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EKG Abnormalities During Partial Seizures in Refractory Epilepsy

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Summary: *Purpose:* This study assessed the frequency and character of ictal cardiac rhythm and conduction abnormalities in intractable epilepsy. Sudden unexpected death in epilepsy (SUDEP) is a major cause of excess mortality in people with refractory epilepsy, and cardiac arrhythmias during seizures may be responsible. The frequency of cardiac abnormalities during seizures in patients with refractory epilepsy must be determined.

Methods: Fifty-one seizures in 43 patients with intractable partial epilepsy were analyzed prospectively from CCTV-EEG monitoring with one ECG channel. Arrhythmias, repolarization abnormalities, and PR and QT_c intervals were determined for preictal (3 min), ictal, and postictal (3 min) periods for one or more seizures per patient. Parametric statistics were used for continuous variables, and nonparametric statistics were used for categoric variables.

Results: Of the patients, 39% had one or more abnormalities of rhythm and/or repolarization during or immediately after seizures. Abnormalities included asystole (one), atrial fibrillation (one), marked or moderate sinus arrhythmia (six), supraventricular tachycardia (one), atrial premature depolarizations (APDs; eight), ventricular premature depolarizations (VPDs; two), and bundle-branch block (three). Mean seizure duration was longer in patients with abnormalities than in those without (204 vs. 71 s; $p < 0.001$). Generalized tonic–clonic seizures were also associated with increased occurrence of ictal ECG abnormalities ($p = 0.006$) as compared with complex partial seizures. There were no clinically significant differences in mean preictal and ictal/postictal PR and QT_c intervals.

Conclusions: Cardiac rhythm and conduction abnormalities are common during seizures, particularly if they are prolonged or generalized, in intractable epilepsy. These abnormalities may contribute to SUDEP. **Key Words:** Epilepsy—SUDEP—ECG—Cardiac—Arrhythmia.

Seizures may directly affect cardiac rate and rhythm. They commonly produce sinus tachycardia and occasionally may cause sinus bradycardia, asystole, and other rhythm disturbances (1–7). However, serious cardiac arrhythmias during seizures appear to be rare (1,8). Studies have focused on cardiac arrhythmias associated with seizures largely because of their possible relation to sudden unexpected death in epilepsy (SUDEP).

People with epilepsy have an increased risk of death compared with the general population (9). SUDEP is a major cause of mortality in patients with epilepsy, particularly in those with refractory epilepsy (10,11). SUDEP may account for perhaps half of the deaths in this population (12,13). A variety of factors have been associated with SUDEP, including uncontrolled seizures, young age, generalized tonic–clonic seizures, seizures during sleep, poor antiepileptic medication (AED) compliance, and use of a larger number of AEDs (14–18). However, the major risk factor appears to be having seizures. People who are not completely controlled have a much higher risk of SUDEP than do well-controlled patients (16).

Both pulmonary and cardiac mechanisms have been implicated as possible contributors to SUDEP (11,19–21). Animal models reveal that significant hypoventilation can occur during prolonged seizures and may contribute to seizure-associated deaths (11,22,23). Thus far, ictal cardiac rhythm disturbances have been primarily reported as case reports or in series of epilepsy patients focusing on heart-rate changes during seizures. However, no studies have been performed to determine how frequently abnormalities of cardiac rhythm and conduction occur during seizures in patients at a relatively high risk for SUDEP, such as those with refractory epilepsy.

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Additionally, it is not known whether specific seizure characteristics, such as seizure type, duration, and laterality, influence the risk for ictal cardiac arrhythmias.

The goals of this study were to evaluate the cerebral mechanisms involved with ictal cardiac arrhythmias, determine how frequently ictal cardiac arrhythmias are seen in patients with refractory epilepsy, and assess whether the risk factors associated with SUDEP correlate with a higher likelihood of occurrence of an ictal cardiac rhythm disturbance. The identification of specific cardiac abnormalities associated with seizures may reveal a potential mechanism of death in some patients with SUDEP and may eventually aid in the prevention of SUDEP.

METHODS

Subjects

Forty-three patients with refractory partial epilepsy who were consecutively admitted to a video-EEG monitoring unit as part of their evaluations for epilepsy surgery were studied prospectively between August 1997 and April 1998. AEDs were tapered as needed to record seizures. No patients had a history of cardiac or pulmonary disease, and all had normal serum potassium, magnesium, and calcium levels on admission.

ECG data

Each patient had a 12-lead ECG performed at admission. In addition, ECG data from at least one complex partial or generalized tonic–clonic seizure per patient was analyzed. ECG data were obtained from lead I recording during video-EEG monitoring by using the Telefactor Corporation (Conshohoken, PA, U.S.A.) TWIN program. ECG data from each seizure were analyzed separately for the following three periods: (a) preictal period: 3 min immediately preceding seizure onset; (b) ictal period: during the entire ictal period, limited to technically satisfactory portions of the recording; and (c) postictal period: 3 min immediately after seizure cessation.

The following data were collected for each of the three periods:

1. Heart rate: Heart rate was the number of consecutive RR intervals during the first minute of each period.
2. Rhythm abnormalities: These included moderate or marked sinus arrhythmia (defined as $\geq$50% increase in heart rate during inspiration as compared with expiration) (24), APDs (atrial premature depolarizations), VPDs (ventricular premature depolarizations), atrial fibrillation, junctional escape complexes, asystole, and supraventricular tachycardia. Blocked APDs were defined as APDs that did not conduct to the ventricles.
3. Conduction abnormalities included bundle-branch block.
4. Repolarization abnormalities included ST-segment elevation or depression and T-wave inversion. ST-segment changes were measured in millivolts, and then converted to the equivalent number of millimeters, as measured on standard 12-lead ECGs.
5. PR and corrected QT (QT_c) measurements were measured by using digital calipers every 20–30 s during the baseline and postictal periods, and every 10 s during the ictal period, as allowed by recording artifact and ictal duration; for a total of five measurements per period when possible. Data were not used for this analysis if five measurements could not be reliably made during a specific period. The QT_c was determined by QT/square root of the RR interval for each QT value (25). PR intervals were considered normal between 120 and 200 ms. QT_c intervals were considered normal at <440 ms.

Comparison variables

EEG was obtained by using the 10–20 system and sphenoidal electrode placement. Variables consisted of (a) laterality of seizure onset, as determined by scalp EEG data, or as determined subsequently by intracranial subdural and depth electrode EEG data; (b) state of consciousness (awake or asleep) before seizure onset; (c) seizure duration, as determined by clinical and EEG data; (d) seizure type: complex partial or secondarily generalized tonic–clonic; and (e) AEDs on admission.

Data analysis

ECGs were classified as abnormal if any abnormalities of rhythm or conduction were found during any period that were not present on the baseline 12-lead ECG; all other ECGs were classified as normal. Isolated sinus tachycardia (heart rate $\geq$100 beats/min) was not considered an abnormality and was analyzed separately.

For each seizure, ECGs were classified as abnormal if a previously mentioned abnormality was found in the ictal or postictal state. The presence of ECG abnormalities was assessed in relation to each of the comparison variables. Parametric and nonparametric statistics were used as appropriate and are specified in the Results.

RESULTS

Fifty-one seizures from 43 patients with intractable partial epilepsy were analyzed for this study. The mean age was 34 years (range, 14–55 years), with 25 men and 18 women. There were 35 complex partial and 16 secondarily generalized tonic–clonic seizures. The mean seizure duration was 123 s (standard error, 23; range, 11–960).

TABLE 1. *ECG abnormalities (ictal/postictal)*

ECG abnormality	Number of patients[a]
Potentially serious abnormalities	
ST-segment elevation (equivalent to >2-mm segment elevation)	3
Junctional escape	2
Asystole (6.5 s)	1
Atrial fibrillation	1
Supraventricular tachycardia	1
Total number of patients with ≥1 of these	6
Generally benign abnormalities	
Atrial premature depolarizations	8
Marked or moderate sinus arrhythmia (inspiratory increase in heart rate by >50%)	6
Bundle-branch block	3
Ventricular premature depolarizations	2
Atrial couplets/triplets	1
Total number of patients with ≥1 of these	13

[a] Some patients had >1 abnormality. See text and Table 2 for details.

Preictal ECG: Preictal ECG was normal in 40 patients and abnormal in three patients. Each of these three had intermittent APDs.

Ictal and postictal ECG: Seventeen (39%) patients had ECG abnormalities during the ictal and/or postictal period (see Tables 1 and 2). Twenty-three (53%) patients had sinus tachycardia (heart rate ≥100 beats/min) during the ictal or postictal period, of whom 10 had ECG abnormalities. Thus a total of 30 (70%) patients had at least one ECG abnormality or sinus tachycardia during the ictal and/or postictal period.

The most common abnormalities were the presence of APDs (eight patients) and sinus arrhythmia (six patients; (Fig. 1). Three of the eight patients with APDs also had APDs during the preictal period; however, APDs markedly increased in frequency during the ictal and/or postictal periods. Six patients had potentially serious ECG abnormalities (ST-segment elevation, junctional escape, asystole, atrial fibrillation, and supraventricular tachycardia), at times in combination with more benign abnormalities. The other 11 patients had generally benign abnormalities (APDs, marked or moderate sinus arrhythmia, bundle-branch block, VPDs, and atrial couplets/triplets). Several patients had more than one abnormality (Table 2).

When abnormalities occurred during the postictal period, they were often noted to persist throughout the entire 3-min period, and noted to persist for several more minutes in some cases.

Baseline 12-lead ECG

Fifteen (35%) patients had one or more abnormalities noted on a baseline 12-lead ECG. Twelve of these patients (T-wave abnormalities in five, bundle-branch block in two, left atrial enlargement in two, left ventricular hypertrophy in one, first-degree atrioventricular block in one, and infarct pattern in two) had normal ictal and postictal ECGs, and three of these patients (incomplete bundle-branch block and infarct pattern in one, T-wave inversion in one, and incomplete right bundle-branch block in one) had abnormal ictal or postictal ECGs. Patients with significant abnormalities on the 12-lead ECG, except for one patient who was lost to follow-up, underwent further evaluation, and none was found to have evidence of coronary artery disease, evidence of myocardial injury by noninvasive studies, or other active cardiac disease requiring intervention.

TABLE 2. *Seizures associated with ECG abnormalities*

Patient	Seizure type	Duration (s)	Onset	Abnormalities
1	CPS	960	Probably R temporal	Bundle-branch block postictally
2	GTC	118	Non-loc	APDs, atrial fibrillation, junctional escape, atrial triplets, atrial couplets
6	GTC	110	R temporal	APDs during preictal and ictal periods; blocked APDs during ictal period
10	GTC	470	Non-loc	APDs during preictal period; increased during ictal and postictal periods
13	GTC	136	Non-loc	1 VPD postictally; heart rate, 122 beats/min
13	GTC	242	Non-loc	25 VPDs postictally, heart rate, 160 beats/min, seizure occurred 27 min after the above seizure
17	GTC	76	Probably L temporal	Sinus arrhythmia
20	CPS	45	R temporal	ST-segment elevation postictally
20	CPS	90	R temporal	ST-segment elevation postictally
23	CPS	115	R temporal	APDS, noncompensatory pauses preictal; APDS, compensatory pauses postictal
24	GTC	153	R temporal	Sinus arrhythmia and APDs postictally
25	GTC	72	R temporal	Sinus arrhythmia and APDs postictally
29	CPS	80	L frontal	Sinus arrhythmia
29	CPS	100	L frontal	Sinus arrhythmia
34	CPS	80	Non-loc	Sinus arrhythmia and APDS postictally
36	CPS	94	L temporal	Sinus arrhythmia, bundle-branch block
37	GTC	110	Non-loc	Supraventricular tachycardia postictally; heart rate, 270 beats/min
38	CPS	55	R temporal	Alternating bundle-branch block, ST-segment elevation, junctional escape, VPDs, APDs
40	GTC	255	L temporal	Asystole for 6.5 s
42	CPS	720	L temporal	ST-segment elevation

CPS, complex partial seizure; GTC, generalized tonic–clonic seizure; R, right; L, left; APD, atrial premature depolarizations; VPD, ventricular premature depolarizations; non-loc, nonlocalizable.

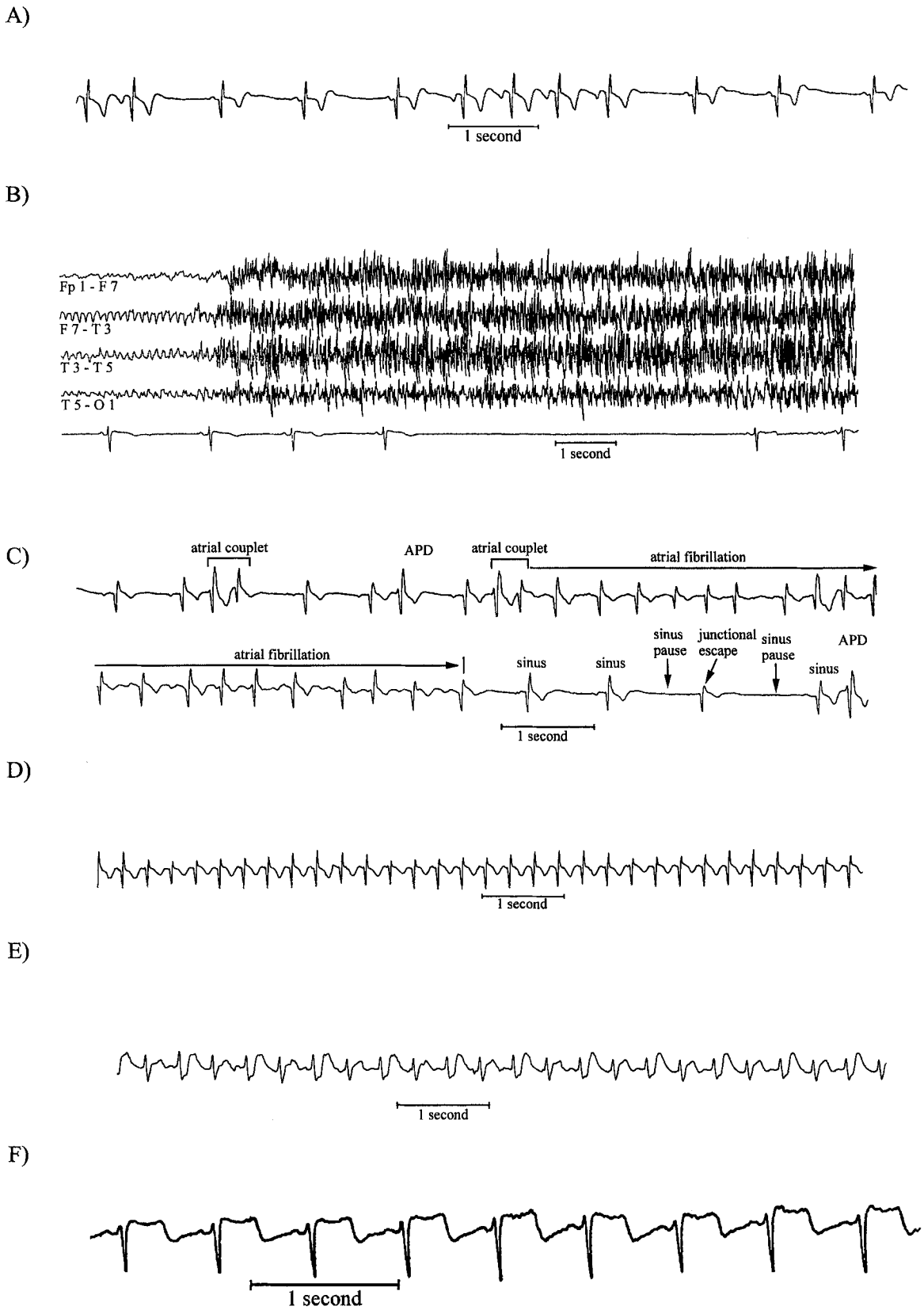

FIG. 1. **A:** Patient 17 (postictal): Marked sinus arrhythmia. **B:** Patient 40 (ictal): Sinus bradycardia occurs at the onset of a seizure, followed by asystole for 6.5 s within 2.5 s of the onset of the tonic phase of a secondarily generalized tonic–clonic seizure. Asystole was then followed by sinus tachycardia. The pattern of progressively slower sinus bradycardia and at times asystole was seen during her other seizures. **C:** Patient 2 (90–110 s postictal): Frequent APDs, and then atrial fibrillation, sinus rhythm, junctional escape, and frequent APDs. **D:** Patient 37 (250 s postictal): Supraventricular tachycardia. **E:** Patient 38 (ictal): Alternating bundle-branch block. **F:** Patient 20 (postictal): ST-segment elevation.

For patients with ictal or postictal abnormalities, 13 (75%) had normal 12-lead baseline ECGs, and four (25%) had abnormal ECGs. For patients without abnormalities, 14 (55%) had normal ECGs, and 12 (45%) had abnormal ECGs. Patients with ictal or postictal ECG abnormalities were not more likely to have abnormalities on a 12-lead ECG ($p = 0.12$, Fisher's Exact test) than were patients with normal baseline ECGs.

Seizure duration and type

Seizures associated with ECG abnormalities lasted longer than those without (204 vs. 71 s; $t = 3.68$; $p < 0.001$). Generalized tonic–clonic seizures were also more frequently associated with ictal ECG abnormalities ($\chi^2 = 5.3$; $p = 0.02$) as compared with complex partial seizures. Using stepwise discriminant function analysis, generalized tonic–clonic seizure type and longer seizure duration were each found to be independent predictors of ECG abnormalities (Wilks' $\lambda = 0.778$; $F(2, 48) = 6.8$; $p < 0.002$).

Additionally, generalized tonic–clonic seizures were also more likely to be associated with sinus tachycardia than were complex partial seizures ($p = 0.035$; Fisher's Exact test).

State of consciousness before seizure onset

The state before seizure onset did not influence whether or not ictal or postictal ECG abnormalities were present. For 20 seizures with ECG abnormalities, eight (40%) were awake, and 12 (60%) were in non–rapid eye movement (NREM) sleep before seizure onset. For 31 seizures without ECG abnormalities, 19 (61%) were awake, and 12 (39%) were in NREM sleep. There was no significant difference between the two groups ($\chi^2 = 2.21$; $p = 0.137$).

Laterality of seizure onset

Side of seizure onset was not related to presence or absence of ictal ECG abnormalities for the 33 seizures in which the side of seizure onset could be reliably determined ($p = 0.35$; Fisher's Exact test). For seizures with ECG abnormalities, eight (73%) began in the right hemisphere, and three (27%) in the left hemisphere. For seizures without ECG abnormalities, 13 (59%) began in the right hemisphere, and nine (41%) began in the left hemisphere.

Anticonvulsant medications

Patients with ictal or postictal ECG abnormalities took similar medications as those without abnormalities: phenytoin (PHT; 35% vs. 35%), valproic acid (VPA; 12% vs. 19%), carbamazepine (CBZ; 29% vs. 42%), lamotrigine (LTG; 18% vs. 19%), gabapentin (GBP; 18% vs. 11%), topiramate (TPM; 35% vs. 27%), phenobarbital (PB; 12% vs. 15%), and tranxene (12% vs. 4%). Additionally, one (4%) patient without abnormalities was taking felbamate (FBM).

The mean number of AEDs per patient at the time of admission was the same, 1.8 medications per patient, for patients with or without ictal ECG abnormalities.

PR and QT_c intervals

We calculated mean values for preictal, ictal, and postictal PR and QT_c intervals for each patient. All mean PR and QT_c values were normal. Mean values were then averaged for each of the three periods for the patients as a whole.

With paired *t* tests, there were no differences between preictal and ictal PR intervals. Similarly, there were no differences between preictal and ictal or postictal QT_c intervals. There was a significant difference between preictal (147 ms) and postictal (141 ms) PR intervals ($t = 2.23$; $p = 0.003$), which is consistent with the general tendency toward increased heart rate during the postictal period as compared with the preictal period.

Patients with two seizures

Eight patients had two seizures reviewed. Two patients had one seizure with ECG abnormalities and another seizure without abnormalities. In both patients, the ECG abnormalities were seen during the longer seizure.

Patient 1 had two complex partial seizures, one of which lasted 110 s, and the other, 960 s. After the 960-s seizure, he developed a bundle-branch block during the postictal period.

Patient 42 had two complex partial seizures (110 and 720 s), with ST-segment elevation occurring during the longer seizure.

In all other patients, both seizures had similar findings [i.e., both ECGs were abnormal or both were normal (Table 2)].

DISCUSSION

The major finding in this study is that cardiac rhythm and conduction abnormalities occur frequently during or after partial seizures in patients with refractory partial epilepsy. In particular, ECG findings consistent with excessive autonomic discharge, including atrial fibrillation, APDs, VPDs, supraventricular tachycardias, sinus tachycardia, and asystole, were common. The primary features associated with the appearance of ECG abnormalities are prolonged seizure duration and the presence of secondarily generalized tonic–clonic seizures. Other factors studied, state of consciousness before seizure onset, laterality of seizure onset, type and number of AEDs, and abnormal baseline 12-lead ECG, were not related to the presence of ictal or postictal ECG abnormalities.

Both generalized seizures and longer seizure duration may increase the risk for cardiac arrhythmias through ictal autonomic hyperactivity. Such changes may be due to increased circulating plasma catecholamines (26) or direct autonomic stimulation of the heart. Both longer

seizure duration and generalized tonic–clonic seizures may involve greater ictal spread than complex partial seizures and thus may be more likely to affect autonomic centers responsible for cardiac control, although a complex partial seizure spreading to autonomic centers could also produce similar ECG abnormalities.

Serial seizures may produce additive autonomic effects, particularly because cardiac rhythm abnormalities often persisted throughout the entire 3-min postictal period. Such a mechanism may explain why both the frequency of VPDs and heart rate increased significantly during the second seizure as compared with the first seizure in patient 13. This study did not specifically review how long the cardiac abnormalities persisted postictally because the postictal study period was limited to 3 min. Recently Tigaran and Dam (27) reported a patient with postictal atrial fibrillation persisting for hours. This requires further study, because late-occurring arrhythmias may have clinical consequences.

Generalized seizures have been associated with higher risk for SUDEP and in this study have been associated with cardiac arrhythmias, suggesting the possibility of a cause-and-effect relation between ictal cardiac arrhythmias and SUDEP. The high frequency of ictal cardiac rhythm abnormalities in this group of patients, who are generally at higher risk for SUDEP, also supports this possible relation.

Seizures could result in lethal arrhythmias by two major mechanisms. Autonomic activity associated with seizures might directly cause lethal arrhythmias. Six patients in this study had potentially serious abnormalities, suggesting that seizures might rarely result in lethal cardiac rhythms. Additionally, in this study, ictal autonomic stimulation was seen in the majority of patients. It is possible that repetitive autonomic stimulation from multiple seizures may damage the heart, resulting in myocardial fibrosis and myofibrillar degeneration, lesions associated with catecholamine toxicity (28,29), which have also been identified in SUDEP patients (14,30). An abnormal cardiac substrate (myofibrillar degeneration and fibrosis) in the setting of a trigger (autonomic discharge associated with seizures) may result in lethal ventricular tachyarrhythmias. Myocardial fibrosis with autonomic imbalance has been proposed as a mechanism of postinfarction ventricular tachycardia (31). Similarly, a seizure may have triggered a lethal arrhythmia in the setting of prior myocardial infarctions in three SUDEP patients reported by Dasheiff and Dickinson (32). Once patients develop myocardial fibrosis through repeated seizures, they may then remain at increased risk for lethal arrhythmias, even if there are only rare isolated seizures. However, this remains speculative.

Prior studies have reported ST-segment and T-wave changes associated with epilepsy in humans and animals (33,34). ST-segment elevation was also found in three study patients. This finding suggests that myocardial ischemia might also occur in association with seizures. However, at this time, the mechanism underlying these changes is unknown, and thus it is difficult to make conclusions regarding their potential clinical relevance.

CBZ was used more frequently than other AEDs in one series of SUDEP patients (35), and prolongation of the QT interval was postulated as one mechanism by which CBZ might cause lethal arrhythmias. In this study, no specific medication was associated with the appearance of ECG abnormalities. Additionally, although this study did not analyze whether specific AEDs may be associated with longer QT_c intervals, the mean QT_c intervals were normal in all cases. There was no evidence that any specific AED causes an abnormal QT_c either interictally or in association with seizures.

Some comments should be made regarding the patients with abnormal 12-lead ECGs. As described in the Results sections, these patients (except one) underwent extensive noninvasive cardiac testing, which revealed no evidence of past or present cardiac disease. This study reveals no association between ictal or postictal ECG abnormalities and abnormal 12-lead ECGs. Thus significant cardiac disease cannot explain the seizure-associated ECG changes seen in this study, although more subtle cardiac changes, such as myofibrillar degeneration, cannot be excluded.

Regarding study limitations, PR and QT_c intervals were not analyzed for individual patients because of the relatively small number of data points obtained per period of study for each patient. Also because each EEG–ECG review was a lengthy process, we limited the number of seizures per patient to one or two to review as many patients as possible. Likewise, the control data were limited to 3 min of preictal recording for similar reasons and were obtained from the immediate preictal period in an attempt to try to control for influences that might arise from differences in time of day, state, and level of physical activity. Data from several seizures per patient may reveal patterns of ECG changes, which are stereotyped for each patient and related to specific patterns of ictal spread. Physical activity during the seizures, particularly generalized tonic–clonic seizures, may also have some influence on the ECG. Further study evaluating the effect of physical activity on the ECG in patients with epilepsy may help to clarify this further.

Additional work in this area is needed to explore more closely the relation between seizures and cardiac rhythm. ECG monitoring should be done routinely in patients admitted for video-EEG monitoring to identify serious ictal cardiac abnormalities, particularly in those with refractory epilepsy. Patients with ictal cardiac arrhythmias may benefit from further cardiac evaluation for a serious underlying cardiac substrate, which may elevate the patient's risk of lethal arrhythmia during a seizure. As more

patients undergo EEG–ECG monitoring, the mechanism of ictal cardiac abnormalities and their possible relation to SUDEP may be eventually elucidated.

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