



## Difficult-to-Localize Intractable Focal Epilepsy: An “In-Depth” Look

### Stereoelectroencephalography in the “Difficult to Localize” Refractory Focal Epilepsy: Early Experience From a North American Epilepsy Center.

Gonzalez-Martinez J, Bulacio J, Alexopoulos A, Jehi L, Bingaman W, Najm I. [Published online ahead of print on September 27, 2012, *Epilepsia*. doi: 10.1111/j. .]

**PURPOSE:** Stereo-electroencephalography (SEEG) enables precise recordings from deep cortical structures, multiple noncontiguous lobes, as well as bilateral explorations while avoiding large craniotomies. Despite a long reported successful record, its application in the United States has not been widely adopted. We report on our initial experience with the SEEG methodology in the extraoperative mapping of refractory focal epilepsy in patients who were not considered optimal surgical candidates for other methods of invasive monitoring. We focused on the applied surgical technique and its utility and efficacy in this subgroup of patients. **METHODS:** Between March 2009 and May 2011, 100 patients with the diagnosis of medically refractory focal epilepsy who were not considered optimal candidates for subdural grids and strips placement underwent SEEG implantation at Cleveland Clinic Epilepsy Center. Demographics, noninvasive clinical data, number and location of implanted electrodes, electrophysiologic localization of the epileptic zone, complications, and short-term seizure outcome after resection were prospectively collected and analyzed. **KEY FINDINGS:** Mean age was 32 years (range 5–68 years); 54 were male and 46 female. The mean follow-up after resection was 15 months. In total, 1,310 electrodes were implanted. Analyses of the SEEG recordings resulted in the electrographic localization of the epileptogenic focus in 96 patients. In the group of 75 patients who underwent resection, only 53 had at least 12 months follow-up. From this group, 33 patients (62.3%) were seizure-free at the end of the follow-up period. The presence of abnormal pathologic finding was strongly associated with postoperative seizure control ( $p = 0.005$ ). The risk of hemorrhagic complications per electrode was 0.2%. **SIGNIFICANCE:** In patients who are not considered to be ideal candidates for subdural grids and strips implantation, the SEEG methodology is a safe, useful and reliable alternative option for invasive monitoring in patients with refractory focal epilepsy, providing an additional mean for seizure localization and control in a “difficult to localize” subgroup of patients.

### Commentary

Monitoring with intracranial electrodes is the gold standard for identification of seizure-onset zones and mapping of eloquent cortex in patients with intractable focal epilepsy. Electrode implantation is guided by hypotheses about localization of the epileptogenic zones that are based on assessment of seizure semiology, interictal and ictal scalp-EEG, functional and anatomic neuroimaging, and neuropsychological testing. Optimal monitoring may be done with depth electrodes if the presumed epileptic focus is deep, and with subdural electrodes if the focus is superficial and if precise, systematic cortical mapping is needed. However, the trends in Europe and the United States over the past several decades have been to use stereoelectroencephalography (SEEG) and subdural electrode

monitoring, respectively, as primary methods for evaluation of intractable epilepsy, regardless of the presurgical hypotheses.

The history of SEEG dates back to 1957, when Jean Talairach built a coordinate system using the anterior and posterior commissures as landmarks and generated a stereotactic atlas of deep brain nuclei. Jean Bancaud soon realized the potential use of stereotactic surgery in localizing epileptic brain regions in three dimensions. Bancaud and Talairach devoted an operating room to stereotactic neurosurgery in 1959, and coined the term stereoelectroencephalography (SEEG) in 1962 (1). Electrodes are implanted stereotactically, targeting areas within and around epileptogenic lesions and areas suspected to be part of the seizure network, thus helping to identify the ictal onset zone and areas of interictal spiking (2). In some European centers, SEEG has been used for evaluation of any intractable epilepsy, including situations when language mapping may be necessary such as in the Sylvian areas (3). Soon afterwards, the use of SEEG became part of the surgical evaluation of intractable epilepsy in the Montréal Neurological Institute (4), but its introduction to the United States was slower,



where the use of subdural electrodes saw more proliferation across the years. In the United States, depth electrodes have been used primarily to record from the mesial temporal structures. Of note, Sperling and O'Connor compared depth with subdural electrodes in temporal lobe epilepsy and found that the ictal discharges were detected initially by depth electrodes before they propagated to subdural electrodes (5).

Gonzalez-Martinez et al. report their recent experience with SEEG at the Cleveland Clinic. Between 2009 and 2011, they implanted 1,310 electrode arrays in 100 patients, including 17 children, who were not ideal candidates for subdural electrode monitoring. The 100 patients included 39 with focal MRI abnormality and 27 who have had prior epilepsy surgery, including subdural monitoring or surgical resection. Forty patients underwent bilateral SEEG implantation. Indications for SEEG use included targeting deep regions, such as the mesial temporal structures, insula, or cingulate gyrus; subjects who failed prior subdural monitoring; bihemispheric implantation for lateralization or localization of the epileptic focus; and nonlesional cases where multiple locations within a network, such as the limbic system, needed to be sampled as suggested by the seizure semiology.

SEEG monitoring allowed localization of the epileptic focus in 96 patients, of whom 75 patients underwent resection. The authors appropriately excluded acute postoperative seizures for up to 1 week after surgery from the classification of the surgical outcome, included patients who had at least 1 year of follow-up, and defined seizure freedom as absence of all kinds of seizures including auras. Only 53 patients completed a 1 year follow-up, including 28 nonlesional patients and 22 with temporal lobe epilepsy. Of the 53 subjects, 33 (62.3%) were seizure free. Complications occurred in 3 patients of the 100, including intraparenchymal hemorrhage in two patients and subdural hemorrhage in one. Each of these complications occurred with one electrode per subject, making the overall risk of complications per electrode 0.2%. As regards surgical outcome, the authors found that the absence of histopathological abnormalities in the resected tissue, but *not* nonlesional or extratemporal epilepsy, was associated with poor surgical outcome. Of interest, the authors also used SEEG for functional mapping, but they did not report the results. They had an impression that SEEG-guided resections may be smaller than resections determined through subdural monitoring, suggesting more specificity of identification of the epileptic focus by SEEG. They also argued that their method may be safer than the traditional SEEG implantation methods described by European authors.

Subdural electrode monitoring has high spatial resolution of the superficial cortex, which constitutes only a small subset of the cerebral cortex that is capable of generating seizures. However, like scalp electrodes, subdural grids sometimes show a diffuse seizure onset. In some of these cases, adequate depth electrode sampling of deep tissue, including the depth of the sulci, may help identify the area of seizure onset before rapid diffuse or multifocal propagation to the superficial cortex. In addition, SEEG can be accomplished by 2.5-mm drill holes of the skull, unlike subdural grid implantation, which requires a craniotomy. While subdural electrode monitoring has contributed to our knowledge about the functional localization of the

cerebral cortex as it facilitates systematic mapping of the superficial cortex, SEEG allows mapping of the depth of the sulci, white matter, and deep brain structures (6). Thus, SEEG allows for studying neuronal networks involved in seizure generation and propagation as well as those important for cognitive or behavioral functions.

A particularly interesting indication of SEEG is in nonlesional patients whose presurgical evaluation suggests involvement of a network, such as the limbic system. In such cases, multiple targets within the same network may be sampled by SEEG to improve accuracy of detecting seizure focus and, consequently, the surgical outcome, which is historically inferior in nonlesional epilepsy than in patients with MRI abnormalities. For example, in patients whose seizure semiology and scalp EEG are consistent with temporal lobe epilepsy, SEEG sampling of the mesial temporal structures as well as areas that have known connectivity with the temporal lobe, such as the posterior cingulate gyrus, the basal temporal cortex, the orbitofrontal cortex, and insula, among others, may help rule out extratemporal seizure onset in a clinically silent region with secondary propagation to the mesial temporal structures (7).

SEEG appears to be a safe procedure with an acceptable rate of surgical risks. It has evolved over the years owing to the introduction of magnetic resonance imaging in the evaluation of patients with epilepsy, and to advanced software that provides accurate coordinates for stereotactic implantation of desired brain targets, and efficiently performs reliable superimposition of cerebral angiograms and brain MRI facilitating avoiding blood vessels during implantation. It would be exciting to see more centers in the United States using SEEG in conjunction with subdural electrode monitoring, as optimal monitoring should be considered with either or both methods depending on the presurgical hypothesis about localization of the epileptogenic zone.

by Mohamad Z. Koubeissi, MD

#### References

1. Kahane P, Arzimanoglou A, Benabid A, Chauvel P. Epilepsy surgery in France. In: *Textbook of Epilepsy Surgery*. (Lüders HO, ed.) London: Informa, 2008:46–53.
2. Bancaud J. Surgery of epilepsy based on stereotactic investigations—The plan of the SEEG investigation. *Acta Neurochir Suppl (Wien)* 1980;30:25–34.
3. Isnard J, Guenot M, Sindou M, Mauguier F. Clinical manifestations of insular lobe seizures: A stereo-electroencephalographic study. *Epilepsia* 2004;45:1079–1090.
4. Crandall PH, Walter RD, Rand RW. Clinical applications of studies on stereotactically implanted electrodes in temporal-lobe epilepsy. *J Neurosurg* 1963;20:827–840.
5. Sperling MR, O'Connor MJ. Comparison of depth and subdural electrodes in recording temporal lobe seizures. *Neurology* 1989;39:1497–1504.
6. Stephani C, Fernandez-Baca Vaca G, Maciunas R, Koubeissi M, Lüders HO. Functional neuroanatomy of the insular lobe. *Brain Struct Funct* 2011;216:137–149.
7. Koubeissi MZ, Jouny CC, Blakeley JO, Bergrey GK. Analysis of dynamics and propagation of parietal cingulate seizures with secondary mesial temporal involvement. *Epilepsy Behav* 2009;14:108–112.



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