Relationship Between Seizure Episode and Sudden Cardiac Arrest in Patients With Epilepsy

A Community-Based Study

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Background—Among patients with epilepsy, sudden cardiac arrest (SCA) is a major cause of death. It is commonly thought that SCA in epilepsy occurs after a seizure, though the strength of evidence supporting this is limited. We sought to evaluate the relationship between seizures and SCA in patients with epilepsy.

Methods and Results—From the ongoing Oregon Sudden Unexpected Death Study, cases of SCA identified using prospective, multisource ascertainment (Portland metropolitan area, Oregon; population ≈1 million; February 1, 2002, to March 1, 2012) were evaluated for history of epilepsy. In the subset with witnessed SCA, clinical presentations were analyzed for evidence of seizure activity immediately before the event as well as lifetime clinical history, including nature of seizures before SCA. Only 34% of patients with history of epilepsy and a witnessed arrest had evidence of seizure activity before the arrest. Rates of survival to hospital discharge after attempted resuscitation were 2.7% in patients with history of epilepsy versus 11.9% for patients without epilepsy (P=0.014). Patients with epilepsy had a significantly lower rate of presentation with ventricular tachycardia/ventricular fibrillation as opposed to pulseless electrical activity/asystole (epilepsy, 26%; no epilepsy, 44%; P=0.002), despite nearly identical response times.

Conclusions—In the majority (66%) of epilepsy patients, there was no relationship between seizure and SCA, implying that SCA in epilepsy patients often may not involve seizure as a trigger. The significantly worse rate of survival from SCA in epilepsy patients warrants urgent investigation. **(*Circ Arrhythm Electrophysiol*. 2013;6:912-916.)**

Key Words: death, sudden, cardiac ■ epilepsy ■ seizures

Among patients with epilepsy, sudden cardiac arrest (SCA) is recognized as a major cause of death. The cause of SCA in patients with epilepsy is not well understood, but it is considered the most common cause of epilepsy-related death.[1] Among the general population, epilepsy is an independent risk factor for SCA compared with the general population. Epilepsy confers a 3-fold higher risk of SCA and is more common in patients suffering from SCA in the setting of normal left ventricular systolic function.[2,3] The role of implantable cardioverter defibrillators in prevention of SCA in patients with epilepsy is unclear, and improved methods of assessing SCA risk are needed.[4]

Clinical Perspective on p 916

Cohort studies of patients in epilepsy clinics or undergoing EEG monitoring have led to the widespread belief that SCA usually occurs in relation to an acute seizure.[5–7] Commonly postulated mechanisms include seizure-induced abnormalities in the autonomic, cortical, or catecholamine systems, as well as respiratory abnormalities and cardiac ischemia.[8] However, there is a possibility that the importance of acute seizure as a trigger of SCA is amplified by bias because of enrollment of higher-risk patients in these cohorts. The present study was based in the community and aims to clarify the frequency of seizure activity immediately before SCA, with the additional ability to compare clinical characteristics and resuscitation outcomes of patients experiencing SCA with and without a diagnosis of epilepsy.

Methods

Study Population

The Oregon Sudden Unexpected Death Study (Oregon SUDS) is an ongoing (2002 to present) study of SCA in the Portland metropolitan area (population ≈1 million) that uses multiple sources of case and control ascertainment.[3,9–15] Records from the regional medical examiner, emergency medical service (EMS) providers, and hospitals were evaluated to identify cases and clinical information to adjudicated cause of death. Available medical records were obtained for all adjudicated cases of SCA.

Definitions

SCA was defined as loss of pulse <1 hour of any onset of new symptoms if arrest was witnessed, or <24 hours of last being seen alive and in baseline health state if arrest was unwitnessed.[16] Cases were

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excluded if terminal medical conditions, trauma, or drug/alcohol overdose were present. Patients were identified as having epilepsy if they had a history of seizure at the time of last medical evaluation before SCA, provided these seizures were unrelated to fever (children) or alcohol withdrawal (adults). Presence or absence of prearrest seizure activity was determined based on a witness's description of patient's movements and behavior at the time of arrest. Movements consistent with generalized seizures (tonic, tonic-clonic, or myoclonic) were defined as presence of prearrest seizure activity. Atonia was not considered to represent seizure activity. Clinically recognized prearrest coronary artery disease (CAD) was defined as coronary disease that had been recognized before SCA (not on autopsy or survivor work-up). This definition was used to maximize relevance to clinicians evaluating patients before SCA and to avoid work-up bias.

Data Collection and Adjudication of SCA and Prearrest Seizure

Records from the medical examiner, EMS, local emergency departments, and most recent outpatient physician documentation were used to evaluate whether a case of sudden death met criteria for SCA. Each case was evaluated by 2 physicians. If consensus was not possible, a third physican's opinion was obtained. Assessment of the presence of seizure activity at the time of SCA was evaluated for all patients with epilepsy who had witnessed arrests with bystander reports available, as well as 50 randomly selected patients without epilepsy. The latter comparison group was created to evaluate the assumption that seizure activity is more frequent among patients with epilepsy than those without (given the potential for SCA-induced cerebral hypoxia to cause seizure-like tonic-clonic movements). Three physicians evaluated each case and consensus opinion was also used to classify presence or absence of seizure before arrest. Full prearrest medical records from hospitals and clinics were then solicited for all cases of adjudicated SCA, including physician notes, laboratory values, cardiac catheterizations, echocardiograms, electrocardiograms, and imaging reports. All patients with records available and adjudicated cases of SCA were included in this analysis.

Statistical Analysis

The frequency of seizure activity immediately before SCA among patients with epilepsy was calculated by dividing the number of patients with observed seizure-like activity by the total number of patients with epilepsy and witnessed arrest and bystander information available. The frequency of seizure-like activity among the 50 sampled patients without epilepsy (all with witnessed arrests and bystander information available) was calculated by dividing the number identified by 50. Univariate comparisons between patients with and without epilepsy were performed using SAS software (version 9.1; SAS Institute, Cary, NC). Independent samples *t* tests were used for continuous variables and χ^2 or Fisher exact tests for categorical variables. Differences with *P* values <0.05 were considered significantly unlikely to be due to chance alone.

Results

Patient Characteristics

Among 2417 patients with SCA identified during the 10-year follow-up of Oregon SUDS, 106 (4.4%) had a history of epilepsy and 2311 (95.6%) did not have epilepsy. Those with epilepsy were younger (55±25 versus 63±19 years; *P*<0.001), more likely to have a history of stroke (20% versus 12%; *P*=0.022), and to be taking antiepileptic medications (79% versus 16%; *P*<0.001). The reasons for patients without seizure disorder to receive antiepileptic medications (as documented in medical records) included chronic pain, movement disorders, and mood disorders. Patients with epilepsy were less likely to have clinically recognized prearrest CAD (18% versus 27%; *P*=0.040) or hypertension (45% versus 55%; *P*=0.039). Of the 106 patients with epilepsy, 36 (34%) had a potential contributing cause of epilepsy identified, the most common of which was prior stroke in 7 patients (Table 1).

Table 1. Characteristics and Prearrest Medical Conditions for Patients With and Without Epilepsy Who Experience Sudden Cardiac Arrest

	Epilepsy (n=106)	No Epilepsy (n=2311)	*P*
Age	55±25	63±19	<0.0001
Female	42%	33%	0.064
White	89%	84%	0.80
Antiseizure medications	79%	16%	<0.0001
Prearrest CAD	18%	27%	0.040
Stroke	20%	12%	0.022
Heart failure	21%	26%	0.27
Hypertension	45%	55%	0.039
Diabetes mellitus	25%	31%	0.18
Hyperlipidemia	31%	37%	0.21

Prearrest CAD includes CAD recognized before arrest, but excludes CAD newly diagnosed at or after arrest. CAD indicates coronary artery disease.

Cardiovascular Characteristics

The assessed cardiovascular characteristics did not differ between patients with and without epilepsy in a statistically or clinically significant manner. A clinical history of myocardial infarction was identified in 14% of patients with epilepsy and 19% without epilepsy (*P*=0.21). Of the 30 patients with epilepsy and an echocardiogram available before and unrelated to SCA event, 60% had left ventricular ejection fraction >0.50. Of the 577 subjects without epilepsy and with prior echocardiogram available, 54% had ejection fraction >0.50 (*P*=0.54). The average QTc (corrected QT interval) from the 12-lead ECG was normal in both groups (Table 2).

Cardiac Arrest Characteristics

Resuscitation was attempted in 75 (71%) patients with epilepsy and 1710 (74%) patients without epilepsy (*P*=0.52). The rate of survival to hospital discharge was 2.7% among resuscitated patients with epilepsy and 11.9% among those without epilepsy (*P*=0.014). This difference occurred in the setting of significantly lower rates of presentation with

Table 2. Cardiac Characteristics for Patients With and Without Epilepsy Who Experience Sudden Cardiac Arrest

	Epilepsy (n=106)	No Epilepsy (n=2311)	*P*
EF >50%	60%	54%	0.54
QTc	442±39	453±40	0.13
Prior MI	14%	19%	0.21
Heart failure	21%	26%	0.27

Denominator modified for EF >50%, which was assessable in 30 patients with epilepsy and 577 without epilepsy, and QTc, which was assessable in 34 with and 493 without epilepsy. CAD indicates coronary artery disease; EF, ejection fraction; MI, myocardial infarction; and QTc, corrected QT interval.

Table 3. Circumstances of Sudden Cardiac Arrest for Patients With and Without Epilepsy

	Epilepsy (n=106)	No Epilepsy (n=2311)	*P*
Witnessed	38%	53%	0.003
Resuscitation attempted	71%	74%	0.52
Response time, min	6.8±3.6	6.9±3.6	0.84
Presenting rhythm			
VT/VF	26%	44%	0.002
PEA	26%	25%	0.86
Bradycardia/asystole	47%	30%	0.002
ROSC	36%	36%	0.91
STHD	2.7%	11.9%	0.014

Denominators are modified for the following: witnessed arrest status that was assessable in 104 patients with and 2277 without epilepsy; response time that was assessable in 80 with and 1617 without epilepsy; presenting rhythm that was assessable in 77 with and 1691 without epilepsy; and survival rates (STHD and ROSC) that were assessable in 75 patients with and 1710 without epilepsy. (Some patients were resuscitated but did not have a recorded presenting rhythm, whereas other patients had a presenting rhythm but were not resuscitated.) PEA indicates pulseless electrical activity; ROSC, return of spontaneous circulation; STHD, survival to hospital discharge; VF, ventricular fibrillation; and VT, ventricular tachycardia.

ventricular tachycardia (VT) or ventricular fibrillation (VF) among patients with epilepsy (epilepsy, 26%; no epilepsy, 44%; *P*=0.002) as opposed to presentation with bradycardia/asystole (epilepsy, 47%; no epilepsy, 30%; *P*=0.002). These differences in presenting arrhythmia were observed despite nearly identical response times (epilepsy, 6.8±3.6 minutes; no epilepsy, 6.9±3.6 minutes; *P*=0.84) and identical rates of return of spontaneous circulation (both groups, 36%; *P*=0.91). When restricted to only witnessed arrests, a trend remained for more frequent bradycardia among patients with epilepsy (31% versus 19%, *P*=0.06), though not for other presenting arrhythmias (Table 3).

Frequency of Seizure Activity Before Arrest

Witnessed arrest with bystander information was present in 32 (30%) patients with epilepsy. Of these, 11 (34%) demonstrated some seizure-like activity in the period shortly before arrest. Among 50 randomly selected patients without epilepsy, 5 (10%) exhibited seizure-like activity at the time of cardiac arrest (*P*=0.01).

Autopsy Findings

Twenty-eight cases with epilepsy and SCA (26%) underwent autopsy. Half (n=14) had a normal postmortem examination. Of the other 14 patients, obstructive CAD was present in 10 and cardiomegaly in 9 cases.

Discussion

This community-based assessment of SCA in the setting of epilepsy from the Oregon SUDS constitutes, to our knowledge, the largest such evaluation to date. Epilepsy was present in 4.4% of all SCA cases from this multisource investigation. The most important findings from this study are: (1) A minority of witnessed arrests in patients with epilepsy was preceded by seizure. (2) The presenting arrhythmia for SCA with epilepsy was less likely to be VT/VF and more likely to be bradycardia/asystole than for SCA without epilepsy. (3) The survival rate for resuscitated SCA in the setting of epilepsy was 4-fold lower despite identical EMS response times and rates of return of spontaneous circulation after resuscitation.

Of the 106 cases of SCA in patients with epilepsy, 32 were witnessed with bystander information regarding prearrest activity. There was a lack of previous seizure activity in the majority (66%), challenging conventional clinical wisdom. In fact, 10% of patients without seizure disorder also had seizure-like activity in the immediate prearrest period, implicating cerebral hypoperfusion as a cause of tonic-clonic activity rather than seizures. This would imply that the rate of primary seizure before cardiac arrest among patients with epilepsy may be even lower than we have observed.

The view that seizure activity often precedes SCA appears to be primarily inferred from a study of 15 patients with sudden unexpected death in epilepsy (SUDEP).[1,5,17] In that study, cases of SUDEP were referred by coroners, neurologists, and advocacy groups. Twelve patients had SUDEP in the setting of a tonic-clonic seizure and 2 had SUDEP in the postictal phase.[17] However, given the nature of the referral population, this study is likely to have a higher seizure burden than a community-based investigation, which may bias or confound results. In fact, an earlier investigation of 23 patients with witnessed SUDEP showed that 39% did not have seizure activity associated with the arrest.[18] Although it was community-based, this study could also have suffered from selection bias because it included only autopsy cases. In addition, because there was discretion in deciding whether to perform an autopsy and because the medical examiner's office was concurrently conducting a prospective study on SUDEP, it is likely that cases would have been preferentially selected for autopsy when seizure activity was reported. Our community-based, multisource study of overall SCA minimizes these selection biases and potential confounders.

Differences in definition are unlikely to account for the lower rate of prearrest seizure activity reported in the present study. When Oregon SUDS cases were restricted to those meeting criteria for definite or probable SUDEP (lack of notable cardiovascular comorbidity, with or without autopsy), 10 of 14 witnessed cases (71%) did not have seizure activity before SCA.

These observations may have important implications for research into SCA in patients with epilepsy. Findings that the trigger for SCA is often not related to seizure and that half of patients with SCA in the setting of epilepsy have obstructive CAD or cardiomegaly on autopsy raises the possibility that conventional SCA substrates/triggers may be more important than previously thought. However, further investigation is required to elucidate whether there are 2 separate pathophysiologic mechanisms of SCA (conventional and epilepsy-specific mechanisms), or whether patients with epilepsy have a different proportion of the same SCA mechanisms. Our observation of frequent cardiomegaly (32% of autopsy cases) provides a potential mechanism for arrhythmia that may not be dependent on a seizure trigger. It could reflect conventional cardiomyopathy or hypertensive heart disease, or could reflect

cardiac remodeling because of sympathetic overload from frequent seizures. Finally, patchy fibrosis was found in both epilepsy- and nonepilepsy-related SCA, but the influence on SCA risk on the initial arrhythmia observed (pulseless electrical activity, asystole, VT, VF) is unknown.

Patients with epilepsy who had SCA had a different clinical profile from patients without epilepsy, lending some support to contention that SCA in the setting of epilepsy may sometimes be because of unique triggers or substrates. Patients with epilepsy were younger, had less CAD, less hypertension, less VT/VF, and more bradycardia/asystole as presenting arrhythmias, despite similar EMS response times. Even when restricted to only witnessed arrests, a trend remained for more bradycardia/asystole among patients with epilepsy (P=0.06). The potential importance of bradycardia in SCA among patients with epilepsy is supported by observations of greater need for temporary cardiac pacing for patients with epilepsy.[19] Asystole, whether from seizure-related respiratory and autonomic abnormalities or from unique nonseizure mechanisms, could represent an important mechanism of SCA in patients with epilepsy. Another unique potential mechanism for future investigation is an abnormality that affects both neuronal and cardiac myocyte ion channels. The presence of KvLQT1, a cardiac ion channel, in mouse forebrain and brainstem and the ability of mutations affecting this channel to cause both epilepsy and ventricular arrhythmias raise the possibility for common genetic mutations to simultaneously confer epilepsy and SCA risk in humans.[20]

Differences in survival between patients with and without epilepsy were notable. Despite nearly identical rates of return of spontaneous circulation and identical response times (Table 3), the survival rates for patients with epilepsy were substantially lower (1.9% versus 8.8%; P=0.003). A trend existed for lower survival among patients with epilepsy when only witnessed arrests were evaluated (5.0% versus 15%; P=0.08). Future research investigating reasons for survival differences could improve outcomes for patients with epilepsy as well as improve understanding of the overall pathophysiology of SCA. Potential roles of antiepileptic medications should also be investigated. These medications have cardiac ion channel properties and could influence susceptibility to SCA or response to resuscitation.

Our study was limited by lack of information about prearrest behavior in some patients. However, sufficient numbers of patients could be evaluated to clearly demonstrate that a significant proportion did not have seizure activity before arrest (no tonic, tonic-clonic, or myotonic activity immediately before arrest). Another limitation is that, despite review of years of medical records in many cases, the nature of epilepsy in the community may not be uniformly characterized for many patients. This is a necessary limitation; if prospective general medical cohorts are used as the denominator, the numbers of arrests could decrease significantly and compromise the feasibility of conducting a useful analysis. If prospective cohorts of patients under care in an epilepsy program are used, the results are not generalizable to the average patient with less severe epilepsy. Accuracy of the diagnosis of epilepsy for patients in this study is no less than that in the average community-based patient care encounter, because the classification of epilepsy for this study was based on manual review of medical records (rather than diagnostic coding or claims data). Restriction to neurology or epilepsy clinics could reduce chances of inaccurate diagnosis, but would introduce selection bias and could distort inferences about SCA in the average patient with epilepsy. An additional limitation is that some seizure activity at the time of arrest could have been misclassified as SCA-related behavior if the seizure initiated with abrupt onset of atonia. This is an unusual manifestation of generalized seizure and, if present, should have minimal influence on results. It is also possible that in the pressured setting of an arrest, witnesses did not discriminate subtle forms of tonic-clonic activity or more subtle manifestations of seizure activity. Differences in rates of witnessed arrests between patients with and without epilepsy could have affected prearrest downtime and confounded presenting arrhythmia and survival data. However, trends persisted for more bradycardia/asystole (P=0.06) and lower survival (P=0.08) among patients with epilepsy when analyses were restricted to only witnessed arrests. Finally, there is always potential for primary cardiac arrhythmia disorders such as long QT syndrome to be misdiagnosed as epilepsy; however, the low incidence of these disorders relative to epilepsy is unlikely to have any significant effects on the results of the study.

Conclusion

A majority of patients with epilepsy did not have seizure activity before SCA, questioning the role of seizure as a dominant trigger of SCA. Compared with patients suffering from SCA without history of epilepsy, those with epilepsy differed in comorbidity profile and clinical presentation and had significantly lower likelihood of survival.

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CLINICAL PERSPECTIVE

Although sudden cardiac arrest is one of the major causes of death for patients with epilepsy, existing information has been derived from small studies. Investigators from the Oregon Sudden Expected Death Study evaluated the characteristics of patients with epilepsy that suffered sudden cardiac arrest in a large community-based study. They found that 4.4% of all sudden cardiac arrests occurred in patients with a clinical diagnosis of epilepsy. Patients with epilepsy had 4-fold lower survival rates that those without epilepsy, in part because of a lower rate of shockable arrhythmias. Among the 32 cases of cardiac arrest in patients with epilepsy in which detailed bystander information was available, only 11 (34%) had prearrest seizure activity. These results call into question the role of seizure as a dominant trigger of sudden cardiac arrest in epilepsy, while supporting observations that bradycardia and asystole are more common mechanisms of cardiac arrest for such patients.

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