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Case Report

Pilot data on responsive epilepsy neurostimulation, measures of sleep apnea and continuous glucose measurements

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ABSTRACT

Objectives: To match responsive neurostimulator (RNS) and polysomnographic data to determine if RNS detections and stimulations correlate with measurements of sleep disordered breathing and continuous glucose measurements (CGM).
Materials and methods: In a patient with an RNS with detection/stimulation leads implanted bi-temporally detection-stimulation counts were matched by time with coinciding polysomnogram and CGM data.
Results: Temporal dispersion of RNS DSC were independent of measures of sleep apnea, hypopnea or glucose.
Conclusion: Hippocampal nighttime responsive neurostimulation therapies did not appear to worsen measures of normal or abnormal sleep.

1. Introduction

The responsive neurostimulation system (RNS, NeuroPace, Mountain View, CA) reduces self-reported seizure frequencies in patients with drug-resistant focal epilepsy [1]. The RNS surveys electrocorticography, which is trained to recognize physician-selected patterns associated with seizure onset, and then triggers electrical stimulation(s) or therapies designed to help mitigate or ideally terminate seizure. Delivered therapies or detection-stimulation counts (DSC) can be used to study treatment efficacies. For example, in the same patient we discuss here, we were previously able to illustrate effects of mirtazapine on increased RNS DSC over both an hourly and daily timeframe [2]. Contemporary RNS programming detects and delivers therapies generously. In the open-label portion of the RNS pivotal trial [1] there was an average of 1175 DSC per day [personal communication]. In this study we used a similar technique to examine DSC and whether or not they correspond to collected polysomnographic data either in sleep staging or measures of sleep disordered breathing.

Obstructive sleep apnea (OSA) and epilepsy have high comorbidity rates and sleep apnea may worsen seizure control [3,4]. Sleep disturbance and deprivation is known to reduce seizure threshold and therefore treatment for OSA can improve seizure control in patients with drug-resistant epilepsy. During convulsive seizures in particular there may be cessation of breathing, particularly during the tonic phase. Independent of seizure-related apnea, it is not well known whether undertreated epilepsy aggravates sleep apnea.

In the medical device literature the apnea hypopnea index (AHI), a key measure of sleep apnea, increased after beginning vagus nerve stimulation (VNS) therapy [4]. In addition, episodic apneas occurred more frequently during VNS. A similar understanding of RNS effects on sleep apnea has yet not been published. Of interest though is RNS data that shows DSC to have a strong circadian pattern, peaking during nocturnal hours regardless of region of onset [5]. In that same study, long nocturnal seizure episodes were increased depending on seizure onset locations. Specifically, temporal neocortical and frontal lobe onsets were more often at night while mesial temporal onsets were more often during daytime.

2. Materials and methods

With informed patient consent, patient data were abstracted and assessed from electronic medical records including RNS logs of DSC and polysomnography (PSG), average DSC, apnea events and other polysomnogram highlights, and stage of sleep were collected [Figs. 1 and 2]. Sleep was scored according to American Academy of Sleep Medicine (AASM) criteria by a licensed sleep medicine technician and further reviewed by a board certified physician specializing in sleep medicine. RNS stimulation settings at the time of polysomnogram included a current of 3.5 ma frequency of 100 Hz, a pulse width of 120 μs, and burst duration of 100 ms with an estimated charge density of 1.3 μC/cm^2. Therapies 1–5 were all the same, and the electrode

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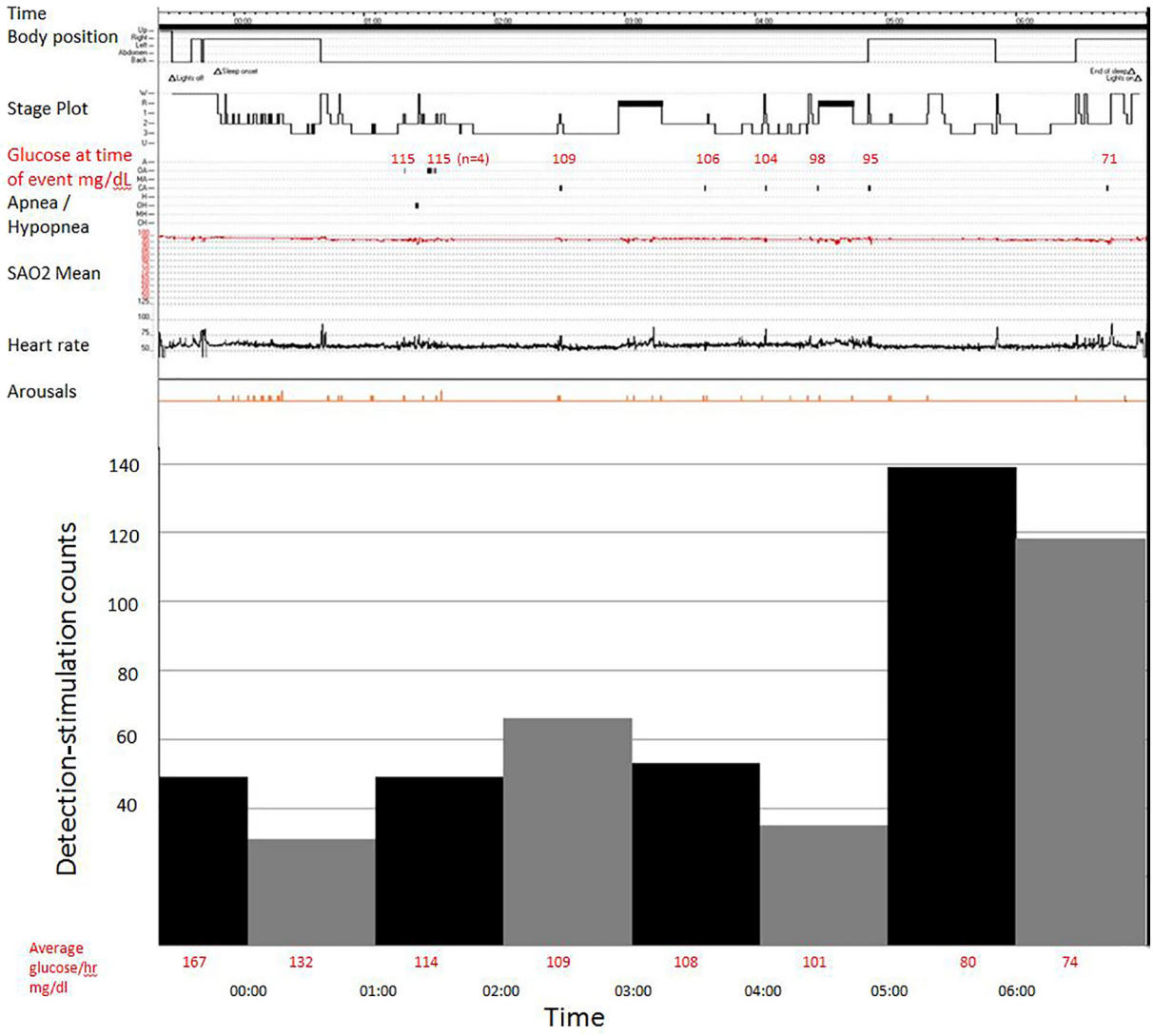

Fig. 1. Total number of detection-stimulation counts recorded by the RNS each hour during the sleep study combined with polysomnographic and glucose data. Glucose data appears as both an hourly average and at time of apnea events and is in red.

configuration and polarity of right and left hippocampal contacts was negative with the RNS device positive. Detection settings on both hippocampi included bandpass assessments with bands set between 2–125 Hz, amplitudes of 12–69% and surveillance durations of 0.256–0.640 s. When first programmed at these settings, post stimulation therapy testing elicited no symptoms. Given the patient had a functional continuous glucose monitoring system with tissue glucose checks every 5 min (CGM, DEXCOM, San Diego, CA), that convenience data was also examined in relation to the RNS and polysomnographic findings. Statistical analysis was formed using two-tailed t-tests or Pearson correlation with significance $p < 0.05$.

3. Case report

A 45-year-old female with drug-resistant bitemporal epilepsy underwent implantation of the RNS device in 2014 after failure of medical and VNS therapies. Seizure types include audiogenic (Johnny Cash's song Ring of Fire, for instance, would trigger focal seizures and potentially convulsions) as well as focal impaired awareness seizures characterized by automatisms of lip smacking and behavior arrest with rarer progression to bilateral tonic-clonic seizures. Her ILAE classification is focal aware and focal impaired awareness seizures with emotional, sensory and behavior arrest with progression to bilateral tonic–clonic seizures. A brother and a second cousin also have epilepsy, however the family LG1 gene status is unknown. MRI scan pre-RNS showed mesial temporal blurring and size diminishment on the left. Comorbid conditions include type I diabetes mellitus, depression, and insomnia. Her RNS detections were recorded from two four-contact depth electrodes placed over the left and the right hippocampus. Those locations were chosen based on intracranial monitoring results suggesting hippocampal involvement in seizure generation. Her VNS device, which historically produced no effect on seizure controls, remained off. A functional insulin pump was used for the duration studied as well as a regularly calibrated CGM.

Because of complaints of non-restorative sleep and excessive daytime sleepiness, she underwent polysomnographic testing in an AASM accredited lab. Sleep data was matched to RNS and CGM data during polysomnography. Anti-seizure medications included topiramate, levetiracetam, clobazam, clonazepam, and gabapentin and were dosed at 09:00 and 21:00. The patient was not on antidepressants during this time period.

No clinical or electrographic seizures were observed by RNS or the 6-lead polysomnographic EEG. The RNS recorded many DSC throughout the night [Fig. 1]. These were not analyzed by side of detection. DSC failed to impact staging of sleep, with progression through various sleep stages independent of DSC activities.