Sudep – Risk Factors, Protective Factors and Pathophysiological Mechanisms: a systematic review

Louise Ferreira Krol¹
Beatriz Chiquito Sacchi¹
Paulo Henrique Pires de Aguiar²

ABSTRACT
Introduction: Sudden Unexpected Death In Epilepsy (SUDEP) is the main cause of premature death in patients with epilepsy. The pathophysiology is not clear, however there are risks and protective factors described in the literature. Objective: To gather the data of these variables and elucidate the pathophysiological mechanisms. Methods: Literature review of free full articles from PubMed database from 2000 to 2019, in English, with an impact factor higher than 1, carried out in humans. As keywords were used “SUDEP”; “Epilepsy”, “Sudden Death”, “Seizure” resulting in 130 articles, and 44 reflecting the objectives. Results: A total of 11 case control and 10 cohort studies was analyzed and the risks and protective factors were presented. Among the risks were found: nocturnal seizure, frequencies, young adults, generalized tonic-clonic (GTCS) type and others. Some of protective factors were adherence to treatment, night supervision and having pets. Discussion: There are evidences that cardiorespiratory and autonomic systems interfere on the phisiopatology. Conclusion: More studies are necessary to elucidate all the involved mechanisms.

Keywords: SUDEP; Epilepsy; Sudden Death; Seizure

RESUMO

Palavras-chave: SUDEP; Epilepsia; Morte súbita; Convulsão

¹ Student of Medicine, Pontifical Catholic University of Paraná, Londrina, Paraná, Brazil
² MD, PhD, Department of Research and Innovation, Laboratory of Cellular and Molecular Biology, Faculdade de Medicina do ABC, Santo André, São Paulo; Department of Neurology, Faculdade de Medicina de Sorocaba, Pontifícia Universidade Católica de São Paulo, Sorocaba; Director of neurosurgery at Santa Paula/Dasa Hospital, São Paulo, Brazil

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SUDEP (Sudden Unexpected Death In Epilepsy) is a type of death in patients with epilepsy. It is defined as a sudden, unexpected, non-traumatic and non-drowning death, which may or may not be witnessed, with no evidence of prior seizures being required. Status epilepticus should be discarded. In the autopsy there is no toxicological or anatomical etiology for death. 

SUDEP is the main cause of premature mortality related to epilepsy, being responsible for 7.5 to 17% of deaths in this population. The incidence varies from 0.35/1000 people-year to 9.3/1000 people-year.

Among the main risk factors, there are: male gender, frequent seizures, age between 20 to 45, generalized tonic-clonic seizures (GTCS), changes in medication doses, polypharmacy, refractoriness to clinical treatment and indication for surgical treatment. In addition, staying at home alone, at night and sleeping in a prone position are other risk factors that are quite prevalent.

Other risk factors reported in several studies are: post-ictal prolonged immobility, antiepileptic drugs in subtherapeutic concentrations, long-term epilepsy, concomitant channelopathies, low heart rate variation, comorbid mental disorder or psychosis, intellectual disability or abnormal neurological findings, acute stages of intoxication and alcohol withdrawal among chronic alcohol-dependent people.

Among the protective factors for SUDEP, controlling seizures is the most effective factor and can be achieved through adherence to treatment with antiepileptic drugs in therapeutic doses, surgical treatment in refractory cases, responsive brain neurostimulation and prevention of seizures triggering factors. In addition to these, the treatment of psychiatric comorbidities, night supervision, specific bathing precautions, monitoring of high-risk patients, maintaining high levels of serotonin, and avoiding the use of drugs or other proarrhythmic conditions have been shown to be satisfactory.

SUDEP, in most cases, is preceded by seizures and a single episode of GTCS may be enough to cause death.

Although the pathophysiology yet not defined, many studies associated SUDEP with central autonomic dysfunction, whose triggering compromises respiratory and cardiovascular systems. Cortical thickening and thinning was also observed in patients with GTCS, especially in the autonomic and respiratory cortical areas, which may contribute to dysfunctional cardiorespiratory patterns during seizures and increase the risk of SUDEP in the long term. Other potentially related mechanisms are: prolonged peri ictal and postictal central apnea, generalized postictal electroencephalogram suppression (PGES), hypoxemia, hydroelectrolytic and acid-base changes and increased concentrations of peri ictal and postictal adenosine.

The purpose of this review was to compile the most recent data available in relation to the risk and protection factors of SUDEP, as well as to elucidate and aggregate its possible pathophysiological effects proposed in different studies.

METHODS

Literature review was performed using as inclusion criteria: free full articles from the PubMed database, published from 2000 to 2019, in English, in international journals with an impact factor higher than 1, with studies carried out in humans. The used keywords were: “SUDEP”; “Epilepsy”; “Sudden Death”; “Seizure”. We found 130 articles; of these, 26 were excluded because they did not meet the inclusion criteria of this review. From the 104 remaining articles, 60 were excluded because they approached specific topics of SUDEP that did not achieved the global approach that was required in this literature review. Finally, 44 articles were selected and included in this study (Figure 1).
In order to elucidate the pathophysiological mechanisms of SUDEP, we evaluated the epidemiological data, such as predominant sex, average age, possible risk factors and protective factors found in case control (Table 1) and cohort studies (Table 2).

**Table 1. Case control studies.**

<table>
<thead>
<tr>
<th>Authors/ year</th>
<th>Type of study</th>
<th>n</th>
<th>Median age and interval</th>
<th>Gender</th>
<th>Risk factors</th>
<th>Protective factors</th>
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<tbody>
<tr>
<td>Cihan et al. 2018 19</td>
<td>Case control</td>
<td>1346 reviewed deaths, 36 definite drowning, 11 possible drowning, 92 SUDEP</td>
<td>41.9 ± 12.9 (definite drowning), 38.2 ± 9 (possible drowning), 40.8 ± 11.6 (SUDEP)</td>
<td>No significant difference</td>
<td>Majority in bathtub/ hot tubs; unwitnessed</td>
<td>Reduce seizure frequency and severity, additional medications, surgery, improved adherence, limiting lifestyle factors, bathing safety</td>
</tr>
<tr>
<td>Ogren et al. 2018 14</td>
<td>Case control</td>
<td>583 cases / 530 control</td>
<td>37.1 ± 12.6</td>
<td>GTCS: 22/53 male, Control: 220/530 male</td>
<td>Frequency of seizures, cortical thickening and thinning</td>
<td>NR</td>
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</tbody>
</table>
Table 1. Case control studies. (continued)

<table>
<thead>
<tr>
<th>Authors/ year</th>
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</thead>
<tbody>
<tr>
<td>Patodia et al. 2018</td>
<td>Case control</td>
<td>40</td>
<td>NR</td>
<td>NR</td>
<td>Impaired respiratory homeostasis; alteration in medullary neuronal groups (including serotoninergic and galaninergic networks); duration of seizures</td>
<td>NR</td>
</tr>
<tr>
<td>Kang et al. 2017</td>
<td>Case control</td>
<td>69</td>
<td>NR</td>
<td>NR</td>
<td>Early nursing intervention</td>
<td>NR</td>
</tr>
<tr>
<td>Zhang et al. 2016</td>
<td>Case control</td>
<td>140</td>
<td>40.2 (8-69)</td>
<td>Cases: 17 female/ 18 male Control: 51 female / 54 male</td>
<td>Early-onset age of seizures, seizure frequency</td>
<td>Attention to early convulsive epilepsy-onset, proper control of convulsive seizures</td>
</tr>
<tr>
<td>Authors/ year</td>
<td>Type of study</td>
<td>n</td>
<td>Median age and interval</td>
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<tr>
<td>Shankar et al. 2014</td>
<td>Case control</td>
<td>48 cases of SUDEP (31 definitive, 9 probable, 8 possible)</td>
<td>42.5 (2-82 years)</td>
<td>33 male / 15 female</td>
<td>Male gender, early-onset age or longer duration of epilepsy, uncontrolled seizures (specially GTCS), recent increase and/or high seizure frequency, unclear treatment/non-compliance history, absence of night surveillance and prone position, psychiatric comorbidity including depression, being on anxiolytic medication and alcohol misuse</td>
<td>NR</td>
</tr>
<tr>
<td>Lamberts et al. 2012</td>
<td>Case control</td>
<td>154 SUDEP 616 controls</td>
<td>NR</td>
<td>NR</td>
<td>If sleep-related: Nocturnal seizures, and unwitnessed</td>
<td>Night supervision</td>
</tr>
<tr>
<td>Terra et al. 2012</td>
<td>Case control</td>
<td>1081 controls 11 case</td>
<td>6.7 (2-16)</td>
<td>5 female 6 male not significant</td>
<td>Younger age at onset of epilepsy, seizure frequency, symptomatic epilepsy – 67% focal. In bed, during sleep</td>
<td>Animals company</td>
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</tbody>
</table>
### Table 1. Case control studies. (continued)

<table>
<thead>
<tr>
<th>Authors/ year</th>
<th>Type of study</th>
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<th>Median age and interval</th>
<th>Gender</th>
<th>Risk factors</th>
<th>Protective factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vlooswijk et al. 2007</td>
<td>Case control</td>
<td>104 controls, 29 cases</td>
<td>29.0 +16.0</td>
<td>16 female 13 male not significant</td>
<td>Younger age at onset of epilepsy, number of seizures, GTCS, mental retardation and psychiatric illness, in bed, prone position</td>
<td>NR</td>
</tr>
<tr>
<td>Nei et al. 2004 26</td>
<td>Case control</td>
<td>21 cases 43 controls</td>
<td>34 years old (14-55)</td>
<td>11 female 10 male not significant</td>
<td>Younger age, seizure frequency, seizures during sleep, low or undetectable antiepileptic drugs (AED) levels, seizure clusters, sinus tachycardia, complex partial seizure, GTCS in SUDEP patients were generally associated with a greater maximal heart rate than were other seizure types, increased autonomic activity, recent seizure before death</td>
<td>NR</td>
</tr>
<tr>
<td>Langan et al. 2000 27</td>
<td>Case control</td>
<td>135 cases, 15 witnessed</td>
<td>32 years (17-47)</td>
<td>9 male 6 female not significant</td>
<td>In bed, GTCS</td>
<td>NR</td>
</tr>
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</table>
The case control study by Cihan et al. reviewed 1346 deaths of people with epilepsy in the water, seeking to differentiate them between drowning and SUDEP. The majority of water-related deaths from SUDEP were reported in bathtubs / hot tubs and without witnesses. Thus, the study reports that reducing the frequency and severity of seizures, using of oral medications correctly, improving adherence to treatment, lifestyle with limiting factors that reduce seizures and safety in the bath could be protective factors for SUDEP and drowning.

Ogren et al. performed a case control study involving 583 individuals. The risk factors reported for SUDEP were cortical thickening and thinning in autonomic and respiratory regions in patients with GTCS, with difference between gender and hemisphere. Various brain sites were evaluated to analyze whether there were pathological thickening or thinning. There was statistical significance in some of its values, but not in all. In addition, the frequency of seizures has also been configured as a risk factor.

Patodia et al. conducted a case control study involving 40 patients. The risk factors evidenced for SUDEP were impaired respiratory homeostasis, changes in spinal respiratory neuronal groups (including serotonin and galaninergic networks), with some of them showing statistical significance. In addition, the duration of seizures was also configured as a risk factor.

Kang et al. elucidated the function of postictal generalized EEG suppression (PGES) with the increased risk for SUDEP. As a result, PGES was found to be an equivocal marker, as it was lower in patients who died of SUDEP and rarely occurred in patients with multiple generalized seizures during monitoring epilepsy monitoring unit. Early nursing interventions can reduce the risk of SUDEP, being related to shorter seizures. Zhang et al. explored the risk factors for SUDEP cases among convulsive epilepsy patients in rural settings. The risk factors found were: age of early onset and frequency of seizures, both with statistical significance. The protective factors demonstrated were attention to the early onset of seizure epilepsy by the others and adequate control of seizures.

According to Shankar et al., SUDEP patients presented as characteristics were male gender, early age of first seizures, refractory seizures, GTCS, prone position, psychiatric comorbidities, all without statistical relevance. The possible protective factors were: treatment of psychiatric comorbidities, education and instruction of patients on the risk of SUDEP and the active search.

Evidences demonstrate that the majority patients who died of SUDEP are found in bed. Therefore, Lamberts et al. concluded that the presence of nocturnal seizures was statistically significant.

The study by Terra et al. sought to assess the relationship between the presence of pets and the SUDEP. According to this study, there is evidence in the literature that there was an improvement in the quality of life and human health status with the presence of pets, because besides to help recovery, the animal company can reduce stress, with psychological improvement and decrease of stress perception. These changes decrease the cardiorespiratory risk and the number of seizures; however, they were not statistically significant.

The study by Vlooswijk et al. observed that SUDEP patients that had young age onset of epilepsy died earlier, being statistically relevant.

The study by Nei et al. sought to evaluate the factors involved in SUDEP through EEG (electroencephalogram) and ECG (electrocardiogram). The heart rate was significantly higher in patients with SUDEP (p <0.005) and the increases in heart rate were much higher in patients with seizures during sleep when compared to awake patients (p <0.05).

Langan et al. searched to identify the deaths by SUDEP that were witnessed, assess the circumstances and to report the possible mechanisms proposed for this outcome. About the unwitnessed cases, most of them were found dead in bed. Some variables were predicted as risk factors such as the absence of witnesses, being in bed and GTCS, although they were not statistically relevant.
Table 2. Cohort studies.

<table>
<thead>
<tr>
<th>Author / Year</th>
<th>Type of study</th>
<th>N</th>
<th>Median age and interval</th>
<th>Gender</th>
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</tr>
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<tbody>
<tr>
<td>Murugesan et al. 2018</td>
<td>Cohort</td>
<td>41 patients with epilepsy</td>
<td>40.6 years ± 14 (range 20-77)</td>
<td>23 female / 18 male</td>
<td>NR</td>
<td>Possibly higher levels of serotonin</td>
</tr>
<tr>
<td>Sveinsson et al. 2018</td>
<td>Cohort</td>
<td>60,952 people with epilepsy (329 SUDEP cases/ non SUDEP deaths: 9276)</td>
<td>73.3 non SUDEP cases / 50.8 SUDEP cases</td>
<td>45% female / non SUDEP cases</td>
<td>Male, night, at home, in bed, prone position, unwitnessed, preceding seizure, living alone or not sharing a bedroom</td>
<td>Nighttime supervision</td>
</tr>
<tr>
<td>Geertsema et al. 2018</td>
<td>Cohort</td>
<td>12 patients with epilepsy</td>
<td>NR</td>
<td>NR</td>
<td>Noncontact seizure detection algorithm</td>
<td></td>
</tr>
<tr>
<td>Lacuey et al. 2018</td>
<td>Cohort</td>
<td>473 patients with epilepsy (completed databases in 126)</td>
<td>40.09 ± 14.71 years (range 16-77)</td>
<td>77 female / 49 male</td>
<td>Possibly prolonged ictal central apnea (&gt;= 60s) and severe hypoxemia</td>
<td>NR</td>
</tr>
<tr>
<td>Latreille et al. 2017</td>
<td>Cohort</td>
<td>20 patients with epilepsy</td>
<td>36.4 ± 11 years</td>
<td>11 female / 9 male</td>
<td>Hypoxemia, PGES, nocturnal seizures</td>
<td>NR</td>
</tr>
<tr>
<td>Kuo J et al. 2016</td>
<td>Cohort</td>
<td>70 patients with GTCS</td>
<td>35.1 ± 12 years</td>
<td>37 female / 33 male</td>
<td>Duration of postictal immobility (PI), PGES, prone position, oxygen saturation nadir (%) , ictal/postictal ETCO₂, ETCO₂ change from preictal baseline, duration of ETCO₂ elevation above preictal baseline.</td>
<td>NR</td>
</tr>
<tr>
<td>Author /year</td>
<td>Type of study</td>
<td>N</td>
<td>Gender</td>
<td>Risk factors</td>
<td>Protective factors</td>
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<tr>
<td>Mostacci et al. 2015 30</td>
<td>Cohort</td>
<td>103 people with NFLE</td>
<td>Mean age at onset of epilepsy: 15 years (range 0-53). Mean age at last observation 43 years (range 9-86).</td>
<td>Duration of postictal immobility (PI), PGES, prone position, oxygen saturation nadir (%), Ictal/postictal ETCO2, ETCO2 change from preictal baseline, duration of ETCO2 elevation above preictal baseline.</td>
<td>No higher risk of SUDEP found on patients with NFLE</td>
<td></td>
</tr>
<tr>
<td>Waddell et al. 2012 31</td>
<td>Cohort</td>
<td>367 (total) / SUDEP was discussed with 14</td>
<td>4.71 of the people (nobody died)</td>
<td>192 female/ 175 male</td>
<td>Male, first seizure under 16, epilepsy for more than 15 years, &gt; 1 GTCS per year, drug resistance, learning difficulties, non-adherence to treatment</td>
<td>NR</td>
</tr>
<tr>
<td>Seyal et al. 2012 32</td>
<td>Cohort</td>
<td>37 patients with GCS</td>
<td>35.4±12.9 years (range 18–66)</td>
<td>17 female / 20 male</td>
<td>Possibly PGES but not sure</td>
<td>NR</td>
</tr>
<tr>
<td>Nilsson et al. 2003 33</td>
<td>Cohort</td>
<td>Non surgery 21 surgery 596</td>
<td>33 years/ (6-53)</td>
<td>6 female/ 4 male</td>
<td>Right temporal gliosis</td>
<td>NR</td>
</tr>
</tbody>
</table>

PGES = postictal generalized EEG suppression; ETCO2 = end tidal carbon dioxide; NFLE = nocturnal frontal lobe epilepsy; NR = no results.
Kuo et al. assessed from a monitoring unit of patients with GTCS whether respiratory dysfunction and/or the characteristics of the ictal period were associated with postictal immobility, which are possible mechanisms of SUDEP. The association between the duration of postictal immobility and the PGES was investigated, in addition to saturation in both the post ictal and ictal periods, the concentration of CO₂ at the end of expiration (ETCO₂), location of epilepsy, duration of both the total seizure seizures and the tonic.

Seizures were assessed and it was observed that the duration of the postictal period was associated with maximum peri ictal ETCO₂, with the duration of oxygen desaturation and with the PO₂ nadir (significantly statistical data), but they were not associated with tonicity, seizure phase or total duration of the seizures.

In seizures with PGES, the duration of the postictal immobility, the change in the ETCO₂ peak and the duration of the ETCO₂ elevation were longer, once SO₂ nadir was shorter; these data were significantly statistical.

Mostacci et al. evaluated whether nocturnal frontal lobe epilepsy represents a high risk condition for SUDEP. Nocturnal frontal lobe epilepsy didn’t represent a higher risk for SUDEP, in fact the low prevalence may reflect the low occurrence of GTCS in this population.

Waddell et al. assessed whether there was an approach to the risk of SUDEP during consultation in patients with epilepsy. Of the risks factors analyzed, only occurrence of more than one GTCS per year and drug resistance had statistically significant results.

Seyal et al. evaluated the relation between PGES and SUDEP. They analyzed the respiratory pattern during video EEG telemetry. There was a significant difference in oxygen desaturation nadir, in duration of desaturation and peak ETCO₂ that was higher.

Nilsson et al. investigated the mortality and incidence of SUDEP in a population of patients with surgical indication to treat epilepsy. From the analysis of medical records, imaging exams and autopsy, they concluded that patients with SUDEP had more right temporal gliosis, greater refractoriness to treatment, were not free of seizures in the last year and patients whose treatment was conservative had a higher mortality rate having SUDEP as a cause, when compared to those submitted to surgery.

Murugesan et al. investigated the changes induced by epileptic seizures in serum serotonin levels and their potential implications for SUDEP. Higher serotonin levels have been reported to be possibly protective factor for SUDEP. The change in serum levels of serotonin (ictal and interictal post) was statistically significant (P = 0.027) between the generalized and focal seizure groups. The difference in the serotonin level (postictal to interictal) was associated with a reduction in the duration of the tonic phase during generalized seizures (p = 0.03) and higher levels of interictal serotonin were related to the shorter duration of the PGES (p = 0.04).

Sveinsson et al. analyzed the circumstances of SUDEP and its incidence in relation to the time of year, week and day. The statistically significant risk factors associated with SUDEP were male gender, being at home, at night, in a prone position, not having witnesses, living alone or not sharing a bed with another person. The protection factor found was night supervision.

Geertsema et al. concluded that the algorithm for detecting seizures without contact has a protective factor of occurrence of SUDEP. However, a detection limit has not yet been established and the performance of the algorithm has not been validated in the new test data. Lacuey et al. investigated central peri ictal apnea as a risk factor. SUDEP was possibly related with prolonged central apnea (≥ 60 seconds) and severe hypoxemia.

Latreille et al. aimed to investigate whether nocturnal seizures are more likely to be associated with respiratory impairment (such as more severe oxygen desaturation) when compared to surveillance seizures. The study demonstrated the following aspects with a higher risk for SUDEP: hypoxemia, PGES, and nocturnal seizures, all with statistical significance.
Review


Although the pathophysiology of SUDEP is not fully established, many studies have sought to investigate the influence that the autonomic nervous system and cardiorespiratory apparatus would have for such an outcome (Figure 2). The results discussed in this review are extremely important to describe the risks and protective factors, which helps to understand better the mechanisms of SUDEP. Besides, it is important to define the group of patients in which the subject must be approached by the doctors, establishing it in an individualized way the best time to talk about SUDEP in patients with epilepsy.

Speaking of pathophysiology, it is known that there are cortical (such as the insula, cingulate and orbitofrontal) and subcortical regions that integrate and influence the central autonomic system, which may be included in a convulsive episode, as demonstrated in Table 1, in the study of Ogren et al. This autonomic involvement can trigger activation or inactivation of certain areas, generating cardiorespiratory clinical manifestations that may be included in the pathophysiology of SUDEP.

Along with the autonomic system, there are several neurotransmitters involved in its pathophysiology. It has been shown that differences in peripheral serotonin levels can lead to different seizure characteristics and different speed of postictal recovery depending on the autonomic response generated. Evidence suggests changes in central respiratory control, carried out by nuclear clusters in the ventrolateral medulla. Greater evidence of a decrease in neuropeptidergic and monoaminergic neurons (including serotonin and galanine) has been demonstrated, possibly related to sudden death, with the need for further investigations in other neuronal groups.

The serotonergic system, for example, is related to the release of substances (such as serotonin) that cause cortical excitation and stimulation of the return of breathing if partial pressure of carbon dioxide ($\text{PaCO}_2$) is at high levels. Thus, it is possible that, in some cases, hyperventilation induced by convulsive episodes is a pathophysiological mechanism of SUDEP.

DISCUSSION

Figure 2. Pathophysiological mechanisms of SUDEP including the autonomic nervous system and cardiorespiratory dysfunction and its consequences. It includes the impairment of amygdala, increase of catecholamines, tachyarrhythmias and bradyarrhythmias, metabolic acidosis, changes in cardiac tissue, participations of postictal generalized EEG suppression (PGES) and using of medicines.
In addition to the substances already mentioned, adenosine also plays a role in the pathophysiological triggering. This substance is related to sedative mechanisms in the body and, due to the increase in the reactive concentration in convulsive episodes this organic response can contribute to SUDEP, suppressing cardiorespiratory functions 34.

In relation to the autonomic nervous system, Brotherstone et al. reported a physiological increase in vagal tone during sleep. When the seizures occur, there may be autonomic instability, further increasing the tone, resulting in bradyarrhythmia and possible asystole 35.

Nei et al. stated that seizures during sleep can cause constant fluctuations in the autonomic nervous system, which would result in lethal cardiac arrhythmias. In addition, other factors that further alter sympathetic vagal stimulation would be GTCS and young individuals, whose tone tends to be increased when compared to older people, justifying the epidemiology of SUDEP cases 26.

As already demonstrated, nocturnal seizures are associated risk factors 12,16,24, which generate more intense and long-lasting episodes of hypoxemia and continue with PGES more frequently 16, which is also a risk factor for SUDEP 16,29,32. According to So, autonomic mechanisms lead to a reduction in cardiac variability which, in addition to being a risk factor, also makes individuals more susceptible to sudden death from acute myocardial infarction 36.

Regarding the cardiorespiratory system, more specifically, Nei et al. demonstrated increased autonomic activity and found abnormalities in heart rhythm and repolarization in half of SUDEP patients, including atrial fibrillation, sinus arrhythmia and ST segment enlargement during and in the immediate post ictal state 29. Singh et al. observed that a specific population was at greater risk of presenting central apnea and consequent desaturation, a mechanism also suggested as a precipitant of SUDEP 15,37. This group included young people 37, with long-term seizures of the temporal lobe 33,37 or generalized seizures 37. Seyal et al. also found changes in the breathing pattern of patients with temporal lobe epilepsy, which was strongly associated with ictal respiratory arrest.

In other words, they concluded that discharges that reach limbic structures are associated with central apnea, regardless of duration of the seizures. Generalized seizures are the most susceptible ones to desaturation and the consequent hypoxemia – a possible contributor to SUDEP 34. In addition, the disseminated convulsive episode to the amygdala is also an important event, which can cause spontaneous breathing loss 38-39. Schuele et al. observed that hypoxia is an inhibitory factor of the seizures, that is, individuals who presented hypoxia had seizures of shorter duration when compared to those who did not have hypoxia. However, the occurrence of an exaggerated inhibitory stimulus can result in ictal asystole and SUDEP. The long periods of asystole lead to cerebral ischemia, found in the EEG of some patients. Cerebral ischemia anoxia causes acidosis, cellular energy failure and increased adenosine, which is an endogenous antiepileptic regulator 40.

There are several changes that may be associated with the cardiac mechanism in the pathophysiology of SUDEP. It is known that alternating T waves are markers of electrical instability of the heart and a higher risk of sudden death in individuals who have cardiovascular disease, possibly also being associated with an increased risk of SUDEP 41.

Semmelroch et al. related the suppression of EEG in the postictal period with the risk of SUDEP. Most of patients with epilepsy were found with respiratory impairment due to airway obstruction or variations in breathing pattern. Patients with postictal suppression of EEG required interventions such as suction, oxygen administration, change of position and check of vital signs by nursing, suggesting that the postictal state was more worrying 42.

Another study that evaluated the impact of interventions on the evolution of respiratory dysfunction, EEG suppression and post ictal immobility was accomplished by Seyal et al. 7. These variables were proposed as triggers for SUDEP. Suppression of EEG as a trigger for post ictal immobility would increase the chance of death from asphyxiation precisely because of the difficulty in repositioning the face. Therefore, the longer the suppression, the greater the duration and severity of postictal desaturation in agreement with the study of Kuo et al. 29. In addition, it was observed that when interventions
were early performed, respiratory dysfunction, the duration of the seizures and its convulsive component and the duration of PGES were shorter. Furthermore, the preventive role of SUDEP was suggested, since hypoxia and hypercapnia, when causing abnormalities of cardiac repolarization and arrhythmias, can result in sudden cardiac death, since several of the patients who died of SUDEP reported the stretching of QT.

The role of the QT interval, previously mentioned, is quite controversial in relation to SUDEP. Nei et al. found no consensus on whether an increase or decrease in the interval occurs. Surges et al. stated that pathological cardiac repolarization is not uncommon in people with epilepsy and may be a plausible mechanism of ventricular tachyarrhythmia leading to SUDEP. In addition, genetic mutations in ion channels can affect both cardiac and brain function, leading to susceptibility to epilepsy and cardiac arrhythmias.

Surges addressed the importance of evaluating the drug interactions, since some drugs metabolized by CYP3A4 can increase the QT interval, and when they interact with drugs that inhibit CYP3A4, such as valproate, it can facilitate ventricular tachyarrhythmia. In addition, he listed factors described in the literature that could both increase QT, such as: hypoxemia, hypercapnia, catecholamines released during the seizures, as well as factors that could cause shortening of QT, such as: medications, catecholamine release, hyperkalemia and acidosis.

So, talking about other cardiac mechanisms, confirmed abnormalities in rhythm and repolarization, citing studies whose patients with intractable epilepsy had sinus arrhythmia with premature atrial depolarization, sinus pause, elevation or depression of the ST segment. Van der Lende et al. demonstrated that postictal arrhythmias (asystole, atrioventricular block, atrial fibrillation and ventricular fibrillation) were observed after episodes of GTCS and appear to be of great importance in the pathophysiological mechanism of sudden death associated with epilepsy. Also, So reported changes found in the autopsy of SUDEP cases such as pulmonary congestion and edema. Apnea and hypoxia are often found during seizures or shortly after because the brainstems respiratory activity may be suppressed directly by the seizures or indirectly by the hypoxia of ictal cardiac arrest. The combination of cessation of inspiratory neuronal discharge from the brain stem associated with reduced lung activity exacerbated the bradycardia induced by carotid chemoreceptors. As the cardiorespiratory reflex is greater in young adults, this confirms the higher incidence of SUDEP in this population.

After all this discussion, it is clear the contribution of GTCS in the occurrence of SUDEP. Besides all the physiopathology mentioned and their related factors, there are more risk factors found in the results that deserves to be mentioned because of their contribution to the final event: male gender, learning difficulties, drug resistance, non-adherence to treatment and early onset of the seizures. Frequent seizures, psychiatric comorbidities, unwitnessed seizures and prone position also leads to the event. Despite of all those risk factors, there are some protective factors that may be achieved for reducing the chance of SUDEP, as: controlling seizures, night supervision and having an animal companionship.

Although the pathophysiology of SUDEP is not well established, there are evidences of involvement of the autonomic nervous system and the cardiorespiratory system. It is extremely important to approach the risk of the occurrence of this event and the possible forms of prevention in patients who are part of the epidemiology, ensuring greater adherence to treatment and better therapeutic success. It is worth remembering that the physician’s decision between talking or not about the risk of SUDEP to their patients with epilepsy should always be individualized, balancing the risks and benefits. Even with the progress made in recent years in the pathogenesis of SUDEP, many further studies will still be necessary to establish in a more specifically way the risks and protection factors of this event and to define more clearly its pathophysiological mechanisms.
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CORRESPONDING AUTHOR

Louise Ferreira Krol
Medical Student
Pontifical Catholic University of Paraná
Londrina, Paraná, Brazil
E-mail: louisefkrol@hotmail.com

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