setting triggering stimulation at an increase in heart rate by 40%. During video-EEG recording, when only tachycardia-based stimulation was active, five simple partial seizures were recorded. In one, seizure heart rate increased by 22.1% above baseline, thus the detection threshold was not reached. Four seizures were accompanied by ictal tachycardia, as defined in the methods (heart rate increases between 43 and 71% above baseline) (*figure 1*). Stimulation was delivered in all these seizures. In three seizures with an EEG pattern present, stimulation was triggered with latencies between 19 and 39 seconds after seizure onset. In one seizure without a clear EEG pattern, the latency was 12 seconds after clinical seizure onset. Stimulation was, however, also triggered by physical activities, *e.g.* in a standardized step exercise (*figure 2*). Over the period of 68.6 hours, the full EMU monitoring period, there were 292 false positive stimulations (4.3/hour).

The mean seizure duration of the two previously recorded seizures was 19 seconds (SD: 4.2) compared to 16.8 seconds (SD: 15.3) during the EMU stay when only auto-stimulation was turned on. Moreover, of the five stimulated seizures, one was

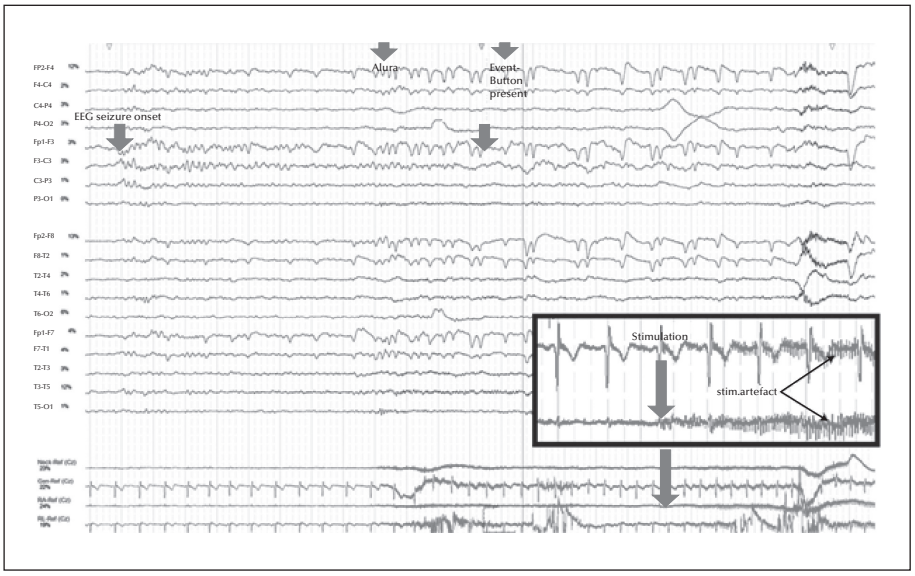

Figure 1. Ictal tachycardia detection and automated activation of vagus nerve stimulation during video-EEG monitoring. Stimulation is visible based on the stimulation artefact (see arrows).

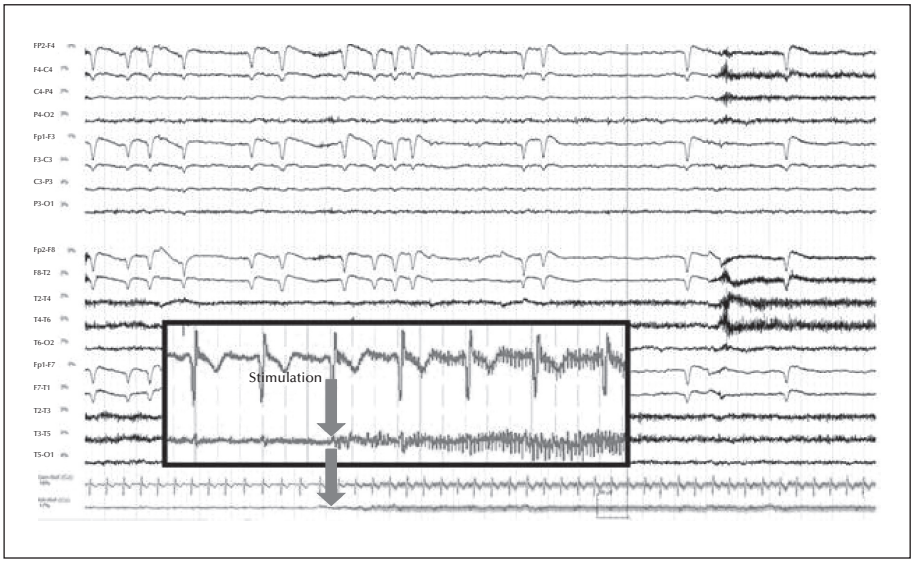

Figure 2. Interictal detection of tachycardia and automated activation of vagus nerve stimulation during video-EEG monitoring. Stimulation is visible based on the stimulation artefact (see arrows).

terminated during the stimulation. Seizure severity assessed using the seizure severity questionnaire improved over time until seizure freedom was reached. The patient reported an improvement in quality of life scores with a baseline score of QOLIE31-P starting at 40.72, fluctuating in the first 12 months, and surpassing the minimally important change threshold of 5 at later time points (18 and 24 months; *table 1*).

At three months follow-up, the patient reported good tolerability of VNS (combined standard stimulation and tachycardia-triggered stimulation) and a perceivable effect on seizure frequency. He reported seizure-free periods of approximately 13 weeks (compared to a maximum of two weeks before implantation). At 24 months follow-up, the patient reported that he had been seizure-free for the last 12 months with unchanged medication. The stimulation intensity at this time was 1.25 mA at normal mode and 1.5 mA with magnet and automated stimulation (frequency: 20 Hz, pulse width of 500 μseconds, signal ON time of 30 seconds, signal OFF time of 5 minutes, magnet pulse width of 500 μseconds, and magnet ON time of

60 seconds). With these settings, VNS was well tolerated with the exception of a mild stimulation-related voice alteration.

Case 3

This patient was a left-handed, 25-year-old female with a cryptogenic left frontotemporal epilepsy who failed two prior resective epilepsy surgeries. Her seizures started at the age of 2 and initially presented with a Lennox Gastaut syndrome. She transiently improved with ACTH treatment, but became refractory to several antiepileptic drugs. Thereafter, she developed a focal left fronto-temporal epilepsy for which she was investigated with invasive monitoring in 2004. Seizures were localized to the superior temporal gyrus and adjacent part of the temporal operculum. MRI showed a left hippocampal sclerosis. PET showed a diffuse hypometabolism in the left frontal and lateral temporal lobe. She underwent a left anterior temporal lobectomy with amygdalo hippocampectomy and multiple subpial transections in the motor and premotor regions of the left arm based on intraoperative electrocorticography findings. She remained seizure-free for four years, but developed the same type of seizures subsequently. Further invasive monitoring, performed in 2010, showed ictal onset in the left anterior part of the SMA and anterior left frontal regions. A left anterior frontal disconnection and cortectomy of the anterior part of the SMA was performed. Seizure burden decreased with disappearance of the secondary generalized seizures, but she was not seizure-free. A treatment with vagus nerve stimulation was proposed and she was implanted with the Aspire VNS system in March 2013. She was randomized to an SDA setting triggering stimulation at an increase in heart rate by 40%. During video-EEG recording, when only tachycardia-based stimulation was active, three complex partial seizures were recorded, which were all accompanied by an ictal tachycardia that varied between a 22% and 35% increase in heart rate. As this increase did not meet the randomised threshold value of 40%, none of these seizures were stimulated. During EMU admission, we recorded 513 false positive stimulations over a period of 86.6 hours of video-EEG monitoring (5.9/hour). As the seizures were not stimulated, no statement can be made regarding the eventual effect of decrease in seizure duration. Clinically, seizure frequency progressively decreased throughout the follow-up period (*table 1*). From Month 6, secondary generalized seizures no longer occurred. Moreover, seizure severity decreased simultaneously with improved seizure severity questionnaire scores. Quality improved in parallel with significant improvement in QOLIE31-P scores (*table 1*).

The stimulation parameters at 24 months of follow-up were programmed as follows: 20 Hz, pulse width of 250 μseconds, signal ON time of 30 seconds, signal OFF time of 5 minutes, magnet pulse width of 250 μseconds, and magnet ON time of 60 seconds. Intensity of stimulation was gradually up-titrated and at 24 months of follow-up, stimulation parameters were programmed to 1.75 mA normal mode, 1.875 mA magnet mode, and 1.875 mA auto-stimulation mode.

Discussion

The AspireSR is designed to provide standard VNS therapy and additionally provide VNS stimulation based on the detection of changes in heart rate during a seizure. It uses the SDA to identify ictal tachycardia and provides automated on-demand stimulation.

The patients reported here show that detection of ictal tachycardia was successful with the algorithm implemented, even if this stimulation is not strictly specific to ictal periods. In cases reported here, IT was detected after seizure onset on surface EEG. However, IT can potentially be detected prior to the EEG and the clinical seizure onset (Hirsch *et al*., 2015). Tachycardia-based detection may thus not only offer advantages in terms of ease of recordings and of computational analyses, as compared to EEG-based seizure detection, but may offer, for certain patients, advantages in the timing of a closed-loop intervention.

Tolerability of additional tachycardia-based stimulation was good, and two out of the three patients described here showed an improvement in seizure frequency. The design of the E36 study (Boon *et al*., 2015) focused on the feasibility of automated ictal stimulation rather than on the efficacy of this additional type of closed-loop stimulation. Automated stimulation was assessed in isolation, only during in-hospital video-EEG monitoring, whereas later stimulation occurred using both standard and closed-loop stimulation. Thus, the differential effect of closed-loop stimulation cannot be judged thus far based on the available outcome data. The patients reported here demonstrate, however, that ictal vagus nerve stimulation based on the SDA implemented in the Aspire stimulator is feasible, even though the algorithm is not strictly specific to ictal tachycardia but is also activated by physiological activities. Notably, none of the patients reported that such non-specific stimulation led to impairments in everyday life.

The additional stimulations caused by detections of physiological tachycardia (false positives; FP) raise the question of how the dosing of VNS increases in comparison to a Normal Mode duty, and of the possible implications on overall effectiveness and battery life. The false positive rates for our patients at the EMU

ranged between 3.4 and 5.9/hour. In the E36 trial, a high sensitivity of detection of IT as low as 20% could be achieved at the price of 7 FP/hour. For a Normal Mode duty cycle of 10%, 11 stimulations are delivered per hour. The increase of the duty cycle through the IT triggered stimulation is limited by an enforced OFF period that follows any delivered closed-loop stimulation. This enforced OFF period, serves as a device refractory period, and is as long as the automatic stimulation, usually 60 seconds. Additionally, when automatic stimulation is triggered, the normal mode OFF period is reset, thus the OFF period countdown of *e.g.* five minutes starts anew. In the long-term follow-up of the E36 study, automatic stimulation increased the overall duty only by <3% (Boon *et al*., 2015). In our patients, maximal false positive rate was 5.9 stimulations/hour, which corresponds to an increase from 10% to 15% duty cycle. For comparison, rapid cycling with a 30-second ON and three-minute OFF paradigm equals a 16% duty cycle.

Our data suggest that settings for ictal tachycardia detection have to be chosen on an individual patient basis in order to improve sensitivity and specificity of ictal stimulations. Even though the company might provide "starting" values for auto-stimulation based on the results of the E-36 trial, we still believe it is important to titrate stimulation parameters individually, as ictal tachycardia and level of physical activity varies amongst patients. Ideally, the threshold for detection is determined on the basis of previous seizures recorded at the monitoring unit and programmed at the correct settings after the implantation. One can assume that possible positive effects of the therapy will be obtained more rapidly if the most appropriate threshold is set as early as possible. In our experience, the threshold for auto-stimulation in the follow-up of patients may need to be adapted, as psychological and environmental factors may induce additional anxiety, which can induce false positive stimulations.

Besides the issue of programming the best SDA setting, neurologists should also take into account that in order to allow the device to detect heart rate correctly, heart detection sensitivity needs to be determined by measuring peak to peak values of R waves in different patient body postures. Based on the minimal amplitude value, the manufacturer provides the appropriate system calibration factor, which is programmed immediately after implantation, independently of the stimulation parameters. This implies an additional intervention, albeit minor, from the neurologist or nurse practitioner in the follow-up of patients. Moreover, we recommend checking heart rate detection on a regular basis, although in the initial trial no major problems were reported on that level.

Concerning the selection of patients, the E-36 trial appeared to have very stringent criteria for ictal tachycardia, as a heart rate increase greater than 100 bpm *and* an increase of at least 55% or 35 bpm from baseline was required. As the lowest SDA setting requires ≥20% increase in heart rate, all patients fulfilling these criteria may benefit from the therapy.

Regarding the choice of stimulation parameters, we recommend, as for the magnet mode, to program the auto-stimulation slightly higher than normal mode intensity, respecting patient tolerability. In addition, the company has recently added a safety measure, which states that auto-stimulation and magnet mode should not be programmed at the same intensities, as there have been reports of malfunctioning of the device whenever this was the case. For Patient 2 and 3, auto-stimulation mode was thus increased after the end of the trial to meet this requirement. Long-term follow-up and additional studies assessing the differential effects of ictal versus standard VNS and increased duty cycles are necessary to improve our understanding of the potential benefit patients may have from this new therapeutic strategy for seizure abatement. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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TEST YOURSELF

(1) What does vagus nerve automatic magnet mode stimulation mean (AMM)?

(2) How was ictal tachycardia defined in the initial E-36 trial (Boon *et al*., 2015) and is this definition of IT required to implant an Aspire model?

(3) How does the neurologist need to titrate individually the seizure detection algorithm (SDA)?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".