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A prospective, multicenter study of cardiac-based seizure detection to activate vagus nerve stimulation☆,☆☆

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ABSTRACT

Purpose: This study investigates the performance of a cardiac-based seizure detection algorithm (CBSDA) that automatically triggers VNS (NCT01325623).
Methods: Thirty-one patients with drug resistant epilepsy were evaluated in an epilepsy monitoring unit (EMU) to assess algorithm performance and near-term clinical benefit. Long-term efficacy and safety were evaluated with combined open and closed-loop VNS.
Results: Sixty-six seizures ($n = 16$ patients) were available from the EMU for analysis. In 37 seizures ($n = 14$ patients) a $\geq$20% heart rate increase was found and 11 ($n = 5$ patients) were associated with ictal tachycardia (iTC, 55% or 35 bpm heart rate increase, minimum of 100 bpm). Multiple CBSDA settings achieved a sensitivity of $\geq$80%. False positives ranged from 0.5 to 7.2/h. 27/66 seizures were stimulated within $\pm$2 min of seizure onset. In 10/17 of these seizures, where triggered VNS overlapped with ongoing seizure activity, seizure activity stopped during stimulation. Physician-scored seizure severity (NHS3-scale) showed significant improvement for complex partial seizures (CPS) at EMU discharge and through 12 months

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($p < 0.05$). Patient-scored seizure severity (total SSQ score) showed significant improvement at 3 and 6 months. Quality of life (total QOLIE-31-P score) showed significant improvement at 12 months. The responder rate (≥50% reduction in seizure frequency) at 12 months was 29.6% (n = 8/27). Safety profiles were comparable to prior VNS trials.

Conclusions: The investigated CBSDA has a high sensitivity and an acceptable specificity for triggering VNS. Despite the moderate effects on seizure frequency, combined open- and closed-loop VNS may provide valuable improvements in seizure severity and QOL in refractory epilepsy patients.

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1. Introduction

Vagus nerve stimulation (VNS) (VNS Therapy®, Cyberonics, Houston, Texas, USA) is a safe and efficacious treatment for refractory epilepsy [1,2]. Currently VNS is delivered in an open-loop fashion with continuous but intermittent ('ON' and 'OFF' cycles) stimulation of the vagus nerve. A hand-held magnet allows on-demand stimulation to interrupt seizure activity [3]. Automated seizure detection that triggers VNS could offer a solution for patients unable to use the magnet due to clinical seizure symptoms, a physical limitation, cognitive impairment, or for nocturnal seizures. EEG and ECG studies have shown that ictal heart rate increases occur in an average of 82% of epilepsy patients [4].

This clinical trial investigates, for the first time in an epilepsy monitoring unit (EMU) setting, the performance of a novel cardiac-based seizure detection algorithm (CBSDA) incorporated in a neurostimulation device (AspireSR®, Cyberonics, Houston, Texas, USA). In addition to standard open-loop VNS, this device provides an automatic stimulation feature which is triggered in response to ictal heart rate increases of at least 20% to deliver VNS in a closed-loop fashion. The automatic stimulation feature delivers the same stimulation waveform as open-loop VNS, although output current, stimulation duration, and pulse width can be set independently. Both open and closed-loop modes can be delivered in combination.

2. Methods

2.1. Study overview

The E-36 study was a prospective, multi-center study in VNS candidates with a history of ictal tachycardia (iTC, 55% or 35 bpm increase in heart rate, to a minimum level of 100 bpm). The primary aim of the study was to demonstrate a seizure detection sensitivity of at least 80% for iTC seizures by at least one detection threshold setting, and to investigate the associated false positive (FP) rate. Secondary outcome measures were latency to seizure detection and effects on seizure duration, severity, frequency and quality of life (QOL) over a 12-month treatment period. Patients were implanted [5] with the new VNS device between April 2011 and June 2013 at 13 European sites (Fig. 2A, see Section 3). Continuous video-EEG and ECG monitoring was performed during 3–5 days when the device was programmed with the closed-loop VNS feature only. The new VNS device monitors the electrical activity of the heart using the generator case and one VNS lead electrode (Fig. 1). When a patient's relative heart rate increases above a programmed threshold for at least 1 s, a single VNS train (preprogrammed to 30 or 60 s duration) is automatically delivered. Six seizure detection algorithm (SDA) thresholds are available to match individual patient ictal heart rate changes. In the trial, patients were randomized to three different SDA settings (≥20%, ≥40%, ≥60% above baseline heart rate) during the EMU stay. During the EMU, open-loop stimulation was disabled to allow assessment of the automatic stimulation feature. Recorded seizures at the EMU were annotated by the clinical investigators. Patients performed a 3-min step test to elicit non-ictal increases in heart rate. The exercise test was not long enough to extrapolate FP rate per hour, but was reviewed to determine the proportion of sessions in which automatic stimulation was triggered. During long-term follow-up, both open- and closed-loop VNS was active using the SDA threshold deemed most appropriate by the physician. Throughout the course of the study medication changes were avoided unless considered medically necessary. Based on records of concomitant medications, no significant medication changes occurred from baseline through long term follow-up. The study was approved by the Competent Authorities and Ethics Committees (EC). All patients signed informed consent. This study is registered with ClinicalTrials.gov (NCT01325623).

2.2. Assessment of device performance

Sensitivity, potential FP rate, and latency were analyzed in two ways: observed and modeled. The observed analysis reflects the real world behavior of the device. As patients were randomized to a specific SDA setting during EMU stay, the detection of each seizure, based on associated cardiac changes, could only be evaluated at the single SDA threshold to which the patient was randomized. For the observed analysis, timestamps from detection logs that were downloaded from the implanted generator were compared to the seizure annotations from the physicians based on EEG. Not all EMU seizures could be included in the observed analysis. To be included, the clinical study site needed to download the detection log from the generator (a daily protocol requirement), the SDA threshold had to be set to the randomized setting dictated by the protocol, and the seizure needed to occur while closed-loop stimulation was activated in isolation of other VNS modes (Normal Mode or Magnet Mode). For the modeled analysis, surface ECG recordings from the EMU stay were post-processed through the seizure detection algorithm to simulate outcomes at all possible device threshold settings ranging from 20 to 70%. ECG was collected as a referential montage with one electrode placed over the lead incision site and one electrode place over the generator implant location. Compared to the observed analysis, more seizures could be included in the modeled analysis, since the only requirement was that surface ECG was available during the time of the seizure.

2.3. Calculation criteria and formulas

Sensitivity was calculated as the number of seizures detected, divided by the number of physician-annotated seizures. A detection window of ±2 min around the annotated seizure onset was established to identify true positives, according to a method previously used in validation of an EEG-based seizure detection software [6]. The observed analysis reports sensitivity based on generator detection logs and the protocol-dictated, randomized, device threshold setting (see Table 2). In the modeled analysis sensitivity is reported by the magnitude of ictal heart rate increase

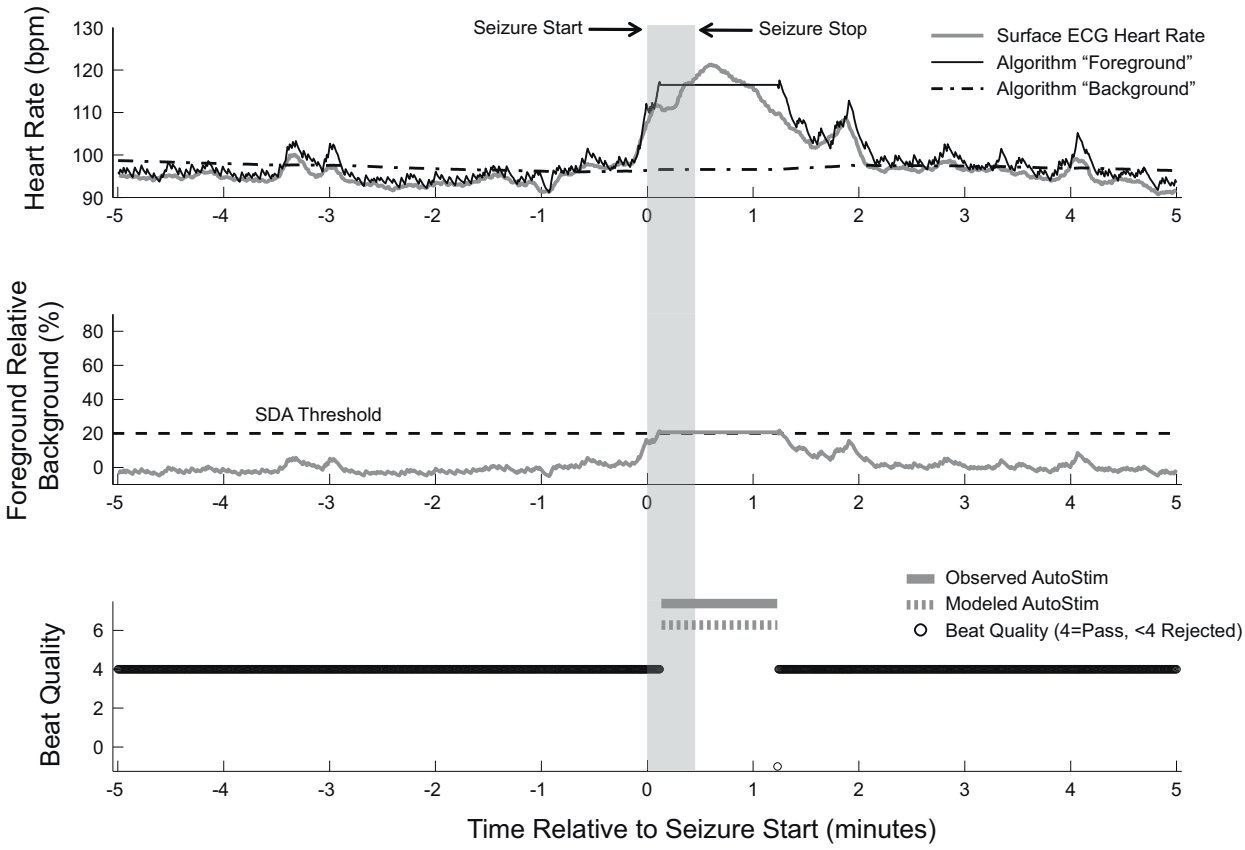


Fig. 1. CBSDA description and demonstration of algorithm behavior. Complex partial seizure, SDA 20% threshold. In the AspireSR device, heart beats are recorded by monitoring the electrical activity of the heart using the generator case and one VNS lead electrode. The device firmware amplifies and filters these signals, identifies the R-waves, and calculates R–R intervals based on the detected beats. These R–R intervals are then processed through the CBSDA, which compares the most recent heart rate data to a background rate established over approximately the previous 5 min of R–R intervals. The threshold above baseline heart rate required for seizure detection can be set in 10% increments (range: 20–70%) according to patient needs. Device performance is shown for a 26 year old female subject experiencing a bilateral temporal lobe complex partial seizure. The upper panel shows the instantaneous heart rate based on surface ECG (gray), and the algorithm calculated foreground (black) and background (black dashed) heart rates, as well as seizure start and stop times. The middle panel shows the relative heart rate, the key patient metric monitored by the device, as well as the SDA threshold required for stimulation. The lower panel shows the R–R interval quality checks which are performed by the device algorithm that are intended to prevent muscle noise from influencing the foreground and background heart rates; on this plot a value of 4 indicates the beat passed all quality checks and was included in the determination of the relative heart rate; lower values (−1 to 3) indicate the beat failed at least one constraint and was excluded from algorithm processing. The lower panel also shows stimulations based on observed (solid gray bar) and modeled detections (dashed gray bar). This seizure was stimulated by AspireSR and ended during the period of stimulation.

(see Table 1), since the modeled analysis allows evaluation of all seizures at all possible device threshold settings.

Latency was calculated as the time between annotated seizure onset, defined as a typical change in behavior or EEG whichever came first, and device detection for each true positive detection. The latency is therefore bounded to 120 s, either positive or negative, the latter indicating that detection preceded seizure onset.

Each detection that occurred outside the ±2-min window was counted as a potential FP, and the average rate was calculated for each SDA threshold setting as the total number of potential FP detections divided by the total monitoring time.

Table 1
Modeled sensitivity and potential false positive rate, based on post-processed ECG.

SDA threshold (%)	Sensitivity for iTC seizures[a] $n=15$ (%)	Sensitivity as a function of percent heart rate increase from baseline						Potential false positive rate[b] (95% CI)[c] (stimulations/h)
		≥70% $n=5$ (%)	≥60% $n=7$ (%)	≥50% $n=11$ (%)	≥40% $n=19$ (%)	≥30% $n=33$ (%)	≥20% $n=45$ (%)	
70	60	**100**						0.4 (0.30, 0.64)
60	60	100	**85.7**					0.6 (0.47, 0.89)
50	80	100	85.7	**81.8**				1.0 (0.78, 1.39)
40	93.3	100	85.7	90.9	**89.5**			1.8 (1.44, 2.35)
30	100	100	100	100	100	**90.9**		3.5 (2.83, 4.37)
20	100	100	100	100	100	97.0	**97.8**	6.9 (5.74, 8.25)

For each magnitude of heart rate increase category, the least sensitive SDA threshold capable of detecting the category is shown in bold. SDA settings that are below the threshold expected for seizure detection are shaded gray.

[a] iTC is defined as ictal heart rate >100 bpm, and at least 55% increase, or 35 bpm increase, from baseline.

[b] Potential false positive rate per hour utilized 2709.5 h of monitoring time at each SDA setting.

[c] 95% confidence interval (CI) calculated using 3000 bootstrap samples.

Seizure severity data was collected using two scales: The National Hospital Seizure Severity Scale (NHS3) [7] and the Seizure Severity Questionnaire (SSQ) [8]. The NHS3 is a physician-scored severity scale (1–27 range; 27 most severe). The Wilcoxon signed-rank test was used to assess statistical significance of changes in seizure severity versus the baseline NHS3 score. The SSQ is completed by patients and caregivers (1–7 range; 7 most severe). Changes in severity versus baseline SSQ score were compared to the minimally important change (MIC) threshold to determine clinical significance [9].

Baseline seizure frequency was reported as the total number of seizures during 3 months prior to enrolment screening. Post-baseline seizure frequency was obtained from seizure diaries reported at each follow-up visit (3, 6, and 12 months post-implant). The responder rate was defined as the proportion of patients with a ≥50% decrease in seizure frequency versus baseline.

QOL data was collected at baseline using the QOLIE-31-P and compared to data collected at post-baseline visits. Changes in QOL from baseline were compared to the minimally important change (MIC) threshold to determine clinical significance [10].

Adverse events were collected and incidence rates tabulated utilizing MedDRA dictionary version 17.0.

3. Results

Thirty-one of 35 enrolled patients were implanted with the AspireSR device that includes a cardiac-based seizure detection feature (Fig. 2B). Study procedures are summarized by Fig. 2A. Data from 29 patients are available through 12 months of follow-up (Fig. 2B). Patient demographics, including seizure types recorded in the EMU, are found in Fig. 2C.

3.1. CBSDA performance

At the EMU, 87 seizures were annotated by the investigators. Observed analysis for seizure detection was possible in 66/87 seizures from 16 patients in whom all protocol procedures were followed, including: device detection logs were downloaded, SDA threshold was set to the randomized setting dictated by the protocol, and the seizure occurred while closed-loop stimulation was activated in isolation of other modes (see Section 2). The ictal heart rate change in these 66 seizures ranged from −14.5% to 100% (decrease $n = 6$, increase $n = 60$). In 37/66 seizures ($n = 14$ patients) a ≥20% increase in heart rate was found, surpassing the lowest detection threshold of the device. 11/37 seizures ($n = 5$ patients) were associated with iTC according to the strict study criteria of 55% or 35 bpm increase in heart rate to a minimum level of 100 bpm. For 11 iTC seizures that occurred in the EMU, observed sensitivities ranged from 75% (SDA = 40%) to 100% (SDA = 20% and 60%; see Table 2). 2/8 iTC seizures that occurred in a patient with SDA = 40%, were not detected. In one case the elevated heart rate was not maintained for more than 1 s (a device design requirement). In the other case, muscle artifact was believed to be the reason for the missed detection.

In 27/66 annotated seizures, the ictal heart rate change surpassed the SDA threshold and VNS was triggered. As latency cannot be calculated in the absence of seizure detection, these 27 true positives only are summarized in the observed (based on device detection logs) latency analysis. In the remaining 39/66 seizures where VNS was not triggered, 23/39 seizures were associated with an ictal heart rate change of <20%, 14/39 had a heart rate change less than the randomized SDA threshold, and the remaining 2/39 had high ECG noise or did not cross the threshold for >1 s (these two cases were described above).

Compared to the observed analysis, more seizures could be included in the modeled analysis, since the only requirement was that surface ECG was available during the time of the seizure (see Section 2). Concurrent ECG and EEG recordings, allowing modeled analysis for seizure detection, were available in 86/87 annotated seizures from 18 patients. In 45/86 ($n = 15$ patients) a ≥20% increase in heart rate was found. 15/45 seizures ($n = 6$ patients) were associated with iTC. Table 1 reports the modeled sensitivity at every available device SDA setting for all seizures with heart rate changes ≥20% ($n = 45$), the types of seizures for which the detection algorithm was designed. Results are presented by magnitude of ictal heart rate increase. The least sensitive SDA threshold capable of detecting seizures with a particular heart rate change is shown in bold (below threshold categories are shaded gray).

Both the observed and modeled sensitivity analyses demonstrate that at least one SDA setting had a ≥80% sensitivity, meeting the primary study endpoint. Ictal heart rate change as observed in this study was highly variable. Of the 18 patients in whom seizures were annotated during the EMU, 13 had more than one seizure. Among patients with multiple seizures, the mean standard deviation (SD) of change in ictal heart rate was 16% (maximum SD 33%, minimum SD 7%).

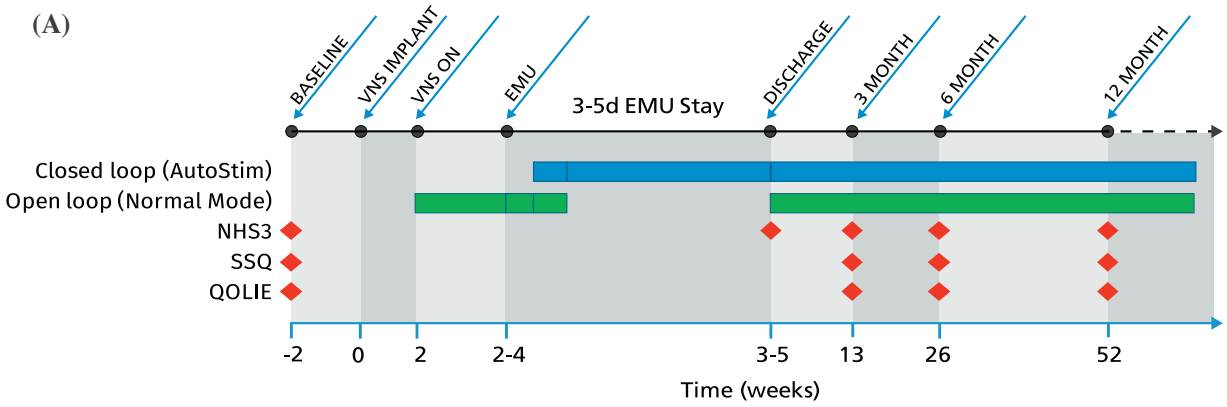
The mean observed (based on device detection logs) potential FP rate ranged from 0.5 to 7.2 per hour, depending on the SDA setting (Table 2). Consistent with the observed clinical results, the modeled analysis indicated a potential FP rate of approximately 0.4–6.9 per hour, depending on the SDA sensitivity setting (Table 1). During the EMU, 28 patients completed 127 exercise sessions which consisted of at least 3 min of stair step exercise. In 55.9% (71/127) of the sessions VNS was not triggered, in 20.5% (26/127) of the sessions one triggered stimulation occurred, and in 23.6% (30/127) of the sessions VNS was triggered twice during the 3 min step exercise. After EMU discharge, patients underwent both open- and closed-loop VNS. The mean overall duty cycle exceeded the Normal Mode setting by <3% at the 3, 6, and 12 month follow-up periods pointing to modest FP rates in the ambulatory setting. The effect on overall duty cycle can be alternately summarized as a mean closed-loop stimulation rate of <2.1/h at each follow-up period. This indicates that normal daily activity such as physical exercise did not compromise performance, and the device safety features limit the addition of automatic stimulation to the Normal Mode duty cycle. It should be noted that physicians most typically selected mid-range detection thresholds during the ambulatory phase; together the 40% and 50% detection thresholds accounted for over 60% of patients at the 12 month follow-up.

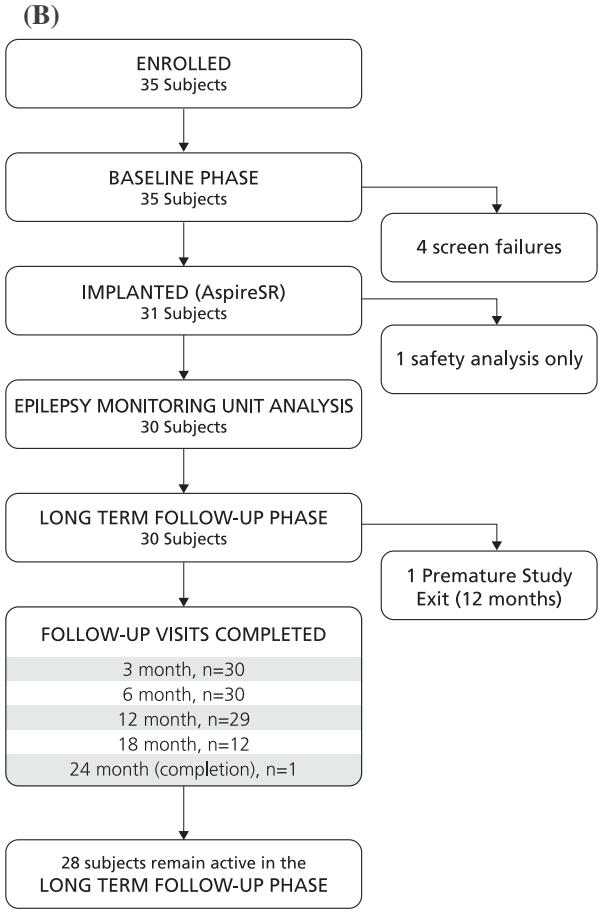
3.2. Latency

The observed latency could be calculated for each true positive detection, i.e. those stimulated within ±2 min of seizure onset. This included 27 seizures from the total of 66 investigator annotated seizures in the observed analysis. The median observed latency ranged from 6 (SDA = 20%) to 35 s (SDA = 60%) after seizure onset (Table 2). For iTC seizures ($n = 11$ seizures), the median observed latency ranged from 14.5 s before seizure onset (SDA = 20%) to 27.5 s (SDA = 40%) after seizure onset. Similar results were collected for modeled data (not shown). Generally, increasing the sensitivity of the SDA threshold resulted in earlier seizure detections.

3.3. Effect of closed-loop VNS on seizure duration and severity during the EMU

In total, 27/66 EMU seizures from the observed analysis were stimulated within ±2 min of seizure onset. In 17 seizures, the triggered VNS overlapped with ongoing seizure activity, and seizure





(C)

VARIABLE	MEASURE
Gender [subjects (%)]	
Female	19 (61.3%)
Male	12 (38.7%)
Race [subjects (%)]	
White	31 (100%)
Ethnicity [subjects (%)]	
Not Hispanic or Latino	31 (100%)
Age [years]	
Mean (st.dev.)	39.6 (13.4)
Min, Max	19, 66
Cognitive Status [subjects (%)]	
Normal	20 (64.5%)
Minimal Impairment	8 (25.8%)
Moderate Impairment	3 (9.7%)
Severe Impairment	0
Age at Epilepsy Onset [years]	
Mean (st.dev.)	15.9 (10.9)
Min, Max	2, 43
Prior Brain Surgery [subjects (%)]	
No	22 (71.0%)
Yes	9 (29.0%)
Seizure Types* [seizures (%)]	
Focal (unspecified)	8 (9.2%)
Simple Partial	26 (29.9%)
Complex Partial	31 (35.6%)
Secondarily Generalized	17 (19.5%)
Generalized Tonic Clonic	0
Other Seizures	5 (5.7%)

* Note: Patients could report mulitple seizure types

Fig. 2. Study protocol overview. Panel A: Seizure diary, SSQ, NHS3, and QOLIE-31-P were collected at baseline. Two weeks following implant surgery, standard open-loop VNS was initiated and titrated for up to 2 weeks. This period allowed patients to acclimate to VNS stimulation, but restricted output to a subtherapeutic level to facilitate seizure recording during a 3–5 day EMU stay (2–4 weeks after implant). As part of EMU procedure the subject received Normal Mode stimulation for 1 h (to increase output to therapeutic levels), Normal Mode plus Automatic stimulation for 2 h (to introduce new feature), and then automatic stimulation only until EMU discharge. The SDA threshold randomization was performed on day 1 of EMU. At EMU discharge, both open- and closed-loop VNS were activated and the SDA threshold was programmed by the physician to the most suitable setting. Follow-up visits occurred at 3, 6, and 12 months. The study will continue to follow patients through 2 years after implant. Panel B shows the status of patients enrolled in the trial. Four screen failures occurred: low seizure rate during baseline (1), underlying cardiac conditions (2), and withdrawn patient consent (1). The first subject was implanted with a first version of the new generator; the remaining 30 subjects were implanted with version 2, which included modified gain and filter settings for heart beat sensing. The population used for safety analyses consists of all subjects who provided consent and were implanted with either generator version (n = 31 subjects). The population used for performance analyses consists of all subjects who were implanted with version 2 and underwent an EMU stay (n = 30 subjects). One patient discontinued the trial prior to the 12 month follow-up visit due to an adverse event (AE) of diarrhea and vomiting. The patient recovered from the AE, but VNS was permanently programmed 'OFF'. Panel C describes patient characteristics.

Table 2
Observed sensitivity, potential false positive rate, and latency, based on device detection logs.

SDA threshold (%)	Sensitivity for iTC[a] seizures (n = 11)	Sensitivity for seizures with ≥20% heart rate change (n = 37)	Sensitivity for all observed analysis seizures (n = 66)	False positive rate per hour[b] (95% CI)[c] (stimulations/h)	Median latency[d] (min, max) (s)
60	1/1 (100%)	3/11 (27.3%)	3/16 (18.8%)	0.49 (0.20, 0.96)	35.0 (4, 40)
40	6/8 (75%)	7/15 (46.7%)	8/23 (34.8%)	2.72 (1.70, 3.91)	27.5 (0, 57)
20	2/2 (100%)	11/11 (100%)	16/27 (59.3)	7.15 (5.31, 9.94)	6.0 (−112, 105)

[a] iTC is defined as ictal heart rate >100 bpm, and at least 55% increase, or 35 bpm increase, from baseline.
[b] Potential false positive rate per hour utilized 609.6, 953.9, and 759.3 h of monitoring time for SDA thresholds 20%, 40%, and 60%, respectively.
[c] 95% confidence interval (CI) calculated using 3000 bootstrap samples.
[d] Results from 27 true positive seizure detections among the 66 seizures available for the observed analysis.

activity stopped during stimulation in 10/17 (58.8%) seizures, including 4/4 (100%) simple partial, 6/11 (54.5%) complex partial, and none of the secondarily generalized seizures (0/2). Fig. 3 (panels A and B) shows an example of the impact of triggered VNS on the EEG and displays the relationship between detection latency and seizure duration (panel C). Seizures stimulated near annotated onset, were shorter in duration ($p < 0.01$).

After 3–5 days of treatment with closed-loop VNS only, patients experienced statistically significant reduction in seizure severity compared to baseline among CPS according to the NHS3 scale (mean change −2.5 points; 19 subjects, $p = 0.002$).

3.4. Long-term changes in seizure severity, seizure frequency and QOL

Twenty-nine patients completed 12 months of follow-up (96.7% compliance rate). Improvement in physician-rated seizure severity (NHS3) at EMU discharge persisted during long-term follow-up at the 3, 6, and 12 month assessments; mean NHS3 severity changes for patients with CPS were −1.6 (20 subjects; $p = 0.037$), −2.5 (20 subjects; $p = 0.004$), and −2.3 points (20 subjects; $p = 0.002$), respectively.

Additionally, several subscales of the SSQ (patient-rated) exceeded the Minimally Important Change (MIC) criteria [9] for clinical significance at 12 months (Fig. 4).

The responder rate was 24.1% ($n = 7/29$) at 3 months, 20.0% ($n = 6/30$) at 6 months, and 29.6% ($n = 8/27$) at 12 months. For partial seizures it was 25.9% ($n = 7/27$) at 3 months, 25.0% ($n = 7/28$) at 6 months, and 32.0% ($n = 8/25$) at 12 months. At 6 months the median Normal Mode stimulation parameters were: 1.250 mA output current, 250 μs pulse width, 30 s 'ON'/5 min 'OFF', 20 Hz signal frequency; automatic stimulation settings: 1.188 mA, 375 μs pulse width, and 60 s 'ON' time. Median parameters were identical at 12 months, except automatic stimulation pulse width decreased to 250 μs and the output increased to 1.375 mA.

Improvement in QOL was found at the 12-month follow-up visit. The following domains exceeded the Minimally Important Change (MIC) criteria for clinical significance [10]: emotional well being (e.g. happiness, decreased anxiety or depression), social function (e.g. visiting friends or relatives), cognitive function (e.g. memory and concentration), seizure worry (e.g. decreased fear of injury or embarrassment), and overall QOL.

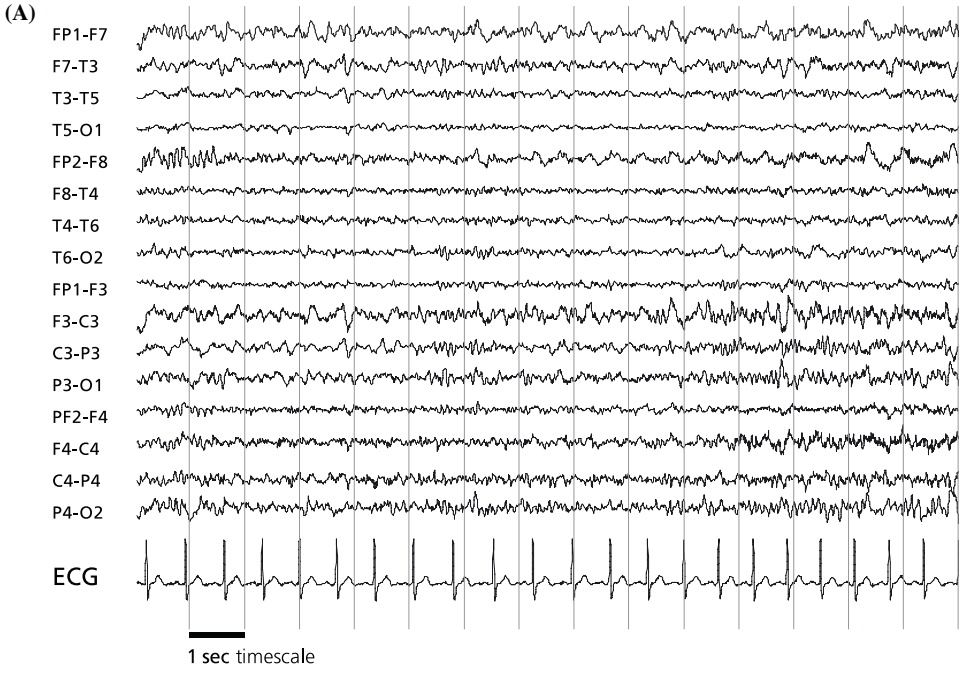


Fig. 3. The impact of triggered VNS following an ictal heart rate increase detection. Panels A (pre-ictal) and B (ictal) show data from a 26-year old female patient experiencing a bilateral temporal lobe complex partial seizure. The device was set to an SDA threshold of 20% and stimulation was triggered 6 s after seizure onset. Following the onset of stimulation, slowing of the focal synchronized sharp- and -slow wave activity is observed, followed by an abrupt and generalized desynchronization of rhythmic activity resembling pre-ictal EEG patterns. Panel C shows the relationship between seizure detection latency and seizure duration. For seizures that ended during stimulation ($n = 10$ in 5 patients), those stimulated near annotated onset, were shorter in duration (linear regression, $p < 0.01$).

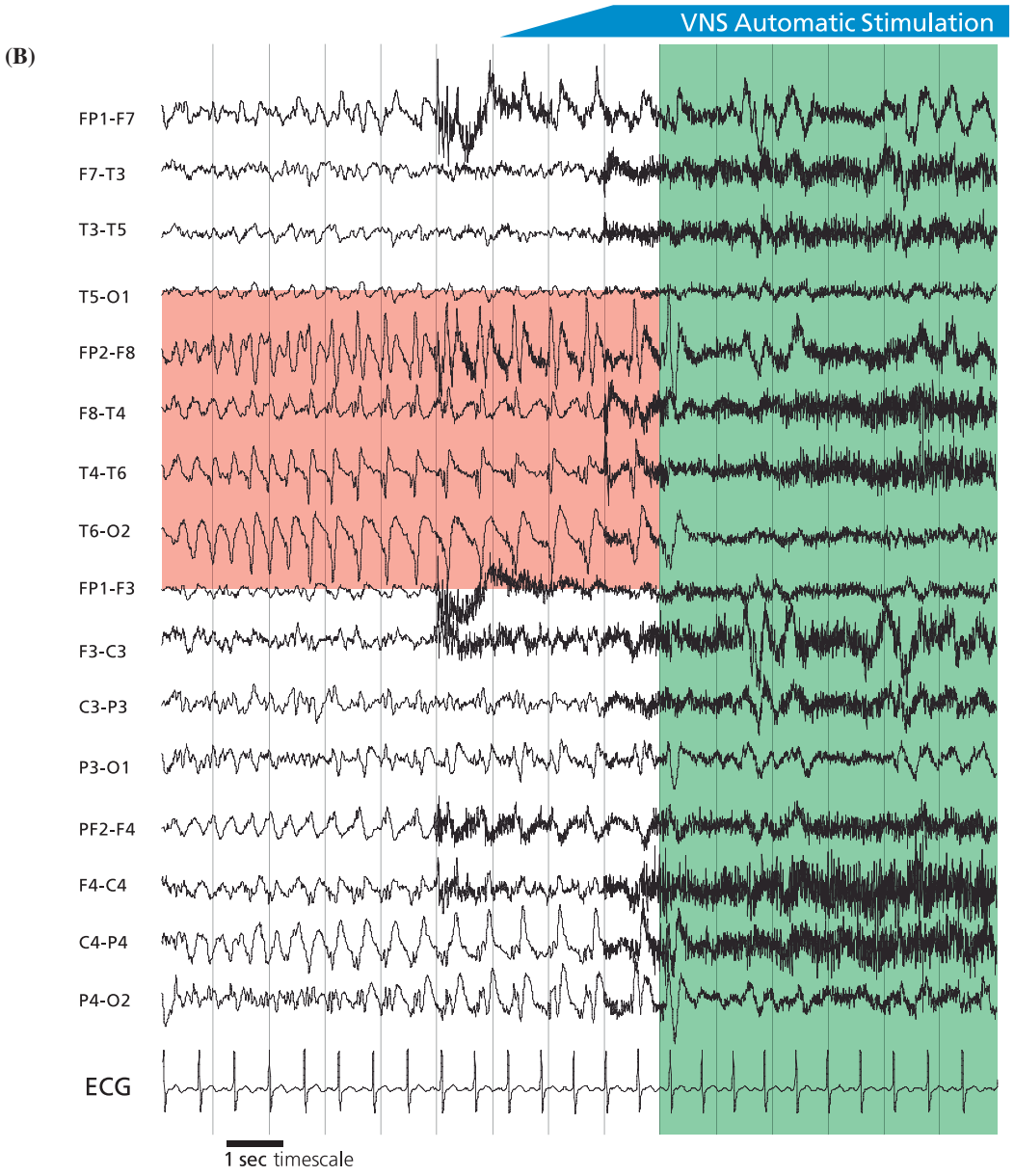


Fig. 3. (*Continued*).

3.5. Safety

The new VNS device did not produce any unanticipated adverse device effects and the surgical implantation was well tolerated. Data were not collected on patients' awareness of stimulation, however the adverse event profile indicates a similar tolerability profile to open-loop VNS. Dysphonia was reported in nine patients (29.0%) and was the most common adverse event after VNS activation. One patient discontinued the trial prior to the 12 month follow-up visit (Fig. 2B).

4. Discussion

This study is the first clinical trial in epilepsy to prospectively evaluate the performance of a CBSDA incorporated into a closed-loop VNS device. A high sensitivity for seizure detection was reached when the appropriate detection threshold was applied, and the FP rate was acceptable.

Seizure detection algorithms have mainly been EEG-based [11], which depending on the type of seizure, requires the capability to detect a wide variety of specific EEG abnormalities. Detection algorithms based on intracranial EEG recordings are promising and currently applied for neurostimulation triggering, but they remain limited to a carefully selected patient population [12]. Heart rate changes associated with seizures have been extensively investigated [4]. ECG is less complex and obtrusive to record, and seizure-related ECG changes are more generic and present in the majority of patients. Therefore, seizure detection based on cardiac recordings would appear a promising alternative.

There have been few studies assessing real-time seizure detection systems based on measures obtained from an ECG alone [13–17] or in combination with EEG [18–20]. Most studies were conducted in small samples of neonates [13,14,16,18] and retrospectively analyzed pre-existing data. Seizure detection sensitivity ranged from a low of 54.5% (corresponding specificity

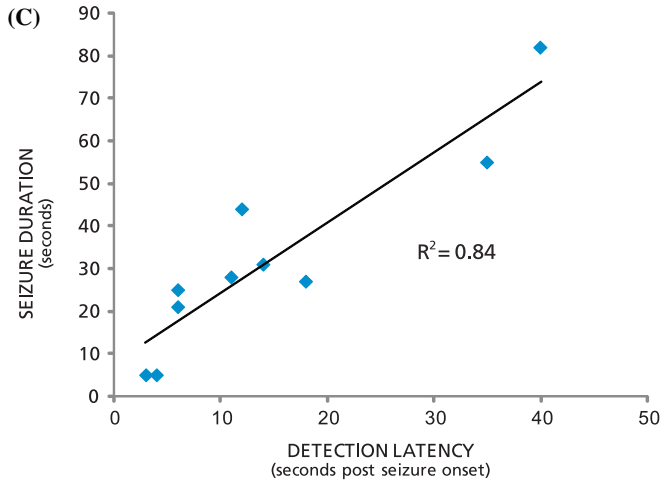


Fig. 3. (*Continued*).

of 77.3%) [14] to a high of 85.7% (corresponding specificity of 84.6%) [16]. In our study, when the patient exhibited large ictal heart rate change and more selective SDA thresholds were used, less than 1 false detection per hour occurred. We considered the combination of sensitivity and FP rate to be clinically appropriate for implementation in a neurostimulation device. Combined recording of other physiological parameters – such as accelerometry leading to multimodal and individualized seizure detection – may be required when the algorithm is to be used solely for seizure alerting purposes or objective seizure counting in therapeutic trials.

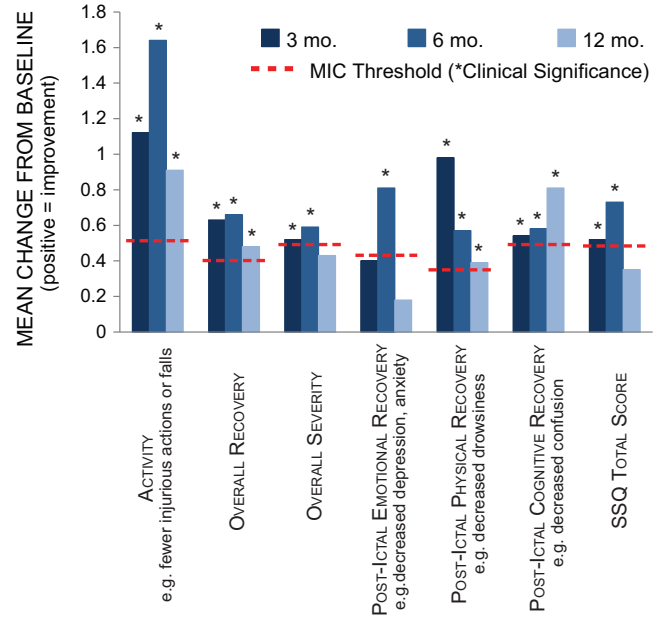


Fig. 4. Clinically significant improvement in patient and caregiver scored seizure severity (SSQ). The plot shows the mean change from baseline SSQ score (dimensionless units) at 3, 6, and 12 months for each of 6 subscales and the overall total score. Positive values indicate improved seizure severity compared to baseline. All subscales and the total SSQ score improved from baseline, and those exceeding the minimally important change (MIC) criteria represent clinically significant improvement in patient health. At 12 months, the full SSQ was completed by 26/30 patients. Each of the categories exceeding MIC at 12 months (activity, overall recovery, post-ictal physical and post-ictal cognitive recovery) previously showed clinically significant improvement at the 3 and 6 month follow-up periods.

Despite the fact that a priori iTC was an inclusion criterion for the study, and that an extensive literature review [4] demonstrated that approximately 82% of epilepsy patients have significant ictal heart rate increase, only approximately one-third of the prospectively recorded E-36 seizures were associated with iTC. This discrepancy reflects a significant variability in ictal heart rate changes in individual patients along with the fact that none of the published studies were prospective studies.

The pulse generator design includes CBSDA thresholds as low as 20%, which supports the consideration that patients with ictal heart rate increases less than the strictly defined iTC could also be considered for closed-loop VNS treatment.

The limitation of the randomization to specific detection thresholds was overcome by performing a modeled analysis in which recorded surface ECG data were reanalyzed post hoc by the detection algorithm for all programmable thresholds ranging from 20% to 70%. The higher the seizure-associated heart rate increases are, the higher the SDA threshold can be programmed, and the lower the FPs are expected to be. On the other hand, seizures associated with heart rate increases of only 20% could be detected with a high sensitivity at the price of 7 FPs per hour. In comparison, a Normal Mode duty cycle of 10% used in isolation of other modes would deliver a similar number of stimulations per hour (approximately 11/h), without the potential benefit of temporal targeting of stimulation to seizure activity. Two design features limit the extent to which the automatic stimulation feature can increase the programmed Normal Mode duty cycle. First, after delivery of an automatic stimulation burst the device enforces an 'OFF' period, equal in duration to the selected automatic stimulation 'ON' time, in which no further automatic stimulation can occur. Secondly, automatic stimulation reschedules or delays the next Normal Mode stimulation, by resetting the Normal Mode 'OFF' period. Taken together the impact of automatic stimulation on the overall duty is modest, increasing the mean Normal Mode setting by <3% during long term follow-up.

During the trial, patients were not limited in physical activity and exercise. On the contrary, they were instructed to perform daily submaximal exercise activities to determine the likelihood of triggering during moderate physical exertion. In more than half of the exercise sessions automatic stimulation was not triggered, since the dynamics of heart rate increase associated with seizure activity (reflected by the rate of change) differs from physiological heart rate increase during exercise and the algorithm is designed to detect rapid relative heart rate changes. At 3, 6, and 12 month follow-up periods, device logs of CBSDA stimulations revealed only modest FP rates in the ambulatory setting. This implies that normal daily activity such as physical exercise did not significantly add to the programmed open-loop duty cycle, and this outcome was likely related to more suitable patient-specific CBSDA settings during the long term follow-up compared to the randomized assignments within the EMU.

In three different patients CPS stopped during triggered VNS. The relatively short mean duration of these CPS [21] suggests a shortening effect for acutely delivered VNS. These durations however could not be compared with historical information from the same patients due to limited availability of historical patient records. Initial reports comparing seizures treated with and without closed-loop VNS in an EMU setting are promising [22].

The design of this study did not allow for direct comparison to patients treated with open-loop VNS alone. However, the impact of automatic stimulation on seizure duration and seizure severity in the EMU (when only closed-loop VNS was active) suggests that acute delivery of VNS at seizure onset may be beneficial. Both seizure severity and QOL were significantly improved early in the trial by combined closed- and open-loop

VNS during the long-term follow-up. Although the magnitude of noted improvements may appear modest compared to the overall range of these scales, many of these improvements were statistically significant or exceeded the minimally important change (MIC) threshold for clinical significance. In this study the responder rate of 30% was relatively low compared to other open VNS trials [23]. One of the reasons could be the relatively low output current that patients were ramped up to at 12 months follow-up due to the study design. Longer follow-up data will have to demonstrate whether responder rates increase which is to be expected from results in long-term studies. Beneficial effects of the closed-loop VNS modality are primarily expected in the QOL and seizure severity assessments as the algorithm has to detect heart rate change before it can trigger stimulation, and this change occurred prior to clinical seizure onset in only a minority of patients.

5. Conclusion

The present study prospectively demonstrated the ability to detect seizures based on cardiac changes as low as a 20% above baseline heart rate with high sensitivity. Limitations of this study include the relatively small sample of seizures captured during the EMU that were associated with iTC. Due to the apparent intra-patient variability of seizure-associated heart rate increases, identification of candidates for this treatment in an outpatient clinical setting may prove challenging. A practical approach would be to select suitable patients during a presurgical EMU admission during which at least one recorded seizure is found to be associated with at least 20% heart rate increase.

Combined open- and closed-loop systems may have differential and additive effects in patients with drug resistant epilepsy. Open-loop treatment might provide neuromodulatory effects which take time to establish, whereas acute treatment via the closed-loop feature may more rapidly terminate or decrease duration and/or severity of the ictal events. Despite the moderate effects on seizure frequency, combined open- and closed-loop VNS may provide valuable improvements in seizure severity and QOL in refractory epilepsy patients. Our results demonstrate that ECG-based seizure detection can provide a valuable addition to the currently available treatment modalities.

Role of funding source

Cyberonics, Inc. is the study sponsor and the manufacturer of AspireSR. This trial was developed in collaboration with the clinical investigators. The sponsor was responsible for data collection and statistical analysis. The sponsor collaborated with investigators to interpret the data and write this report. The corresponding author had full access to all the data and final responsibility for the decision to submit for publication.

Author contributions

All authors meet all four criteria for authorship in the ICMJE recommendations including:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work;
   - P. Boon, K.S. Eggleston – design of the trial, interpretation of data.
   - K. Vonck – design of the trial, data acquisition, interpretation of data.
   - K. van Rijckevorsel, R. El Tahry, C.E. Elger, N. Mullatti, A. Schulze–Bonhage, G.L. Wagner, B. Diehl, H.M. Hamer, M. Reuber, H. Kostov, B. Legros, S. Noachtar, Y.G. Weber–data acquisition, interpretation of data.
   - V.A. Coenen, H. Rooijakkers, O. Schijns, R. Selway, D. Van Roost, W. Van Grunderbeek – data acquisition.
   - K. Jayewardene – data analysis.
   - R.M. McGuire – design of the trial, data acquisition, data analysis, interpretation of data.
2. P. Boon, K. Vonck, K.S. Eggleston, and R.M. McGuire contributed to drafting manuscript. All authors contributed to reviewing and revising the manuscript.
3. All authors approve the final version to be published.
4. All authors agree to be accountable for all aspects of the work.

Conflict of interest

This study was sponsored by Cyberonics, Inc.

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Dr. El Tahry reports no disclosures.

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Dr. Mullatti, reports no disclosures.

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References

[1] Ben-Menachem E. Vagus-nerve stimulation for the treatment of epilepsy. Lancet Neurol 2002;1:477–82.
[2] Englot DJ, Chang EF, Auguste KI. Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response. J Neurosurg 2011;115:1248–55.
[3] Tatum WO, Helmers SL. Vagus nerve stimulation and magnet use: optimizing benefits. Epilepsy Behav 2009;15:299–302.
[4] Eggleston KS, Olin BD, Fisher RS. Ictal tachycardia: the head-heart connection. Seizure 2014;23:496–505.
[5] Schneider UC, Bohlmann K, Vajkoczy P, Straub HB. Implantation of a new Vagus Nerve Stimulation (VNS) Therapy® generator, AspireSR®: considerations and recommendations during implantation and replacement surgery-comparison to a traditional system. Acta Neurochir (Wien) 2015;157:721–8.
[6] Kelly KM, Shiau DS, Kern RT, Chien JH, Yang MC, Yandora KA, et al. Assessment of a scalp EEG-based automated seizure detection system. Clin Neurophysiol 2010;121:1832–43.
[7] O'Donoghue MF, Duncan JS, Sander JW. The National Hospital Seizure Severity Scale: a further development of the Chalfont Seizure Severity Scale. Epilepsia 1996;37:563–71.
[8] Cramer JA, Baker GA, Jacoby A. Development of a new seizure severity questionnaire: initial reliability and validity testing. Epilepsy Res 2002;48:187–97.
[9] Cramer JA, de la Loge C, Brabant Y, Borghs S. Determining minimally important change thresholds for the Seizure Severity Questionnaire (SSQ). Epilepsy Behav 2014;31:286–90.
[10] Borghs S, de la Loge C, Cramer JA. Defining minimally important change in QOLIE-31 scores: estimates from three placebo-controlled lacosamide trials in patients with partial-onset seizures. Epilepsy Behav 2012;23:230–4.
[11] Binder DK, Haut SR. Toward new paradigms of seizure detection. Epilepsy Behav 2013;26:247–52.
[12] Morrell MJ, Group RSiES. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology 2011;77:1295–304.
[13] Doyle OM, Temko A, Marnane W, Lightbody G, Boylan GB. Heart rate based automatic seizure detection in the newborn. Med Eng Phys 2010;32:829–39.
[14] Greene BR, de Chazal P, Boylan GB, Connolly S, Reilly RB. Electrocardiogram based neonatal seizure detection. IEEE Trans Bio-Med Eng 2007;54:673–82.
[15] Kerem DH, Geva AB. Forecasting epilepsy from the heart rate signal. Med Biol Eng Comput 2005;43:230–9.
[16] Malarvili MB, Mesbah M. Newborn seizure detection based on heart rate variability. IEEE Trans Bio-Med Eng 2009;56:2594–603.
[17] van Elmpt WJ, Nijsen TM, Griep PA, Arends JB. A model of heart rate changes to detect seizures in severe epilepsy. Seizure 2006;15:366–75.
[18] Greene BR, Boylan GB, Reilly RB, de Chazal P, Connolly S. Combination of EEG and ECG for improved automatic neonatal seizure detection. Clin Neurophysiol 2007;118:1348–59.
[19] Shoeb A, Pang T, Guttag J, Schachter S. Non-invasive computerized system for automatically initiating vagus nerve stimulation following patient-specific detection of seizures or epileptiform discharges. Int J Neural Syst 2009;19:157–72.
[20] Sturm K, Knake S, Schomburg U, Wakat JP, Hamer HM, Fritz B, et al. Autonomic seizures versus syncope in 18q-deletion syndrome: a case report. Epilepsia 2000;41:1039–43.
[21] Afra P, Jouny CC, Bergey GK. Duration of complex partial seizures: an intracranial EEG study. Epilepsia 2008;49:677–84.
[22] Hampel KG, Vatter H, Elger CE, Surges R. Cardiac-based vagus nerve stimulation reduced seizure duration in a patient with refractory epilepsy. Seizure 2015;26:81–5.
[23] Elliott RE, Morsi A, Kalhorn SP, Marcus J, Sellin J, Kang M, et al. Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: long-term outcomes and predictors of response. Epilepsy Behav 2011;20:57–63.