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Sudden unexpected death in epilepsy. A critical view of the literature

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Bullet points

- The incidence of SUDEP ranged from 0.09 to 2.4 per 1,000 person-years, with differences attributed to age and disease severity.

-Young age, disease severity, symptomatic epilepsy and the response to antiseizure medications could be independent predictors of SUDEP.

-Hypothesized pathophysiological mechanisms are cardiac, respiratory and neuromodulator dysfunction, postictal EEG depression and genetic.

Abstract

Sudden unexpected death in epilepsy (SUDEP) is a sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus in which postmortem examination does not reveal other causes of death. Lower diagnostic levels are assigned when cases met most or all of these criteria, but data suggested more than one possible cause of death. The incidence of SUDEP ranged from 0.09 to 2.4 per 1,000 person-years. Differences can be attributed to the age of the study populations (with peaks in the 20-40 year age group) and the severity of the disease. Young age, disease severity (in particular, a history of generalized TCS), having symptomatic epilepsy, and the response to antiseizure medications (ASMs) are possible independent predictors of SUDEP. The pathophysiological mechanisms are not fully known due to the limited data available and because SUDEP is not always witnessed and has been electrophysiologically monitored only in a few cases with simultaneous assessment of respiratory, cardiac and brain activity. The pathophysiological basis of SUDEP may vary according to different circumstances that make that particular seizure, in that specific moment and in that patient, a fatal event. The main hypothesized mechanisms, which could contribute to a cascade of events, are cardiac dysfunction (included potential effects of ASMs, genetically determined channelopathies, acquired heart diseases), respiratory dysfunction (included postictal arousal deficit for the respiratory mechanism, acquired respiratory diseases), neuromodulator dysfunction,postictal EEG depression and genetic factors.

Keywords: Epilepsy, SUDEP, Incidence, Pathophysiological mechanisms.

Introduction

One of the first documented cases of sudden unexpected death in epilepsy (SUDEP) is that of Patsy Custis, the stepdaughter of George Washington. Patsy, a 17-year-old woman, who had long-standing epilepsy refractory to the available medications. In a letter to a family member, Washington gave a lucid and evocative picture of his daughter's death: " … *She rose from Dinner about four o'clock in better health and spirits than she appeared to have been in for some time; soon after which she was seized with one of her usual Fits, and expired in it, in less than two minutes without uttering a word, a groan, or scarce a sigh*…".[1] The description of Patsy's death summarizes the main diagnostic criteria for SUDEP, a fatal complication of epilepsy, which is defined as the sudden and unexpected, non-traumatic and non-drowning death of a person with epilepsy, without a toxicological or anatomical cause of death detected during the post-mortem examination. The mechanisms underlying SUDEP are still poorly understood and the causes seem to be multifactorial, including respiratory, cardiac and cerebral factors, as well as the severity of epilepsy and seizures.

In this article, a comprehensive review of the literature will be performed to illustrate the definition, frequency and mechanisms of SUDEP. In doing so, published reports will be critically appraised to define the current state of knowledge, in light of the quality of each contribution, to suggest preventive measures and indicate the future directions of the research.

Definition

Sudden unexpected death in epilepsy (SUDEP) is "sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicologic or anatomic cause of death".[2]

The proposed Unified SUDEP Definition and Classification[3] contains nine main recommendations:

Unified SUDEP definition and classification

1- The word "unexpected," and not the word "unexplained," should be uniformly used in the term SUDEP.

2-The SUDEP category should be applied when appropriate, whether or not a terminal seizure is known to have occurred.

3- The "Possible SUDEP" category should be used only for cases with competing causes of death, with cases left unclassified when data are insufficient to reasonably permit their classification.

4- Cases that would otherwise fulfill the definition of SUDEP should be designated as "SUDEP Plus" when evidence indicates that a preexisting condition, known before or after autopsy, could have contributed to the death, which otherwise is classified as SUDEP (e.g., coronary insufficiency with no evidence of myocardial infarction or long-QT syndrome with no documented primary ventricular arrhythmia leading to death).

5- To be considered SUDEP, the death should have occurred within 1 hour from the onset of a known terminal event.

6- For status epilepticus as an exclusion criterion for SUDEP, the duration of seizure activity should be 30 minutes or more.

7- A specific category of SUDEP due to asphyxia should not be designated, the distinction being largely impractical on circumstantial or autopsy evidence, with more than one mechanism likely to be contributory in many cases.

8- Death occurring in water but without circumstantial or autopsy evidence of submersion should be classified as "Possible SUDEP." If any evidence of submersion is present, the death should not be classified as SUDEP.

9- A category of "Near-SUDEP" should be agreed to include cases in which cardiorespiratory arrest was reversed by resuscitation efforts with subsequent survival for more than 1 hour.[3]

In summarizing, the new categories proposed by Nashef et al. [3] are:

Diagnostic criteria for SUDEP

1. Definite SUDEP: sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus (seizure duration ≥30 minutes or seizures without recovery in between), in which postmortem examination does not reveal a cause of death.

1a. Definite SUDEP Plus: satisfying the definition of Definite SUDEP, if a concomitant condition other than epilepsy is identified before or after death, if the death may have been due to the combined effect of both conditions, and if autopsy or direct observations/recordings of the terminal event did not prove the concomitant condition to be the cause of death.

2. Probable SUDEP/Probable SUDEP Plus: same as Definite SUDEP but without an autopsy. The victim should have died unexpectedly while in a reasonable state of health, during normal activities, and in benign circumstances, without a known structural cause of death.

3. Possible SUDEP: a competing cause of death is present.

4. Near-SUDEP/Near-SUDEP Plus: a patient with epilepsy survives resuscitation for more than 1 hour after a cardiorespiratory arrest that has no structural cause identified after investigation.

5. Not SUDEP: a clear cause of death is known.

6. Unclassified: incomplete information available; not possible to classify.

If disagreement exists about which category fits a particular case, we suggest the use of consensus decision by a panel of informed reviewers to adjudicate the classification of the case.[3]

Autopsy findings

SUDEP is a challenge for death investigators because unwitnessed events occurred mostly overnight. A 2018 position paper of the National Association of Medical Examiners about this topic suggested seven questions to address epilepsy-related deaths.[4] Detailed seizure history from clinicians can greatly assist the accuracy of death certification by a medical examiner.

In a large Instanbul study[5] with 20.334 autopsied patients between 2007 and 2011, 112 had a prior diagnosis of epilepsy and SUDEP was the cause of death in 35.7% of cases (n=40). 95% of them underwent a toxicological analysis and no antiseizure agent was detected in 33.5% of these. Incidence of SUDEP determined by autopsy data on epilepsy-related deaths was 0.7 per 1,000 person-years (95% CI 0.5-1.2 per 1,000 person-years) in Queensland (Australia), and in 55% of cases subtherapeutic levels of antiseizure medications (ASMs) were found. This study reported that an unwitnessed overnight seizure is a key factor in autopsy-confirmed SUDEP.[6]

In a retrospective study conducted in Ontario (Canada) between 2014 and 2016, two neurologists examined autopsy reports and classified deaths with Nashef criteria to verify the under-identification of SUDEP as a cause of death. A significant association was found between neurologists' classification and autopsy reports, with definite cases younger than definite plus, who were younger than possible SUDEP cases. Concordance decreased in the most complex cases and SUDEP could be underestimated in older adults.[7]

Conversely, Verducci et al.[8] found discordance between forensic investigators and epileptologists in SUDEP classification (higher discordance in possible and probable cases), because coroners favoured non-epilepsy-related diagnosis in case of more than one cause of death (cardiac and psychiatric comorbidity, substance abuse and toxicology findings for drugs of abuse).[8]

Methods of the review

This is a narrative review and the scientific literature on SUDEP was examined. The databases used were MEDLINE (since 1966) and EMBASE (since 1974) to June 2021, searching for the key words “Sudden unexpected death in epilepsy”, “SUDEP”, "Epilepsy", “Seizure Disorder", "Death”, “Sudden Death",

“Epidemiology”, “Epidemiologic Studies" Heart Diseases", “Heart Defects, Congenital", "Cardiac Disease”, "Cardiac Disorder”, "Heart Disorder", "Congenital Heart Defect", "Malformation Of Heart”, "Heart Abnormalities”, "Congenital Heart Disease, “Risk Factors", "Risk Factor”, "Risk

Score" "Risk Factor Score", "Population at Risk", "Molecular mechanisms" "Focal myocytolysis", "Physiopathology", "Therapy", "Anticonvulsive Drug", "Anticonvulsant", "Anticonvulsant Drug", "Anticonvulsive Agent", "Antiepileptic Agent", "Antiepileptic" "Antiepileptic Drug", "Antiepileptic Agent, "Diagnosis", "Prognosis", "Prognostic factor", "Surveillance video", "Video surveillance", "Baby monitor", "Remote listening device", "Wearable seizure detection device", "Movement monitor", "Sleeping tablet", "Mat on mattress", "Mat under mattress".

Incidence of SUDEP

The reported incidence of SUDEP varies significantly depending on the study design, the level of diagnostic certainty, the source of cases, and the size of the population at risk. The most representative estimates are provided by community-based studies (Table 1). A total of 16 studies have been examined. Most studies were done in North America (USA or Canada) followed by Northern Europe and Australia. In two instances (four studies), the same population was examined in two different periods. The predominant source of cases were the coroners' archives. National or local registries of patients with epilepsy were the source of cases in the remaining studies. In these latter cases, patients with definite, probable or possible SUDEP were included. In most studies the diagnosis of SUDEP was made with reference to Nashef 1997[2] or Leestma 1997.[9] SUDEP cases were identified retrospectively in the majority of studies. The observation period ranged from 1 to 40 years. The number of patients with epilepsy ranged from 44 to 33,022 and the number of patients with SUDEP from 1 to 66. The populations at risk (patients with epilepsy) were reported in eight studies and calculated on the basis of the expected prevalence of epilepsy in the area in seven others. In community-based studies, the incidence of SUDEP ranged from 0.09 to 2.4 per 1,000 person-years. Differences can be largely explained by the study design and methods. Studies reporting the lowest rates were based on small samples and newly diagnosed epilepsy,[10] young age at death,[11] an unknown definition of SUDEP,[12] or a small sample with some unclassified cases.[13]

On this basis, the most credible incidence of SUDEP in a well-defined prevalent population ranges between 1 and 2 cases per 1,000 person-years. In two studies[13,14] the incidence of SUDEP was compared to the expected incidence of sudden death in the same origin population. In the study by Ficker et al.[13] the standardized mortality ratio (SMR) was 24 times higher in epilepsy patients than in the general population. Fairly similar values were found by Holst et al.[14] who found an hazards ratio (HR) of 27.6 (95% confidence interval 18.1-41.9) after adjustment for sex and an HR of 16.3 (95% CI 9.8-26.9) after adjustment for comorbidities. This indicates a strong independent effect of epilepsy on the risk of sudden death.

More variable, mostly higher SUDEP rates can be found in selected populations represented by patients seen in secondary or tertiary referral centers, individuals with drug-refractory epilepsy, or patients included in drug trials or surgery registers (Table 2). Nineteen studies have been included. Only one-fourth of the studies have been done prospectively. The studies were performed in USA (7), UK (6) China (2), Italy (1), Spain (1), The Netherlands (1), Sweden (1), or in other countries in the context of drug developments programs (3). The sources of cases varied across studies, being mostly represented by the records of referral centers. The lowest incidence of SUDEP was found in patients with newly diagnosed epilepsy (1.0 per 1,000 person-years),[15] or seen at the primary care level in China (0.2-1.0 per 1,000).[16]

Slightly higher rates (1.2-2.0 per 1,000 person-years)[17,18] were found among mixed populations including newly diagnosed and chronic epilepsy patients. Even higher rates (2.5-3.4 per 1,000 person-years)[19,20] were found in patients with chronic epilepsy. Incidence rates ranging from 2.1 to 5.9 per 1,000 person-years were found in patients with mental retardation and/or learning disabilities.[21,22] Cohorts of patients with refractory epilepsy (some of them participating in drug development programs) incurred in SUDEP rates ranging from 2.2 to 3.8 per 1,000 person-years[23,24] and surgical candidates from 2.2 to 9.3 per 1,000 person-years.[23,25]

In general, up to 17% of deaths in people with epilepsy can be attributed to SUDEP,[26] the highest fractions being found in patients with idiopathic/cryptogenic epilepsies with or without relevant comorbidity.

A recent review reporting previous studies in pediatric cohorts, showed that SUDEP incidence was five times lower than in adults (between 0.02 and 0,34 per 1,000 person-years) even if more recent studies suggested similar incidence rates than in adulthood (between 1.20 / 1,000 and 1.45 / 1,000 person per years). (Mastrangelo 2022 review)[27]

In a recent US study, a decreasing monotonic trend in medical examiner-investigated SUDEP incidence over 8 years has been observed, with a 28% reduction in incidence from 2009–2012 to 2013–2016. (Cihan et al 2020)[28]

Risk factors

A number of patient and disease-related factors have been investigated in patients who died of SUDEP. These include, among others, a history of TCS (including generalized tonic-clonic seizures/focal to bilateral tonic-clonic seizures) (presence, number and nocturnal occurrence), young age at epilepsy onset, longer duration of epilepsy, male sex, symptomatic aetiology of epilepsy, history of alcohol abuse, number of ASMs, selected drugs, low drug levels, low IQ, epilepsy treatment and vagus nerve stimulation (VNS) therapy. The circumstances of death have been also investigated. All putative risk factors were assessed in the context of reports on the incidence of SUDEP or in specifically designed case-control studies. The controls were represented by living patients with epilepsy or by patients with epilepsy who died of known causes. Several reviews and meta-analyses were also performed and are discussed here. Key findings from the studies on the risk factors for SUDEP are presented in Table 3.

The data from four case-control studies were combined by Hesdorffer and co-workers[29] and the factors found to be significant in the pooled analysis included an increased frequency of TCS, polytherapy, duration of epilepsy, young age at onset, male gender, symptomatic etiology, and treatment with lamotrigine (LTG). In a subsequent combined analysis of the three case-control

studies with data on both ASMs and generalized tonic-clonic seizures, the authors found that, when adjusting for TCS, none of the ASMs considered in the studies were associated with an increased SUDEP risk as monotherapy or polytherapy.[30]

Clark et al, identified 123 cases of SUDEP in all autopsy reports from Queensland for a 5-year period from January 1, 2004 to December 31, 2008 confirming the increased association between SUDEP and nocturnal seizures and the absence of witnesses.[6]

Chen et al.[31] in a retrospective case-control study from the database of the Convulsive Epilepsy Control and Management Program in West China identified 41 probable SUDEP cases and for each probable SUDEP case included, they assigned five controls from the database matched for age, sex and seizure frequency. The study conducted from May 2005 to December 2015 focused on patients with epilepsy treated with phenobarbital. The authors found that the SUDEP group had more seizures before they died than the control group (Mann–Whitney U test, $p = 0.023$) and that the SUDEP group had significantly higher non-seizure-free incidences than the control group [probable SUDEP: 0 (0, 10)/y vs control group: 0 (0, 0)/y; $p= 0.023$- Mann–Whitney U test].

Van der Lende et al.[32] selected 60 cases of SUDEP in two epilepsy residential care units in Nederland. They identified four controls per case matched on age (±5 years) and residential alive at the death of cases. The authors found that both the presence of nocturnal convulsive seizures and their frequency were associated with a higher risk of SUDEP [presence: cases 34/44 (77%) *vs* control 47/146 (32%); $p < 0.001$]. When comparing SUDEP incidence between the two centers which used the different level of supervision, that with the lowest grade of supervision had significantly higher SUDEP rate (6.12/1,000 patient-years) than the other (2.21/1,000 patient-years).

In a recent Swedish case-control study in adult patients with epilepsy, Sveinsson et al.[33] identified 255 SUDEP cases among deaths recorded during 2006-2008 by the National Cause of Death Registry: 167 definite SUDEP and 88 probable SUDEP according to the Annegers classification.[34] The 76 cases of possible SUDEP were not analyzed. SUDEP cases were matched 1:5 to epilepsy

patients alive at case death. Experiencing TCS during the preceding year, presence of nocturnal TCS during the last year and living alone were associated with increased risk of SUDEP and interaction analysis showed that the combination of not sharing a bedroom and having TCS TCS conferred a greater risk than that of the individual factors considered.[33] Others proposed risk factors such as young age at epilepsy onset, longer duration of epilepsy and structural etiology were not associated with SUDEP after adjustment for TCS frequency. In individuals who had had exclusively non-convulsive seizures during the previous year, no higher risk of SUDEP was seen (OR 1.15, 95% CI 0.54-2.46).

In a comprehensive review of published reports, integrated with some personal data, Hughes[35] investigated the incidence and risk factors of SUDEP. The most extensively investigated factor was the number of seizures, followed by subtherapeutic ASM levels followed. Other factors, in decreasing order, were history of TCS , young-adult age , polytherapy , early onset of seizures, male gender , duration of epilepsy , mental retardation , alcohol abuse, death on bed/floor, congenital neurological defects, and exposure to carbamazepine.

In a pooled analysis of risk factors, a high frequency of tonic-clonic seizures was related to a higher risk of SUDEP.[36] In a systematic review of published reports,[37] also being in bed proved to be a strong risk factor for SUDEP. Weak risk factors were prone position, one or more sub-therapeutic ASM blood levels, being in the bedroom, having a structural brain lesion and sleeping. Devinsky et al.[38] in a non-systematic review of the literature suggested that the strongest SUDEP risk factor is poor control of "primary or secondary generalized tonic-clonic seizures".

Ali et al.[39] in a systematic review of published reports evaluated the relationship between sleep and SUDEP by selecting 67 studies. Of the 880 SUDEP cases, 69.3% occurred during sleep and 30.7% occurred during wakefulness with a significant association between SUDEP and sleep as compared to wakefulness ($p< 0.001$). This association could be related to the reported greater desaturation that occurs during TCS in sleep compared with those that recur in wakefulness.[40]

Subsequent systematic and non-systematic literature reviews confirmed that a major risk factor for SUDEP is the presence, frequency of TCS and/or their nocturnal occurrence.[38,41-45-43]

The role of ASMs in affecting the risk of SUDEP is not completely defined. In the study by Aurlien et al.,[46] the incidence of SUDEP in patients receiving LTG was 3.9 per 1,000 patient-years, with an incidence rate ratio (vs. patients not exposed to LTG) of 8.6 (16.5 in women). However, on autopsy six of the seven women with SUDEP had inadequate or absent LTG levels.[47] The lack of control for TCS has been indicated as a possible explanation of the study findings. Clark et al.[6] came to a similar conclusion. Edey et al.[48] analyzed the report of the United Kingdom Confidential Enquiries into Maternal Deaths (2006-2008) and evidenced a risk of maternal mortality 10 times higher compared to the general population. In the English study, out of 14 epilepsy-related deaths, 11 (79%) were probably SUDEP and 9/11 (64%) were in women taking LTG seven as monotherapy.[48] This finding may simply reflect the current United Kingdom prescribing practice, but also could be related to the pharmacokinetic changes that LTG undergoes throughout pregnancy with resulting lack of seizure control.

Ryu et al.[49] in a retrospective study evaluated 35,638 patients aged 5-70 years referred for epilepsy at Asan Medical Center, University of Ulsan College of Medicine, Korea and identified SUDEP cases defined according to Leestma criteria.[9] Inclusion criteria was follow-up > 5 years. Control subjects were patients with epilepsy alive at the date of case death matched for age, sex and initial date of enrollment at the medical centre recruited in a 1:3 ratio to cases. For all subjects, demographic and clinical characteristics were assessed. Univariate analysis showed that seizure frequency (odds ratio: 3.1; P=0.021) and number of ASMs (odds ratio: 2.0; P=0.009) were significantly associated with SUDEP. Only the number of ASMs remained significant in the multivariate analysis (odds ratio: 1.83; P=0.026)[49] One possible explanation hypothesized was that polypharmacy is a marker of poor seizure control.

In a meta-analysis by Ryvlin et al.,[50] the authors compared patients randomized to ASMs at efficacious doses, to ASMs at not-efficacious doses and to placebo. “Efficacious” was intended as

the antiepileptic potency shown in randomized trials. Adjunctive therapy with ASMs at efficacious doses was found to reduce the incidence of SUDEP more than seven times compared with placebo in patients with refractory epilepsy.

In the retrospective study of Kloster et al.,[51] in which the causes of death in an outpatient population of a tertiary referral centre were reviewed, significant risk factors were aetiology, high seizure frequency and signs of seizure preceding death (see Table 3). A prone position at death was seen in 71% of SUDEP patients and sub-therapeutic ASMs concentrations were found in 57% of 23/42 SUDEP patients for whom this information was reported.[51]

Data from existing surgical series with respect to SUDEP are conflicting, and SUDEP has been reported in patients who have undergone surgical treatment but whose presence and possible frequency of seizures is not known.[52.53]

Casadei et al.[54] retrospectively evaluated patients referred for pre-surgical evaluation at Columbia University Medical Center from 1996 to December 31, 2014 and identified 590 patients who underwent surgical treatment and 122 patients who did not undergo surgical treatment because they were deemed unfit or refused surgery. There were 14 SUDEP cases in the surgery group and 5 SUDEP in comparison group. The SUDEP risk was significantly greater in non-surgical group in comparison with in the surgery group (cases: 7371.7 patient-years and 14 SUDEP deaths, comparison group: 1096 patient-years and 5 SUDEP deaths, Fisher's exact test, $p = 0.04$). 4/14 SUDEP death death occurred 10 years or more after the surgery date, with an average of 10.1 years (range: 4.6–15.8 years). Nevertheless, the presence/absence of TCS at the time of death in both groups is not well understood.

Ryvlin et al.[55] evaluated the outcome of 40,443 patients implanted with VNS Therapy systems in the United States between November 16, 1988 and December 31, 2012 and followed up to 10 years post-implantation, accumulating 277,661 person-years of follow-up. 632 cases of SUDEP have been identified. The authors evaluated whether SUDEP rates decrease during the post-implantation follow-up period using the Mann-Kendall nonparametric trend test and by comparing SUDEP rates

of the first 2 years of follow-up (years 1-2) to longer follow-up (years 3-10). Age-adjusted SUDEP rates decreased significantly over time (by over 30%) from years 1 to 2 (2.47/1,000 person-years) to years 3 to 10 (1.68/1,000 person-years) suggesting a protective effect of VNS over time.

Pathophysiological mechanisms

The pathophysiology underlying SUDEP is yet to be fully understood[56, 57], partly because of the limited available data given the rarity of SUDEP recordings.

However, several putative mechanisms have been identified. They will be discussed separately in the next paragraphs, although they are not mutually exclusive and they might coexist, or indeed be chained, in a cascade of consequential events.

1. Heart mechanisms

Both seizures and chronic epilepsy may affect heart function.

The anatomo-functional correlates of the ictal/inter-ictal cardiac effects rely on the central autonomic network that exerts descending control over the peripheral autonomic neurons innervating the heart.[58-63]The involvement of the cortical and subcortical autonomic centers, such as insular, orbitofrontal, and cingulate areas, amygdala, and hypothalamus, during the spread of seizures, may provoke peri-ictal cardiac anomalies. Alterations in blood pressure and heart rate[64] after repeated stimulation of the insular and cingulate cortices, and the amygdala were demonstrated.[65,66]

Both structural and functional abnormalities involving the central autonomic network might predispose to sudden death.[58] Specifically, thinning of the mesial and orbitofrontal cortices, and intrinsic or acquired insular damage have been reported in patients with refractory epilepsy who died from SUDEP.[67] Disruption of the functional connectivity between cingulate and orbitofrontal cortices, amygdala, and thalamus has been also broadly associated with the cardiovascular dysregulation that may lead to SUDEP. [44,68] The imbalance between the two vegetative components

or dysfunction in the heart innervation of one autonomic component might lead to abnormal heart function and be responsible for sudden death. [69]

The autonomic instability that comes from these aberrant nervous circuits has a direct effect on heart function and seizure by seizure may alter heart structure in a way that in turn perpetuates the cardiovascular deterioration where a superimposed acute event may find its breeding ground for sudden death.

1a Acute cardiac effects of seizures

Tachycardia and autonomic storm

Seizures are frequently associated with rate, rhythm, and conduction abnormalities.[70]

The most common is sinus tachycardia.

Sinus tachycardia is considered a benign phenomenon resulting from autonomic stimulation during the ictal phase, sometimes persisting post-ictally for up to a few minutes. [71-74]

Notably, sinus tachycardia is observed more frequently in TCS, the kind of seizures most often related to SUDEP, especially if of a long duration.[72,75]. However, these events are accompanied by an actual autonomic storm characterized by an enhanced sympathetic tone and raised plasmatic catecholamines.[76] Sudden vegetative imbalances are known to increase the risk of sudden death.[64,77-79] Beyond the arrhythmias, acute myocardial sympathetic stimulation may cause transient left ventricular dysfunction similar to Takotsubo cardiomyopathy.

Cardiac Troponin I (TnI) is elevated in up to 25% of cases after TCS. A raise of Creatine kinase-MB (CK-MB) and Brain-Type Natriuretic Peptide (BNP) plasmatic levels following a TCS has been detected also when TnI was not increased, suggesting the presence of a slight cardiac acute dysfunction even in the absence of myocyte necrosis.[80-82]

High plasmatic levels of catecholamines cause microdamage to the myocardial tissue such as vacuolating focal myocytolysis, [64,83-87] which represents, together with interstitial edema, a more common autoptic finding in patients who died of SUDEP than in controls.[51,88-92]

Myocardium distress is supposed to result from the augmentation of oxygen demand due to the increase in heart rate, blood pressure, and cardiac output during sympathetic hyperactivity. [93-96] As a further element, S-T segment depression in the ECG correlates with TCS and their duration.[75,88,94,97]

Bradycardia/Asystole

Ictal bradycardia has been reported in 1.4% of seizures in epilepsy patients.[98] Ictal asystole has been found in 0.27% of patients undergoing video-electrographic monitoring,[99,100] appearing most often some years after the disease onset,[100] probably as a consequence of the remodeling of the anatomical epileptic circuits.

Ictal bradycardia and asystole are usually triggered by focal temporal seizures[71,75,99,101-105] and are probably related to the discharge propagation into the central autonomic network.[106] Currently, the occurrence of asystole and bradycardia during seizures is considered of limited importance to the pathophysiology of SUDEP since these ictal arrhythmias appeared self-limiting.[107]

Bradycardia can also occur in the immediate postictal phase, representing an autonomic breakdown phenomenon evolving from benign tachycardia[101,108-110 111], often accompanied by hypoxia.[112]

ASMs may also have an impact on heart conduction. Phenytoin and carbamazepine by inducing blockade of sodium channels may produce bradycardia, sinus arrest, and atrioventricular block, while lamotrigine could cause QT prolongation through its effect on potassium channels.[113]

1.b Chronic cardiac dysfunction in epilepsy

In people with epilepsy (PWE), the recurrence of many seizures might cause repeated hypoxemia and catecholaminergic toxicity to the heart thus provoking permanent cardiovascular changes. The term "Epileptic Heart" has been indeed adopted to describe the heart and coronary vasculature damage resulting from chronic epilepsy and leading to mechanical dysfunction and electrical instability.[114]

The chronically heightened sympathetic tone might elevate interictal heart rate and diastolic blood pressure, promoting left ventricular stiffness and heart failure with preserved ejection fraction-like phenotype.[115,116]

Moreover, PWE, particularly those with more severe disease, presented a reduction in cardiovascular fitness.[117] The decrease in functional capacity contributes to the progressive decline of the cardiac vagal tone as assessed through heart rate variability (HRV). While HRV is normal in newly diagnosed patients, it is significantly lower in patients with drug-resistant epilepsy, especially during sleep.

Low HRV scores indicate a reduction of cardiovascular autonomic efficiency and have been associated with increased risk for SUDEP. It has been argued that the shortening of RR intervals may facilitate cardiac conduction reentrance networks causing tachyarrhythmia or, conversely, lead to a paradoxical rebound with an excessive increase in vagal tone during a seizure causing bradyarrhythmia, conduction block, or asystole.[118]

In addition, elevated levels of lipids and accelerated atherosclerosis, partly reflecting the metabolic effects of certain ASMs, have been reported in people with epilepsy.[114]

Pathologic studies showed that the recurrence of catecholamine stimulation in chronic epilepsy determines permanent structural damage to the heart as evidenced by myofilament damage, extracellular matrix deposition, and myocardial fibrosis. The yet described focal myocytolisis, initially transitory, evolves into irreversible focal fibrosis. Overall, among SUDEP cases, interstitial myocardial fibrosis and myocyte hypertrophy are the most frequent pathological abnormalities. Myocardial fibrosis predisposes to arrhythmias such as atrial fibrillation, supraventricular tachycardia, bundle branch block, ventricular or premature atrial depolarizations.[119,120] It has been hypothesized that a sympathetic stimulation during a long tonic-clonic seizure over a fibrotic myocardium may result in a lethal tachyarrhythmia.[75,121]

Some reports exist of SUDEP or near-SUDEP cases due to ictal ventricular fibrillation. In most cases with severe tachycardia, the heart rate undergoes irregular and sudden oscillations in the post-

ictal phase [75,101,109,110] and thus the final condition preceding death could be a severe autonomic and electric instability with temporary dispersion of recovery of ventricular excitability.[122]

As consequence, SUDEP might represent the epiphenomenon of self-organizing criticality where a slow chronic process can suddenly bring to death.[123]

It is worth noting that SUDEP diagnosis excludes, by definition, known causes of mortality as cardiac comorbidities and sudden cardiac death, although chronic epilepsy itself predisposes to heart disease and increases the risk of sudden cardiac death by means of the structural and functional changes mentioned above.[114]

2. Respiratory mechanism

Witnesses of SUDEP have frequently reported breathing difficulties.[124,125] Limited data on monitored patients display a higher frequency of ictal central or mixed apneas compared to the obstructive ones.[112,126-128] . However, the difficulties in the identification of laryngospasm are of particular concern as it could be underestimated. Ictal and postictal bradypnea, apnea, and/or hypoxia [93,109,112,129-131] could play a pathogenetic role in SUDEP (Table 65).[51,93,109,112,124,132] The extent of desaturation during a seizure has been related to the appearance of repolarization anomalies (ie: QT interval prolongation or shortening).[133] The SpO2 threshold value associated with an increased SUDEP risk is reported as 80-86%.[96] Therefore, the respiratory mechanism may initiate the cascade of events that eventually ends with a fatal arrhythmia and death.

In some patients, a role for primary pulmonary dysfunction has been postulated since hypoxia and hypercapnia have been observed despite an increase in respiratory rate.[134]

SUDEP postmortem examination frequently revealed pulmonary abnormalities, most commonly congestion together with an increased lung weight.[51,132] Pulmonary edema is more likely to occur with prolonged TCS, though it is still not clear if it is a potential contributor to death or merely a consequence of seizures.[135] Several mechanisms have been proposed as responsible for pulmonary

edema such as central respiratory inhibition, brainstem sympathetic output, negative intrathoracic pressure related to ictal laryngospasm, and increased pulmonary vascular pressure.[136]

2.a Ictal Central Apnea

Ictal central apnea was reported in 40% of TCS in patients with refractory epilepsy and is mainly associated with temporal seizures. Hypoxemia occurred in 86% of TCS in patients with drug-resistant epilepsy and it was more severe in temporal epilepsies.[137] The desaturation level depends on the duration and the contralateral spread of the seizure.[120,131]

The respiratory involvement might result from the seizure spreading into the networks connecting the cortical regions to the brainstem autonomic centers. Several proofs come from stimulation studies in monkeys and from the CACNA1A model of SUDEP, which demonstrated the major role of spreading depolarization into the brainstem in initiating apnea and hypoxia.[133,138] In humans, amygdala activation by seizure propagation or electrical stimulation produced apnea without subjective dyspnea.[139] However, respiratory depression may precede or follow by more than 2 minutes the spreading of the discharge to the amygdala[140] , reflecting the necessity of bilateral involvement of the amygdala to effectively suppress the volitional control of breathing, at least in some seizures.

Neuroimaging investigations revealed increased right-sided gray matter volumes of the amygdala in SUDEP cases and a reduction of the functional connectivity between the amygdala and brainstem in patients at high risk for SUDEP. This disconnection may prevent the amygdala to trigger inspiratory efforts and recover from hypoventilation during seizures leading to terminal apnea. In addition, the gray matter volume of the posterior thalamus, which is involved in oxygen sensing and in relaying afferent signals essential for breathing, is decreased in epilepsy patients by a degree that is proportional to disease duration.[68]

2.b Ictal Obstructive Apnea

A severe laryngeal-esophageal spasm leading to death was reported in a single monitored case of SUDEP. Some investigators sustain laryngospasm as the consequence of the seizure-induced activation of recurrent laryngeal nerves.[141] The prone position contributes to the mechanical obstruction of nose and mouth because of their pressure on the pillow [51,109,142].

2.c Post-Ictal Apnea

Postictal central apnea was detected in 22% of seizures in both focal and generalized epilepsies.[137] Seizures from sleep have been associated with more severe and prolonged hypoxemia. The reasons may rely on the reduction of chemosensitivity and respiratory drive as well as the increase in upper airway resistance.[40]

Chemoreflex failure acquires special relevance during sleep when conscious control of respiration withdraws thus causing breathing impairment and sudden death.[143] This could be one of the reasons for the greater occurrence of SUDEP during sleep. Moreover, the postictal phase represents a condition of arousal deficit that may result in postictal immobility. Under these circumstances, especially if the patient lies in a prone position, the loss of protective reflexes to airway obstruction or aspiration, such as moving and coughing, and of recovery responses to cardiorespiratory collapse increase the risk for SUDEP.[96,144]

The serotoninergic system which adapts both breathing and arousal during hypercapnia states.[145] could be implicated as postictal serotoninergic dysfunction would compromise the head repositioning in case of airway obstruction due to the prone position.

3. Neuromodulator dysfunction

Experimental evidence from transgenic mice and clinical studies in humans sustain a role in impaired serotonergic transmission in SUDEP.[146,147] The serotonergic system defect is one of the similarities between SUDEP and sudden infant death syndrome (SIDS).[148]

Seizure propagation in the brainstem affects both serotonergic neurons in the midbrain, which participate in the ascending arousal system, and those in the medulla involved in breathing control, and then might impair arousal as well as respiration.[149]

The recurrence of spreading depolarization within the medulla is thought to be responsible for its volume loss in SUDEP cases as revealed by MRI scans[38]. A post-mortem investigation in SUDEP patients demonstrated a reduction of pre-Botzinger complex neurons (preBotC) - generators of inspiratory rhythm - in the ventrolateral medulla, which determines an impairment of 5-HT synthesis and delivery and first manifests with respiratory disturbances during sleep. [150]

In line with these findings, drugs that modulate serotonin may have a great impact on SUDEP prevention. In animal models, selective serotonin reuptake inhibitors (SSRIs) prevented the postictal respiratory arrest.[147,148] Nonetheless, in epilepsy patients, SSRIs have reduced the postictal oxygen desaturation in focal seizures but not in generalized ones.[151]

Adenosine exerts an important anticonvulsant effect by A1 receptor (A1R) stimulation, however it promotes respiratory depression. The A1 receptors are responsible for tolerance to hypoxia and may mediate the apnea without dyspnea induced by amygdala electrical stimulation. Conversely, the A2a receptors are expressed in astrocytes and exert a modulation of adenosine effects. The adenosine levels rise during seizures, especially if prolonged, and could therefore trigger sudden death when accompanied by a metabolic impairment of its clearance. As further evidence, the administration of caffeine, an adenosine receptor antagonist, increased survival times in a kainic acid model with altered adenosine clearance. Surgical pathology in hippocampal sclerosis specimens demonstrated an imbalanced expression of A1R/A2aR receptors in patients with high SUDEP risk, suggesting that chronic epilepsy may alter adenosine neurotransmission with potentially fatal consequences.[152]

Finally, central apnea might partly depend on the release of endogenous opioids during seizures and activation of brainstem opioid receptors, whose response is also influenced by medications, recreational drugs (including alcohol), and gene polymorphisms.[141]

4. Postictal Generalized EEG Suppression (PGES)

Another putative mechanism involved in SUDEP is prolonged postictal generalized EEG suppression (PGES). According to Lhatoo,[153] PGES consists of the immediate postictal (within 30 seconds of seizure cessation) generalized reduction of the cerebral EEG activity below 10 uV in amplitude. Then, the minimum duration criterium of 1 second was added to this definition.

PGES was observed in several cases of SUDEP and near SUDEP.[127,151,153-156,] Despite this association, its significance is yet to be defined. The causal role that the "cerebral shutdown" may have on cardiorespiratory dysfunction is under debate [161].[157]

However, PGES has been proposed as an electrophysiological marker for SUDEP. As support, several SUDEP risk factors, such as TCS frequency, are strongly associated with PGES.[158]

In a small study, PGES was significantly longer in patients who later died of SUDEP, and the odds of SUDEP were augmented by a factor of 1.7% with every second of the increase in PGES.[153] Nonetheless, this was not confirmed by subsequent research[159] and prolonged PGES might be simply related to seizure severity.[38]

Some hypotheses have been postulated about the triggers of PGES: it may reflect brainstem spreading depolarization, passively come from cortical neuronal exhaustion, or represent the activation of inhibitory networks responsible for seizure termination.[160,161]

4.a Brainstem spreading depolarization

The association of PGES with TCS (40-66% of cases) rather than with focal seizures (1-2% of cases) and particularly with the occurrence of symmetric tonic arm extension and oral tonicity suggested the involvement of brainstem and medulla.[153-155, 162] According to some authors, PGES might correlate with the duration of the seizure specifically in its tonic phase.[163]

Another proof for seizure-induced brainstem depolarization derives from the observation that PGES of any duration co-occurs with ictal and post-ictal respiratory depression.

Seizure propagation to the upper brainstem with consequent inhibition of the ascending reticular arousing system may give rise to PGES, while its spreading to the lower brainstem might lead to central apnea, hypoxia, and eventually autonomic dysfunction.

On the other hand, since PGES could be prevented or limited in duration by early oxygen administration, it might directly represent the effect of hypoxia and hypercapnia on cerebral function.[163,164]

4.b Cerebral neuronal exhaustion

It has been found that postictal immobility occurs more frequently and lasts for a longer time in seizures followed by PGES than in those without. This correlation may be explained by the cerebral exhaustion that originates from the depletion of energy substrates after prolonged and hypersynchronous neuronal excitation or the decreased cerebral blood flow from postictal cardiorespiratory dysfunction.[148,165]

However, the abrupt onset of PGES and its lack of correlation with seizure duration argues against the hypothesis of such a passive process.

4.c Activation of inhibitory networks

Eventually, PGES might come from the activation of a reticular-thalamo-cortical inhibitory network responsible for switching off cortical activity. As support, PGES preferentially occurs after CTS during sleep than wakefulness thus reflecting circadian differences in the neurovegetative response or, otherwise, the sleep-related facilitation to activate these inhibitory pathways in the postictal phase.[166,167] Then, the profound neuronal inhibition related to endogenous mechanisms of seizure termination may be enhanced during a low arousal state like sleep. It also might act more strongly if the seizure is more severe, for example, after drug withdrawal.[168]

In addition, the combination of this inhibitory neuromodulation with the dysfunction of 5-HT system and cholinergic transmission to the frontal cortex could determine both arousal deficit and immobility in the post-ictal phase.[165]

A common pathway in the pathophysiology of SUDEP: the hyperactivation of the Mammalian Dive Response and data from the MORTEMUS study

It has been hypothesized that the hyperactivation of the mammalian dive response (MDR) follows the convergence of unanticipated events and brings together all the mechanisms yet described in a sequence that finally leads to death. MDR as an oxygen-conserving reflex represents a life-preserving safety feature that combines parasympathetically mediated bradycardia with sympathetically mediated positive ventricular inotropy and peripheral vasoconstriction. However, the high drive to the heart from both autonomic limbs may be arrhythmogenic and result in sudden death.[169] In the context of epileptic seizures, the ictal sympathetic storm that co-occurs with TCS extends into the postictal period and it might combine with parasympathetic hyperactivation, as shown in animal and human studies.[38] More closely, the MDR could be triggered by hypoxia secondary to ictal apnea coupled with a rapid increase in the demand by muscle for oxygen. The loss of consciousness that accompanies TCS prevents the MDR attenuation by mental processes. The hyperventilation, which usually precedes apnea, might cause QT prolongation within 1 minute. When QT is prolonged, the bradycardia of the MDR increases the risk of Torsade de Pointes and ventricular fibrillation. In addition, the shift of the blood to the central organs may result in pulmonary edema.[124]

Accordingly, the MORTEMUS study sheds light on a consistent and previously unrecognized pattern common to all monitored SUDEP and near-SUDEP. After TCS, a short period of rapid breathing (18-50 respiratory acts per min) developed and was followed within 1-3 min by a combination of central apnea, severe bradycardia, and most often transient asystole together with

PGES. This cardiorespiratory collapse was terminal in a third of patients. In most cases, transient restoration of cardiac function occurred while ineffective respiration, probably aggravated by the prone position, progressively deteriorated within 11 min of the end of the seizure until terminal apnea, which always preceded terminal asystole. Thus, SUDEP primarily follows an early postictal, centrally mediated, neurovegetative breakdown that may be induced by mechanisms leading to seizure termination and associated with PGES. Since oximetry data were not available, the contribution of ictal hypoxia in determining the occurrence and severity of this process is unknown, though the early postictal tachypnea might reflect such hypoxia.[109]

The prone position and postictal arousal deficit influenced by the sleep state as well as the co-occurrence of genetically determined channelopathies, heart or respiratory acquired diseases, and the potential effects of ASMs are potential contributors. These elements account for a wide inter-subject variability since different circumstances could make a particular seizure a fatal event for each individual.

5. Genetic factors

Current literature supports the hypothesis that the existence of specific predisposing conditions could determine the susceptibility to develop a terminal arrhythmic event during or immediately after an epileptic seizure.[170] There is increasing interest in the contribution of genes expressed in the heart and brain tissue, in which membrane ion channels play a fundamental role.[171] Indeed, genetic abnormalities involving these channels are associated with sudden death, epilepsy, and arrhythmias. Recently, the identification of genes encoding for ion channels that are co-expressed in the heart and brain supports the existence of a possible shared genetic susceptibility between epilepsy, arrhythmias (particularly, long QT syndrome [LQTS]), and SUDEP. However, the complex genetic background of SUDEP also involves other genes with cardiac or brain expression.[36]

5a. SUDEP and ion channels

Among SUDEP-associated genes, the major research focus has been made on those encoding sodium and potassium ion channels. A peculiar example is represented by Dravet syndrome (DS), a disease characterized by a high incidence of SUDEP and associated with a high percentage of anomalies of the SCN1A gene, which encodes for the sodium channel Nav1.1.[172] Other sodium channel mutations, e.g., SCN5A, SCN8A, and SCN1B, have been associated with an increased risk of SUDEP (Table 4). In particular, SCN5A mutations have been reported in patients with epilepsy, Brugada syndrome (BS), and found in individuals who have died from SUDEP, thus highlighting the existence of complex interactions responsible for the genetic susceptibility to cardiac and brain dysfunction.[173.174]

Genes encoding for KCHQ/KCHN potassium channels have also been associated with an increased risk of arrhythmias, epilepsy, and SUDEP. [175-179] There has been increased interest in a possible association between epilepsy and cardiac arrhythmias, such as LQTS,[180] and in a recent post-mortem study six out of 68 (13%) SUDEP patients exhibited mutations in genes previously associated with LQTS (KCNH2, KCNQ1, or SCN5A).[177]

Finally, also genes encoding for other ion channels, including calcium channels and the cationic HCN channels have been associated with SUDEP.[181-183]

5b. Other SUDEP-associated genes and research perspectives

Recent studies have identified other genes associated with an increased risk of SUDEP, which encode for proteins expressed in the heart and brain tissue or both.[181-184] From a systematic review by Chahal et al.[176] it emerges that SUDEP occurs in individuals with epilepsy carrying mutations associated with different cardiac disorders, including arrhythmias (LQTS, short QT syndrome, BS, and others) and cardiomyopathies (hypertrophic cardiomyopathy, dilated cardiomyopathy) and genes associated with primary brain SUDEP.

Moreover, the expanding use of next-generation sequencing (NGS) and whole-exome sequencing (WES) techniques allowed the identification of other candidate genes potentially associated with SUDEP, including HCN1, SCN4A, CACNA1A, and others.[185-188]

All these observations suggest the utility of an active search for a personal history of cardiac disorders and family history of sudden death, SUDEP, and cardiac disease in first-degree family members of epileptic individuals. Indeed, the identification of selected patients carrying a higher risk of SUDEP could lead to appropriate genetic testing and cardiologic screening.

How to prevent SUDEP

Shankar et al.[189] wrote an evidence-based safety checklist for clinicians to quickly identify well-recognized risk factors of SUDEP (subdivided into static and modifiable risk factors) in order to minimize them and promote safety: 1) static factors: male sex, duration of epilepsy, unclear treatment history, primary generalized epilepsy, intellectual disability; 2) modifiable factors: severity of seizures, number of ASMs, compliance with treatment, frequent ASM prescribing changes, sub-therapeutic ASM levels, use of lamotrigine and/or carbamazepine, alcohol addiction, treatment for depression and anxiolytic medications; 3) moderate risk-static factors: younger age; 4) moderate risk-modifiable factors: no surveillance at night, prone position, failed assessment for epilepsy surgery; 5) established risk-static factors: early onset of epilepsy; 6) established risk-modifiable factors: high seizure frequency with special reference to tonic-clonic seizures.[189]

Verma and Kumar[190] proposed hypothetical preventive measures such as optimal medical management and patient education, use of lattice pillow, nocturnal supervision (especially in high-risk patients), reinforcement of interictal serotoninergic tone lowering opiate- or adenosine-induced postictal brainstem depression.

Nevertheless, excluding the role of ASMs in preventing SUDEP, in a recent review conducted on randomized controlled trials and cohort and case-control non-randomized studies, Maguire et al.[191]

demonstrated the lack of evidence in the previous literature about the effectiveness of different interventions in preventing SUDEP. Only one case-control study at high risk of bias[122] was identified by the authors, suggesting a protective effect of nocturnal supervision, i.e. the risk of SUDEP seemed to be reduced if another person of at least 10 years old was in the room and if frequent night-time checks or listening devices were used. As said above, van der Lende et al.[32] compared two epilepsy facilities with different devices and methods of nocturnal supervision, showing a higher incidence of SUDEP in the center with the lowest grade of supervision.

The utilization of wearable devices detecting seizure activity has lately increased intending to improve PWE quality of life and reduce SUDEP risk. In contrast to technological development, the lack of scientific evidence about these devices is still an issue.[192] According to some studies, their use increases the level of safety and security for PWE, especially pediatric patients and young adults, despite technical difficulties and the occurrence of false alarms due to the sensitivity of the device.[193,194] The alarm does not stop the seizure but determines a quicker intervention allowing the administration of rescue medicines or the prevention of injuries. Non-EEG devices (accelerometers, surface electromyography, automatic video detection and bed alarms) have been growingly used, even though their utility in detecting focal seizures (identification of non-movement variables) is not as accurate as in TCS. For example, in a preliminary study involving patients with temporal lobe seizures, the sensitivity rate was 70%, with a very high false-alarm rate of 50 per day.[195] Despite the numerous marketed devices, an available caregiver able to provide early peri-ictal intervention is required,[196] but barriers to socialization and loneliness are quite common in most PWE.[197] Moreover, SUDEP may occur even in the absence of a seizure.[198]

Among non-pharmacological interventions to prevent SUDEP, the large longitudinal study conducted by Ryvlin et al.[199] has already been mentioned above, showing that VNS could potentially contribute to decrease SUDEP rate over time through several mechanisms, i.e., reducing the frequency of TCS, as the duration and severity of ictal and postictal phases. VNS showed SUDEP rate similar to other neuromodulation treatments, as deep brain stimulation (DBS) or RNS

(Responsive Neurostimulation) system.[200] However, data about non-pharmacological interventions need to be further investigated.

If we consider the role of anti-seizure treatment in the prevention of SUDEP, according to the guidelines of the American Academy of Neurology and the American Epilepsy Society,[41] there is not sufficient evidence to support or refute the prognostic value of polypharmacy for SUDEP as well as it is not possible to surely state that a specific ASM is associated with an increased SUDEP risk.[41] Recently, a warning by the Food and Drug Administration addressing the arrhythmogenic potential of LTG created great concern in the neurologic community .[201] A recent systematic search stated that there is insufficient evidence to support or refuse the association between LTG and SUDEP due to the high risk of bias and low precision and inconsistence in the examined studies.[202] Notably, none of the studies examined the risk of lamotrigine in people with pre-existing cardiac conditions.

To prevent or modify the above-mentioned risk factors and reduce SUDEP events, the caring physician should discuss them with the patient and the family. A pilot study on this topic was performed:[203] 28.35% of the respondents claimed that SUDEP should be discussed with all or almost all their patients. Patients' reaction after SUDEP discussion was emotional and negative (73.8%). Physicians decided to give information about SUDEP because of specific clinical situations or therapeutic choices (47%), but other reasons included patient's request and nonclinical reasons, such as ethical (the subjective view of the doctor as a person) or deontological issues (the objective view of the doctor as an healthcare professional).[203] Also for Kruja and Wyshka[204] disclosing the risk of SUDEP is necessary and it should be personalized and situation-related, using a more helpful and psychologically acceptable step-by-step approach.[204]

In the U.S. and Canadian survey by Friedman et al.,[205]neurologists rarely discuss SUDEP with patients or caregivers. More experienced neurologists encounter fewer negative reactions and they could minimize patient/caregiver distress.[203]A UK study[206] involving child neurologists showed that 93% of interviews provided SUDEP information, with 20% giving this to all patients. 63% of

neurologists preferred to provide information to children with intractable epilepsy, 30% preferred to inform about SUDEP at diagnosis whereas 50% only when seizures become intractable. 91% of parents wanted to know about it at the time of diagnosis (74%) or when seizures were poorly controlled (16%); the remaining parents were not sure about receiving information or did not want to know about SUDEP.[206]The authors concluded that the best way to provide SUDEP information is through discussion with the parents followed by giving an information leaflet.

According to the previous literature, patients claim the right to know about SUDEP,[207] but it seems that the decision to talk about it still relies on the clinician's ability to identify the "right time" to discuss such a delicate and not completely known matter.[208] Moreover, the subjective discomfort and perceived pressure with SUDEP, the lack of confidence on communication quality and the potential patients' negative reactions may explain why clinicians prefer not to talk about SUDEP at all or to do it only in specific situations.[208]

Conclusions

SUDEP is a rare event, not always observed by witnesses and poorly monitored with reference to respiratory, cardiac and electrophysiological activities. In line with the reports on the incidence of SUDEP, young age, disease severity (TCS), symptomatic etiology and poor response to ASMs are negative predictors. Seizures and epilepsy can affect cardiac function and in particular frequency, rhythm and conduction. Also, cardiac abnormalities are in relationship with epileptic seizures, but a lower number of SUDEP cases has been observed in these patients. Seizures can also modify the respiratory function through tachypnea, apnea/ipopnea and hypoxia and SUDEP was observed in patients with increased lungs' weight, edema and pulmonary congestion. Prone position is considered a risk factor for SUDEP, too. Cardiac defects may be responsible for death or may be the result of an impaired respiratory mechanism that may act as a trigger. Another mechanism that can be involved is prolonged PGES, but its role in SUDEP is still to be confirmed.

Regarding SUDEP prevention, clinicians should identify and aim to reduce the potential risk factors for SUDEP. According to The National Institute for Health and Clinical Excellence, SUDEP should be discussed "from the time of diagnosis onwards",[209] even though it may have a negative emotional impact on patients and caregiver.[210]

It is not clear which is the most suitable moment to discuss SUDEP, but educating patients about it could help in reducing the risk of seizures - and SUDEP as well - because a properly informed patient can modify dangerous behaviors.[211]

Author contributions

GG, ALN, EB wrote the first draft of the manuscript. GF, BM, AS, PS, GC, GG, ALN reviewed and updated the entire manuscript. GG added the paragraph about autopsy findings, reviewed and updated the defintions, methods and incidence paragraph; GC and PS added the paragraph about genetic and reviewed and updated the entire manuscript, GF added the paragraph about SUDEP prevention, reviewed and updated the entire manuscript. BM and AS reviewed and updated the paragraph about pathophysiological mechanisms and the entire manuscript; ALN reviewed and updated the paragraph about risk factors and entire manuscript.

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Ethical Publication Statement

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

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Table 1. Study design and incidence of SUDEP in community-based studies

Author, year	Design	Sources	Country	Target population	Definition	Population size	N. of cases
Ficker, 1998	Population-based study	Register of patient with epilepsy	Rochester MN, USA	Patients with seizure disorders in Rochester population in the period 1954-1994	Leestma, 1997 [5]	1,353 PWE	9
Aurlien, 2012	Retrospective study	Autopsy reports and data from the Norvegian Cause of Death Registry	Rogaland County, Norway	Patients resident in Rogaland County with SUDEP in the period 1995-2005	Nashef, 1997 [2]	2612 PWE (in 2000) 268 deaths in PWE	26 (all types of SUDEP) 19 (definite and probable
Holst, 2013	Retrospective study	Danish National Patient Registry, Danish Registry of Causes of Death and Danish Registry of Medicinal Products and deaths certificates	Denmark	All Danish residents in the age group 1-35 years in the period 2000-2006	Nashef, 1997 [2]	33,022 PWE 685 deaths in PWE	50 (definite 26; probable 37 (possible)
Leetsma, 1989	Prospective study	Coroners archives	Cook County, Illinois, USA	All SUDEP cases falling under the jurisdiction of the medical examiner in 1983.	Not specified	26250 PWE 360-432 deaths 79 SUD	60
Langan, 1998	Retrospective and prospective study	Coroners archives	South Dublin and Wicklow, Ireland	Population residing in South Dublin, South County Dublin and County Wicklow	Not specified	680,000 population area	15
Opeskin, 2003	Prospective study	Coroners archives	Victoria, Australia	Deaths occurred in Victoria, Australia between 1997 and 1999. Average yearly population 4,674,467	Nashef, 1997 [2]	4,375 deaths 166 deaths in PWE	50
Opeskin, 2000	Retrospective study	Coroners archives	Victoria, Australia	Deaths occurred in Victoria reported to the coroner and autopsied between 1991 and 1997.	Nashef, 1997 [2]	15,751 deaths 357 deaths in PWE	50

				Average yearly population 4,517,229			
Salmo and Connolly, 2002	Retrospective study	Coroners archives	West Ireland	All autopsies performed between 1991 and 2000 in the University College Hospital of Glasgow	Nashef, 1997 [2]	188,500 population area 3,103 autopsies 44 PWE	22 (21 residents)
Donner, 2001	Retrospective study	Coroners archives, Ontario Pediatric Forensis Pathology Unit, Division of Neurology, Hospital for Sick Children, Toronto	Ontario, Canada	Children less than 18 years of age with epilepsy occurring over the period 1988-1998 in the province	Leestma, 1997 [5]	13,862 PWE	27
Tennis, 1995	Retrospective study	Coroners archives	Saskatchewan, Canada	Primary epilepsy 15-49 years of age, based on ASMs prescriptions	Not specified	3,688 PWE	45 (definite/probable=18; possible=21)
Lhatoo, 2001	Prospective study	Register of patients with epilepsy	UK	Patients with newly diagnosed epilepsy between 1 and 90 years of age in the period 1984-1987	Nashef, 1997 [2]	792 PWE 214 deaths	1 SMR 1.9 (1.6-2.2)
Jick, 1992	Retrospective study	Coroners archives Medical records, autopsy reports, death certificates	Seattle, Washington area, USA	Members of Group Health Cooperative of Puget Sound (GHC),15-49 years of age, with primary epilepsy. Based on ASMs	Not specified	1,840 PWE 43 deaths	11
Camfield, 2002	Retrospective study	Local register of Nova Scotia Epilepsy cohort study.	Nova Scotia, Canada	Children with epilepsy resident in Nova Scotia at the time of the first two unprovoked epileptic seizures between 1977 and 1985 aged from 28 days and 16 years. Population 850,000.	Hauser, 1997 [4]	692 PWE 26 deaths	1

Leestma, 1984	Retrospective study	Coroners archives	Cook County, Chicago, Illinois, USA	SUDEP cases examined by the Office of the Medical Examiner during a 3-year period.	Not specified	NC	66
Lear-Kaul, 2005	Retrospective study	Coroners archives	Denver, Colorado, USA	SUDEP cases from autopsies performed from 1993 to 2000 at the Arapahoe County Coroners and from 1996 to 2000 at the Denver Office of the Medical Examiner	Nashef, 1997 [2]	67 SD in PWE	8
Derby, 1996	Retrospective	General Practice Research Database. Deaths certificates, coroner reports (autopsies)	United Kingdom	Patients with refractory epilepsy younger than 50 years, between 1989 and 1992. Based on ASMs. Population: >4 M of residents	Leestma, 1997 [5]	4,150 PWE	15 10
Burns, 2020	Retrospective	Sudden death in the Young Case Registry	USA	Sudep cases from the registry with autopsy 2015-2016	NS	1319 sudden deaths in infant	32 + 9 possible cardiac/SUD
Cheng 2020	Retrospective	National Health Insurance Research database (NHIRD)	Taiwan	Patients with epilepsy 1997-2013	Nashef, 1997	5411 PWE	157
Ge, 2017	Prospective	Genetic study on Epilepsy and Verbal autopsy questionNeire	China	PWE aged 2-80 years between 2010 and 2011	Annegers, 1997	1562 PWE	13 probable and 3 possibl
Panelli, 2019	Retrospective	Coroners archives	Australia and New Zealand	Cases between 2001 and 2013	Nashef, 2012	4149	53
Einarsdottir , 2018	Retrospective	Coroners archives	Iceland	PWE died between 1991 and 2010	Nashef, 2012	3514	37

Sveinsson, 2017	Retrospective	Swedish National Patient Registry and National Cause of Death Registry	Sweden	PWE between 1998-2005	Annegers, 1997	1230 PWE deceased	99

*Recalculated.

NC= not calculable; PWE= patients with epilepsy; SD= sudden death; SUD= sudden unexpected death; SUDEP= sudden unexpected death in epilepsy; SCD sudden cardiac deathNS not specified.

The source references are available upon request to the corresponding author

Table 2. Study design and incidence of SUDEP in selected cohorts of patients with epilepsy

Author, year	Design	Sources	Country	Target population	Definition	Population size	N. of cases
Ding, 2013	Prospective study	Follow-up survey, primary health level	China	Patients with convulsive epilepsy between 2000 and 2004. Population 3,185,000.	Nashef, 1997 [2]	1,986 PWE 206 deaths	2
Nashef, 2012	Retrospecitve study	Tertiary referral center	Italy	Patients with nocturnal frontal lobe epilepsy, 90% seizures during sleep, 1 year of follow-up		103 PWE, 2 death	1
Nashef, 1995	Retrospective study	School specializing in the education of children and adolescents with epilepsy and learning disorders	United Kingdom	Children and adolescents with epilepsy and learning disorders followed from1970 to 1993.	Not specified	601 PWE 24 deaths	11
Nashef, 1995	Retrospective study	Three tertiary referral center	United Kingdom	Patients with active epilepsy seen in 1990 until June 30 1993 in the epilepsy clinics at the National Hospital for Neurology and Neurosurgery	Nashef, 1997 [2]	310 PWE 28 deaths	14
Walczac, 2001	Prospective study	Three upper mid-western epilepsy centers: MINCEP Epilepsy Care, Minneapolis MN; Mayo Clinic Epilepsy Division, Rochester MN; Marshfield Clinic Epilepsy Section, Marshfield WI.	USA	Deaths of people with epilepsy enrolled in three epilepsy centers between June 1 1991 and December 31 1996	Leestma, 1997 [5]	4,578 PWE 110 deaths	20
Mu, 2011	Prospective study	Epilepsy program at primary health care level	Sichuan, China	People with convulsive epilepsy in seven counties from 2005 to 2009	Nashef, 1997 [2]	2,998 PWE 106 deaths	15
Klenerman, 1993	Retrospective study	Epilepsy center	London, UK	Deaths at the Chalfont Centre for Epilepsy between 1980 and 1990.	Not specified	113 deaths	7

Annegers, 2000	Retrospective study	Coroners archives	USA	Vagal nerve stimulation cohort (refractory cohort) between July 16 1997 and August 15 1999	Annegers, 1997 [3]	1,819 PWE 29 deaths	13 definite and
Sperling, 1999	Prospective study	Data of patients with epilepsy surgery	USA	Seizure recurrence after epilepsy surgery in the period 1986-1996 (10 years)	Leestma, 1997 [5]	393 PWE	6 Probable SU
Racoosin, 2001	Prospective study	Pooled data from New Drug Applications (NDAs) submitted to FDA	International	Refractory patients in add-on trials	Leestma, 1997 [5]	9,144 PWE 124 deaths	52
Leppik, 1995	Retrospective study	Pooled data from five clinical trial with tiagabine	International study	Five clinical trial with tiagabine	Not specified	1,000 PWE	7
Leestma, 1997	Retrospective study	Drug trials with lamotrigine in refractory epilepsy	International study	Death of subjects participating in trials with lamotrigine with diagnosed refractory epilepsy	Leestma, 1997 [5]	4,700 PWE 45 deaths	20
Mohanraj, 2006	Retrospective study	Epilepsy Unit at the Western Informary	Glasgow, UK	Newly diagnosed (and chronic patients) with epilepsy and treated chronically at the epilepsy unit between August 31 and May 1 and followed until Oct 1 2003.	Nashef, 1997 [2]	890 PWE (93 deaths) 2689 PWE (216 deaths)	7 55
Vlooswijk, 2007	Retrospective study	Tertiary referral center	Heeze, Netherlands	Deaths occurred within the epilepsy population treated in the period between Jan 1999 and April 2004	Leestma, 1997 [5]	4,400 PWE mean/year 179 deaths	29 (definite probable) 50 (all SUD
Timmings, 1993	Retrospective study	Medical records and death certificates of epilepsy unit	Cardiff, UK	PWE in Cardiff Epilepsy Unit	Not specified	1,820 PWE	14
Hennessy, 1999	Retrospective study	Maudsley Hospital	London, UK	Cohort study in patients with temporal lobe epilepsy surgery from Dec 1 1975 to Dec 1 1995	Nashef, 1997 [2]	299 PWE 20 deaths	6 (definite/p
Nilsson, 2003	Retrospective and prospective study	Swedish National Epilepsy surgery register	Sweden	Case series based on hospital admissions in six operating centers in Sweden	Nashef, 1997 [2]	212 non surgery 596 surgery	4 (definite/p SUDEP in n surgery pati

				between 1990 and 1994 and between 1995-1998.			6 (definite/p SUDEP in s patients)
McKee, 2000	Retrospective study	Medical records of patients with epilepsy and mental retardation	USA	Death of resident patients with epilepsy and mental retardation from 1978 to 1997 in an intermediate care facility for mentally retarded.	Leestma, 1997 [5]	180 PWE (55 deaths in PWE) 125 non-PWE (25 deaths in non-PWE)	11
Terrence, 1975	Retrospective study	Autopsy records of the Allegheny County Coroner's office	USA	Death being due to epilepsy from 1969 to 1973 in Allegheny County (1.6 million of people)	Not specified	8,000 expected PWE (assuming a prevalence of epilepsy of 5 per 1,000)	37
Dasheiff, 1991	Prospective and retrospective study	Medical records of the University of Pittsburgh Epilepsy Center (UPEC)	USA	Deaths in epilepsy surgery candidates from mid-1985 to mid-1990	Not specified	103 adult PWE candidates for epilepsy surgery	7
Sanchez-Larsen, 2019	Retrospective study	Spanish epilepsy reference centre	Spain	Deaths between 2010-2018	Nashef et al 2012	1250 PWE	6
Ryvlin, 2017	Retrospective study	VNS therapy device tracking database	USA	Deaths in patients with drug-resistant epilepsy and VNS from 1988-to 2012	Annegers, 1997	40443 PWE with VNS	632

*Recalculated.

PWE= patients with epilepsy; SUDEP= sudden unexpected death in epilepsy.

The source references are available upon request to the corresponding author

Table 3. Significant risk factors for SUDEP

Author, year	Design	Sources	Risk factor
Hesdorffer, 2012	Combined analysis	Case-control studies: Walczac, 2001 [26], Nilsson, 1999 [43] and Langan, 2005 [44]	Carbamazepine polytherapy
Aurlien, 2012	Retrospective study	Cause of death registry	Comorbidity
			History of complex partial se
			History of simple partial seizu
			History of GCTS
Hesdorffer, 2011	Combined analysis	Case-control studies from the United States (Walczac, 2001) [26], Sweden (Nilsson, 1999) [43], Scotland (Hitiris, 2007) [46], England (Langan, 2005) [44]	Young age at onset
		Case-control studies from the United States (Walczac, 2001) [26], Sweden (Nilsson, 1999) [43], Scotland (Hitiris, 2007) [46], England (Langan, 2005) [44]	Longer duration of epilepsy
		Case-control studies from the United States (Walczac, 2001) [26], Sweden (Nilsson, 1999) [43], Scotland (Hitiris, 2007) [46], England (Langan, 2005) [44]	Politherapy
		Case-control studies from the United States (Walczac, 2001) [26], Sweden (Nilsson, 1999) [43], Scotland (Hitiris, 2007) [46], England (Langan, 2005) [44]	Male sex
		Case-control studies: Nilsson, 1999 [43] and Langan, 2005 [44]	Alcohol abuse
		Case-control studies: Walczac, 2001 [26], Hitiris, 2007 [46] and Langan, 2005	Lamotrigine
		Case-control studies: Walczac, 2001 [26], Nilsson, 1999 [43] and Langan, 2005 [44]	GCTS (frequency)
Ryvlin, 2011	Meta-analysis	112 randomized trials	ASMs at not efficacious dose
Montè, 2007	Systematic review	27 papers about SUDEP	Being in bed/prone position/sl

Kloster, 1999	Retrospective study	Cause of deaths in an outpatient population of a tertiary referral centre	Aetiology High seizure frequency Signs of seizure preceding de
Ruy HU, 2014	Retrospective study	Cause of death in an epileptic population the tertiary hospital in Korea	GCTS (frequency) ASMs politherapy

* Recalculated

GTCS= generalized tonic-clonic seizures; ASMs= antiepileptic medications; COR= conditional Odds Ratio; SUDEP= sudden unexpected death in epilepsy.

The source references are available upon request to the corresponding author

Table 4: Genes associated with SUDEP

Authors (year)	Sodium channels	Potassium channels	Other ion channels	Non-ion channel genes	Chromosomal rearrangement
Glasscock et al, 2014	*SCN1A, SCN5A,SCN8A*	*KCNQ1, KCNH2, KCNA1*	*RYR2, HCN2*	*PRRT2*	
Bagnall et al, 2015	*SCN1A, SCN5A, SCN8A*	*KCNQ1, KCNH2, KCNA1*			
Devisnky et al, 2016	*SCN1A, SCN2A, SCN5A, SCN8A*	*KCNQ1, KCNH2*	*RYR2, HCN4, HCN2*	*TSC1, TSC2, NOS1AP, PRRT2, CSTB, DEPDC5*	
Goldman et al, 2016	*SCN1A, SCN5A, SCN8A, SCN1B*	*KCNQ1, KCNH2, KCNQ2, KCNA1*	*RYR2, HCN4, HCN2*		
Bagnall et al, 2017	*SCN1A, , SCN2A, SCN5A, SCN8A*	*KCNQ1, KCNH2, KCNA1*		*DEPDC5*	
Thorn et al, 2018	*SCN1A, SCN2A, SCN5A, SCN8A*	*KCNQ1, KCNH2, KCNE1, KCNT1*	*RYR2, HCN4, HCN2*	*TSC1, TSC2, NOS1AP, DSC2, LDB3, PRRT2, CSTB, DEPDC5*	5q14.3 Del/dup15q11
Li et al, 2019	*SCN1A, SCN2A, SCN5A, SCN8A*	*KCNQ1, KCNQ2, KCNA1*	*RYR2, HCN2*	*SENP2*	

The source references are available upon request to the corresponding author

Table 5. Respiratory mechanisms in SUDEP in animal studies

Author, year	Study type	Animal models	Mechanism
Venit, 2004	Experimental study	Three mouse strains: DBA/2J, B6SAS and primed 57BL/6J	Oxygenation prevent fatal audiogenic seizure in each mouse strain
Faigold, 2010	Experimental study	DBA1 mice	Audiogenic seizures followed by sudden death associated with respiratory arrest
Johonston, 1995 [183]	Experimental study	Sheep	Striking hypoventilation demonstrated in the sudden death group
Johonston, 1996	Experimental study	Sheep	Postictal pulmonary edema in the sudden death group
Johonston, 1997	Experimental study	Sheep	Central apnea in the sudden death group
St.-John, 2006	Experimental study	Rats	Seizures result in recurrent periods of obstructive and central apnea

The source references are available upon request to the corresponding author

Table 6. Respiratory mechanisms in SUDEP

Author, year	Design	Sources of cases	Mechanism	Sources of clinical evidence
Hewertson, 1994	Retrospective study	Inpatients undergoing VET	Decrease in SaO2	Data from EEG and oximetry
Nashef, 1996	Prospective study	Inpatient undergoing VET	Hypoxemia, apnoea	Data from VET, oximetry and plethysmography
Walker, 1997	Prospective study	Inpatients undergoing presurgical evaluation	Central, mixed and obstructive (8%) apnea	Data from EEG polysomnography
Kloster, 1999	Retrospective study	Died epileptic outpatients	Pulmonary oedema	Clinical and pathological data
Langan, 2000	Case-control study	Coroners archives, British Neurological Surveillance Unit and charity "Epilepsy Bereaved"	Difficulty in breathing	Data from withnessed
Blum, 2000	Retrospective study	Inpatients undergoing VET	Desaturation related to seizure duration	Data from VET, oximetry and plethysmography
So, 2000	Case report	Inpatient	Apnoea	Data from VET and oximetry
O'Regan, 2005	Retrospective study	Inpatients undergoing VET	Decrease in SaO2 and respiratpry rate	Data from VET, oximetry and plethysmography
Langan, 2005	Retrospective case-control study	Coroners archives, British Neurological Surveillance Unit and charity "Epilepsy Bereaved"	Protective effect of nocturnal supervision	Data from semistructured questionnaire
Bateman, 2008	Prospective study	Outpatient undergoing EEG polysomnography	Desaturation related to seizure duration	Data from VET and oximetry

Seyal, 2009	Prospective study	Inpatient undergoing VET with intracranial electrodes	Desaturation related to controlateral spread	Data from VET and oximetry
Pezzella, 2009	Case-report	Outpatient	Bilateral pulmonary congestion	Chest X-ray
Ryvlin, 2013	Retrospective study	Inpatients undergoing VET	Complex cardiorespiratory dysfunction	Data from VET and investigator observation
Seyal, 2013	Prospective study	Patients undergoing VET	Reduced duration of respiratory disfunction by periictal interventions	Data from VET
Singh, 2013	Prospective study	Inpatients undergoing VET	Ictal apnoea/ipopneoea	Data from VET, oximetry and plethysmography

The source references are available upon request to the corresponding author