Interdisciplinary Neurosurgery: Advanced Techniques and Case Management 23 (2021) 101003

Contents lists available at ScienceDirect

Interdisciplinary Neurosurgery: Advanced Techniques and Case Management

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

Research Article

Closed-loop vagus nerve stimulation. Patient-tailored therapy or undirected treatment?

Philipp Spindler *, Peter Vajkoczy, Ulf Cristoph Schneider

Department of Neurosurgery, Charité – University Medicine Berlin, Germany

ARTICLE INFO

Keywords:
AspireSR(®)
Automatic stimulation (AutoStim)
Cardiac-based seizure detection (CBSD)
Pharmacoresistant epilepsy
Vagal nerve stimulation (VNS)

ABSTRACT

Background: In multi-drug-resistant epilepsy vagus nerve stimulation (VNS) is an efficacious additional treatment to reduce seizure frequency and severity. A recently developed cardiac-based seizure detection (CBSD) algorithm triggers automate stimulation (AutoStim) upon heart rate increases of at least 20%. Yet, long term sensitivity and specificity of the CBSD-algorithm remain unclear. We present a case series of 15 adult patients with epilepsy with AutoStim VNS therapy.

Methods: We reviewed CBSD-settings, operating hours and battery status of the devices. Percentage of AutoStim was assessed in comparison to continuous but intermittent stimulation. If seizure diaries were available, we verified whether a high rate of AutoStim was present during the documented seizures.

Results: We reviewed 15 patients with a mean age of 34 years (±11y). Mean duration since implantation was 47 months (±12 m). Of 1296 (±686) continuous intermittent stimulations per week, 4.8 (±3.9)% were AutoStim. Proportion of AutoStim varied substantially. While 9 patients had a mean of 1.5% (±1.4%), 6 patients had a significantly higher proportion of AutoStim 9.0% (±1.6%). Seizure-frequency was higher in patients with higher AutoStim frequency. Adverse events occurred in none of the patients.

Conclusion: We provide long-term results for sensitivity and specificity of the CBSD algorithm. While sensitivity seems to be high, we presume specificity to be poor. An extremely high number of AutoStim is supposedly false-positive. Yet, treatment was well tolerated by the patients without any adverse events, despite the high number of AutoStim. CBSD is a promising development, yet the algorithm should be revised to provide a better specificity.

1. Introduction

According World Health Organisation (WHO) around 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally. Approximately 30% of patients remain multi-drug resistant. While 450.000–600.000 of those patients worldwide might be suitable for epilepsy surgery, over 1.4millions remain candidates for other therapies such as VNS [1]. VNS was approved in the EU in 1994 for use as an adjunctive therapy in reducing the frequency of seizures in patients whose epileptic disorders are dominated by partial seizures (with or without secondary generalization) or generalized seizures, which are refractory to anti-epileptic medications [2]. VNS therapy normalizes the inter-ictal EEG: Inter-ictal spikes, theta-synchronization, frequency and duration of spikes as well as spike-and wave activity are gradually reduced while the power spectrum, inter-hemispheric synchronization of the gamma band and the duration of spike-free intervals are increased [3–5]. Acute effects of VNS on electrical ictal activity have driven the development of automated responsive VNS therapy [6,7]. In 2014 a responsive VNS therapy was introduced that delivers automate stimulation (AutoStim) in response to a rapid heart rate increase that may be associated with seizures. AutoStim is delivered according a cardiac-based seizure detection (CBSD) algorithm. Therefore R-waves are identified and a baseline (background) heart rate according to R-R intervals of approximately 5 min as well as near-term (foreground) heart rate for comparison is established. In case the foreground heart rate exceeds the background heart rate above a programmed threshold, a VNS train is automatically delivered [8]. 82% of patients with epilepsy experience rapid heart rate increase associated with a seizure, especially in terms of generalized tonic-clonic seizures [9–11], so heart rate increase is thought as a

Abbreviations: AutoStim, automate stimulation; CBSD, Cardiac-based seizure detection; VNS, Vagus nerve stimulation; WHO, World Health organisation.

* Corresponding author.
E-mail address: Philipp.spindler@charite.de (P. Spindler).

https://doi.org/10.1016/j.inat.2020.101003
Received 26 October 2020; Accepted 1 November 2020
Available online 7 November 2020

biomarker of seizure activity. Ictal tachycardia occurs when hyperexcitation (seizure activity) affects brain regions, located in or directly connected to the mesial temporal lobe, responsible for autonomic control of cardiac rhythm [12]. Responsive VNS therapy combines open-loop-stimulation that delivers a long-term neuromodulatory effect in order to reduce seizure frequency and -severity and automatic stimulation by CBSD in attempt to terminate seizures and reduce seizure propagation. The CBSD's threshold of AutoStim is customizable to individual patients between 20 and 70% heart rate increase, thereby influencing detection latency. A prospective, unblinded study in patients with multi-drug-resistant partial onset seizures and history of ictal tachycardia has shown over 60% of seizures treated with automatic stimulation ended during stimulation [13]. Hamilton et al described an increased responder rate when patients switched from standard to automated stimulation [14]. Ravan et al showed that responsive VNS therapy reduces seizure duration by reducing generalization of focal onset seizures [15]. Automatic stimulation seems to improve therapy of multi-drug-resistant epilepsy. Yet, long term sensitivity and specificity of the CBSD-algorithm remain unclear. We present long term results of a case series of 15 adult patients with epilepsy with AutoStim VNS therapy. Aim of our study is to figure out whether CBSD-algorithm which depends on the patient's physiology in real time leads to a more suitable therapeutic value for each patient.

2. Methods

Patients were seen in the outpatient clinic or at their care facilities to review individual VNS data and seizure diaries. All patients had the same Closed-loop VNS device (Aspire SR ®, Liva Nova, Houston, Texas, USA)) implanted in our center. Open- and closed-loop VNS was active in all patients. We reviewed CBSD-settings, operating hours and battery status of the devices. Percentage of AutoStim was assessed in comparison to continuous but intermittent stimulation. If seizure diaries were available, we verified whether a high rate of AutoStim was present during the documented seizures. GraphPad Prism software was used for data analysis with Pearson correlation calculations and students *t*-test, alpha = 0.05.

3. Results

We reviewed 15 patients with a mean age of 34 years (±11y). Ten patients were men. Mean age at implantation of VNS therapy system was 31 years (±11y). Mean duration since implantation was 47 months (±12 m). Mean operating time was 4276 h (1766–8907 h). CBSD thresholds ranged between 20% and 70% (20% in one, 30% in one, 40% in three, 50% in one, 60% in five and 70% in four patients). Stimulation pattern (per week) was: 1296 (±686) continuous intermittent stimulations, 4.8 (±3.9)% AutoStim. Remaining battery life was 50–75%, consistently. Pearson correlation calculation showed no correlation between CBSD thresholds and percentage of AutoStim ($r^2 = 0.12$, $p = 0.2$) (Fig. 1). Proportion of AutoStim varied substantially. According to seizure diaries and reports from patients and caregivers, patients had more AutoStim in case of higher seizure frequency (>5 seizures/week). One female patient with 1.88% AutoStim was seizure free since VNS, six patients with high proportion of AutoStim had > 5 seizures/week, two patients with 1.4% and 1.49% AutoStim reported > 5 seizures/week as well (Fig. 2A). Nevertheless, Pearson calculations showed no correlation between number of AutoStim and seizures per week ($r^2 = 0.1$, $p = 0.24$) (Fig. 2B). 46.7% of the patients had an existing VNS replaced to an AutoStim VNS. Regarding seizure-frequency there was no difference between patients who received AutoStim VNS as their first model or had a replacement of a previous model. Neither was there a difference in percentage of AutoStim (3.43 vs 6.44%, p = 0.14, Fig. 3). 66.6% reported an improvement following AutoStim VNS. Although three of those patients still experience > 5seizures/week severity of seizures were reduced. Four patients report no further generalized seizures following AutoStim VNS. Adverse events occurred in none of the patients.

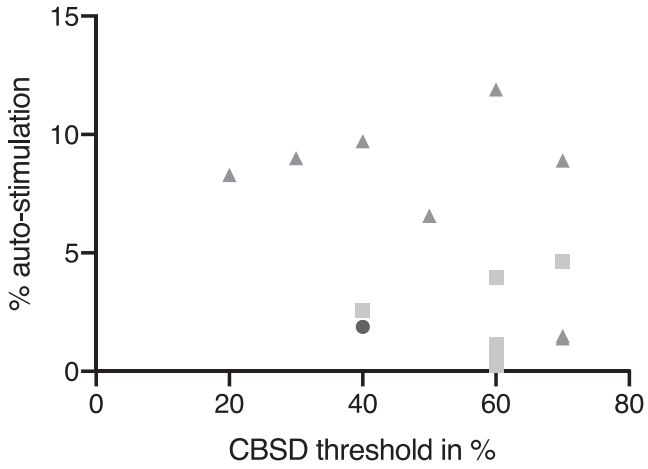

Fig. 1. Pearson correlation calculation showed no correlation between CBSD thresholds and percentage of AutoStim ($r^2 = 0.12$, $p = 0.2$). Triangles indicate patients with > 5 seizures / week, squares indicate patients with < 5 seizures / week, circles indicate seizure free patients.

4. Discussion

Our data provide long-term results of 15 patients who received CBSD AutoStim VNS. CBSD thresholds, proportion of AutoStim and seizure frequency varied substantially within a relatively small cohort. We chose >/< 5 seizures / week as surrogate parameter for meaningful clinical response because precise reports from seizure diaries were not available from the majority of patients. Furthermore, the relative long duration since VNS implantation impeded assessment of seizure frequency reduction in comparison to patient's situation before VNS treatment. In our data sensitivity of AutoStim VNS appears to be good since patients who report more seizures per week have a higher percentage of AutoStim although no correlation of seizure frequency and percentage of AutoStim was found (Fig. 2). Reports in which treatment of seizures with and without AutoStim were evaluated in epilepsy monitoring units (EMU) revealed good results. Beside a significant reduction of seizure duration, high sensitivity and specificity of 92% and 13,5% respectively were described in a case report by Hampel et al[16]. In 2015 Boon et al published a prospective multicenter study (E-36 Trial) including 31 patients one month after implantation of the VNS System. A very reliable correlation of seizures and AutoStim with a sensitivity of > 80% was found [17]. A parallel prospective multicenter study (E-37 Trial) with 20 patients was divided into an assessment on the EMU two–four weeks after device implantation and a follow-up period three, six and twelve months after implantation. During the EMU assessment 34.8% of detected seizures were treated with AutoStim on detection and 61.3% seizures ended during the stimulation. In the follow-up period the authors described an increasing responder rate, which they defined as > 50% seizure reduction, during the time of observation. 20% responder rate after three months developed to 50% after one year. Additionally a significant reduction of seizure severity and an improvement in quality of life was reported [13]. A main difference between our data and the afore mentioned studies is, that in contrast to data that was recorded during hospitalization, we provide long-term data based on reports of patients and caregivers. We found an extremely high number of stimulations despite relatively few seizures, which indicates specificity to be poor (Fig. 2B). An average of 53.9 (±41.9) AutoStim / week appears inappropriate for significantly fewer reported seizures. Our assumption is supported by a case series in which three patients who were part of the E-36 Trial were described in further

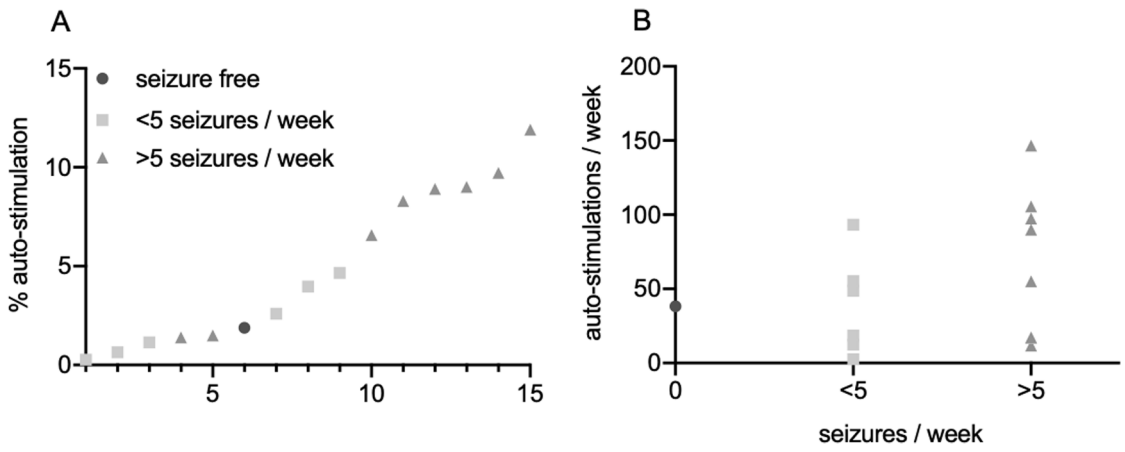

Fig. 2. A Percentage of AutoStim for each patient. B No correlation between number of AutoStim and seizure frequency. Pearson correlation $r^2 = 0.1$, $p = 0.24$.

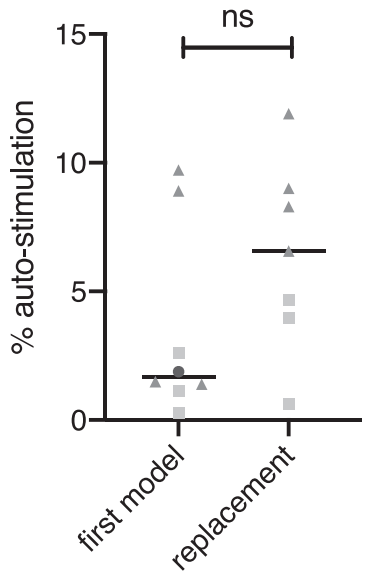

Fig. 3. No significant difference in percentage of auto-stimulation between patients who received AutoStim VNS as their first model or had a replacement of a previous model (3.43 vs 6.44%, $p = 0.14$).

detail: On EMU CBSD AutoStim settings and seizures were recorded. Detection of ictal tachycardia was found to be successful but stimulation not strictly specific to ictal periods due to a high number of false-negative stimulations (mean 4.6 ± 0.96/h) [18]. In our data three patients mentioned an improvement in seizure severity even though seizure frequency wasn't reduced. Four patients who experienced secondary generalization prior to AutoStim VNS had no generalized seizures ever since. This observation matches an observation by Ravan et al, that seizures which were acutely stimulated using VNS had a reduced ictal spread [15]. Our data provide long-time consolidation of Kulju et al who found less energy consumption of VNS with AutoStim compared to previous models, since even some patients had a follow-up of more than five years since implantation, battery status was still > 75% charge [19]. A limitation of our study is, that compared to recordings of an EMU seizure detection might be underrepresented since it is completely based on reporting of patients and caregivers. Furthermore, the mismatch of lot AutoStim and much fewer detected seizures in our data could be explained by unnoticed seizures during sleep. In a short-term observation one month after VNS implantation Ravan et al. found reduced epileptiform activities during sleep [20]. In our data patients and caregivers mentioned, that seizures that occur at night might not be detected and thus are not represented in seizure.

5. Conclusion

From our perspective sensitivity of closed loop VNS appears to be good since patients who report more seizures per week have a higher percentage of AutoStim. On the other hand, an extremely high number of AutoStim despite relatively few seizures indicates poor specificity. Yet, treatment is well tolerated by the patients without any adverse events. We found AutoStom to be a promising feature in the development of a patient-tailored therapy but the CBSD algorithm should be revised to provide better specificity.

Funding

We acknowledge support from the German Research Foundation (DFG) and the Open Access Publication Funds of Charité – Universitätsmedizin Berlin.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] World Health Organization. WHO | Epilepsy: a public health imperative. Who, 2019.
[2] LivaNova. Physician' s Manual VNS Therapy® Programming Software, 2019.
[3] F. Marrosu, et al., Increase in 20–50Hz (gamma frequencies) power spectrum and synchronization after chronic vagal nerve stimulation, Clin. Neurophysiol. 116 (2005) 2026–2036.
[4] T. Hallböök, J. Lundgren, G. Blennow, L.G. Strömblad, I. Rosén, Long term effects on epileptiform activity with vagus nerve stimulation in children, Seizure 14 (2005) 527–533.
[5] Betty Koo, EEG Changes With Vagus Nerve Stimulation, J. Clin. Neurophysiol. 18 (5) (2001) 434–441.
[6] H. Wang, et al., Long-term effect of vagus nerve stimulation on interictal epileptiform discharges in refractory epilepsy, J. Neurol. Sci. 284 (2009) 96–102.
[7] P.W. Olejniczak, et al., The effect of vagus nerve stimulation on epileptiform activity recorded from hippocampal depth electrodes, Epilepsia 42 (2001) 423–429.
[8] A. Mertens, et al., Recent advances in devices for vagus nerve stimulation, Expert Rev. Med. Devices 15 (2018) 527–539.
[9] W. Chen, F.G. Meng, Ictal heart rate changes and the effects of vagus nerve stimulation for patients with refractory epilepsy, Neuropsychiatr. Dis. Treat. 13 (2017) 2351–2356.
[10] M. Zijlmans, D. Flanagan, J. Gotman, Heart rate changes and ECG abnormalities during epileptic seizures: Prevalence and definition of an objective clinical sign, Epilepsia 43 (2002) 847–854.
[11] K.S. Eggleston, B.D. Olin, R.S. Fisher, Ictal tachycardia: The head-heart connection, Seizure 23 (2014) 496–505.

[12] F. Chouchou, et al., The neural bases of ictal tachycardia in temporal lobe seizures, Clin. Neurophysiol. 128 (2017) 1810–1819.
[13] R.S. Fisher, et al., Automatic Vagus Nerve Stimulation Triggered by Ictal Tachycardia: Clinical Outcomes and Device Performance - The U.S. E-37 Trial, Neuromodulation 19 (2016) 188–195.
[14] P. Hamilton, et al., Clinical outcomes of VNS therapy with AspireSR® (including cardiac-based seizure detection) at a large complex epilepsy and surgery centre, Seizure 58 (2018) 120–126.
[15] M. Ravan, S. Sabesan, O. D'Cruz, On quantitative biomarkers of VNS therapy using EEG and ECG signals, IEEE Trans. Biomed. Eng. 64 (2017) 419–428.
[16] K.G. Hampel, H. Vatter, C.E. Elger, R. Surges, Cardiac-based vagus nerve stimulation reduced seizure duration in a patient with refractory epilepsy, Seizure 26 (2015) 81–85.
[17] P. Boon, et al., A prospective, multicenter study of cardiac-based seizure detection to activate vagus nerve stimulation, Seizure 32 (2015) 52–61.
[18] R.El Tahry, et al., Early experiences with tachycardia-triggered vagus nerve stimulation using the AspireSR stimulator, Epileptic Disord. 18 (2016) 155–162.
[19] T. Kulju, J. Haapasalo, S. Rainesalo, K. Lehtimäki, J. Peltola, Autostimulation in Vagus Nerve Stimulator Treatment: Modulating Neuromodulation, Neuromodulation 22 (2019) 630–637.
[20] M. Ravan, J. Begnaud, Investigating the Effect of Short Term Responsive VNS Therapy on Sleep Quality Using Automatic Sleep Staging, IEEE Trans. Biomed. Eng. 66 (2019) 3301–3309.