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How might tissue glucose influence responsive neurostimulation detection?

We previously reported a drug-resistant focal epilepsy patient who had both a responsive neurostimulator (RNS) and continuous glucose monitoring (CGM) device for type I diabetes mellitus[1]. We found lower relative glucose and earlier morning onsets for right temporal seizures when compared to left temporal seizures. The RNS detects provider-defined ictal patterns on electrocorticography (ECoG) and stimulates the brain in response to those patterns. These are automatically recorded as ***detections*** and are summated hourly [2]. RNS monitoring shows various ultradian, infradian or multidien rhythms apparent in both detection and seizure events. The ictal patterns on ECoG varies by location of seizure onset [1–3].

We evaluated 24-hour RNS ***detection*** data in our previously report and correlated hourly average tissue glucose levels over two months of consistent RNS detection parameters, insulin production and antiseizure medications. The study period *did not* overlap with that used in the prior report which focused on RNS detection *and* stimulation changes [1]. Hourly glucose was averaged from consecutive 5-minute glucose records. Plots of hourly glucose by hourly RNS detection over 24 h are depicted in linear and polar graphic formats (Fig. 1a, b). Electrographically determined "long events" identified by the RNS device were reviewed and classified as probable seizures. Whether the events were clinically subtle or subclinical remains unknown.

Average glucose through the study period was 146 mg/dl (range 46–356 mg/dl; SD = 53); hemoglobin A1c during study period was 6.7%. RNS stimulations do not appear to increase glucose elevations, detections increased with decreased glucose (Pearson correlate −0.94; $p < 0.001$), (Fig. 1a,b).

A total of 20 focal seizures were recorded. For right-sided seizures (n = 16) glucose levels at the time of a seizure, when available (n = 14), averages 143 mg/dl. For seizures that spread bilaterally (n = 3) the glucose was 119 mg/dl. No obvious left-sided seizures were noted during this study, though event origins may have been overwritten if the RNS device recorded the last 90 s of an event. Larger events that spread bilaterally (n = 3) occurred between 12:00 and 17:00. Most seizures occurred between 22:00 and 03:00, times where detections were increasing and glucose decreasing. Of the 8 events that don't occur in that time, 3 may perhaps have been related to missed antiseizure medications in the preceeding 36 h.

RNS and CGM devices allow complex individualized therapies. From one patient, we found peaks of RNS DSC increased during nocturnal circadian patterns similar to a previous reports [2]. We add to that observation that DSC within a 24-hour cycle appears to correlate inversely with tissue glucose *in our patient*. The majority of her seizures tended to occur when RNS detections were increasing, a finding previously noted in cohort of RNS patients studied by Baud et al. [3] and a pattern that is involved in circadian rhythms though more complex than sleep/wake cycling alone.

In RNS patients, detections may be triggered by abundant interictal abnormalities [2]. Interictal abnormalities may not always translate into ictal events [4]. It's an important concept though to separate the interictal-ictal spectrum, as the reasons for the transition may suggest clues to seizure prediction and subsequent control. In our prior report we showed circadian glucose variances may predispose to focal seizures and confer a time-based risk. In this case report, tissue glucose and RNS detections demonstrate a circadian relationship between glucose levels, sleep, and RNS events. The relationship between the data may help individualize epilepsy and diabetes management. Understanding when glucose, sleep and RNS event detection and seizures show similar correlations and polar relationships in broader populations with focal (or generalized) epilepsy might give new perspectives on seizure prediction and management. This may be particularly relevant for patients with anti-epilepsy therapies that rely on carbohydrate regulation such as the ketogenic diet. It's likely that understanding the influence of glucose on ictal and interictal epileptiform activity remains contingent on analyzing long durations of ambulatory ECoG recorded by continuous surveillance devices.

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Declaration of competing interest

Kyla Wright, Devon Kollmyer as well as Drs. Michael Doherty and Alan Haltiner have no disclosures. Nicole Fortier, ARNP and Dr. Ryder Gwinn have consulted for NeuroPace. All authors are responsible for data collection, analysis, drafting of manuscript and critical input.

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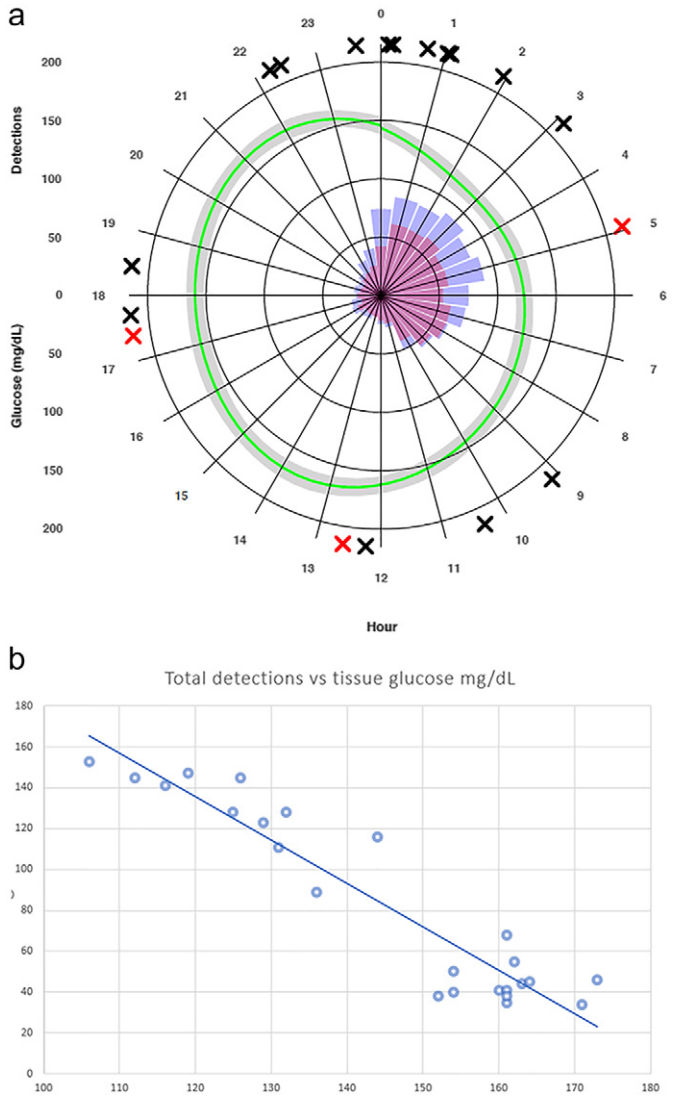

Fig. 1. a: Polar relationship between left (blue) and right (red) detections per hour and average glucose (green) over a 24 hour cycle. Seizures are labeled with X, a red X is a seizure within 36 h of missed antiseizure medication. Two of twenty seizure times overlapped. The gray error bar for glucose data corresponds to 95% confidence interval with the median value indicated by the solid green line. The y-axis *values* for glucose *or* detections use the same plot circles for reference. b: Plot of hourly average tissue detections (y axis) by hourly average glucose concentration (x-axis) with line of best fit. Hourly averages were calculated from the 61st day in the study period. The two-tailed Pearson correlation was significant (-0.94, $p < 0.001$).

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