Epilepsy & Behavior Reports 16 (2021) 100471

Contents lists available at ScienceDirect

Epilepsy & Behavior Reports

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

Network radiofrequency ablation for drug resistant epilepsy

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ARTICLE INFO

Article history:
Received 18 May 2021
Revised 6 July 2021
Accepted 7 July 2021
Available online 14 July 2021

Keywords:
Epilepsy
Radiofrequency ablation
Minimally invasive epilepsy surgery
sEEG
Epileptogenic network

ABSTRACT

Radiofrequency ablation (RFA) is a minimally invasive procedure for drug-resistant focal epilepsy. Although well tolerated, seizure outcomes are less favorable than standard resection. RFA is commonly performed following stereoencephalography (sEEG) identification of the seizure onset zone (SOZ). We hypothesized RFA outcomes can improve by adding RFA of seizure spread regions to the SOZ as identified by sEEG, an approach we term network RFA. Four patients underwent network RFA at our institution from 8/2017 to 9/2019. There were two Engel IB outcomes and two Engel III outcomes. The median follow-up length was 25.5 months (range 17–35). No permanent neurological deficits occurred. Etiologies consisted of polymicrogyria (1), mixed malformation of cortical development (MCD) (2), and cryptogenic (1). This study provides descriptive results regarding the efficacy and safety of network RFA. Network RFA can be considered in patients with focal epilepsies with large MCDs that may not be amenable to standard resection.

1. Introduction

Radiofrequency ablation (RFA) is a minimally invasive epilepsy surgery technique first proposed more than 30 years ago for drug resistant temporal lobe epilepsy. Although well tolerated, seizure outcomes are less favorable compared to standard resection [1]. Radiofrequency ablation has been utilized in conjunction with stereoencephalography (sEEG) to improve seizure outcomes through targeted RFA of the seizure onset zone (SOZ). Prior studies of patients with heterogenous etiologies have demonstrated varied therapeutic outcomes [2,3]. Expectedly, a previous study demonstrated anterior temporal lobectomy superior to RFA [4]. Still, studies examining single types of malformation of cortical development (MCD) such as periventricular nodular heterotopia (PVNH) have suggested sEEG guided RFA to be potentially useful [5].

Efforts are ongoing to identify treatments that could benefit these drug resistant large MCDs which are less optimal for conventional surgical resection [6]. As such, RFA can be a palliative option to patients with epileptogenic lesions that are surgically difficult to resect or when the epileptogenic network either involves or is adjacent to eloquent cortex. Taking these groups together, we hypothesize that clinical outcomes for patients with large MCDs or SOZ involving eloquent regions can be improved by RFA of select seizure spread regions in addition to the area of onset as identified by sEEG, a concept we term network RFA. We describe four patients with drug-resistant epilepsy who underwent network RFA at our institution, three of whom have large MCDs.

2. Materials and methods

We retrospectively reviewed all patients with drug-resistant focal epilepsies who underwent network RFA at the University of Kansas Medical Center from 08/2017–09/2019. Patient demographics, sEEG characteristics, neuropsychology outcomes, RFA procedural data, and seizures outcomes were abstracted from the electronic medical record. Prior to RFA, all patients underwent extensive evaluation with high resolution structural MRI, fMRI, scalp video EEG, neuropsychology testing, cortical mapping, and sEEG monitoring. Stereoencephalography implantation sites were selected based on clinical, electrophysiologic, and radiologic characteristics as well as potential alternatives to the hypothesized epileptogenic region.

The neurosurgeon (JC) and epileptologist (PL) reviewed the implantation plan together (as standard) to maximize coverage of both superficial and deep cortical structures and malformation regions. The number of areas able to be explored were limited by either proximity to another electrode or inability to safely place the electrode in the desired area (ie. due to cerebral vascularity).

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https://doi.org/10.1016/j.ebr.2021.100471
2589-9864/

The sEEG electrodes used were Integra Auragen depth electrodes (Integra NeuroSciences, Princeton, NJ USA) in some cases with later cases utilizing PMT sEEG Depthalon depth electrodes (PMT, Chanhassen, MN USA). Each implanted depth electrode terminus was plugged into a PMT mini-connector cable (or Integra connector cable for those with Integra electrodes). These cables were then individually attached to the monitoring equipment with the male end of the Integra/PMT cable plugged into the Natus Quantum headbox (Natus Medical, Middleton, WI USA) in sequential fashion starting at the first contact.

The decision to proceed with network RFA instead of resection was made based on either proximity of target lesions to eloquent areas or large MCDs that made patients poor candidates for surgical resection. Ablation areas were chosen in a tailored manner for each patient following identification of both the SOZ and seizure spread regions as identified by sEEG. Post-operative CT scans with implanted depth electrodes were fused to preoperative MRI using neuronavigational software (BrainLab, Munich, Germany). Electrodes for planned RFA were visually verified to be in gray matter. Cortical mapping studies ensured a lack of eloquent function of identified RFA targets. Cortical mapping was performed using bipolar stimulation at a stimulation frequency of either 5 Hz or 50 Hz with stimulation current beginning at 1 mA with increases by 1 mA up to a maximum of 4 mA. Stimulation duration would vary depending on factors including stimulation frequency, stimulation current, and stimulation intent (function vs seizure stimulation). Cortical stimulation was primarily performed for functional evaluation while electrophysiological characteristics of elicited seizures and after-discharges were also noted and compared to spontaneously recorded interictal and ictal discharges. EEG seizure onset and spread patterns were identified by published intracranial seizure onset patterns: low voltage fast activity, sharp activity at $\leq$13 Hz, or high amplitude polyspikes [7]. Spread regions were arbitrarily defined as spread within 15 seconds of ictal onset.

Radiofrequency ablation was performed at patient's bedside using the Cosman RFG-1B radiofrequency generator (Cosman Medical, Burlington, USA), with a grounding pad connected to the patient's thigh and a radiofrequency electrode directly connected to the connector for each depth electrode contact (monopolar setup). We began with RFA of ictal onset regions followed by seizure spread regions. For each electrode contact, the impedance was noted when connected to the Cosman generator. During ablation, the appropriate male connector on the cable corresponding to the specific electrode contact to be ablated was detached from the Quantum Headbox. We manually placed the tip of the RF lesioning probe into the male end of the connector and held it in place to ensure continued contact during the ablation. Using the continuous radiofrequency mode, we manually increased output until we achieved a power of 1 watt, noting the voltage and current needed to achieve this power. We manually increased output by 1 watt every 30–60 seconds until ablation occurred. Ablation occurred when the electrode impedance increased significantly, with the patient usually reporting a crackling or popping sound. When the electrode contact was reconnected for sEEG monitoring, we confirmed that ablation flattened the waveform. During RFA, we monitored the intracranial EEG, neurological examination, and continually interacted with the patient. Tissue temperature was not monitored as the implanted depth electrodes do not have temperature sensors.

The primary outcome measure was seizure outcome following RFA as defined by the Engel classification system. Secondary outcome measures included neurological deficit (transient or permanent), number of anti-seizure medications (ASM) pre and post RFA, sEEG characteristics, neuropsychological changes, length of hospital stay for sEEG monitoring, length of hospital stay following RFA, and number of RFA lesions in both the early onset and ictal spread regions. The sEEG characteristics included spike, ictal onset, and ictal spread regions. Spike, ictal onset, seizure spread, and RFA regions are defined contiguous contacts within an individual electrode. Descriptive statistics were used to analyze baseline characteristics. This study was approved by the local institutional review board.

3. Results

A total of four patients underwent network RFA (Table 1). All MCD diagnoses are radiographic only, as no patient has undergone resection or biopsy. Two patients (patients 2 and 4) had prior vagus nerve stimulator implantations and one patient (patient 4) had 2 prior right temporal lobectomies. All previous surgeries were performed under the care of the patients' previous neurologists.

The RFA areas for patient #1 were in PMG only. For patient #1, only 2 of the 3 identified seizure pathways were ablated since the third spread pathway was eloquent, so risks of RFA outweighed the benefit. The RFA areas for patient #2 targeted FCD and PVNH cortex, although more FCD received RFA. The RFA areas for patient #3 targeted both FCD and PMG cortex, although more FCD cortex received RFA. The RFA areas for patient #4 were MRI normal cortex.

Median length of sEEG monitoring was 17.5 days (range 16–22) and median length of stay after surgery was 1.5 days (range 1–2). Median follow up period was 25.5 months (range 17–35). Median number of ASMs before and after surgery was 2 (range 1–3). There was no physician directed ASM changes, although two patients (patients 2 and 3) self decreased their ASM dosing without change in their Engel outcome.

Median number of regions with sEEG sharp waves was 5.5 (range 3–7). Median number of regions demonstrating ictal onset by sEEG was 2 (range 1–5). Median RFA lesion areas in the seizure spread areas was 2.5 (range 2–4) and in ictal onset regions was 2 (range 1–5). Fig. 1 provides an example of sEEG identified ictal onset and spread areas and post RFA MRI results. No white matter areas received RFA.

No surgical complications from RFA occurred. One patient (right frontal operculum) had expected transient dysphagia that resolved within one week. No patients had permanent neurological deficit or cognitive complaints. Three patients working prior to RFA remained employed. The fourth patient is a stay at home parent who indicates improved function in that role. Patients 1 and 4 had follow up neuropsychological testing. Patient 1 showed mildly improved memory as well as mildly worsened naming performance. Patient 4 had improved verbal memory. Patient 4 is considering further resection based on his positive network RFA outcome.

4. Discussion

In this study we report four patient outcomes after sEEG guided RFA of both seizure onset and seizure spread regions intended as a palliative measure, with two patients having better than expected Engel IB outcome. Prior studies have shown 41% of patients attain $\geq$50% decrease in seizure frequency following sEEG guided RFA at one year follow up [1]. While that improvement is laudable on its own, the use of RFA has shifted more as an initial test of a potential resective strategy [6].

Still, there are previously described cohorts where RFA was the only intended surgical intervention as resection was not deemed feasible due to assessed risk of resection, cohorts worth reviewing given the similar assessment to our four patients. Most specific in comparison to our cohort, Mirandola et al reported a RFA cohort of PVNH patients, ranging from single unilateral heterotopias to complex cortical malformations with associated PVNH. Their four

Table 1
Clinical, EEG, and RFA characteristics.

Patient	Gender and age (years)	Age of onset (years)	Epilepsy localization	Etiology	Seizure semiology	# sEEG electrodes implanted (contacts)	# Interictal spike regions	# Ictal onset regions	# Seizure spread pathways	# RFA ictal onset (# contacts ablated)	# RFA spread regions (# contacts ablated)	Time to seizure spread (s)	EEG ictal pattern	Engel outcome	F/U period after RFA (months)
1	F 27	13	Left perisylvian	PMG and band heterotopia	R arm/face somatosensory aura → aphasic seizure → automotor seizure → R head version → BTC	14 (62)	7	2	3	2 (6)	2 (4)	3	SA ≤ 13 Hz	IB	35
2	F 34	18	Right posterior temporal and posterior insula	FCD, PVNH	Auditory aura → gastric/ psychic aura → complex motor seizure → BTC	14 (106)	5	2	2	2 (11)	2 (6)	3	LVFA, HAP	IIIA	21
3	M 37	21	Left perisylvian	FCD and PMG	Olfactory / auditory / psychic aura → automotor seizure → BTC	11 (101)	3	1	3	1 (2)	3 (8)	10	SA ≤ 13 Hz	IB	30
4	M 31	7	Right posterior perisylvian	Cryptogenic	L arm somatosensory aura → dyscognitive seizure → auditory aura → L head version → BTC	15 (128)	6	5	4	5 (23)	4 (24)	4	LVFA, SA at ≤13 Hz	IIIA	17

Legend: BTC = bilateral tonic clonic seizure; PMG = polymicrogyria; PVNH = periventricular nodular heterotopia (PVNH); FCD = focal cortical dysplasia; LVFA = low voltage fast activity; SA ≤ 13 Hz = sharp activity ≤ 13 Hz; HAP = high amplitude polyspikes; RFA = radiofrequency ablation.

patients with complex MCD all had Engel 1 outcomes with RFA as part of the treatment plan, although three patients required associated resection, leading those authors to conclude PVNH with complex MCD have good outcomes only with resection [8]. The one other patient in the Mirandola cohort as well as the two Engel IB outcomes in this presented cohort could suggest isolated RFA to be a possible alternate course. The Lyon group reported 17 patients receiving multifocal RFA within their 162 patient cohort, of which ten patients saw benefit [2,6], although further data was not presented for that subcohort. Dimova et al described ten patients undergoing RFA for whom resection was not deemed feasible, of whom six saw benefit (with two having >80% improvement). They also noted improved outcome when MRI lesions were present [9], a finding with which our cohort agrees as our two Engel 1B patients both had lesional MRI findings. Lastly, Chipaux and colleagues reported a pediatric cohort, of whom nine were not deemed candidates for resection. They reported two seizure free patients, four with improvement, and three without improvement. Interestingly, the Chipaux study specifically excluded patients with a large epileptogenic zone as RFA was not expected to interrupt the diffuse epileptogenic network [10]. Conversely, our four patients were specifically selected for RFA due to a presumed large epileptogenic network we hoped to disrupt.

There is a growing trend to view focal epilepsies as a disorder of large-scale functional brain networks [11,12]. These epileptic networks are thought to consist of "nodes" or "hubs" that play an important role in seizure onset and propagation [13]. The reconceptualization of the epileptic network versus epileptogenic zone may better describe the synchronization of the seizure onset zone with various seizure spread areas that eventually lead to the full expression of the patient's electroclinical seizure [14]. This consideration may suggest epileptic networks are more expansive than previously thought, even when structural etiologies are evident on MRI [15]. For example, both normotopic and heterotopic cortices have been shown to be epileptogenic in patients with nodular heterotropia [16].

When examining the seizure itself, the ictal onset area is defined by an inherent propensity to shift from an inter-ictal to ictal state [17]. The initial ictal onset then aberrantly propagates through existing neuronal pathways belonging to the epileptic network. Seizure propagation can structurally affect non- epileptogenic pathways by repeated pathological activation [11]. Indeed, cortical morphology alterations have been shown in anatomic regions distant from the seizure onset zone [6]. Additionally, it is hypothesized that epileptic network nodes could become independent foci of epileptogenic activity [11]. This is beginning to be unraveled, as a recent study noted patients with high node abnormality in surgically spared areas following unilateral temporal lobe resection had a significantly higher seizure recurrence rate at one year follow up [18].

From a surgical perspective, as epileptic networks expand, standard resective strategies become more challenging, particularly if a network is associated with a large MCD, associated with eloquent cortex, or is simply a presumed large network. Our four patients were identified to have a large epileptic network by sEEG monitoring, three expectedly given their large MCDs. When considering treatment options, we hypothesized that epileptic network disruption could be expanded by pairing RFA of seizure spread pathways with the seizure onset areas. Specifically, we considered RFA of seizure spread regions may better disrupt aberrant neuronal synchronization, possibly limiting seizure initiation and progression.

As our patients mostly had either large MCDs +/- association with eloquent cortex, complete resection of these areas would likely have resulted in permanent deficit. With our RFA approach,

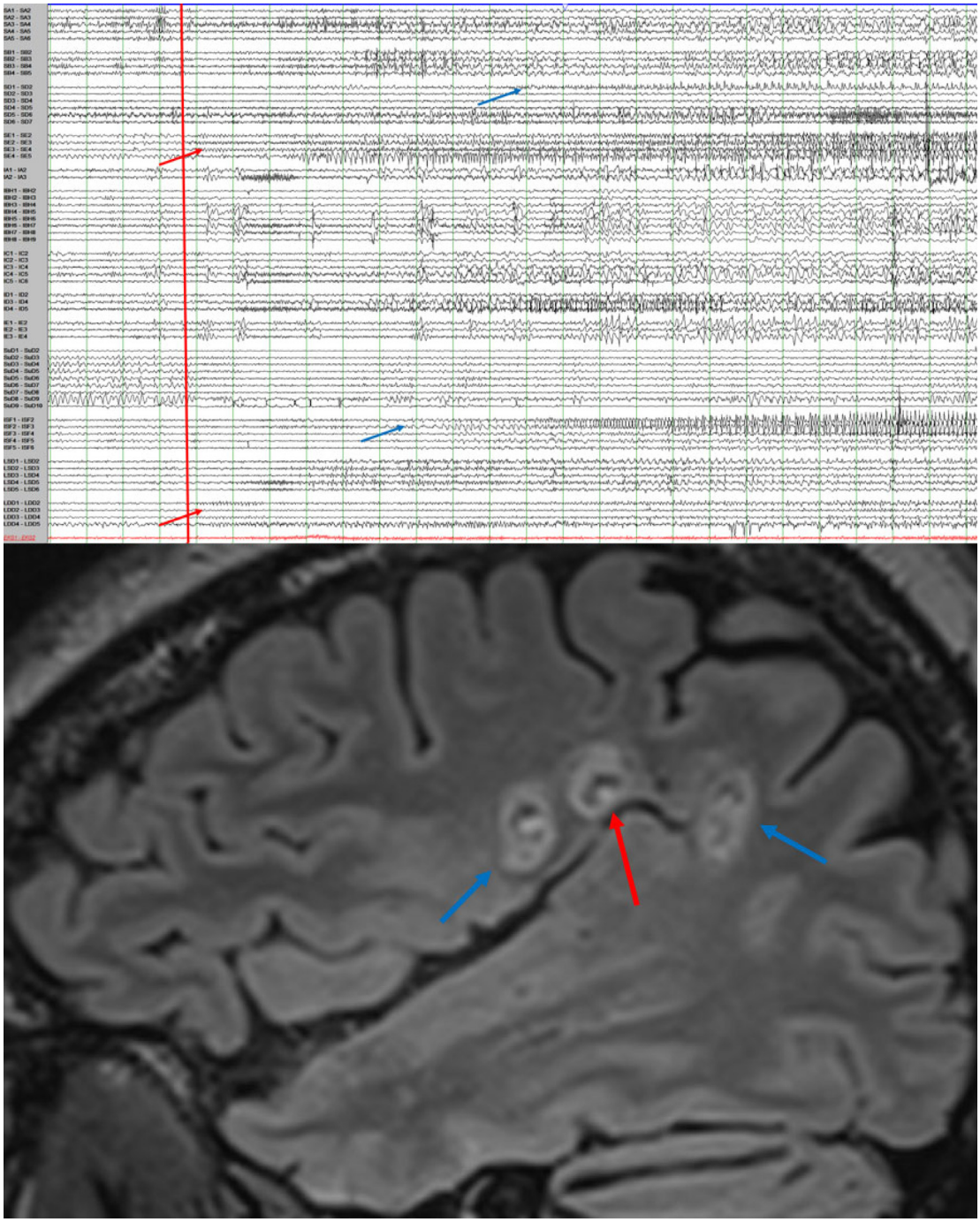

Fig. 1. SEEG (top) and post RFA MRI (bottom) with seizure onset area (red arrows) and spread regions (blue arrows) and red line in EEG denoting seizure onset [one ablation area not visible].

no permanent deficit occurred while all four patients maintained at least >50% improvement. Furthermore, the two Engel 1B outcomes were better than expected outcomes for a palliative surgery type, of which RFA is considered [19,20]. Our outcomes very preliminarily suggest network RFA may provide an additional treatment consideration for such epilepsy patients.

Our study is limited by the small sample size. Our center does not perform RFA on its own except in these very isolated situations, so we do not have a comparison group. Due to the lack of comparison, it cannot be rigidly concluded our four patients could not have had equally good outcomes with RFA of the seizure onset zones only. Due to the small cohort size, a direct comparison of patient lesions volumes was not under-taken. As is inherent to sEEG investigations, limited sampling can impact the potential efficacy of surgical interventions. While our patients had no permanent neurological deficit, the small sample size also limits the ability to conclude that network RFA will always be without permanent deficit. However, we suggest that network RFA performed in tandem with cortical mapping, as is our center's standard of care, can significantly limit patient risk. Our study also was comprised of mostly large MCDs which narrows the potential applicability of our results. Lastly, cortico-cortical evoked potentials were not performed and could be an additive diagnostic technique when considering network RFA.

5. Conclusion

This study provides descriptive results regarding the safety, efficacy, and tolerability of network RFA in patients with drug resistant focal epilepsy. There was at least a 50% seizure improvement and no permanent side effects in our four patient cohort. Subsequent studies are needed to further examine the safety, efficacy, and patient selection for network RFA.

Disclosure of funding

None.

Ethical statement

"The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Kansas University Medical Center STUDY00145162, approval date 3/5/2020".

Author contributions

Author.	Location.	Role
Daniah Shamim.	Department of Neurology, University of Kansas Medical Center.	Design of study, drafting of manuscript, major role in acquisition of data, analysis of data.
Jennifer Cheng.	Department of Neurosurgery, University of Kansas Medical Center.	Major role in acquisition of data, revising the manuscript for intellectual content.
Caleb Pearson.	Department of Neurology, University of Kansas Medical Center.	Interpretation of data, revising the manuscript for intellectual content.
Patrick Landazuri.	Department of Neurology, University of Kansas Medical Center.	Design and conceptualization of study, analysis of the data, revising the manuscript for intellectual content.

Acknowledgements

None.

Institutional Review Board Statement

"The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Kansas University Medical Center STUDY00145162, approval date 3/5/2020"

Data Availability

N/A; all collected data in this case series is presented in the paper.

Informed Consent Statement

"Patient consent was waived due to this study being a retrospective chart review using non identifiable data for publication.

Disclosure of Conflicts of Interest

Dr. Landazuri, Dr. Shamim, Dr. Cheng and Dr. Pearson have nothing to disclose.

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