

Single Pulse Electrical Stimulation in Presurgical Assessment of Epilepsy: A New Diagnostic Tool

Epilepsy is a major source of disability amongst all age groups. Although most epilepsies are well controlled on antiepileptic drugs, around 20% of patients fail to gain medical control, and are potential candidates for surgery. However, despite recent technical advances, the overall success rate of surgery for epilepsy remains at about 75%.

At the department of Clinical Neurophysiology at King's College Hospital, we have developed single pulse electrical stimulation (SPES) as a method to identify epileptogenic cortex in the human brain. Cortical responses to SPES (1msec duration pulses, 4-8mA, 0.1-0.2Hz) were studied in 125 consecutive patients evaluated with intracranial electrodes as candidates for resective surgery for the treatment of their epilepsy.

Two main groups of cortical responses were generated by SPES: 1) early responses (ER), starting immediately after the stimulus and considered as responses of normal cortex to stimulation; and 2) late responses (LR), cortical responses seen in some areas after the initial ER. Two different types of LR were seen: a) delayed responses (DR): responses resembling spikes or sharp waves occurring between 100 milliseconds and 1 second after stimulation; and b) repetitive responses (RR): two or more consecutive sharp-and-slow-wave complexes, each resembling the initial early response. DR were seen when stimulating temporal and extratemporal structures and RR when stimulating frontal structures. Late responses to SPES are related to areas where spontaneous seizure onset occurs. They can identify epileptogenic cortex and predict surgical outcome, especially when a frontal or temporal focus is suspected.

Single-pulse electrical stimulation (SPES) could be an important additional investigation during presurgical assessment and can be particularly useful in patients who have widespread or multiple epileptogenic areas, normal neuroimaging, or few seizures during telemetry.

Introduction

Epilepsy is one of the most common neurological disorders, with a prevalence of 4-10/1000 and an incidence of 50-70/100,000 per year.^{1,2} About 20% of patients with epilepsy are not satisfactorily controlled by medical treat-

ment and are potential candidates for surgery.

In focal epilepsies, there is a localised area of abnormal nervous tissue from which seizures originate (epileptogenic cortex). A successful outcome of resective epilepsy surgery depends on accurate identification of the epileptogenic cortex which is structurally and functionally abnormal. Recent developments in medical imaging provide powerful means to localise structural lesions. Identification of functional abnormalities still requires electroencephalographic (EEG) recordings of seizure onset. Despite technical advances in surgical procedures and presurgical assessment over recent decades, the overall success rate of resective surgery of epilepsy remains at about 75% even in the best centres.³ The reasons for a 25% failure rate are unclear, but might be related to difficulties in identifying the area from which the seizures originate. Its location is inferred from clinical, imaging and electrophysiological findings. Sometimes seizure recordings with intracranial electrodes are necessary to identify epileptogenic cortex. As the number of intracranial electrodes implanted is necessarily limited and seizures can rapidly propagate between regions, intracranial recordings can sometimes be misleading in seizures arising from areas where no electrodes were implanted.

Since epilepsy is due to an imbalance between excitation and inhibition, an alternative is to map cortical excitability in order to identify hyperexcitable areas that could be epileptogenic. This can in principle be achieved by recording EEG responses to electrical stimulation in patients with intracranial recordings. Electrical stimulation with trains of pulses at 50-60Hz is routinely used in some centres to map cortical function and after-discharge threshold, and to elicit habitual seizures. However, it is difficult to study cortical excitability with such stimulation parameters because they are likely to produce massive and widespread cortical activation. In the Departments of Clinical Neurophysiology and Neurosurgery at King's College Hospital, we have developed a method to identify hyperexcitable cortex through the study of EEG responses to single pulse electrical stimulation (SPES).^{4,6} In the present article we review the



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Table 1: Cross tabulation between type of late response and seizure onset.

DR/RR type	Ictal Onset Zone type					Total
	Focal	Regional	Diffuse	Bilateral Indep.	No sz	
Focal DR	18	7	0	3	2	30
Regional DR	6	33*	1	0	0	40
Bilateral DR	4	4**	0	7	3***	18
Only RR	0	5	0	0	0	5
No DR/RR	3	18	7	2	2	32
Total	31	67	8	12	7	125

Patients showing focal and regional ictal onset zones were considered as having regional ictal onset zone. Patients showing focal and regional DR were considered as having regional DR. The ictal onset zone was defined as the region where the initial ictal changes were seen in intracranial recordings.

* Two patients also had repetitive responses (RR).

** One patient also had repetitive responses (RR).

*** One patient had delayed and repetitive responses when stimulating both medial frontal regions.

DR=Delayed Responses; Bilateral DR=independent DR seen on both hemispheres; RR=Repetitive Responses; Indep=independent; sz=seizures.

results of SPES from 125 consecutive patients evaluated with intracranial recordings between 1999 and 2006.

Experimental protocol

SPES was performed between adjacent electrodes with a constant-current neurostimulator (Medelec ST10 Sensor, Oxford Instruments) using monophasic single pulses of 1ms duration and current intensity ranging between 4mA and 8mA (4mA was most often used). A single pulse was delivered every 5-10s and EEG responses to each pulse were recorded by the electrodes not used for stimulation. At least ten pulses were applied to each intracranial electrode. In each patient, all available electrodes located in grey matter were used to stimulate.

SPES responses

Two main groups of cortical responses were generated by SPES:

- 1) Early responses (ER): Responses resembling single sharp-and-slow waves following the stimulus artefact, sometimes associated with a low amplitude sharp wave with a fixed latency. ER can be considered as responses of normal cortex to stimulation (Figure 1).
- 2) Late responses (LR): cortical responses seen in some areas after the initial ER. Two different types of LR were seen:
 - 2.a) Delayed responses (DR): responses resembling spikes or sharp waves occurring between 100 milliseconds and one second after stimulation (Figure 1). DR were not always seen after every identical stimulus and their latency is always variable after each stimulus. DR were seen when stimulating temporal and extratemporal structures.
 - 2.b) Repetitive responses (RR): two or more consecutive sharp-and-slow-wave complexes, each resembling the initial early response (Figure 2). RR were mainly seen when stimulating frontal structures.

Among the 125 patients, 93 had shown late responses to SPES, 84 had exclusively DR, five had exclusively RR, and four patients had both DR and RR (Table 1).

Relation between late responses to SPES and seizure onset

Apart from early responses, DR were the most commonly observed responses to SPES. The relation between the topography of DR and ictal onset zone can be seen in Table 2. The ictal onset zone was defined as the region where the initial ictal changes were seen in intracranial recordings. Ictal onset zone was classified as focal (involving less than three contiguous electrodes), regional (involving three or more contiguous electrodes on one hemisphere), diffuse (involving most electrodes bilaterally), or bilateral independent (different focal seizures starting on different hemispheres). Among the 83 patients with DR and seizures during telemetry, 70 showed DR exclusively within the ictal onset zone (Figure 3), 10 showed DR within and outside the ictal onset zone, and only three showed

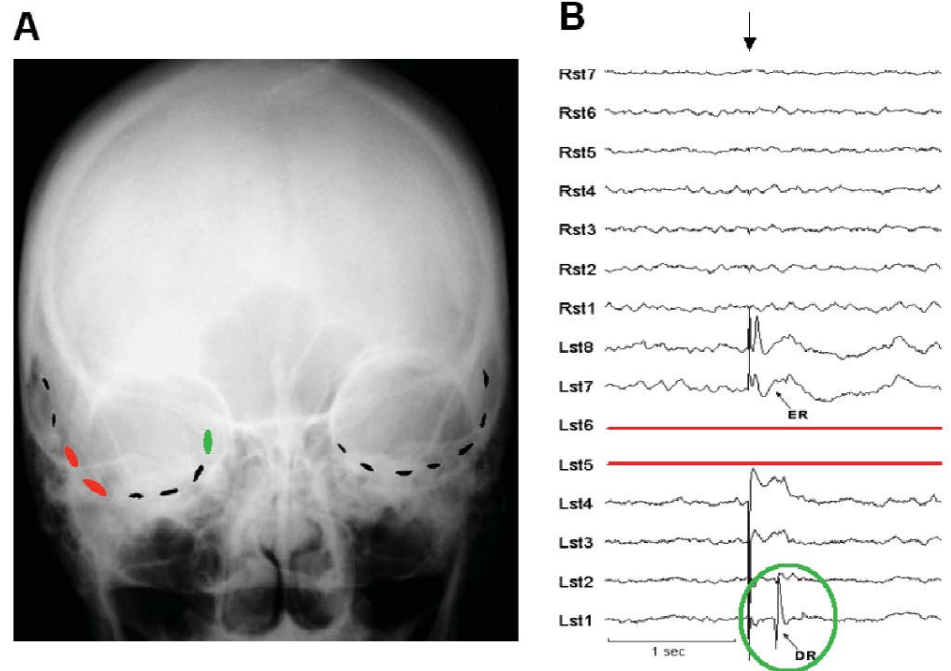


Figure 1: Early and Delayed responses to SPES

A: Frontal radiograph showing implanted subdural subtemporal strips in a patient with left temporal lobe epilepsy. All the contacts of the subdural strips are highlighted. B: Intracranial recordings of early and delayed responses to SPES. Delayed responses were seen at electrode 1 of left subtemporal strip (LsT1, marked as green) when stimulating through electrodes 5 and 6 of same strip (LsT5 and LsT6, marked as red). Early responses were mainly seen at electrodes 3, 4, 7, and 8 of same strip. Electrode 1 was the most distal electrode to the insertion burr hole and closest to mesial temporal structures. Recording displayed in common reference to Pz.

Arrow=electrical stimulation; RsT=right subtemporal strip; LsT=left subtemporal strip; ER=early response; DR=delayed response.

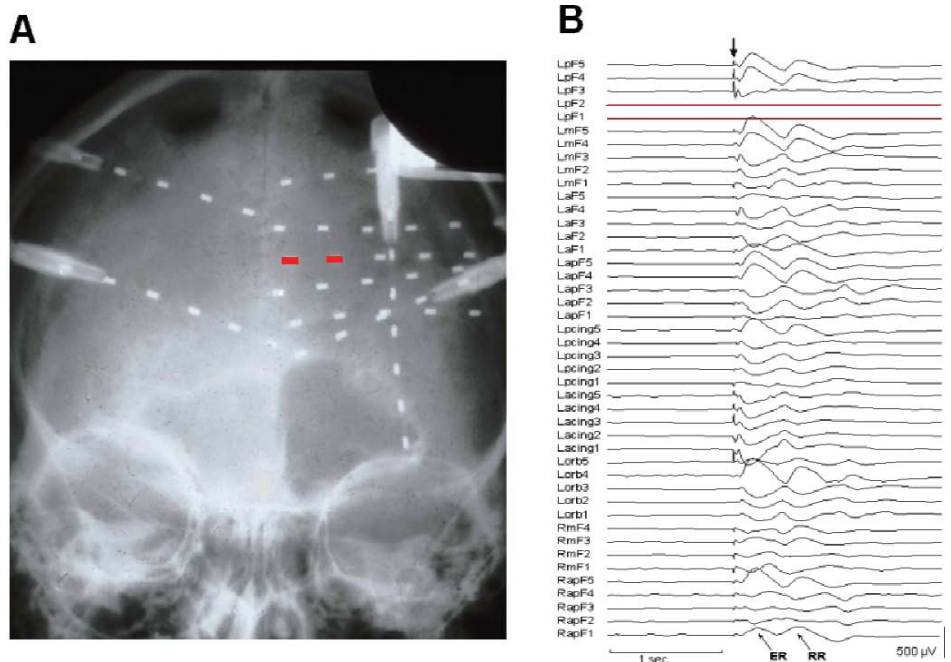


Figure 2: Repetitive responses to SPES

A: Frontal radiograph showing implanted intracerebral (depth) electrode bundles. B: Intracranial recordings of early and repetitive responses to SPES. Repetitive responses were evident when stimulating through electrodes 1 and 2 of the left posterior frontal electrode bundle (LpF1 and LpF2, marked as red). Electrode 1 was the most distal electrode to the insertion burr hole and closest to medial frontal structures. Recording displayed in common reference to Pz.

Arrow=electrical stimulation; RapF=right anterior polar frontal; RmF=right mid frontal; LmF=left mid frontal; LpF=left posterior frontal; LaF=left anterior frontal; Lorb=left orbitofrontal; Lpcing=left posterior cingulate; Lacing=left anterior cingulate; ER=early response; DR=delayed response.

DR exclusively outside the ictal onset zone. Moreover, the vast majority of patients (27/30) without DR did not have a focal onset, probably implying that the electrodes were not in contact with the area of origin for the seizures (Table 1). Therefore, DR appear to be associat-

ed with the ictal onset zone and can be considered as a reliable marker of epileptogenicity.

In a further study of 30 patients with frontal intracranial electrodes, RR and/or frontal DR were seen exclusively in patients with frontal seizure onset.⁵ The best match between seizure

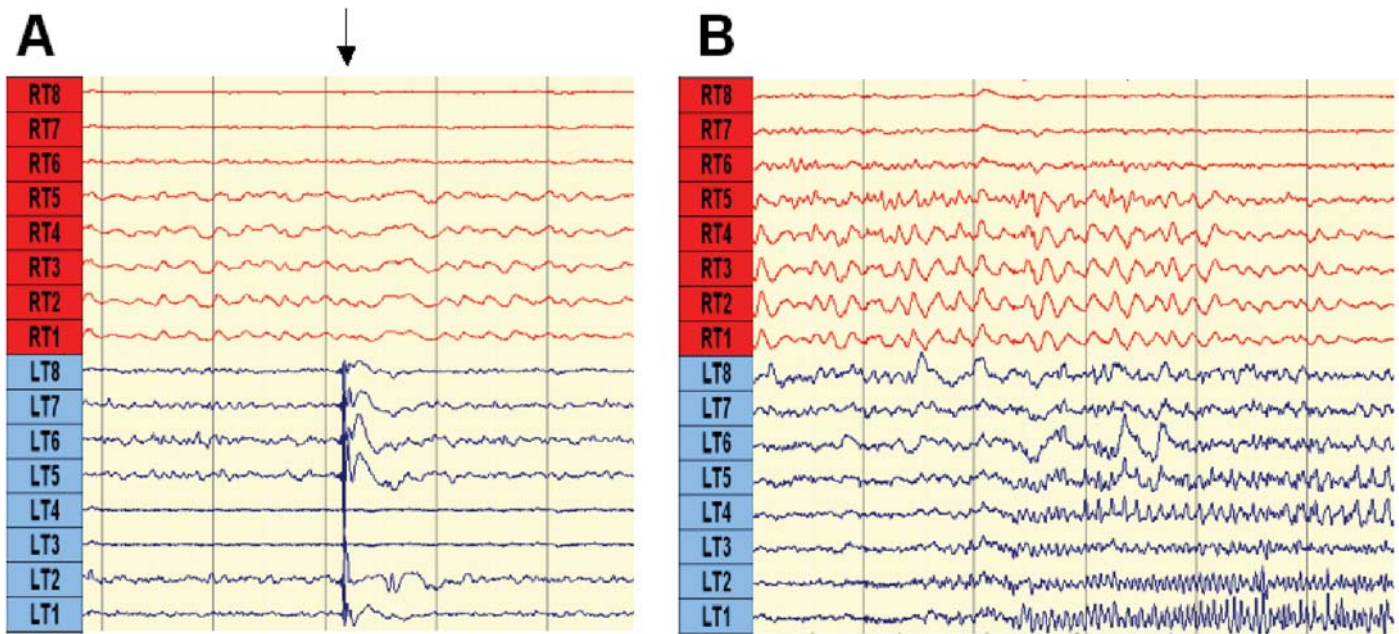


Figure 3: Relation between the distribution and topography of late responses to SPES and seizure onset in a patient with bitemporal subdural strips. A: Intracranial recordings of early and delayed responses to SPES. Delayed responses were seen at contact 2 of left subtemporal strip (LT2) when stimulating through electrodes 3 and 4 of same strip (LT3 and LT4) B: Subdural recording of a focal seizure onset. Note the fast activity building up at electrodes 1 and 2 of the left subtemporal strip (LT1 and 2). Electrode 1 was the most distal electrode to the insertion burr hole and closest to mesial temporal structures Recording displayed in common reference to Pz. Arrow=electrical stimulation; RT=right subtemporal strip; LT=left subtemporal strip.

onset and responses to SPES was seen in the areas where DR were recorded and those which, when stimulated, gave rise to RR (abnormal SPES areas).

Neuropathology and prediction of outcome:

We have studied 40 consecutive patients operated on at King’s College Hospital who had previous SPES, and have more than 12 months of follow-up.⁶ A strong relationship between favourable post-surgical seizure control and removal of the abnormal SPES areas was found. Whereas around 96% of patients who had complete removal of abnormal SPES areas enjoyed a favourable outcome, only 71% of patients where these areas were partially removed had a favourable outcome. The three patients where abnormal SPES areas were not removed had poor outcomes (Table 3). More specifically, a

similar relation has been observed after frontal lobe resections.⁵ An important finding was the consistent presence of structural abnormalities demonstrated by neuropathology in the removed abnormal SPES areas despite normal neuroimaging.⁶ This means that delayed and repetitive responses arose from structurally and functionally abnormal regions.

SPES in children

In a study performed in King’s College Hospital and in Great Ormond Street Hospital for Sick Children (London UK), the utility of SPES in the paediatric population has been evaluated in 35 children. We identified cortical responses to SPES that were similar or identical to those reported in adults.⁷ These results are especially important because in children with focal epilepsy there is a compromise between safety and early surgical intervention. SPES

could reduce the duration of intracranial monitoring by optimising electrode placement and by providing reliable information during the interictal period, avoiding long waiting time for multiple seizures to occur.

Early responses and brain connectivity

Since early responses appear to be normal responses to SPES, they can be used to assess connectivity between different cortical regions.⁸⁻¹⁰ We have studied connections between temporal and frontal cortices in 51 patients.¹⁰ Our findings suggest that connections between temporal and ipsilateral frontal regions were relatively uncommon (seen in up to 25% of hemispheres) whereas connections between frontal and ipsilateral temporal cortices were more common, particularly from orbital to ipsilateral medial temporal regions (40%). Contralateral bi-temporal connections were rare (<9%) whereas contralateral bi-frontal connections were very frequent (up to 88%). These findings were assumed to be representative of human brain as no differences were found between epileptogenic and non-epileptogenic hemispheres.

Practical limitations of SPES

We have identified practical limitations of SPES. When stimulating through medial electrodes from subtemporal strips, about 25% of patients experienced brief ipsilateral facial pain or muscle contraction associated with each stimulating pulse. This effect was sometimes disagreeable and the intensity of stimulation had to be reduced, decreasing the sensitivity of SPES. The second limitation applies to patients with focal cortical dysplasia who show regions with nearly continuous spontaneous interictal epileptiform discharges. In these regions it is very difficult to identify DR, since they often have a morphology and topography similar to

Table 2: Comparison between the topographies of DR and ictal onset zones in the 83 patients with DR and seizures during telemetry.

DR topography	Ictal onset zone topography							Total
	Focal		Regional		Bilateral Indep.		Diffuse	
	in	out	in	out	in	out		
Focal	17	1	7	0	3*	0	0	28
Regional	6	0	31**	2	0	0	1	40
Bilateral	4***	0	4***	0	7	0	0	15
Total	27	1	41	2	10	0	1	83

Patients showing focal and regional ictal onset zones were considered as having regional ictal onset zone. Patients showing focal and regional DR were considered as having regional DR
in=DR inside the ictal onset zone; out=DR seen outside ictal onset zone and not within the ictal onset zone; indep=independent
 * All three patients had unilateral focal DR and bilateral seizures.
 ** Two patients had DR inside and outside the ictal onset zone
 *** All patients had DR inside and outside the ictal onset zone

