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Seizure Duration Determined by Subdural Electrode Recordings in Adult Patients with Intractable Focal Epilepsy

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Background and Purpose: To investigate the duration of seizures and its relationship to seizure type, epilepsy syndrome, and seizure clustering.

Methods: We examined 1,251 seizures from 152 patients who underwent video-electrocorticographic monitoring with subdural electrodes. Their seizure duration, seizure types, epilepsy syndromes, and seizure clusters were analyzed.

Results: The median seizure duration was 91.5s (4-1016s). There were 34 (2.7%) seizures lasting > 5 minutes in 20 (13.2%) patients. There was a significant difference in seizure duration according to seizure types ($p < 0.0001$), but not to epilepsy syndromes. There were 99 seizure clusters in 67 (44.1%) patients. The first seizure in a cluster of seizures tended to last longer than non-cluster seizures (median 98s versus 89s, $p = 0.033$). Seizure duration was significantly longer in mesial temporal lobe epilepsy than in neocortical lobe epilepsy (median 103s versus 87s, $p = 0.041$). Rate of seizure cluster was lower in mTLE (38.0%) than in NLE (47.1%), but this difference was not significant.

Conclusions: Seizure durations were different among seizure types. Seizure clustering also differ between patients with mTLE and those with NLE, which suggests different seizure generation and propagation among different epileptogenic foci. This study has implications for the identification of abnormally prolonged seizures. **(2011;1:57-64)**

Key words: Epilepsy; Seizure duration; Seizure cluster; Subdural grid

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Introduction

Epileptic seizures are common paroxysmal electrical phenomena that are usually self-limiting. If the brain mechanism that normally terminates seizures fails, the seizure becomes longer and can develop into status epilepticus, which is a serious medical emergency requiring prompt treatment. However, there is no consensus regarding the typical seizure duration.[1,2] Data from video-electroencephalographic (EEG) monitoring of patients with refractory focal epilepsy show that most secondarily generalized tonic-clonic seizures last for <2 minutes and that seizures lasting for >5 minutes are quite uncommon.[1,3,4] This has led some to propose that the definition of status epilepticus should be changed from a seizure or series of seizures lasting for ≥30 minutes to a seizure lasting for ≥5 minutes.[1] However, approximately one-half of all prolonged seizure episodes lasting from 10 to 29 minutes stop spontaneously.[5] There is insufficient data on seizure duration to determine whether the 5-minute criteria would be reasonable for patients in certain populations.

Most reports on seizure duration were based on scalp EEG findings or clinical events. These measures usually cannot determine seizure duration accurately. Epileptic activity in relatively small area or within deep cortical structures may not recorded with scalp electrodes.[6,7] Duration of aura, dialeptic seizures, negative motor seizures, or autonomic seizures frequently cannot be determined according to the clinical event per se.

In the present study, we investigated seizure duration in patients with subdural electrode arrays according to seizure type, focal

epilepsy syndrome, and seizure cluster. The establishment of a well-defined seizure duration will help physicians decide when to initiate treatment for ongoing seizure activity and will lead to a better understanding of the pathophysiology of epilepsy.

Methods

Subjects

We studied a consecutive series of 152 adult patients (median age of 28 years, ranging 18-61; 54 women) using long-term video-electrocorticographic (ECoG) monitoring with subdural electrode arrays at the Samsung Medical Center, Sungkyunkwan University School of Medicine (Seoul, Korea) from January 1995 to July 2006. The patients were admitted for invasive presurgical evaluation after subdural electrode placement. The median age at epilepsy onset was 14 years (range, 1-60). The patients had been refractory to adequate doses of antiepileptic medications for more than 1 year. The median duration of epilepsy was 14 years (range, 1-42). Pathologic diagnosis of the resected specimens revealed hippocampal sclerosis in 48 (31.6%) patients, focal cortical dysplasia in 44 (28.9%), neoplasm in 19 (12.5%), cavernous malformation in 7 (4.6%), focal encephalomalacia in 9 (5.9), neurocysticercosis in 2 (1.3%), Sturge-Weber syndrome in 1 (0.7%), paragonimiasis in 1 (0.7%), and nonspecific findings in 21 (13.8%). We analyzed 1,251 seizures (median number a patient, 7; range 1-39) that were clearly recorded on subdural electrode arrays in all patients. The patients' epileptic syndromes were determined according to their epileptogenic zones and divided into the following categories: frontal lobe epilepsy (FLE), parietal lobe epilepsy (PLE), occipital lobe epilepsy (OLE), mesial temporal lobe epilepsy (mTLE), lateral temporal lobe epilepsy (latTLE), and multifocal epilepsy (ME). Twenty-six (17.1%) patients had FLE, 16 (10.5%) patients had PLE, 2 (1.3%) patients had OLE, 50 (32.9%) patients had mTLE, 22 (14.5%) patients had latTLE, and 36 (23.7%) patients had ME.

Invasive video-ECoG monitoring

The patients were previously admitted for non-invasive presurgical evaluation of the epileptogenic zone. All patients underwent video-EEG monitoring with scalp electrodes, ictal video, ictal EEG and ictal single photon emission computerized tomography (SPECT). Additional studies, such as magnetic resonance imaging (MRI), positron emission tomography (PET) or interictal SPECT, had been performed to ensure the detection of the most probable epileptogenic zone. Neuropsychological tests, functional MRI or intracarotid amobarbital tests were performed to evaluate the eloquent area. The decision to perform invasive ECoG monitoring was made at the epilepsy management conference, where all non-invasive presurgical evaluations were reviewed.

After craniotomy was performed, invasive electrodes (PMT electrodes; PMT Co., MN) were placed to fully cover the epileptic foci, probable regions where ictal activity spreads, and nearby eloquent areas, such as speech, motor, somatosensory and visual areas. The electrodes were 5 mm in diameter, and the center-to-center distance between neighboring electrodes was 10 mm. Intraoperative electrocorticographic (ECoG) recording was also performed during subdural electrode placement, and subdural grids, strips, or both electrodes were used. If the mesial temporal structures needed to be covered, the mesial contact electrodes were placed as close to the mesial side as possible. Simple skull X-ray images and evoked potential mapping were used to localize the subdural electrodes in relation to the underlying brain structures. Moreover, post-implantation CT scans were fused with pre-implantation MR images, and the 3D-rendered MR images of the electrodes were compared with electrode position as determined by intraoperative digital photography in most of the patients.

Invasive monitoring (Vangard, Cleveland, OH) began one day after subdural electrode implantation. The patients were instructed to push an alarm button if they experienced an aura. Monitoring was carried out according to the standard protocol for medication withdrawal. Antiepileptic medication was reduced or withdrawn if seizures were not recorded by the second or third day of monitoring. This approach does not appear to have significant effects on the topography of electroencephalographic manifestations of seizure onset.[8] An intravenous line with heparin lock was established in the forearm prior to monitoring. Intravenous midazolam (0.05 mg/kg) was given when two consecutive secondarily generalized seizures or three complex partial seizures occurred within a few hours.

Seizure analysis

The clinical features of the seizures were analyzed by reviewing video recordings and structured interview descriptions, which included aura, responsiveness, memory impairment, and other clinical findings. If an electrographic seizure was recorded without aura or objective manifestations, it was classified as a subclinical ECoG seizure (SES). The clinical seizure types were classified in accordance with the International League Against Epilepsy (ILAE)

Table 1. Number of seizure types according to epilepsy syndrome

Seizure types	Epilepsy syndromes						Total
	FLE	PLE	OLE	mTLE	latTLE	ME	
Subclinical (%)	18 (7.9)	3 (2.4)	2 (7.1)	85 (20.2)	4 (2.4)	23 (8.1)	135 (10.8)
SPS (%)	109 (48.0)	41 (32.3)	0 (0.0)	60 (14.3)	16 (9.6)	32 (11.3)	258 (20.6)
CPS (%)	35 (15.4)	22 (17.3)	21 (75.0)	213 (50.7)	94 (56.6)	156 (55.1)	541 (43.2)
SGS (%)	65 (28.6)	61 (48.0)	5 (17.9)	62 (14.8)	52 (31.3)	72 (25.4)	317 (25.3)
Total	227	127	28	420	166	283	1,251

FLE, frontal lobe epilepsy; PLE, parietal lobe epilepsy; OLE, occipital lobe epilepsy; mTLE, mesial temporal lobe epilepsy; ME, multifocal epilepsy; Subclinical, subclinical electrographic seizure; SPS, simple partial seizure; CPS, complex partial seizure; SGS, secondarily generalized seizure.

guidelines for the classification of epileptic seizures (1981). There were 135 (10.8%) SESs, 258 (20.6%) simple partial seizures (SPS), 541 (43.3%) complex partial seizures (CPS), and 317 (25.3%) secondarily generalized seizures (SGS).

Seizure duration was determined from the electrocorticographic recordings during monitoring. Seizure duration was defined as the time of the earliest sustained ictal activity until the termination of activity in all subdural electrodes. Intervals between consecutive seizures were measured to determine whether the seizures occurred in a cluster. A seizure cluster was defined as two SGS or three CPS in 4 hours.[9]

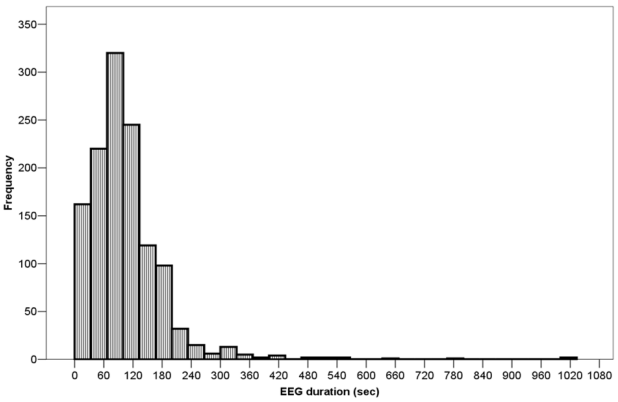

Figure 1. Distribution of the duration of all seizures. This histogram shows seizures lasting for > 5 minutes.

Data analysis

Because the data were non-normal, we utilized medians and ranges, rather than mean and SD, for summary purposes. Comparisons of seizure duration as a function of seizure type, epilepsy syndrome, and seizure cluster were performed using mixed model analysis. Mixed model analysis with Bonferroni's correction was used for posterior analysis. Mann-Whitney U test was used for comparisons between non-cluster and cluster seizures. Chi-square test was used to compare the frequency of seizure types and clustered seizures between patients with neocortical lobe epilepsy (NLE) and those with mTLE. Mann-Whitney U test was used to compare seizure duration between NLE and mTLE. Two-tailed p-values of <0.05 were accepted as significant. Statistical analyses were performed with SAS 9.13 (SAS Institute, Cary, NC).

Results

Seizure frequency according to epilepsy syndrome

The frequency of SES was 20.2% in mTLE, but less than 10% in NLE. The frequency of SPS was 48.0% in FLE and 32.3% in PLE, but less than 15% in mTLE, ME, latTLE, and OLE. The frequency of CPS was more than 50% in OLE, latTLE, mTLE and ME, but less than 20% in FLE and PLE. The frequency of SGS was the highest in PLE (48.0%) and the lowest in mTLE (14.8%) (Table 1).

Seizures lasting for >5 minutes

The median duration of all seizures was 91.5s (range, 4-1016). The lower and upper quartiles for seizure duration were 57 and 131s. The 5% trimmed mean was 96.6s. Figure 1 shows the distribution of seizures according to duration. Thirty-four (2.7%) seizures in 20 (13.2%) patients lasted for >5 minutes. Seventeen (4.0%) seizures were recorded in 9 (18.0%) patients in the mTLE group, 5 (2.2%) seizures were recorded in 3 (11.5%) patients in the FLE group, 2 (1.6%) seizures were recorded in 2 (20.0%) patients in the PLE group, 1 (0.6%) seizure was recorded in 1 (4.5%) patient in the latTLE group, and 9 (3.2%) seizures were recorded in 5 (13.9%) patients in the ME group. There were 6 (4.4%) SES, 9 (2.8%) SGS, 14

Table 2. Numbers of seizures lasting for more than 5 minutes according to epilepsy syndrome and seizure type

Seizure types	Epilepsy syndromes						Total (%)
	FLE	PLE	OLE	mTLE	latTLE	ME	
Subclinical	1	0	0	5	0	0	6 (4.4)
SPS	2	1	0	2	0	0	5 (1.9)
CPS	0	0	0	7	0	7	14 (2.6)
SGS	2	1	0	3	1	2	9 (2.8)
Total (%)	5 (2.2)	2 (1.6)	0 (0.0)	17 (4.0)	1 (0.6)	9 (3.2)	34 (2.7)

FLE, frontal lobe epilepsy; PLE, parietal lobe epilepsy; OLE, occipital lobe epilepsy; mTLE, mesial temporal lobe epilepsy; latTLE, lateral temporal lobe epilepsy; ME, multifocal epilepsy; Subclinical, subclinical electrographic seizure; SPS, simple partial sizure; CPS, complex partial seizure; SGS, secondarily generalized seizure.

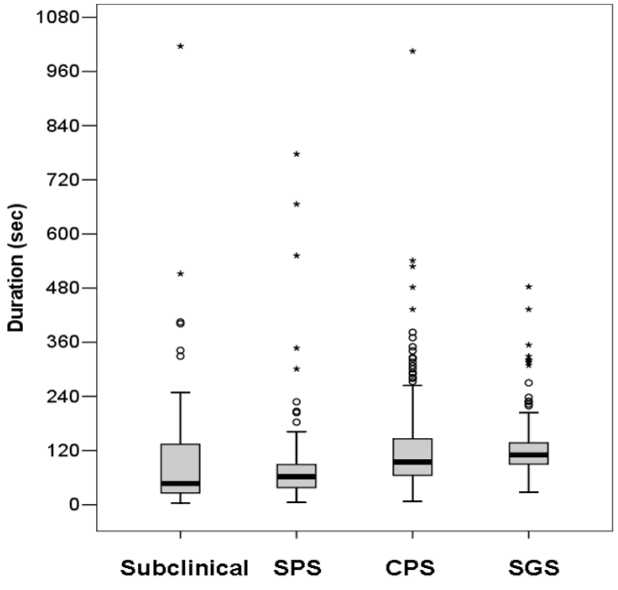

Figure 2. Seizure duration according to seizure type. Subclinical, subclinical electrographic seizure; SPS, simple partial seizure; CPS, complex partial seizure; SGS, secondarily generalized seizure.

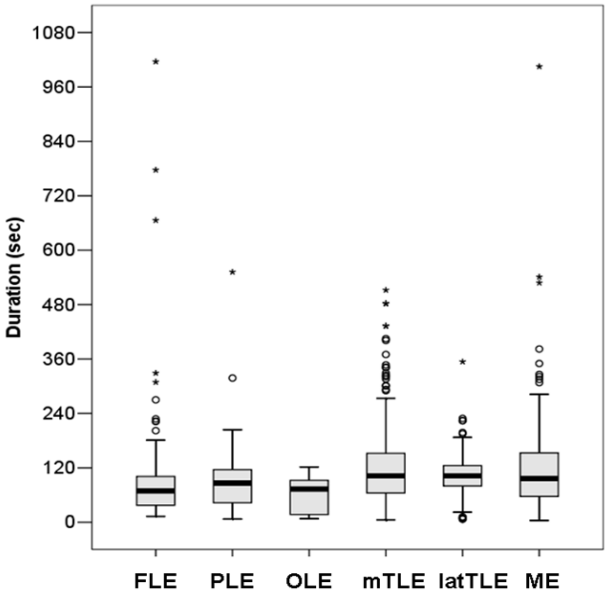

Figure 3. Seizure duration according to epilepsy syndrome. FLE, frontal lobe epilepsy; PLE, parietal lobe epilepsy; OLE, occipital lobe epilepsy; mTLE, mesial temporal lobe epilepsy; latTLE, lateral temporal lobe epilepsy; ME, multifocal epilepsy.

(2.6%) CPS, and 5 (1.9%) SPS (Table 2). Four (0.3%) seizures in 4 (2.6%) patients (1 SES and 2 SPS in the FLE group, and 1 CPS in the ME group) lasted for 10 to 20 minutes.

Seizure duration according to type of seizure

The median seizure duration was 47.0s (range, 4-1016s) for SES, 62.5s (range, 5-777s) for SPS, 95.0s (range, 7-1005s) for CPS, and 110.0s (range, 28-483s) for SGS (Figure 2). Mixed model analysis revealed a significant difference in seizure duration according to seizure type (p<0.0001). Mixed model analysis with Bonferroni's correction for seizure duration showed that seizure duration differed significantly according to seizure type. SGS and CPS lasted longer than SPS, and SPS lasted longer than SES (p=0.0001). SGS tended to last longer than CPS but this trend was not statistically significant.

Seizure duration and type according to epileptic syndrome

The median seizure duration was 69s (range, 13-1,016s) in FLE, 86s (range, 7-552s) in PLE, 73s (range, 8-122s) in OLE, 102s (range, 5-512s) in mTLE, 102s (range, 7-354 s) in latTLE, and 96.0s (range, 4-1005s) in ME (Figure 3). There was no difference in seizure duration according to epileptic syndrome (analysis of mixed mode, p=0.1025).

Seizure clusters

Ninety-nine seizure clusters were identified in 67 (44.1%) patients. The type of epileptic syndrome did not have a significant influence on the frequency of clusters (analysis using generalized linear mixed model, $p<0.4975$). The median duration of the first seizure in a cluster was 98s (range, 14-246s). The median duration of the second seizure was 104s (range, 7-329s), that of the third seizure was 101s (range, 7-354s), that of the fourth seizure was 100s (10-370s), and that of the fifth seizure was 98s (117-433s) (Figure 4). The duration of seizures in a cluster (median, 101s; range, 7-433s) was typically longer than that of seizures that did not cluster (median, 89s; range 4-1016s), but this trend was not statistically significant (Mann-Whitney U, $p=0.351$). There was a significant difference in seizure duration between the first seizure in a cluster of seizures and non-cluster seizures (Mann-Whitney U, $p=0.033$).

Comparison of NLE and mTLE

We reclassified the epilepsy syndromes into two types: neocortical epilepsy (NLE: FLE+PLE+OLE+latTLE+ME) and mTLE. There was a difference in seizure frequency between the NLE and mTLE groups. SPS (23.8%) and SGS (30.7%) were more frequent in the NLE group than in the mTLE group (14.3% and 14.8%, respectively), whereas SES (20.2%) and CPS (50.7%) were more frequent in the mTLE group than in the NLE group (6.0% and 39.5%, respectively) (chi-square test, $p=0.0001$) (Figure 5). Seizure duration was significantly shorter in NLE (median, 87s; range, 4-1016s) than in mTLE (m edian, 103s; range 5-512s) (Mann-Whitney U, $p=0.041$) (Figure 6). Seizure clusters were more frequent in NLE (47.1%) than in mTLE (38.0%), but this difference was not statistically significant (Mann-Whitney U, $p=0.303$).

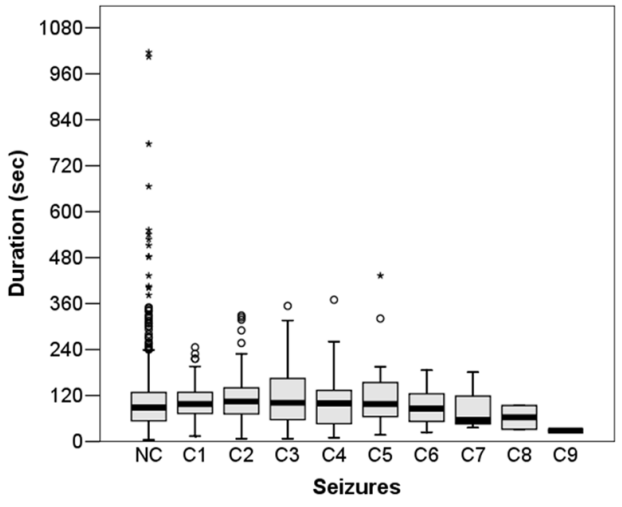

Figure 4. Seizure duration in cluster and non-cluster seizures. NC, non-cluster seizure; C1-9, the first to the ninth seizure in a seizure cluster.

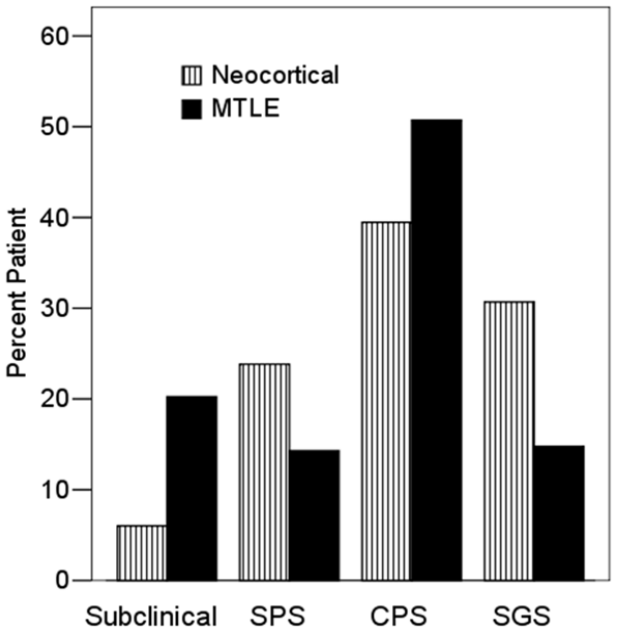

Figure 5. Comparison of seizure types between neocortical and mesial temporal lobe epilepsy. Neocortical, neocortical epilepsy; MTLE, mesial temporal lobe epilepsy; Subclinical, subclinical electrographic seizure; SPS, simple partial seizure; CPS, complex partial seizure; SGS, secondarily generalized seizure.

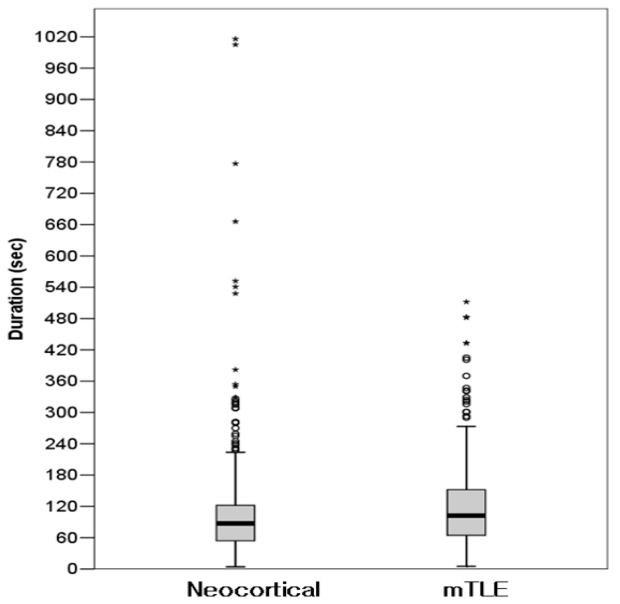

Figure 6. Comparison of seizure duration between neocortical and mesial temporal lobe epilepsy. Neocortical, neocortical lobe epilepsy; mTLE, mesial temporal lobe epilepsy.

Discussion

In the present study, we investigated the seizure duration in adult patients with intractable focal epilepsy using subdural electrodes. The invasive recording technique can detect seizure onset earlier and the end of a seizure more clearly than the scalp recording technique. The recordings can also easily detect subclinical seizures. In addition, subjects of this study represent selected group of patients with intractable focal epilepsy. It is, however, not known whether intractability affects seizure duration.

The median duration of all seizures was 91.5s (range, 4-1016s). Only 2.7% of seizures in 20 of 152 (13.2%) patients lasted for more than 5 minutes. Patients with mTLE had a higher percentage of seizures lasting >5 minutes (4.0%) than those with NLE (2.0%). In a previous study, among 696 seizures recorded from 161 patients who were monitored with scalp electrodes, 27 (3.9%) seizures lasted >5 minutes.[9] SGS usually lasted for less than 6 minutes, with the exception of 2 of 317 (0.9%) seizures. CPS typically lasted for less than 7 minutes, except for 4 of 542 (0.7%) seizures.

Seizure duration was significantly different according to seizure type. The median duration of seizures was 110.0s in SGS, 95.0s in CPS, 62.5s in SPS, and 47.0s in SES. In addition, the range of seizure duration was wider in SES (1012s) or partial seizures (CPS, 998s; SPS, 772s) than in generalized seizures (455s), suggesting that the duration of generalized seizures is relatively regular. One study compared the duration of different types of seizures recorded during video-EEG monitoring.[10] They reported that the median seizure durations were 78s in CPS and 28s in SPS, which were shorter than those found in the present study. An invasive study of CPS with subdural and depth electrode arrays showed that the duration of CPS was 106s in mTLE, 82s in neocortical TLE, and 78s in neocortical extratemporal lobe epilepsy, which was in agreement with our data.[11] A semi-invasive study of temporal lobe epilepsy showed that ictal changes occurred earlier at sphenoidal contacts than on the scalp in 20.1% of seizures.[12] Those results suggest that the seizure duration measured by scalp recording could be shorter than that measured in invasive or semi-invasive studies. Moreover, our subdural recordings demonstrated 135 (10.8%) subclinical electrographic seizures. Since ictal discharges at seizure onset gradually increase in amplitude during the course of a significant proportion of partial seizures, a larger proportion of neurons may have to be recruited in order to generate identifiable EEG signals on the scalp. An in vitro cadaveric study showed that significant signals would be obtained on the scalp provided that the sum of the cortical areas recruited is about 6 cm^2 and that the coherent regions are close together.[6] A study on simultaneous ECoG with scalp EEG suggested that ictal ECoG discharges recorded on at least 8-15 subdural electrodes, which correspond to 8-15 cm^2, were observed on scalp EEG. In terms of the amplitude of the ictal ECoG potentials, ictal ECoG discharges with amplitudes of 200-2,000 μV could be recorded on scalp EEGs. However, even though ictal ECoG activities were recorded on 10 electrodes with maximum amplitudes of 500-600 μV, any corresponding ictal discharge could not be recorded on EEG. These findings suggest that various factors can be involved in determining the appearance and amplitude of ictal EEG activities, although the extent of the area involved in ictal activities and the amplitude of the ictal discharges are obviously important factors.[13] Those features support that subdural ECoG recordings can differ from those of scalp EEG when evaluating ictal electrophysiologic recordings and when detecting subclinical seizures.

The clinical expression of a seizure depends largely on its site of origin.[14] The proportion of each seizure type differed between epileptic syndromes. SPS was the most frequent type of seizure in patients with FLE. SGS was the most frequent type of seizure in patients with PLE. CPS was the most frequent type of seizure in patients with OLE, ME, and TLE, regardless of whether they were classified as mesial or neocortical. Especially, SPS and SGS were more frequent in the NLE group, whereas SES and CPS were more frequent in the mTLE group. The duration of each seizure may be related to the type of epilepsy syndrome. CPS is brief in FLE[15] and shorter than in TLE. Sagi *et al.*[16] observed short frontal lobe seizures in adults, with an average duration of less than 1 min. An intracranial EEG study revealed that the median duration of CPS was 106s in mTLE and 78s in neocortical extratemporal lobe epilepsy.[11] Laskowitz *et al.* reported that the average seizure duration in FLE was 68s.[17] In our study, basic descriptive statistics showed that the median seizure duration was shortest in FLE (69s) and longest in TLE (102s). Statistical analysis showed no significant difference in seizure duration according to epileptic syndrome, but the duration of seizures was significantly longer in mTLE than in NLE. The mesial temporal structures are interconnected by an organized fiber system that creates a reverberating loop involving the entorhinal cortex, dentate gyrus, CA3 and CA1 regions, and the subiculum.[14] Dreier and Heinemann showed that this full circuit is both necessary and sufficient to sustain persistent epileptic activities,[18] Experiments in various animal models have shown that sprouted mossy fibers make

synaptic contacts in ectopic locations, and thus form an excitatory feedback circuit.[19] Mesial temporal lobe seizures can maintain epileptic discharges through normal or pathological hippocampal circuitry, which can have implications for seizures of long duration.

Seizure clustering implies that the occurrence of one seizure may influence the probability of subsequent seizures.[20] Reports concerning relations between seizure clustering and status epilepticus, however, were inconsistent. A previous study reported that seizure clustering was associated with a significantly higher risk of prolonged seizure and status epilepticus.[21] Another study found no statistically significant increase in status epilepticus or prolonged seizure in patients with seizure clusters.[9] Moreover, the prevalence of seizure clustering varies widely between studies and definitions, ranging from very low up to 60%.[22] We used the clinical 4-hour period definition for seizure clustering. The rate of seizure clusters in the present study was similar to that reported in subjects who underwent presurgical evaluations.[9,23] The duration of the first seizure in a cluster of seizures (median, 98s; range, 14-246s) was significantly longer than that of non-cluster seizures (median, 89s; range 4-1016s). This suggests that a prolonged seizure may be another risk factor for the next seizure to be followed by clusters. The localization of the epileptic zone was considered to be a risk factor for seizure clustering. The rate of seizure cluster was higher in NLE than in mTLE. A previous report suggested that extratemporal epilepsy, especially FLE, was significantly associated with seizure clustering.[17,24] Interestingly, we demonstrated that NLE had shorter duration and more frequent seizure clustering, compared to mTLE. Therefore, the longer seizure duration, as a risk factor for seizure clustering, should be related to a measureable increase over typical seizure duration of the epilepsy syndrome.

Although a duration of 5 min for the operational definition of status epilepticus is most widely adopted by clinicians for initiating emergency therapy,[2] we do not have adequate data for choosing a time point that differentiates seizures at risk of prolonged or repetitive seizures from self-limiting seizures. In our study, the duration of seizures differed according to seizure type and site of origin. The appropriate time point for early intervention in patients with status epilepticus may differ according to these factors. Prolonged seizure duration needs to be taken into greater consideration in patients with mTLE. A prolonged initial seizure can be followed by a cluster of seizures, especially in patients with NLE.

In this study, we classified the subjects according to their epileptogenic zones with a high degree of certainty. In addition, invasive ECoG monitoring provided a more sensitive means of detecting the onset of ictal electrographic activity. The majority of our patients had intractable localization-related epilepsy and were candidates for epilepsy surgery. Though this population may not represent all patients with epilepsy, our electrocorticographic results have implications for the identification of abnormally prolonged seizures and different seizure durations according to seizure type in selected groups of patients. Seizure duration and seizure clustering can differ between patients with mTLE and NLE, which suggests that seizure generation and propagation to underlying structures may differ according to epileptogenic foci.

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We have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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