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Editorial

Responsive neurostimulation for epilepsy: More than stimulation

In the last two decades, neurostimulation has emerged as a safe and effective therapeutic option for patients with pharmacoresistant epilepsy who are not suitable candidates for surgery because they have more than one epileptic focus or a single focus over eloquent cortex.

There are three main neurostimulation techniques for epilepsy – vagus nerve stimulation (VNS), deep brain stimulation (DBS) and responsive neurostimulation (RNS). Compared to the first two types of neurostimulation, which are open-loop systems providing intermittent stimulation throughout the day at sites distant from the epileptic focus, RNS involves a closed-loop system that delivers an electrical stimulus directly to the epileptic focus only when the patient has a seizure. In order to do this, it includes a system for recording and detection of brain electrical activity. One or two subdural or intracerebral depth electrodes, each consisting of 4 contacts, are placed over the epileptic focus and parameters are adjusted to optimize the sensitivity and specificity for detecting seizures. It can be used for patients with 1–2, unilateral or bilateral epileptic foci.

Apart from neurostimulation, the RNS system provides an opportunity for chronic ambulatory electrocorticography (ECoG). Such recordings obtained through the RNS system can be useful in several ways, including lateralization of the predominant epileptic focus in patients with bilateral epilepsy (King-Stephens et al., 2015), seizure counting and reporting, determination of timing of seizures and identification of temporal patterns (Anderson et al., 2015), assessing drug response and planning surgical resection at a later date.

The effectiveness of neurostimulation for seizure control and the value of the chronic recordings for other purposes depend on the precise localization of the epileptic focus. This requires detailed presurgical evaluation, usually including intracranial recordings, and determination of the seizure onset zone(s) in most patients. Patients typically undergo video-EEG monitoring in the epilepsy monitoring unit over 2–3 weeks, during which antiepileptic medications are often reduced or withdrawn to provoke seizures. Despite these approaches, seizures are not recorded in some patients. How can the location of the epileptic focus be determined in such patients?

In this issue of *Clinical Neurophysiology Practice*, Chan and colleagues address this question by describing two patients with pharmacoresistant epilepsy who had no seizures recorded during invasive monitoring, but subsequently underwent RNS, with placement of leads determined by interictal and neuroimaging data (Chan et al., 2018). Seizures were later localized during chronic ambulatory ECoG.

This is a short, well-written and timely paper describing a new approach to this infrequent but important clinical issue. Their observation that clinical seizures documented by patients in seizure diaries after RNS lead implantation were always associated with electrographic changes in the RNS ECoG recordings suggests that RNS indeed provided adequate localizing information for all seizures, and that these patients did not have additional foci that were not localized.

In their first patient, the region of interictal spiking (hippocampus and periventricular nodular heterotopia) was chosen for placement of the RNS depth leads, but subsequent recordings determined that the seizures actually started in the temporal neocortex overlying the nodular heterotopia, highlighting the limitations of using interictal data to identify the seizure onset zone. The authors were fortunate to have proximal contacts of the RNS leads in this region and obtain localizing information.

The authors appropriately acknowledge the limitations of their study, including the limited number of contacts used in the RNS system and the possibility that the recorded seizures could have reflected a spread pattern from brain regions not sampled by the electrodes rather than the ictal onset zone. One way to distinguish between the two is to determine if clinical seizure onset follows or precedes ictal EEG onset. The former would suggest placement of leads directly over the focus, while the latter would indicate a spread pattern. This can be accurately determined during video-EEG monitoring studies in the hospital. However, there are practical constraints to doing so during chronic ambulatory ECoG in the outpatient setting, since patients are not on video camera and impairment of consciousness associated with a seizure may result in patients being unaware of and unable to document the exact clinical onset.

The clinical response was relatively modest in Patient 1 (30% reduction of seizure frequency after 15 months) and better in Patient 2 (50% reduction after 14 months). This could be related to the natural variability of clinical response to RNS among individuals with epilepsy, the location of the focus (neocortical temporal versus mesial temporal) or to the less precise localization of the focus in Patient 1. Two recent studies have addressed the latter two possibilities. Over a mean follow-up period of 6.1 years, Geller et al. (2017) reported a median seizure reduction of 70% for patients with mesial temporal onset, while Jobst et al. (2017) found a 58% reduction in those with neocortical temporal onset. Interestingly, Geller et al. (2017) also noted that the clinical response was similar in patients with leads placed directly over the focus (hippocampus) or near to the focus. Therefore, accurate localization may not be critical for RNS lead placement.

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Since this is a novel application of a relatively new technology in only two patients, it remains unclear whether chronic ambulatory ECoG with RNS can be routinely used to provide localizing information. However, this study should stimulate further discussion regarding the advantages and limitations of their approach. It also adds to the growing literature on other ways to use RNS besides providing therapeutic neurostimulation.

Conflicts of interest and funding sources

None.

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