Seizure 22 (2013) 198–204

Contents lists available at SciVerse ScienceDirect

Seizure

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

Role of single pulse electrical stimulation (SPES) to guide electrode implantation under general anaesthesia in presurgical assessment of epilepsy

Vasileios Kokkinos [a,b], Gonzalo Alarcón [a,c,d], Richard P. Selway [a,e], Antonio Valentín [a,c,*]

[a] Department of Clinical Neuroscience, Institute of Psychiatry, King's College Hospital, London, UK
[b] Epilepsy Monitoring Unit, St. Luke's Hospital, Thessaloniki, Greece
[c] Department of Clinical Neurophysiology, King's College Hospital, London, UK
[d] Departamento de Fisiología, Facultad de Medicina, Universidad Complutense, Madrid, Spain
[e] Department of Neurosurgery, King's College Hospital, London, UK

ARTICLE INFO

Article history:
Received 9 August 2012
Received in revised form 4 December 2012
Accepted 7 December 2012

Keywords:
Refractory epilepsy
Epilepsy surgery
Electrocorticography
Cortical electrical stimulation
SPES

ABSTRACT

Purpose: Single-pulse electrical stimulation (SPES) during intracranial recordings is part of the epilepsy presurgical evaluation protocol at King's College Hospital (London). Epileptiform responses correlated to the stimulus (delayed responses – DRs) tend to occur in areas of seizure onset, thereby allowing interictal identification of epileptogenic cortex in patients suffering refractory epilepsy. This preliminary study investigated the validity of SPES in the operating theatre under general anaesthesia (GA) during the implantation procedure, aiming to improve the positioning of intracranial electrodes.
Methods: Twelve drug-resistant epilepsy patients implanted with depth and/or subdural electrodes were studied. SPES (1 ms pulses, 4–8 mA, 0.2 Hz) was performed during both intra-operative electrode implantation under GA and chronic intracranial ECoG recordings, and the two recordings were compared in terms of cortical responses produced by stimulation and their electrode location.
Results: In 8/12 patients, SPES during chronic recordings produced DRs positively correlated to seizure onset and/or early seizure propagation areas. Of those eight patients, four showed DRs during electrode implantation under GA over the same electrode contacts. Among the four patients without DR during GA, three had continuous localized spontaneous epileptiform discharges, which made interpretation of SPES responses unreliable.
Conclusion: This study showed that, under GA, DRs can be reliably replicated, without false positive epileptiform responses to SPES, although the method's sensitivity is greatly reduced by spontaneous discharges.

Results support SPES as a complementary technique that can be used to improve electrode placement during epilepsy surgery when no profound interictal activity is present.

1. Introduction

Epilepsy is one of the commonest neurological disorders worldwide, exhibiting a prevalence of 4–10/1000 and an incidence of 50–70/100,000 per year.[1,2] An estimated 10–20% of patients fail to gain adequate seizure control on anti-epileptic drug treatment, with 50% of them fulfilling criteria for epilepsy surgery.[3,4] The utmost objective of resective surgery in epilepsy is the complete removal or disconnection of the cortical area responsible for the generation of seizures, without inducing permanent neurological deficits to the patients. A variety of methods are available for the identification of the seizure focus, including interictal and ictal scalp electroencephalography,[5,6] magnetic resonance imaging, positron emission tomography[7] and neuropsychology.[8] Patients where these methods fail to demonstrate a single seizure focus may require video monitoring with intracranial electrodes. Cortical electrical stimulation via intracranial electrodes has been used to localize function, induce habitual seizures and study cortical excitability.

More specifically, single-pulse electrical stimulation (SPES) has been used to study differences in cortical excitability between epileptogenic and normal cortical tissue[9–15] and to identify functional connections.[16–21] Two main types of cortical responses were evoked by SPES: early and late responses. Early responses usually consisted of a sharp deflection immediately after the

* Corresponding author at: Department of Clinical Neuroscience, Institute of Psychiatry, King's College London, De Crespigny Park, Denmark Hill, London SE5 8AF, UK. Tel.: +44 0207 8485161; fax: +44 0207 8480988.
E-mail addresses: info@vasileioskokkinos.gr (V. Kokkinos), antonio.valentin@iop.kcl.ac.uk (A. Valentín).

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http://dx.doi.org/10.1016/j.seizure.2012.12.012

stimulus artefact or occasionally merging with it, followed by a slow wave. As early responses are seen when stimulating through most areas, they are considered as normal cortical responses to SPES. Late responses arise after the early response and they are of two types: delayed and repetitive responses. Delayed responses consisted of one or several typical spike-and-slow waves, resembling interictal epileptiform discharges with a delay longer than 100 ms after stimulation. Repetitive responses are seen mainly when stimulating frontal structures in some patients with frontal epilepsy. They consisted of two or more consecutive waves, each resembling the initial early response. Delayed and repetitive responses to SPES were found to be significantly associated with the location of ictal onset and post-surgical seizure control.[13]

SPES can confirm findings from other presurgical evaluation methods, possibly reducing the number of seizures required for localization, which may shorten the duration of the invasive studies. Currently, SPES is carried out in alert patients with chronically implanted electrodes. The present study was carried out in order to explore the usefulness of SPES under general anaesthesia in the operating theatre. If so, the technique could be used intraoperatively, at the time of electrode implantation, in order to assess whether the sites chosen for implantation are likely to include the seizure onset area(s). By moving or adding electrodes during implantation according to SPES results, SPES could increase the accuracy of seizure onset identification.

In the present work, we have compared responses to SPES recorded with the same intracranial electrodes and at the same positions under two different conditions: (a) under general anaesthesia in the operating theatre at the time of electrode implantation (*acute recordings*), and (b) during chronic telemetry recordings obtained without anaesthesia (*chronic recordings*). The latter contain ictal additional recordings.

2. Methods

2.1. Patients

We studied 12 consecutive patients (8 males, 4 females, mean age 33, range 12–52 years) who were evaluated as candidates for surgical treatment for their epilepsy in the Department of Clinical Neurophysiology at King's College Hospital, London. All patients suffered from drug-resistant epilepsy (see Supplementary material and Table 1 for details on clinical data and procedures) and were admitted for video-monitoring with intracranial electrodes. The experimental procedure was approved by the ethical committee of King's College Hospital (ref. no. 99-017) and is now part of our clinical protocol for assessment of epilepsy with intracranial recordings.

2.2. Electrode placement

Subdural and/or intracerebral (depth) electrodes were surgically implanted in the 12 patients recruited. The type, number and location of the electrodes were determined by the suspected location of the ictal onset region, according to non-invasive evaluation: clinical history, scalp EEG recordings obtained with the Maudsley system[22,23] neuropsychology and neuroimaging. The selection criteria and implantation procedure have been described previously.[24]

In 3 patients, multicontact flexible bundles of depth electrodes (AdTech Medical Instruments Corp., WI, USA) were implanted stereotactically under MRI guidance. Electrodes consisted of 6–10 cylindrical 2.3 mm long platinum contacts located at a distance of 0.5 cm between centres of adjacent electrodes in the same bundle. In 6/12 patients, electrode strips and/or grids (AdTech Medical Instruments Corp., WI, USA) were used. Each strip consisted of a single row of 4–8 platinum disk electrodes spaced at 1 cm between centres of adjacent electrodes in the same strip. The disks were embedded in a 0.7 mm thick polyurethane strip which overlapped the edges, leaving a diameter of 2.3 mm exposed, recessed approximately 0.1 mm from the surface plane. Grids were formed by similar platinum electrode rectangular arrays of 1 cm centre-to-centre distance across rows. Details on the particular sites of electrode placement are provided in Table 1. In the rest 3/12 patients, combinations of depth and subdural grids/strips were used.

2.3. EEG recording

Acute recordings during implantation in the operating theatre (obtained under general anaesthesia) were obtained with an Xltek EMU128 system (Xltek, Oakville, Canada). The 32-channel intraoperative EEG signals were amplified (maximum input range of $\pm$8 mV), digitized by a 18-bit analog-to-digital converter (accuracy of 0.03 μV) at 500 Hz, and bandpass-filtered (0.3–70 Hz), before being saved on hard disk.

Chronic recordings (obtained without general anaesthesia) begun when the patient had recovered from the implantation operation, that is, usually 24–48 h after, under conditions of relaxed awareness. Cable-telemetry with up to 64 recording channels was used for data acquisition with simultaneous video monitoring. Data were amplified (max input range of $\pm$10 mV), digitized by a 16-bit analog-to-digital converter (accuracy of 0.153 μV) at 256 Hz with an anti-aliasing filter of 100 Hz, and bandpass-filtered (0.16–70 Hz) by a NicoletOne system (Nicolet Biomedical Inc., Madison, WI, USA) and saved on hard disk for further off-line reviewing and analysis.

2.4. Experimental protocol

The SPES protocol was applied through a constant-current (or current-controlled) neurostimulator, commercially approved for use in human subjects (Medelec ST10 Sensor, Oxford Instruments, Old Woking, UK). Electrical stimulation was performed between adjacent electrodes with single monophasic pulses of 1 ms duration and current intensity which varied between subjects from 1 to 8 mA. A single 1 ms electrical pulse was applied every 5 s and the EEG responses were monitored over the electrodes not used to stimulate. Neuronal stimulation was assumed to occur over the cathode electrode. Five to 20 stimuli (typically 10) were applied at each location for each polarity. Unless side-effects were observed (facial pain when stimulating through subtemporal electrodes; or stimulation induced myoclonic jerks when stimulating primary motor cortex), the stimulation intensity was kept the same for all stimuli applied to each patient. If any side-effects were observed, stimulus intensity was decreased or stimulation at the corresponding site was abandoned.

Anaesthesia was induced with propofol and maintained with isoflurane without opioids (usually at around MAC 1.0). If epileptiform activity was scanty, general anaesthesia was lightened to a minimum of MAC 0.5.

Since time available during acute recordings is necessarily limited, only a selected number of electrodes were used for stimulation. Based on previous clinical history, examination, imaging, EEG findings, and interictal activity during the acute recording, the areas presumed to be epileptogenic were stimulated during acute recordings. In temporal lobe implantations, these included medial temporal structures (hippocampus and amygdala) on either side. In contrast, during chronic recordings in telemetry, all implanted electrodes in contact with grey matter were used to stimulate the cortex.

Table 1
Patient data, implantation, stimulation and seizure onset results.

Patient No.	Age	Sex	Extracranial EEG-based seizure onset	Implanted electrodes	Location of spontaneous discharges under GA	Location of evoked SPES responses under GA	Location of spontaneous discharges without GA	Location of evoked SPES responses without GA	Intracranial seizure onset
1	36	F	Left posterior temporal/occipital	Depth					
				- 10c: LposH	LposH1-3	LposH1-3	LposH1-3	LposH1-3	LposH1-3
				- 8c: LinfO	–	–	LinfO1-3	–	–
				- 8c: LantH	–	–	–	–	–
				- 8c: RantH	RantH1-3	–	RantH1-2	–	–
				- 10c: LantP	–	–	–	–	–
				- 10c: LsupO	–	–	–	–	–
2	20	F	Left frontal	Depth					
				- 10c: LasupF	LasupF1-3	–	LasupF1-3	–	–
				- 7c: LainfF	–	–	–	–	–
				- 6c: LposF	–	–	–	–	–
				- 10c: LpinfF	–	–	–	–	–
				- 7c: LposC	LposC1-3	–	LposC1-2	LposC1-2	LposC1-2
				- 10c: LantP	LantP1-2	–	LantP1-6	–	–
				- 10c: LsupP	LsupP2-6	–	LsupP2-5	–	–
				- 10c: LposP	LposP1-7	–	LposP1-7	–	–
3	35	M	No clear onset	Depth					
				- 4x10c: LF1-4	–	–	–	–	Widespread onset
				- 4x10c: RF1-4	–	–	–	–	–
				- 10c: LorbF	–	–	–	–	–
				- 10c: RorbF	–	–	–	–	–
4	12	M	Left mid-parietal/ posterior frontal	Depth					
				- 10c: LlsupP	–	–	–	–	–
				- 10c: LmsupP	–	–	LmsupP1	–	LmsupP1-3
				- 10c: LlinfP	LinfP6	–	LinfP1-6	–	LinfP1-3
				Subdural					
				- 8c: LsupP	–	–	–	–	–
				-8c: LlatP	LlatP1-8	–	–	–	–
5	40	M	Right temporal	Depth					
				- 8c: Lam	–	–	–	–	–
				- 10c: LantH	LantH1-4	–	LantH1-2	–	–
				- 10c: LposH	LposH1-3	–	–	–	–
				- 10c: Ram	–	–	–	–	–
				- 10c: RantH	RantH1-2	RantH1-2	RantH1-2	RantH1-2	RantH1-2
				- 10c: RposH	RposH1-2	RposH1-2	RposH1-2	RposH1-2	–
				Subdural					
				- 8c: Lcing	–	–	Lcing1-5	–	–
6	40	M	Left temporal	Subdural					
				- 8c: LsubT	LsubT1-7	–	LsubT1-7	–	LsubT2-3
				- 8c: RsubT	RsubT1	–	RsubT1	–	–
7	20	M	Right temporal	Subdural					
				- 8c: LsubT	LsubT1-5	–	LsubT3-4	–	–
				- 8c: RsubT	RsubT1-7	–	RsubT1-6	RsubT3	RsubT1-3
8	52	M	Right temporal	Subdural					
				- 4c: RantT	RantT1-4	–	Rant3-4	–	–
				- 8c: RmidT	RmidT1-7	–	RmidT5-6	–	–
				- 4c: RposT	RposT1-3	–	RposT1-2	–	–
				- 8c: LmidT	LmidT1-3	–	LmidT4-7	LmidT4-7	LmidT5-6
9	43	M	Left temporal	Subdural					
				- 8c: LantT	LantT1-5	–	LantT1-5	–	–
				- 8c: LmidT	LmidT1-3	LmidT1-3	LmidT1-2	LmidT1-6	–
				- 4c: RantT	–	–	–	–	–
				- 8c: RmidT	RmidT1-3	RmidT4-5	RmidT1-7	RmidT2-5	RmidT3-5
10	22	M	Right frontal	Subdural					
				- 32c: RlF	RlF30-32	–	–	–	Widespread onset
				- 4c: RsF	–	–	–	–	–
				- 8c: RaF	–	–	–	–	–
				- 8c: RiF	–	–	–	–	–
				- 8c: RmF	–	–	–	–	–
				- 4c: LmF	–	–	–	–	–
11	34	F	Right frontal	Subdural	RlF1-3,9-11	RlF1,2	RlF1-23,31	RlF1-3,9-10, 18-19,25-26	
				- 32c: RlF	–	–	RiF1-4	RiF1-4	RlF1-3,9-12, 17-19,25-26
				- 8c: RiF	–	–	–	–	
				- 8c: RaF	–	–	–	–	RiF2,3,4
				- 8c: RmF					–
									–

Table 1 (*Continued*)

Patient No.	Age	Sex	Extracranial EEG-based seizure onset	Implanted electrodes	Location of spontaneous discharges under GA	Location of evoked SPES responses under GA	Location of spontaneous discharges without GA	Location of evoked SPES responses without GA	Intracranial seizure onset
12	42	F	Right frontal	Subdural					
				- 32c: RlF	RlF4-6,11-14, 20-22,28-30	–	RlF7,8,16,24	RlF7,12,14,15,23	RlF3-5,13-15,24
				- 4c: RmF	–	–	–	–	–
				- 10c: LmF	–	–	–	–	–
				- 4c: RmantP	–	–	–	–	–
				- 4c: RmposP		–	–	–	–
				Depth					
				- 2x10c: RmantF	–	–	$RmantF_1$1,2	–	–

L: left, R: right, H: hippocampus, am: amygdale, cing: cingulated gyrus, F: frontal, T: temporal, P: parietal, O: occipital, orb: orbitofrontal, ant or a: anterior, pos or p: posterior, lat or l: lateral, m: medial, sup: superior, inf: inferior, mid: middle, sub: sub, c: contact.

2.5. Delayed responses to SPES

Delayed responses consisted of one or several spike-and-slow waves, often resembling spontaneous interictal epileptiform discharges, and showing latencies greater than 100 ms and less than 1.5 s after the stimulus artefact. The use of 1.5 s is arbitrary, and it was chosen as a time window during which delayed responses are likely to occur if present, according with our experience in more than 250 patients (Figs. 1 and 2, see also[11] for a thorough description of DRs).

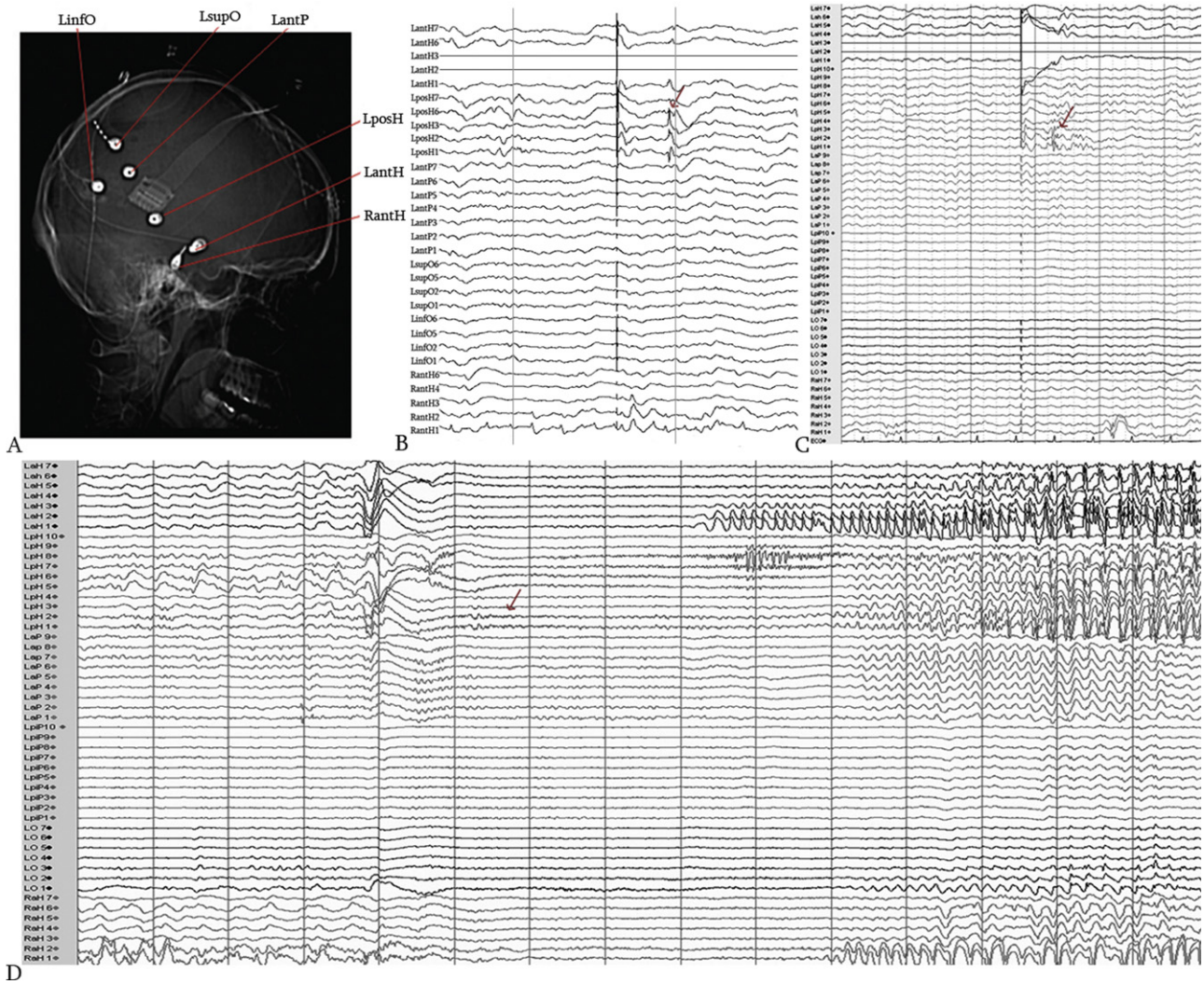

Fig. 1. (A) X-ray image showing depth electrode positions of Patient 1. (B) Single pulse stimulation (SPES) under GA produced DRs over the deep contacts of the left posterior hippocampal electrode (LposH1-3). (C) SPES during chronic recordings resulted in DRs over the same electrode contacts. (D) Ictal electro corticography (ECoG) showing SWDs over the deep contacts of the left posterior hippocampal electrode that precede the development of an ictal rhythm over the superficial contacts of the same electrode (arrows denote DRs in B and C, and seizure onset in D).

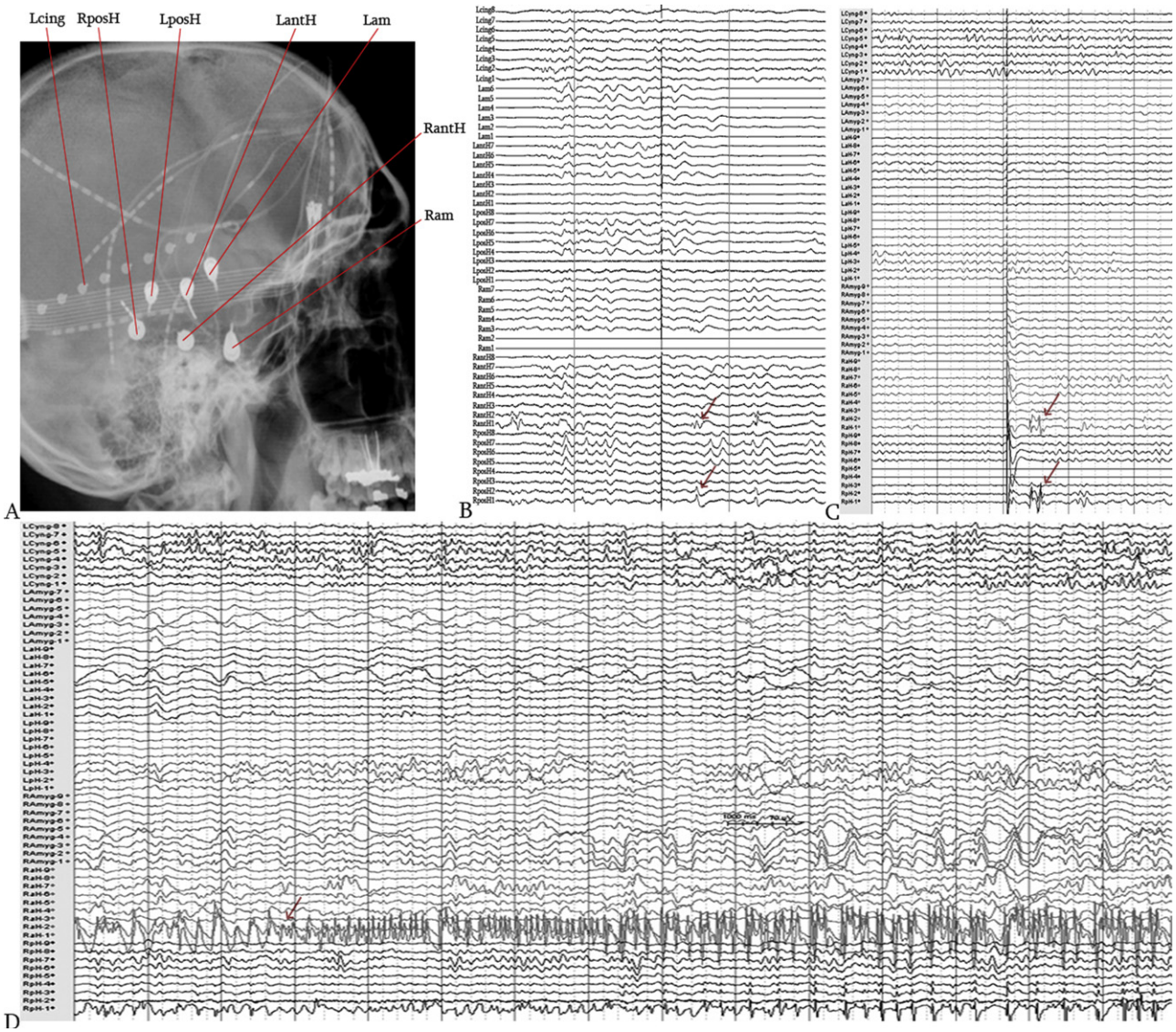

Fig. 2. (A) X-ray image showing depth and subdural electrode positions of Patient 5. (B) Single pulse stimulation (SPES) under GA evoked DRs over the deep contacts of the right anterior and the right posterior hippocampal electrodes (RantH1-2, RposH1-2). (C) SPES during chronic recordings resulted in DRs of a similar distribution. D: Ictal ECoG showing the development of an ictal rhythm over the right anterior temporal (RantH1-2) electrodes (arrows as in Fig. 1).

2.6. Seizure onset

The seizure onset area was determined by the electrodes showing initial sustained ictal activity.

2.7. Statistical analysis

As DRs often resemble spontaneous interictal discharges and are not systematically produced by each stimulus applied, the association between stimulation and DRs was established by comparing the occurrence of spikes during 1.5 s before and 1.5 s after each pulse. We assumed that spikes were related to stimulation if the number of stimuli showing spikes during the 1.5 s following stimulation was greater than the number of stimuli showing spikes during the 1.5 s before stimulation (with $p < 0.05$ one tail Sign Test). The non-parametric Sign Test has the advantage that can be tabulated and significance can be checked during recordings without complicated calculations. DRs were visually evaluated, without the use of filters or other EEG processing means.

3. Theory

Single pulse electrical stimulation (SPES) in the operating theatre under general anaesthesia (GA) can evoked similar abnormal responses to SPES under chronic recordings. This finding would help to improve the positioning of intracranial electrodes during the implantation procedure.

4. Results

Out of the 12 patients selected for this study, 3 were implanted with depth electrodes only, 6 were implanted with subdural electrodes only, and 3 were implanted with a combination of depth and subdural electrodes (Table 1). Of the two varieties of late responses, repetitive responses[12] were not seen neither in chronic nor in acute recordings. DRs were induced in patients with all three implantation categories. Implantation sites varied according to pathology and covered all lobes, although the majority of patients were implanted in the temporal and the frontal lobes.

4.1. Patients with DRs

In 8 patients out of the total 12 (P1, P2, P5, P7, P8, P9, P11, P12), DRs were reliably produced during chronic recordings without anaesthesia. Among these 8 patients, four showed DR under general anaesthesia, three (P7, P8, P12) showed continuous spontaneous epileptiform discharges under general anaesthesia which made interpretation of SPES responses unreliable, and one patient (P2) did not show DRs nor continuous spontaneous epileptiform discharges. In the four patients showing DR under anaesthesia, the position of DR was at the same electrodes and contacts as the DR seen during chronic recordings. Among these four patients, three (P1, P5, P11) showed DRs exclusively at the site of seizure onset, and one (P9) showed DR in both temporal lobes.

In summary, when seen under general anaesthesia, DRs showed similar topography to that seen under chronic recordings (Table 1). In all four patients with DR under anaesthesia, they occurred in areas involved in seizure onset as determined by chronic telemetry recordings. In one case (patient 9) independent DRs were seen in both hemispheres during anaesthesia and during chronic telemetry.

4.2. Patients without DRs

Among the 12 patients recruited, four (P3, P4, P6, P10) did not show DRs during acute or chronic recordings. Among these four patients, two (P4, P6) showed frequent spontaneous interictal activity under both conditions and, consequently, it was not possible to confirm the existence of DRs. The remaining two patients (P3, P10), showed no focal seizure onset (Table 1) nor spontaneous epileptiform activity, neither during anaesthesia nor during chronic telemetry recordings, suggesting that electrodes in these two patients may not have been in contact with epileptogenic tissue.

5. Discussion

The aim of this study was to evaluate SPES as a method to identify epileptogenic cortex under general anaesthesia. SPES responses were studied with the same electrodes and positions under two conditions: (a) during implantation under general anaesthesia (acute recordings) and (b) during chronic telemetry recordings without anaesthesia (chronic recordings). DRs could be induced by SPES under general anaesthesia in 4 of the 8 patients who had DRs without anaesthesia. Moreover, DRs occurred at the same contacts under both conditions. Since SPES is time consuming and time is necessarily limited in the operating theatre, not all implanted contacts were used for stimulation under general anaesthesia. In addition, during implantation we were necessarily blind to results from chronic recordings. These factors may have contributed to the discrepancy observed between the number of patients showing DRs during chronic and acute recordings, since the optimal contacts might have not be chosen for stimulation in the latter.

Nevertheless, the results demonstrate that abnormal responses to SPES can be induced under general anaesthesia and that, when present, the topography of DRs is not altered by anaesthesia. The efficacy of intracranial recordings highly depends on electrode placement. At present, there are no electroencephalographic methods to confirm at the time of implantation that electrodes are positioned in contact with epileptogenic cortex, with the exception of recording spontaneous epileptiform discharges which are not very specific markers for seizure onset.[22,25] Consequently, a proportion of seizures recorded with intracranial electrodes may show a non-localized or ill-localized seizure onset, resulting in misleading or non-interpretable findings. This is highly undesirable because chronic intracranial recordings are time consuming, expensive and not risk-free. For these reasons, in most patients, chronic recordings are carried out only once or perhaps twice. Any method that could increase the likelihood of recording focal seizure onset and abnormal SPES responses in chronic recordings by improving electrode positioning during implantation will be highly valuable. Our findings suggest that SPES could be effective in achieving this goal. In addition, SPES may also have a role during acute electrocorticography recorded to tailor resection.

As shown in Table 1, DRs always occurred in areas with spontaneous interictal discharges and, therefore, it could be claimed that DRs do not provide more information. However, spontaneous discharges are rather ubiquitous, appearing independently at a number of sites, including at seizure onset and elsewhere, often bilaterally (Fernández Torre et al., 1999[22]; Alarcon et al., 1994[26]). Under these circumstances it is difficult to identify the spontaneous spikes that have clinical significance. DRs are usually more specific, mostly occurring at sites showing seizure onset, and, therefore, could be used interictally to identify the areas with the interictal discharges associated with seizure onset.

Interestingly, in six of the 12 patients, DRs to SPES could not be determined reliably either under anaesthesia only (4 patients) or under both conditions (2 patients), as spontaneous interictal activity was nearly continuous and DRs were difficult to distinguish from coincidental spontaneous epileptiform discharges. However, in this patient group, SPES findings are perhaps less relevant, as nearly continuous epileptiform discharges are unequivocal markers of epileptogenic cortex.[27]

In summary, it appears that abnormal responses to SPES can be recorded under general anaesthesia with similar topography to that seen without anaesthesia, and this could be used to guide electrode implantation in order to increase the likelihood of recording focal seizure onset and abnormal SPES responses during chronic recordings.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2012.12.012.

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