Relationship between Seizure Episode and Sudden Cardiac Arrest in Patients with Epilepsy: A Community-Based Study

Running title: Stecker et al.; Seizure and Sudden Death

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Abstract

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

Methods and Results - From the ongoing Oregon Sudden Unexpected Death Study, cases of SCA identified using prospective, multi-source ascertainment (Portland, Oregon metropolitan area population approximately 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 preceding the event as well as lifetime clinical history including nature of seizures preceding SCA. Only 34% of patients with history of epilepsy and a witnessed arrest had evidence of seizure activity prior to the arrest. Rates of survival to hospital discharge following 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.

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

Cohort studies of patients in epilepsy clinics or undergoing electroencephalographic (EEG) monitoring have led to the widespread belief that SCA usually occurs in relation to an acute seizure. Commonly postulated mechanisms include seizure-induced abnormalities in the autonomic, cortical or catecholamine systems, as well respiratory abnormalities and cardiac ischemia. However, there is a possibility that the importance of acute seizure as a trigger of SCA is amplified by bias due to 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 preceding 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-present) study of SCA in the Portland metropolitan area (population approximately 1 million) that utilizes multiple sources of case and control ascertainment. Records from the regional medical examiner, emergency medical response 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 within 1 hour of any onset of new symptoms if arrest was witnessed, or within 24 hours of last being seen alive and in baseline health state if arrest was unwitnessed.\(^6\) Cases were excluded if terminal medical conditions, trauma, or drug or alcohol overdose were present. Patients were identified as having epilepsy if they had a history of seizure at the time of last medical evaluation prior to SCA provided these seizures were unrelated to fever (children) or alcohol withdrawal (adults). Presence or absence of pre-arrest seizure activity was determined based on SCA witness’ description of patients’ movements and behavior at the time of arrest. Movements consistent with generalized seizures (tonic, tonic-clonic or myoclonic) were defined as presence of pre-arrest seizure activity. Atonia was not considered to represent seizure activity. Clinically recognized pre-arrest coronary artery disease (CAD) was defined as coronary disease that had been recognized prior to SCA (not on autopsy or survivor work-up). This definition was used to maximize relevance to clinicians evaluating patients prior to SCA and to avoid work-up bias.

**Data collection and adjudication of SCA and pre-arrest seizure**

Records from the medical examiner, emergency medical service, 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 two physicians. If consensus was not possible, a third physician’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 prior to arrest. Full pre-arrest 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 preceding 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 Chi-square or Fisher exact tests for categorical variables. Differences with p-values less than 0.05 were considered significantly unlikely to be due to chance alone.

**Results:**

**Patient characteristics (Table 1)**

Among 2,417 patients with SCA identified during the 10 year follow-up of Oregon SUDS, 106 (4.4%) had a history of epilepsy and 2,311 (95.6%) did not have epilepsy. Those with epilepsy
were younger (55 ± 25 years vs. 63 ± 19 years; p<0.001), more likely to have a history of stroke (20% vs. 12%; p=0.022) and to be taking anti-epileptic medications (79% vs. 16%, p<0.001).

The reasons for patients without seizure disorder to receive anti-epileptic medications (as documented in medical records) included chronic pain, movement disorders and mood disorders.

Patients with epilepsy were less likely to have clinically recognized pre-arrest coronary artery disease (CAD; 18% vs. 27%, p=0.040) or hypertension (45% vs 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.

**Cardiovascular characteristics (Table 2)**

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 the patients with epilepsy and 19% without epilepsy (p=0.21). Of the 30 patients with epilepsy and an echocardiogram available prior 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 EKG was normal in both groups.

**Cardiac arrest characteristics (Table 3)**

Resuscitation was attempted in 75 (71%) of the patients with epilepsy and 1710 (74%) of the 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 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 min, no epilepsy – 6.9 ± 3.6 min; 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.

**Frequency of seizure activity preceding arrest**

Witnessed arrests with bystander information was present in 32 (30%) of the patients with epilepsy. Of these, 11 (34%) demonstrated some seizure-like activity in the period shortly before the 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 patients with epilepsy and SCA (26%) underwent autopsy. Half (n=14) had a normal post-mortem examination. Of the other 14 patients, obstructive coronary artery disease 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 multi-source investigation. The most important findings from this study are: 1) A minority of witnessed arrests in patients with epilepsy were preceded by seizure, 2) The presenting arrhythmia for SCA with epilepsy was less likely VT/VF and more likely bradycardia/asystole than for SCA without epilepsy, 3) The survival rate for resuscitated SCA in the setting of epilepsy was four-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 pre-arrest activity. There was a lack of preceding 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 pre-arrest period, implicating cerebral hypoperfusion as a cause of tonic clonic activity rather than seizures. This would imply that the rate of primary seizure prior to 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).\textsuperscript{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 two had SUDEP in the post-ictal phase.\textsuperscript{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.\textsuperscript{18} Although it was community-based, this study could also have suffered from selection bias since 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, multiple-source study of overall SCA minimizes these selection biases and potential confounders.

Differences in definition are unlikely to account for the lower rate of pre-arrest 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 prior to 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 substrate/triggers may be more important than previously thought. However further investigation is required to elucidate whether there are two 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 due to sympathetic overload from frequent seizures. Finally, patchy fibrosis was found in both epilepsy- and non-epilepsy-related SCA but the influence on SCA risk and on the initial arrhythmia observed (PEA, asystole, VT, VF) is unknown.

Patients with epilepsy who had SCA had a different clinical profile from patients without epilepsy, lending some support to contentions that SCA in the setting of epilepsy may sometimes be due to unique triggers or substrate. 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.\textsuperscript{19} Asystole, whether from seizure-related respiratory and autonomic abnormalities, or from unique non-seizure 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 a 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 raises the possibility for common genetic mutations to simultaneously confer epilepsy and SCA risk in humans.\textsuperscript{20}

Differences in survival between patients with and without epilepsy were notable. Despite nearly identical rates of ROSC and identical response times (table 3), the survival rates for patients with epilepsy were substantially lower (1.9\% vs 8.8\%, \textit{p}=0.003). A trend existing for lower survival among patients with epilepsy when only witnessed arrests were evaluated (5.0\% vs 15\%, \textit{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 pre-arrest behavior in some patients. However, sufficient numbers of patients could be evaluated to clearly demonstrate that a significant proportion did not have seizure activity prior to arrest (no tonic, tonic-clonic or myotonic activity immediately preceding 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 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 the patients in this study is no less than that in the average community-based patient care encounter, since 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 pre-arrest 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 prior to SCA, questioning the
role of seizure as a dominant trigger of SCA. Compared to patients suffering 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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**Table 1.** Characteristics and pre-arrest medical conditions for patients with and without epilepsy who experience sudden cardiac arrest

<table>
<thead>
<tr>
<th></th>
<th>Epilepsy (n=106)</th>
<th>No epilepsy (n=2311)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>55 ± 25</td>
<td>63 ± 19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>42%</td>
<td>33%</td>
<td>0.064</td>
</tr>
<tr>
<td>White</td>
<td>89%</td>
<td>84%</td>
<td>0.80</td>
</tr>
<tr>
<td>Anti-seizure medications</td>
<td>79%</td>
<td>16%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pre-arrest CAD</td>
<td>18%</td>
<td>27%</td>
<td>0.040</td>
</tr>
<tr>
<td>Stroke</td>
<td>20%</td>
<td>12%</td>
<td>0.022</td>
</tr>
<tr>
<td>Heart failure</td>
<td>21%</td>
<td>26%</td>
<td>0.27</td>
</tr>
<tr>
<td>Hypertension</td>
<td>45%</td>
<td>55%</td>
<td>0.039</td>
</tr>
<tr>
<td>Diabetes</td>
<td>25%</td>
<td>31%</td>
<td>0.18</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>31%</td>
<td>37%</td>
<td>0.21</td>
</tr>
</tbody>
</table>

CAD – coronary artery disease. “Pre-arrest CAD” includes coronary artery disease recognized prior to arrest, but excludes coronary artery disease newly diagnosed at or after the arrest.

**Table 2.** Cardiac characteristics for patients with and without epilepsy who experience sudden cardiac arrest

<table>
<thead>
<tr>
<th></th>
<th>Epilepsy (n=106)</th>
<th>No epilepsy (n=2311)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF&gt;50%</td>
<td>60%</td>
<td>54%</td>
<td>0.54</td>
</tr>
<tr>
<td>QTc</td>
<td>442 ± 39</td>
<td>453 ± 40</td>
<td>0.13</td>
</tr>
<tr>
<td>Prior MI</td>
<td>14%</td>
<td>19%</td>
<td>0.21</td>
</tr>
<tr>
<td>Heart failure</td>
<td>21%</td>
<td>26%</td>
<td>0.27</td>
</tr>
</tbody>
</table>

CAD – coronary artery disease; EF – ejection fraction; MI – myocardial infarction; QTc – corrected QT interval. 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.
**Table 3.** Circumstances of sudden cardiac arrest for patients with and without epilepsy

<table>
<thead>
<tr>
<th></th>
<th>Epilepsy (n=106)</th>
<th>No epilepsy (n=2311)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Witnessed</td>
<td>38%</td>
<td>53%</td>
<td>0.003</td>
</tr>
<tr>
<td>Resuscitation attempted</td>
<td>71%</td>
<td>74%</td>
<td>0.52</td>
</tr>
<tr>
<td>Response time (min)</td>
<td>6.8 ± 3.6</td>
<td>6.9 ± 3.6</td>
<td>0.84</td>
</tr>
<tr>
<td>Presenting rhythm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VT/VF</td>
<td>26%</td>
<td>44%</td>
<td>0.005</td>
</tr>
<tr>
<td>PEA</td>
<td>26%</td>
<td>25%</td>
<td>0.86</td>
</tr>
<tr>
<td>Bradycardia/asystole</td>
<td>47%</td>
<td>30%</td>
<td>0.002</td>
</tr>
<tr>
<td>ROSC</td>
<td>36%</td>
<td>36%</td>
<td>0.91</td>
</tr>
<tr>
<td>STHD</td>
<td>2.7%</td>
<td>11.9%</td>
<td>0.014</td>
</tr>
</tbody>
</table>

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