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

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Abstract

Sudden unexplained 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 (seizure duration ≥30 minutes or seizures without recovery in between), in which postmortem examination does not reveal a cause 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 yr age group) and the severity of the disease. Young age, disease severity (in particular, a history of generalized tonic-clonic seizures), having symptomatic epilepsy, and the response to AEDs 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 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 are cardiac dysfunction (included potential effects of antiepileptic drugs, genetically determined channelopathies, acquired heart diseases), respiratory dysfunction (included postictal arousal deficit for the respiratory mechanism, acquired respiratory diseases) and postictal EEG depression.

KEY WORDS: 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 to George Washington. Patsy, a 17-year old woman, 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.

Definitions

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).

Annegers (3) explained the criteria as follows:

Explanatory features for SUDEP diagnostic criteria

1. *The victim must have had epilepsy, defined as recurrent unprovoked seizures.*
2. *The victim died unexpectedly while in a reasonable state of health.*
3. *The death occurred "suddenly" (in minutes), when known.*
4. *The death occurred during normal activities (e.g., in or around bed, at home, at work) and benign circumstances.*
5. *An obvious medical cause of death was not found.*
6. *The death was not directly caused by the seizure or status epilepticus.*

The criteria included death with or without evidence of seizure near the time of death, although many SUDEP cases have evidence of a recent seizure by observation or clinical signs such as a bitten tongue or cheek.

Annegers classified also SUDEP in different categories based on the level of diagnostic accuracy: "Definite SUDEP" includes cases meeting different criteria (victim suffering from epilepsy, victim dying unexpectedly, death occurring suddenly, during normal activities and benign circumstances, no obvious cause of death found, death not the direct cause of seizure or status epilepticus) and having sufficient descriptions of death and postmortem status;"Probable SUDEP" refers to cases having no postmortem data;"Possible SUDEP" includes cases having insufficient evidence on the circumstances of death and no post-mortem data available;"Unlikely/not SUDEP" refers to cases having a cause of death clearly established, or to circumstances making SUDEP highly improbable.
According to Hauser (4), it is important to include in the classification the category "unknown" to allow categorization of individuals in whom information is insufficient.

Criteria for SUDEP were revised also by Leestma et al. (5) and were as follows:

Revised SUDEP criteria

The criteria for SUDEP (definite or highly probable) were as follows:

1. *The subject had epilepsy, as defined by Gastaut and the World Health Organization (WHO): "a chronic disorder characterized by recurrent seizures due to excessive discharge of cerebral neurons". Because all patients had chronic and usually intractable epilepsy (according to their physicians, who had prescribed one or more AEDs for many years for their patients' seizures), it was assumed that Gastaut/WHO criteria were met.*
2. *The subject died unexpectedly while in a reasonable state of health.*
3. *The fatal attack occurred "suddenly". The complexity of this definition was discussed. It was recognized that the final ictus must occur precipitously and unexpectedly, but that death might not occur for several hours. Death may have occurred presumably from a seizure-associated cardiorespiratory arrest and its complications and not from status epilepticus. Sudden collapse and death may also have occurred without an observable seizure.*
4. *The death occurred during normal activities (e.g., at work, at home, in or around bed) in benign circumstances.*
5. *An obvious medical cause of death was not found. (An exception would be the presence of sudden cardiac arrhythmia, which may be related to the mechanism of SUDEP. Death in water if the victim does not show evidence of drowning may also be attributable to SUDEP).*
6. *SUDEP was excluded in the presence of status epilepticus or acute trauma in the setting of a seizure.*

The classification of "possible SUDEP" was assigned when cases met most or all of these criteria for SUDEP, but data suggested more than one possible cause of death (e.g., deaths associated with seizures while in the bath or swimming, or aspiration (confirmed or suspected) occurring concurrently with a seizure). It was recognized that the classification of drowning deaths is difficult, and unless such deaths were witnessed or other information was available, a level of indeterminateness of classification was appropriate. The "other (non-SUDEP)" classification was assigned to cases in which the criteria for SUDEP (definite or highly probable) or possible SUDEP were not met and another obvious cause of death had been established. The classification "insufficient data" was assigned to cases that could not be properly interpreted because of missing or ambiguous data related to the circumstances of death or concurrent medical condition.

The proposed Unified SUDEP Definition and Classification (6) 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 fulfil 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 one 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 one hour* (6).

Summarizing, the new categories proposed by Nashef et al. (6) are:

New 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 post mortem 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 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 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 one 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 (6).

Methods of the review

The scientific literature on SUDEP was examined. The databases used were MEDLINE (since 1966) and EMBASE (since 1974), searching for the key words "sudden unexpected death in epilepsy", "epidemiology", "cardiac defects", "electrodes", "heart disease", "risk factor", "focal myocytolysis", "molecular mechanisms", "physiopathology" and in the Pubmed Clinical Queries "sudden unexpected death in epilepsy", "systematic reviews", "therapy", "diagnosis" and "prognosis".

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 (Tab. 1) (2, 4, 5, 7-22). A total of sixteen 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 (10/15). 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 (2) or Leestma (5). 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 (17), young age at death (15), an unknown definition of SUDEP (21), or a small sample with some unclassified cases (7). 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 (7, 9) 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. (7) 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. (9) 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

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	Person-years	Incidence rate (per 1,000)
Ficker, 1998 (7)	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	25,939.70	0.35
Aurlien, 2012 (8)	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)	2,612 PWE (in 2000) 268 deaths in PWE	26 (all types of SUDEP) 19 (definite and probable SUDEP)	26,120 Estimated 0.7% of prevalence of epilepsy in Western countries	1.0 (all SUDEP classes) 0.7 (definite and probable SUDEP) epi
Holst, 2013 (9)	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 24) 37 (possible)	120,096 with epilepsy prevalence of 0.7%	0.41 (definite and probable SUDEP) 0.72 (all SUDEP classes)
Leetsma, 1989 (10)	Prospective study	Coroners archives	Cook County, Illinois, USA	All SUDEP cases falling under the jurisdiction of the medical examiner in 1983.	Not specified	26,250 PWE 360-432 deaths 79 SUD	60	5,250,000 14-16% SUD are SUDEP	2.3
Langan, 1998 (11)	Retrospective and prospective study	Coroners archives	South Dublin and Wicklow, Ireland	Population residing in South Dublin, South County Dublin and	Not specified	680,000 population area	15	10,200 Estimated prevalence of 0.5%	1.5

to be continued

Table 1 - *Continue*

				County Wicklow					
Opeskin, 2003 (12)	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	62,326 Estimated with prevalence of 0.5%	0.8*
Opeskin, 2000 (13)	Retrospective study	Coroners archives	Victoria, Australia	Deaths occurred in Victoria reported to the coroner and	Nashef, 1997 (2)	15,751 deaths 357 deaths in PWE	50	Estimated prevalence in Victoria of 0.5%	0.3 * (1 per 3000 patient years)
				autopsied between 1991 and 1997. Average yearly population 4,517,229					
Salmo and Connolly, 2002 (14)	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)	8,687 Estimated prevalence of epilepsy of 0.46%	2.4
Donner, 2001 (15]	Retrospective study	Coroners archives, Ontario Pediatric Forensis	Ontario, Canada	Children less than 18 years of age with epilepsy occurring	Leestma, 1997 (5)	13,862 PWE	27	138,620 Assuming prevalence 0.59%	0.2 children

to be continued

Table 1 - *Continue*

		Pathology Unit, Division of Neurology, Hospital for Sick Children, Toronto		over the period 1988-1998 in the province					
Tennis, 1995(16)	Retrospective study	Coroners archives	Saskatchewan, Canada	Primary epilepsy 15-49 years of age, based on AEDs prescriptions	Not specified	3,688 PWE	45 (definite/probable=18; possible=21)	33,299	0.54 definite/probable 1.3 possible
Lhatoo, 2001 (17)	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)	11,400	0.09
Jick, 1992 (18)	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 AEDs	Not specified	1,840 PWE 43 deaths	11	8,460 Estimated from the 5% sample of their computer files in which 56% of person aged 15-49 years using AEDs have epilepsy	1.3 estimated 0.9 after excluding drowning
Camfield, 2002 (19)	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	Hauser, 1997 (4)	692 PWE 26 deaths	1	9,090.9*	0.11

to be continued

Table 1 - *Continue*

				between 1977 and 1985 aged from 28 days and 16 years. Population 850,000					
Leestma, 1984 (20)	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	78,750	0.8 (3 years) 2.0 (1 year)
Lear-Kaul, 2005 (21)	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	34,115*	0.2
Derby, 1996 (22)	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 AEDs. Population: >4 M of residents	Leestma, 1997 (5)	4,150 PWE	15 10	6,784 (Estimated) (with refractory epilepsy)	2.2 1.5 per highly probable SUD Acquired 1.0 Idiophatic (all) 2.4 (1.7 highly probable)

*Recalculated.

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

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 (Tab. 2) (2, 3, 5, 23-40). Nineteen studies have been included. Only 1/4 of studies have been done prospectively. The studies were performed in the UK (6), USA (6), China (2), 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 number of patients with epilepsy ranged from 103 to 9,144. SUDEP cases ranged from 2 to 52. The lowest incidence of SUDEP was found in patients with newly diagnosed epilepsy (1.0 per 1,000 person-years) or seen at the primary care level in China (0.2-1.0 per 1,000). Slightly higher rates (1.2-2.0 per 1,000 person-years) were found among mixed populations including newly diagnosed and chronic epilepsy patients. Even higher rates (2.5-3.4 per 1,000 person-years) 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. Cohorts of patients with refractory epilepsy (some of them participating in drug development programs) incurred in SUDEP rates ranging from 2.2 to 3.9 per 1,000 person-years and surgical candidates from 2.2 to 9.3 per 1,000 person-years. Although the differing rates within each category at risk could be explained in part by the study design and methods, a correlation can be confirmed between the risk of SUDEP and the underlying disease severity and its response to drug treatment.

In general, up to 17% of deaths in people with epilepsy can be attributed to (41), the highest fractions being found in patients with idiopathic/cryptogenic epilepsies and/or no relevant comorbidity.

Incidence of SUDEP

1. *In community-based studies, the incidence of SUDEP ranged from 0.09 to 2.4 per 1,000 person-years.*
2. *Differences in the incidence of SUDEP can be attributed to the age of the study populations (with peaks in the 20-40 yr age group) and the severity of the disease.*
3. *Rates partly overlap across studies and periods of time.*
4. *SUDEP is the result of the effects of disease-related factors in individuals with genetically determined predisposition to cardiac arrhythmia or other structural or functional cardiac defects.*

Risk factors

A number of patient and disease-related factors have been investigated in patients died of SUDEP. These include, among others, history of generalized tonic-clonic seizures (presence and number), young age at epilepsy onset, longer duration of epilepsy, male sex, symptomatic aetiology of epilepsy, history of alcohol abuse, number of antiepileptic drugs, selected drugs, and low drug levels. 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 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 (8, 26, 42-49).

Walczac et al. (26) followed 4,578 patients in three US epilepsy centers and found 20 SUDEP cases. For each case, the Authors randomly selected four living controls from the same centers. Occurrence of tonic-clonic seizures, treatment with three or more AEDs, and mental retardation were independent risk factors. In a Swedish case-control study in adult patients with epilepsy, Nilsson et al. (43) identified 57 SUDEP cases among patients aged 15-70 years admitted in the period 1980-89 in any hospital of the Stockholm country, in Sweden. These patients were matched 1:3 to living epilepsy patients. In this study, SUDEP was associated with an increasing number of AEDs, early onset epilepsy and frequent changes of AED daily dose. In a study done in the UK, Langan et al. (44) studied 149 SUDEP cases, which were matched to 958 living controls. The risk of SUDEP was higher in patients with a history of generalized tonic-clonic seizures in the previous three months. Hitiris et al. (46) reported 62 SUDEP deaths among 6,140 mostly adult patients seen at the Epilepsy Unit of the Western Infirmary in Glasgow, UK in a 23-year period. These cases were matched 1:2 to living epilepsy controls. Mean duration of epilepsy was significantly longer in cases compared to controls and more cases than controls had a seizure in the antecedent year. All other putative factors were equally represented in cases and controls.

The data from these four case-control studies were combined by Hesdorffer et al. (45) and the factors found to be significant in the pooled analysis included an increased frequency of generalized tonic-clonic seizures, 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 AEDs and generalized tonic-clonic seizures, the authors found that, when adjusting for generalized tonic-clonic seizures, none of the AEDs considered in the studies were associated with an increased SUDEP risk as monotherapy or polytherapy (42).

In a comprehensive review of published reports, integrated by some personal data, Hughes (50) investigated the incidence and risk factors of SUDEP. The author found 48 studies and scored each of the main risk factors subtracting from the total number of studies the number of reports with negative or uneventful findings. The most extensively investigated factor was the number of seizures (19 studies, 14 of which with positive findings). Subtherapeutic AED levels followed

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	Person-years	Incidence rate (per 1,000)
Ding, 2013 (23)	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	9,930*	0.2 (probable SUDEP) *
Nashef, 1995 (24)	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	1,849	5.9 * Status epilepticus 4
Nashef, 1995 (25)	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	4,135	3.4 * 7/11 evidence of seizure
Walczac, 2001 (26)	Prospective study	Three upper mid-western epilepsy centers: MINCEP Epilepsy Care, Minneapolis MN; Mayo Clinic Epilepsy Division, Rochester MN; Marshfield Clinic	USA	Deaths of people with epilepsy enrolled in three epilepsy centers between June 1 1991	Leestma, 1997 (5)	4,578 PWE 110 deaths	20	16,463	1.2 (definite and probable SUDEP) 0.6 (definite SUDEP)

to be continued

tTable 2 - *Continue*

		Epilepsy Section, Marshfield WI		and December 31 1996					
Mu, 2011 (27)	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	14,990*	1.0 *
Klenerman, 1993 (28)	Retrospective study	Epilepsy center	London, UK	Deaths at the Chalfont Centre for Epilepsy between 1980 and 1990.	Not specified	113 deaths	7	3,392	2.1
Annegers, 2000 (29)	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 probable	3,176 + 375.2 after deactivation	4.1 5.0 (all SUDEP)
Sperling, 1999 (30)	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 SUDEP	1,502.6	4.0
Racoosin, 2001 (31)	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	13,617.1	3.8
Leppik, 1995 (32)	Retrospective study	Pooled data from five clinical trial with tiagabine	International study	Five clinical trial with tiagabine	Not specified	1,000 PWE	7	1,810	3.9
Leestma, 1997 (5)	Retrospective study	Drug trials with lamotrigine in refractory epilepsy	International study	Death of subjects participating in trials with	Leestma, 1997 (5)	4,700 PWE 45 deaths	20	5,747	3.5

Table 2 - *Continue*

				lamotrigine with diagnosed refractory epilepsy					
Mohanraj, 2006 (33)	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) 2,689 PWE (216 deaths)	7 55	6481.5* 22357.7*	1.08 (definite and probable SUDEP) 2.46
Vlooswijk, 2007 (34)	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 and probable) 50 (all SUDEP)	23387.1*	1.24 (definite and probable SUDEP)
Timmings, 1993 (35)	Retrospective study	Medical records and death certificates of epilepsy unit	Cardiff, UK	PWE in Cardiff Epilepsy Unit	Not specified	1,820 PWE	14	7,000	2.0
Hennessy, 1999 (36)	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/probable)	2,729	2.2

to be continued

tTable 2 - *Continue*

Nilsson, 2003 (37)	Retrospective and prospective study	Swedish National Epilepsy surgery register	Sweden	Case series based on hospital admissions in six operating centers in Sweden between 1990 and 1994 and between 1995-1998	Nashef, 1997 (2)	212 non surgery 596 surgery	4 (definite/probable SUDEP in non-surgery patients) 6 (definite/probable SUDEP in surgery patients)	634.9* 2,500*	6.3 2.4
McKee, 2000 (38)	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	3,012	3.6 in epilepsy 1.3 in non-PWE
Terrence, 1975 (39)	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	40,000*	0.9*
Dasheiff, 1991 (40)	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	752.7*	9.3

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

Table 3 - Significant risk factors for SUDEP.

Author, year	Design	Sources	Risk factor	Odds Ratio	95%CI
Hesdorffer, 2012 (42)	Combined analysis	Case-control studies: Walczac, 2001 (26), Nilsson, 1999 (43) and Langan, 2005 (44)	Carbamazepine polytherapy	1.40	0.70-2.70
Aurlien, 2012 (8)	Retrospective study	Cause of death registry	Comorbidity History of complex partial seizures History of simple partial seizures History of GCTS	1.8 (COR) 1.5 (COR) 1.8 (COR) 4.2 (COR)	0.6-5.4 0.5-4.4 0.5-6.2 0.5-34.2
Hesdorffer, 2011 (45)	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	1.72	1.23-2.40
		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	1.95	1.45-2.63
		Case-control studies from the United States (Walczac, 2001) (26), Sweden (Nilsson, 1999) (43), Scotland (Hitiris, 2007) (46), England (Langan, 2005) (44)	Politherapy	1.95	1.09-3.47
		Case-control studies from the United States (Walczac, 2001) (26), Sweden (Nilsson, 1999) (43), Scotland (Hitiris, 2007) (46), England (Langan, 2005) (44)	Male sex	1.42	1.07-1.88
		Case-control studies: Nilsson, 1999 (43) and Langan, 2005 (44)	Alcohol abuse	1.86	0.99-2.66
		Case-control studies: Walczac, 2001 (26), Hitiris, 2007 (46) and Langan, 2005	Lamotrigine	1.86	1.22-2.84
		Case-control studies: Walczac, 2001 (26), Nilsson, 1999 (43) and Langan, 2005 (44)	GCTS (frequency)	5.07 for 1-2 GTCS 15.46 for ≥3 GTCS	2.94-8.76 9.92-24.10

to be continued

tTable 3 - *Continue*

Ryvlin, 2011 (47)	Meta-analysis	112 randomized trials	AEDs at not efficacious doses	6.90	3.80-11.60
Montè, 2007 (48)	Systematic review	27 papers about SUDEP	Being in bed/prone position/sleeping	1.16 *	-
Kloster, 1999 (49)	Retrospective study	Cause of deaths in an outpatient population of a tertiary referral centre	Aetiology High seizure frequency Signs of seizure preceding death	2.36* 1.23* 1.96*	0.95 - 5.85* 0.38 - 3.96* 0.66 - 5.76*

* Recalculated

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

(positive 17/18). Other factors, in decreasing order, were history of generalized tonic-clonic seizures (10/12), young-adult age (11/11), polytherapy (7/11), early onset of seizures (6/7), male gender (3/6), duration of epilepsy (5/6), mental retardation (4/5), alcohol abuse (4/4), death on bed/floor (5/5), congenital neurological defects (4/4) and exposure to carbamazepine (1/4).

In a pooled analysis of risk factors, high frequency of tonic-clonic seizures was related to high risk of SUDEP (51). In a systematic review of published reports of Montè et al. (48), also being in bed was shown to be a strong risk factor for SUDEP. Weak risk factors were prone position, one or more sub-therapeutic blood levels, being in the bedroom, having a structural brain lesion and sleeping.

The role of AEDs in affecting the risk of SUDEP is controversial. In the study by Aurlien et al. (8), 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 (52). The lack of control for generalized tonic-clonic seizures has been indicated as a possible explanation of the study findings.

In a meta-analysis by Ryvlin et al. (47), the Authors compared patients randomized to AEDs at efficacious doses to AEDs at not-efficacious doses and to placebo. “Efficacious” was intended as the antiepileptic potency shown in randomized trials. Adjunctive therapy with AEDs 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. (49), in which the causes of deaths 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 (Tab. 3). A prone position at death was seen in 71% of SUDEP patients and sub-therapeutic AEDs concentrations were found in 57% of 23/42 SUDEP patients for whom this information was reported (49).

Risk factors for SUDEP

1. *Young age, disease severity (in particular, a history of generalized tonic-clonic seizures), having symptomatic epilepsy, and the response to AEDs are possible independent predictors of SUDEP.*
2. *The scarcity of the available data prevents any study of interactions between different factors.*
3. *Although the number of AEDs can be considered a proxy for the disease severity, one cannot exclude that drugs themselves have an independent role.*

Pathophysiological mechanisms

The pathophysiological mechanisms underlying SUDEP are not fully known or understood (51, 53, 54). This depends on the limited data available since SUDEP is a rare event that is not always attested,

whose electrophysiology is monitored in few cases with regard to both respiratory and heart function as well as cerebral electrical activity. Even when monitored by video-EEG data are often incomplete due to the lack of contemporary monitoring of the arterial pressure and respiratory function, often evaluated exclusively by visual observation of respiratory movements.
Moreover, heart activity monitoring is also generally limited to a single electrocardiographic channel, which may provide information about heart rate but not on the morphology of the QRS complex;finally the electrocardiographic track is often masked by movement artifacts. In addition, SUDEP is temporarily related to generalized tonic-clonic seizures only in certain cases (49). Its pathophysiological causes may therefore vary according to different circumstances that make that particular seizure, in that specific moment and in that patient, a fatal event. It can be assumed that the main mechanisms are: heart, respiratory and postictal depression (cerebral electrical shutdown). Each of these mechanisms includes also subcategories such as: potential effects of antiepileptic drugs, genetically determined channelopathies, acquired heart diseases that may account for the heart mechanism and postictal arousal deficit for the respiratory mechanism.

Pathophysiological mechanisms

1. *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 few cases with simultaneous assessment of respiratory, cardiac and brain activity.*
2. *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.*
3. *The main hypothesized mechanisms are cardiac dysfunction (included potential effects of antiepileptic drugs, genetically determined channelopathies, acquired heart diseases), respiratory dysfunction (included postictal arousal deficit for the respiratory mechanism, acquired respiratory diseases) and postictal EEG depression.*

Heart mechanisms

There are experimental and clinical evidences that acute seizures and chronic epilepsy may be associated with changes in heart functions that, in rare cases, may lead to death.
The acute involvement of the heart activity during epileptic seizures is supported by anatomical and functional links that connect cerebral districts (both cortical and subcortical) to autonomic networks (55, 56). Upper brain areas, such as insular, orbitofrontal and cingulate cortex, together with amygdala and hypothalamus, exert descending control over the autonomic neurons going towards the heart, as shown by experimental (57-61), clinical and electrophysiological (62-67), and functional neuroimaging (68, 69). The final heart homeostasis depends on the balance between the two components of the autonomic nervous system, the sympathetic and the parasympathetic, which determine each ionotropic and chronotropic effects on the heart opposites, respectively positive and negative.
This system of anatomical pathways creates a heart-brain link, which constantly regulates the activity of the cardiovascular system in response to every external or internal stimulus and, intuitively, to any pathological condition, which will severely affects the central nervous system, interfering with the optimal functioning of this network (56).
The vegetative nervous system modulates heart activity and its nuclei/centers are likely to be involved during the spread of epileptic seizures, resulting in the appearance of peri-ictal autonomic cardiac symptoms and/or signs (70-73). There is experimental evidence for alterations in arterial blood pressure and heart rate (59) and for a strong sympathetic activation (which becomes persistent after its stimulation or parasympathetic resection) after repeated stimulation of the insular cortex and the amygdala (74, 75).
The imbalance between the two vegetative components or a dysfunction in the heart innervation of one autonomic component represents a predisposing condition leading to abnormal heart function and consequently to sudden death (SD). It should be pointed out that the literature has not shown unequivocal evidence of a possible cerebral lateralization, that is to say a different effect of the two hemispheres in the autonomic cardiovascular control (75-87), and it has been assumed that the intact connectivity of mesial temporal structures, particularly the insula, of the two hemispheres is essential for a balanced interhemispheric and cardiovascular control (88).
The most frequently involved autonomic conditions in SD resulting from cardiac arrhythmia are said to be secondary to an increase of the sympathetic tone, an increase of the plasmatic concentrations of chatecolamines and a decrease of the vagal activity (74, 89-91).
The cardiac anomalies, which occurred in patients with epilepsy during epileptic seizures, can involve rate, rhythm and conduction.

Heart mechanisms

1. *The acute involvement of the heart activity during epileptic seizures is supported by anatomical and functional links that connect cerebral districts (both cortical and subcortical) to autonomic networks.*
2. *The autonomic nervous system modulates cardiac activity and its nuclei/centers are likely to be involved during the spread of epileptic seizures, resulting in the appearance of peri-ictal autonomic cardiac symptoms and/or signs.*
3. *The imbalance between the two vegetative components (sympathetic and parasympathetic) or a*

dysfunction in the heart innervation of one autonomic component represents a predisposing condition leading to abnormal heart function and consequently to sudden death.

4. *The most frequently involved autonomic conditions in sudden death resulting from cardiac arrhythmia are secondary to an increase of the sympathetic tone, an increase of the plasmatic concentrations of catecolamines, and a decrease of the vagal activity.*

Tachycardia

The most frequently cardiac anomaly, which occurs in adults and children during epileptic seizures, is the increase of the heart rate. An ictal sinus tachycardia occurred in 73-99% of epileptic seizures and in 92-100% of patients with epilepsy and some of them subsequently died of SUDEP (64, 76, 85, 87, 92-99).

Sinus tachycardia seems to be particularly related to generalized tonic-clonic seizures or focal seizures with secondary generalization, to the duration of these seizures and to their appearance in clusters (96, 100). Tachycardia can occur immediately before (which would exclude its relation with motor activities linked to the same epileptic seizure) or at the same moment of the appearance of an epileptic seizure and it can last, after the seizure, for a few minutes or even a few hours (86, 87, 99, 100). The appearance of other seizures before the heart rate settles down could result in an incremental increase of heart rate and fatal arrhythmia. Although sinus tachycardia is benign in most cases (93), severe tachycardia at a higher rate (>150 bpm) (100) and a slower recovery of the normal heart rate in the post-acute phase (101) occur more frequently during seizures of patients who subsequently died of SUDEP.

There is evidence that may explain how a cardiac dysfunction, such as sinus tachycardia, whose evolution is generally benign when occurring during a single epileptic seizure, can be potentially a predictive factor of SUDEP in patients with recurring seizures because, at some time of the patient's life, it can evolve into lethal arrhythmia.

- First, epileptic seizures, particularly those generalized tonic-clonic and focal secondarily generalized, especially if of long duration, are associated to an autonomic storm, which is frequently characterized by an increase of the sympathetic tone associated with higher plasmatic levels of catecholamines (102).
- Second, there is experimental (59, 103) and clinical (104, 105) evidence that sudden and acute vegetative imbalances are associated with a high risk of SD. Moreover, high levels of plasmatic catecholamines have been proved to cause severe micro damage to the myocardial tissue. If this damage, which is initially transitory, occurs repeatedly, it may evolve into permanent structural damage of the heart. As a matter of fact, high plasmatic levels of catecholamines experimentally obtained through direct infusion, stimulation of the sympathetic centers such as the stellate ganglion, or stress can be associated with reversible myocardial lesions such as focal myocytolysis or fibrillary degeneration (59, 89, 106-108). Stimulations of the nervous system, particularly the hypothalamus, the limbic cortex, the mesencephalic reticular formation and the sympathetic ganglion have been also associated with focal myocytolysis (108, 109). It has been pointed out that, in the same experimental conditions, vagotomy and removal of the adrenal gland do not prevent its formation, consequently excluding in their genesis the humoral or parasympathetic autonomic role in favor of the sympathetic (108-110).
- Third, post-mortem studies have confirmed that reversible cardiac lesions such as vacuolating focal myocytolysis associated with interstitial edema and irreversible cardial lesions such as foci of fibrosis occurred more often in patients who died of SUDEP than in control groups (49, 111-117).

Multifocal vacuolating myocytolysis is a potentially reversible form of myocardial damage and though it may be associated to transitory ischemic pain, is not to be considered as cardiac necrosis (118, 119).

The occurrence of focal myocytolysis in patients who died of SUDEP is consistent with the presumption that an epileptic seizure, generating sympathetic hyperactivity, would increase heart rate, cardiac output and blood pressure. The myocardium demands an overall higher oxygen level when any of these conditions occurs (120). If this demand is not fully met, the myocardium may suffer from an ischemic pain (121). The activation of the autonomous nervous system can result in vasospasm of the coronary arterioles, finally leading to cardiac ischemia (122). Concomitant hypoxia caused by central or obstructive sleep apnea may worsen the patient's condition.

In agreement with these observations, there is evidence that epileptic seizures can be associated with myocardial distress, as highlighted by the S-T segment depression in the ECG (111, 121, 123, 124), which particularly correlates with generalized tonic-clonic seizures and their duration (96) and by reports of precordial pains during complex partial epileptic seizures (125).

Alehan et al. (126) also evaluated, in a pediatric population, biomarkers of cardiac ischemic injury such as cardiac troponin I (cTnI) for myocardial necrosis, creatine kinase-MB (CK-MB) and Brain-Type Natriuretic Peptide (BNP) (126), which are two specific cardiac proteins. Besides normal cTnI levels, the authors also observed a statistically significant increase of CK-MB and BNP plasmatic levels within 12 hours following a generalized tonic-clonic seizure compared to a control group. The same results were confirmed at a subsequent evaluation carried out 7 days after the ictal event (126). Normal cTnI levels exclude an irreversible necrosis of myocardiocytes, but high levels of BNP and CK-MB, which are biomarkers signaling transitory myocardial injury (127-130), are a sign of slight cardiac dysfunction. The Authors concluded that the

observed cardiac anomaly was likely related to the recurrent epileptic seizures because of the temporal relation of its occurrence and the absence of cardiovascular risk factors as the study concerned a pediatric population.

It is likely that patients with recurrent generalized seizures be exposed to the risk of focal myocardial lesions that are first transitory, as it is the case of focal myocytolysis, but may evolve over time into an irreversible focal fibrosis. Focal myocytolysis and cardiac focal fibrosis, damaging the anatomic-functional uniformity of the myocardial tissue, may cause a predisposition to cardiac arrhythmias such as atrial fibrillation, supraventricular tachycardia, bundle branch block, ventricular or premature atrial depolarizations (131, 132). Myocardial fibrosis is thought to be one of the mechanisms leading to postinfarction ventricular tachycardia (133, 134). Such anatomic-functional myocardial condition, when associated with a specific increase of the sympathetic tone as it occur during a long secondarily generalized epileptic seizure, because of an increase of the circulating plasmatic cathecolamines (102) or a direct autonomic stimulation of the heart, may progress to a lethal tachyarrhythmia (96, 135).

This hypothesis is corroborated by the fact that patients suffering from neurological conditions (including patients with epilepsy in the interictal phase) showed ECG anomalies predictive of SD: QT prolongation, late or premature ventricular potentials, ventricular tachycardia and Q wave inversion (66, 90, 91, 100, 136). The risk for ECG anomalies is thought to be dependent on the duration of the seizure (98).

The literature has shown very few cases of monitored tachyarrhythmias during SUDEP or near-SUDEP (100, 134, 137, 138); among these cases, one patient had antecedents of ischemic cardiac disease and another had a first-degree AV block on the ECG, suggesting that a structural cardiac pathology can be considered a predisposing factor.

Literature reports indicate that in the event of SUDEP or near-SUDEP, death or the need for intensive care are rarely due to an ictal ventricular fibrillation (137, 138). In most cases with severe tachycardia, heart rate does not gradually and regularly decrease, but rather appears disturbed by irregular and sudden oscillations (64, 96, 138-140), suggesting that the final condition which leads to death is a severe autonomic instability. This condition could explain the *lockstep phenomenon*, that is the synchronization of ictal and interictal cortical seizures with cardiac postganglionic sympathetic and unsympathetic seizures, especially in its unstable pattern, which would cause a temporary dispersion of recovery of ventricular excitability, resulting in an electric instability and finally in ventricular arrhythmia (141-143). As a result of this, an irregular series of sudden variations of the heart rate in the postictal phase may indicate a risk marker for SUDEP.

Tachycardia

1. *The most frequently cardiac anomaly, which occurs in adults and children during epileptic seizures, is ictal sinus tachycardia (IST).*
2. *IST is particularly related to generalized tonic-clonic seizures or focal seizures with secondary generalization, to the duration of these seizures and to their appearance in clusters.*
3. *IST is benign in most cases;severe tachycardia at a higher rate (>150 bpm) and a slower recovery of the normal heart rate in the post-acute phase occur more frequently during seizures of patients who subsequently died of SUDEP.*
4. *Patients with recurrent generalized seizures seem to be exposed first to the risk of focal transitional myocardial lesions (focal myocytolysis) and then to irreversible focal fibrosis that damage the anatomic-functional uniformity of the myocardial tissue;this condition may predispose to cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia, bundle branch block, ventricular or premature atrial depolarization).*
5. *Alternatively, the final condition which leads to death could be a severe autonomic instability linked to the lockstep phenomenon which would cause a temporary dispersion of recovery of ventricular excitability, resulting in an electric instability and finally in ventricular arrhythmia. As a result of this, an irregular series of sudden variations of the heart rate in the postictal phase may indicate a risk marker for SUDEP.*

Bradycardia/bradyarrhythmia

As part of the ictal/peri-ictal heart rate disease, bradycardia was observed by different Authors (96, 97, 99, 136, 144-147). However, it appears to occur less frequently than tachycardia (64, 98, 148). It was found in 0.27-0.40% of patients who were monitored with video-EEG (146, 149) or in <6% of patients with complex partial seizures (96, 139, 148). However, a long-term ECG monitoring study with implantable loop recorder showed that 21% of patients had periods of bradycardia or asystole. These, apart from one patient with an atypical pattern of secondary generalization, were observed during typical epileptic seizures, and were usually associated with benign tachycardia (85). During this study, bradycardia was usually an evolution of tachycardia, as previously reported (64, 138-140).

Although the value of this study is limited by the small number of cases, the results suggest that periods of bradycardia/asystole may occur more frequently than previously thought and, for undefined reasons, especially in patients with a different ictal ECG pattern. Nashef et al. (150) found 4 cases of bradycardia associated with respiratory problems and hypoxia and assumed that bradycardia was induced by a cardiorespiratory reflex after activation of chemoreceptors by hypoxia.

Among all the studies shown in the literature that report periods of reduction of heart rate leading up to asystole during epileptic seizures, different patterns

can be identified. For example, bradycardia which occurs in the immediate postictal phase and which appears to be an evolution of cardiac anomalies, most commonly tachycardia, can be considered an autonomic breakdown phenomenon (64, 138-140) and bradycardia associated with disorders of the respiratory rhythm may cause hypoxia (150). There were also reported cases of bradycardia directly associated with the ictal electrical discharge, the so-called ictal bradycardia syndrome, in which the alteration of the cardiac rhythm is supposed to be determined directly by the action of the ictal activity on autonomic networks.

The ictal bradycardia syndrome, defined by Reeves et al. is characterized by proved bradycardia or asystole, which are temporally associated with an EEG ictal discharge (144). In the cases shown in the literature, it is usually associated with complex partial seizures, rarely secondarily generalized, especially those of the temporal lobe origin (64, 96, 99, 136, 145, 146, 151-159). This does not seem to be a lateralized phenomenon (136, 145). Indeed, according to some studies, its onset is said to be associated with the bilateral spread of the ictal discharge (136, 155, 159).

Despite having available ECG and EEG data, the literature provides little information on the characteristics of the cerebral electrical activity when bradycardia begins. Moreover it is difficult to evaluate any possible lateralized organization of cardiac control for different reasons. One is the presence of a cerebral lesion that may modify the functional anatomical organization of the region; the other is the possibility of the discharge to spread contralaterally; in most cases, the patient's dominance was not shown and, at last, the scalp EEG is not always capable of detecting the involvement of contralateral mesial temporal structures. Moreover, in very few cases the respiratory activity was evaluated during bradycardia/asystole and specifically no pO2 value was reported in any patient. Consequently, it is not possible to exclude with certainty that the respiratory function may have a role in the initial slowing down of the cardiac rhythm.

Ictal bradycardia is potentially dangerous for patients as it can progress to a terminal asystole (141, 160-162); it would be important to identify markers, which can be easily detected in clinical practice, to recognize patients at risk and consider them for second level cardiological screening and/or an implanted cardiac pace-maker. Ictal bradycardia usually occurs in the same patient in 40% of seizures (149, 163). Very rarely seizures with and without bradycardia are semeiologically identical. In most of the cases, ictal bradycardia/asystole coincides with a sudden atonia, which is sometimes followed by short and bilateral myoclonic jerks in the arms; sometimes relapse is associated with tonic posturing (145, 149, 163).

The sudden loss of postural tone occurs usually during a patient's typical seizure after the appearance of the first usual symptoms/signs, it is preceded by a few seconds of asystole and is associated with the EEG changes usually observed during cardiac arrest and cerebral hypoperfusion. More rarely atonia appears as the only clinical manifestation of a seizure. More often it is associated with other, more frequent manifestations (149). Ictal asystole appears frequently some years after the onset of epilepsy (149), probably because the anatomical circuits, which are involved in the seizure, have changed. The appearance of atonia in the course of a patient's clinical history, complicating the sequence of symptoms/signs of their habitual seizures, or inexplicable relapses can be considered as an important clinical marker for ictal bradicardia/asystole.

Bradycardia/bradyarrhytmia

1. *Reported in 0.27-0.40% of monitored patients and in <6% of patients with complex partial seizures; it may occur more frequently.*
2. *Most common occurrence: first, in the immediate postictal phase as evolution of cardiac anomalies, most commonly tachycardia;second, associated with disorders of the respiratory rhythm involving hypoxia;third, directly associated with the ictal electrical discharge (ictal bradycardia syndrome).*
3. *Ictal bradycardia syndrome (IBS) is usually associated with complex partial seizures, rarely secondarily generalized, especially those of the temporal lobe origin.*
4. *IBS appears frequently some years after the onset of epilepsy probably because the anatomical circuits, which are involved in seizures, have changed.*
5. *In most of the cases IBS clinically coincides with sudden atony;with respect to this, the appearance of sudden loss of postural tone in the course of a patient's clinical history, complicating the sequence of symptoms/signs of their habitual seizures, or inexplicable relapses can be considered important clinical markers for ictal bradicardia/asystole.*

Genetic factors

Cardiac abnormalities are frequently associated with epileptic seizures;the incidence of SUDEP is very low compared to the frequency of the seizures and it only concerns a very small number of patients. It can be assumed that some predisposing conditions exist which make patients with epilepsy susceptible to develop a terminal arrhythmic event during or immediately after an epileptic seizure.

Heart and brain are organs whose function is based on the production of electrical potentials. Membrane channels especially the voltage-gated sodium and potassium channels play a fundamental role (164). Genetic abnormalities of these channels can result in cardiac and neurological diseases (164).

Dravet syndrome is a drug-resistant epileptic syndrome, which occurs in the patient's early years of life and is characterized by a high mortality rate. Dravet syndrome is associated with a high percentage of anomalies of the SCN1A gene (165, 166). There have been cases of patients with some epileptic syndromes

belonging to the GEFS+, who died of SUDEP or have a family history of SUDEP, where abnormalities of sodium and potassium channels were found (167-170). One of the patients suffering from GEFS+ had a family history of SUDEP involving the maternal and the paternal branch of the genealogic tree.
These observations suggest that an active search of SD in first-degree family members would allow the identification of patients at potential risk of SUDEP, who should undergo generic testing and cardiologic screening.
Arrhythmogenic cardiac diseases in fact have been associated with channelopathies and in particular mutations of genes encoding the KCHQ/KCHN potassium channel and the SCH sodium channel have been associated with long QT syndrome, short QT syndrome and Brugada syndrome (164, 171, 172).
In the recent years, there has been increased interest in a possible association between epilepsy channelopathies and cardiac arrhythmias, such as long QT syndrome (LQTS) (173). A 'seizure phenotype' was recorded in about 30% unrelated patients from two independent cohorts with genetically confirmed (KCNH2 mutations) LQT2 (174). A recent post-mortem study identified mutations in KCNH2 or SCN5A genes, all previously associated to LQTS, in six out of 68 (13%) SUDEP patients (175). Moreover, mutations in KCNH2, encoding the potassium channel hERG-1 (human ether-à-go-go-related gene-1) that generates the rapid component of cardiac delayed rectifier potassium current, have been recently reported in patients with recurrent seizures and prolonged QTc interval (176, 177). In addition, mouse lines bearing dominant mutations in the Kv1.1 Shaker-like potassium channel, associated to long QT syndrome type 1 in humans, exhibit severe epilepsy and premature death (173, 177, 178). Finally, Partemi et al. (179) have recently shown that, in a group of patients with epilepsy and cardiac arrhythmic disease or family history with SUDEP, 21% carried channelopathies related to the SCN and KCN genes (179).

Genetic factors

1. *Predisposing conditions make patients with epilepsy susceptible to develop a terminal arrhythmic event during or immediately after an epileptic seizure.*
2. *Membrane voltage-gated sodium and potassium channels play a fundamental role in the production of electrical cerebral and cardiac potentials.*
3. *Genetic abnormalities of these channels can result in neurological and cardiac diseases such as epilepsy and sudden death.*
4. *SUDEP may be the result of the effects of disease-related factors in individuals with genetically determined predisposition to cardiac arrhythmia or other structural or functional cardiac defects.*
5. *With respect to this, an active search of sudden death in first-degree family members would allow the identification of patients at potential risk of SUDEP, who should undergo generic testing and cardiologic screening.*

Respiratory mechanism

Differently from the cardiac function, there is no evidence of an interictal impairment of the respiratory function in patients with epilepsy (180). Variations of the respiratory function during a seizure were found in some experimental studies, which were carried out in animals (Tab. 4) (181-186) and in clinical studies on adults and children who suffered from tachypnea (187), apnea/hypopnea and/or hypoxia during or after epileptic seizures (120, 138, 150, 188-196). The role of the respiratory mechanism in the pathogenesis of SUDEP was confirmed in SUDEP or near-SUDEP cases, where an increased weight of the lungs was observed, or pulmonary edema or congestion occurred (10, 49, 197).
Anatomical and functional links, which connect cortical regions to autonomic centers of the brainstem, seem to explain the involvement of the respiratory function during an epileptic seizure. The stimulation of the temporal pole, the insular cortex, the orbital surface of the frontal lobe and the cingulate gyrus affect respiratory movements in the monkey (198, 199). These seem to influence cardiorespiratory function through efferents directed, at the bulbar level, to the nucleus of the solitary tract and the trapezoid nucleus, which are also involved in baroreceptor and chemoreceptor reflexes (200, 201). The tracts descending from the cortical regions toward the respiratory centers of the brainstem are mainly ipsilateral (202).
Tachypnea seems to be a benign sign; in contrast, breath difficulties, bradypnea/apnea and/or desaturation may play a potential role in the SUDEP (Tab. 5) (44, 49, 120, 138, 150, 188-197).
The available literature offers little evidence concerning the cases monitored, as there have been very few prospective studies and studies based on the analysis of the respiratory function through a complete cardiorespiratory monitoring with an evaluation of pO2 and pCO2. More frequently, the respiratory function is evaluated visually by the expert.
In relation to the circumstances and the details of the event, witnesses of SUDEP reported a high percentage of breathing difficulties (44, 190).
The patients monitored during a seizure suffered more frequently from central or mixed apnea and less frequently from obstructive apnea (150, 189, 191, 192, 196).
The role of mechanic obstruction would be consistent with the signaling of a higher number of cases of SUDEP in prone position, rather than in supine position (49, 138). In prone position the nose or the mouth may be obstructed because of their pressure on the pillow. Some authors suggest that the prone position is a weak risk factor for SUDEP (48). Only one case with SUDEP was found, during an EEG-video monitoring, to have a severe laryngeal-esophageal spasm, which was considered to be the cause of death (203).
Ictal apnea and hypoxemia were mainly associated with focal seizures originating from the temporal lobe and the level of desaturation was found to be dependent on the duration of the seizure (191, 193, 196), the

Table 4 - Respiratory mechanisms in SUDEP in animal studies.

Author, year	Study type	Animal models	Mechanism
Venit, 2004 (181)	Experimental study	Three mouse strains: DBA/2J, B6SAS and primed 57BL/6J	Oxygenation prevent fatal audiogenic seizure in each mouse strain
Faigold, 2010 (182)	Experimental study	DBA1 mice	Audiogenic seizures followed by sudden death associated with respiratory arrest
Johnston, 1995 (183)	Experimental study	Sheep	Striking hypoventilation demonstrated in the sudden death group
Johnston, 1996 (184)	Experimental study	Sheep	Postictal pulmonary edema in the sudden death group
Johnston, 1997 (185)	Experimental study	Sheep	Central apnea in the sudden death group
St.-John, 2006 (186)	Experimental study	Rats	Seizures result in recurrent periods of obstructive and central apnea

contralateral spread of the seizure (194, 196), and the younger age in a pediatric population (196). A recent study analyzed retrospectively the electrophysiological data of 16 SUDEP and 9 near SUDEP cases (138). In 10 cases with SUDEP with available cardiac and respiratory data, an initial postictal tachypnea progressed and evolved to a deterioration of cardiorespiratory function which was characterized by apnea and bradycardia within 3 minutes after the end of the seizure. This event was terminal for 4/10 patients and in the other 6 it progressed to a late cardiorespiratory arrest after an initial recovery of the cardiac and respiratory function (138). It could be assumed that the initial tachypnea results from the ictal hypoxia, which was responsible for a neurovegetative alteration possibly leading to death, although the lack of data on pO2 and pCO2 in this study cannot corroborate this hypothesis. The Authors remarked that no patient in prone position showed any sign of movement which would have improved their position (138).

Postictal immobility can play a role in the physiopathology of the SUDEP (195). This observation supports the protective role of supervision at night and the importance, in a postictal phase, of simple interventions such as repositioning of patients or acoustic and tactile stimuli (44). A longer postictal immobility resulting in a postictal condition of arousal deficit may be related impairment of the serotoninergic systems, which stimulate part of the respiratory centers of the brainstem involved in the breath regulation and part of the arousal during hypercapnia (204, 205). A postictal depression of the serotoninergic systems would compromise the reflex repositioning of the head in case of upper airway obstruction caused by the prone position. This hypothesis is supported by the observation that the administration of SSRI to patients with epilepsy reduces the desaturation during a generalized tonic-clonic seizure (206). A respiratory deficit, therefore, when severe enough, could lead to SUDEP;there are few available data to determine whether or not the respiratory mechanism contributes with other mechanisms to cause SUDEP. The studies showed a relation between the extent of desaturation during a seizure and the appearance of QT-interval anomalies (prolongation or shortening) (207). This observation requires caution as it opens up different possible scenarios. Cardiac abnormalities may be the mechanism responsible for death or may be the result of a respiratory impairment, which is impossible to detect without adequate cardiorespiratory monitoring. Therefore, the respiratory mechanism would act as the primum movens of the cascade of events. Also hyperventilation, caused by a primary respiratory event, could trigger a fatal arrhythmia in a genetically predisposed patient. It is also important to point out that there are no available data concerning the presence in patients, who died of SUDEP, of pulmonary comorbidities such as chronic obstructive bronchopneumopathy, emphysema, bronchial asthma and smoke addiction.

Respiratory mechanisms

1. *The acute involvement of the respiratory function during epileptic seizures is supported by anatomical and functional links that connect cerebral districts (both cortical and subcortical) to autonomic networks.*
2. *The autonomic nervous system modulates respira-*

Table 5 - Respiratory mechanisms in SUDEP.

Author, year	Design	Sources of cases	Mechanism	Sources of clinical evidence
Hewertson, 1994 (188)	Retrospective study	Inpatients undergoing VET	Decrease in SaO2	Data from EEG and oximetry
Nashef, 1996 (150)	Prospective study	Inpatient undergoing VET	Hypoxemia, apnoea	Data from VET, oximetry and plethysmography
Walker, 1997 (189)	Prospective study	Inpatients undergoing presurgical evaluation	Central, mixed and obstructive (8%) apnea	Data from EEG polysomnography
Kloster, 1999 (49)	Retrospective study	Died epileptic outpatients	Pulmonary oedema	Clinical and pathological data
Langan, 2000 (190)	Case-control study	Coroners archives, British Neurological Surveillance Unit and charity "Epilepsy Bereaved"	Difficulty in breathing	Data from withnessed
Blum, 2000 (191)	Retrospective study	Inpatients undergoing VET	Desaturation related to seizure duration	Data from VET, oximetry and plethysmography
So, 2000 (192)	Case report	Inpatient	Apnoea	Data from VET and oximetry
O'Regan, 2005 (120)	Retrospective study	Inpatients undergoing VET	Decrease in SaO2 and respiratpry rate	Data from VET, oximetry and plethysmography
Langan, 2005 (44)	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 (193)	Prospective study	Outpatient undergoing EEG polysomnography	Desaturation related to seizure duration	Data from VET and oximetry
Seyal, 2009 (194)	Prospective study	Inpatient undergoing VET with intracranial electrodes	Desaturation related to controlateral spread	Data from VET and oximetry
Pezzella, 2009 (197)	Case-report	Outpatient	Bilateral pulmonary congestion	Chest X-ray
Ryvlin, 2013 (138)	Retrospective study	Inpatients undergoing VET	Complex cardiorespiratory dysfunction	Data from VET and investigator observation
Seyal, 2013 (195)	Prospective study	Patients undergoing VET	Reduced duration of respiratory disfunction by periictal interventions	Data from VET
Singh, 2013 (196)	Prospective study	Inpatients undergoing VET	Ictal apnoea/ipopneoea	Data from VET, oximetry and plethysmography

tory activity and its nuclei/centers are likely to be involved during the spread of epileptic seizures, resulting in the appearance of peri-ictal autonomic respiratory symptoms and/or signs.
3. *Tachypnea is a benign sign;in contrast, breath difficulties, bradypnea/apnea and/or desaturation may play a potential role in the SUDEP;central or mixed apnea is more frequent than obstructive apnea.*
4. *A longer postictal immobility caused by a postictal condition of arousal deficit may worsen desaturation.*
5. *Ictal apnea and hypoxemia are mainly associated with focal seizures originating from the temporal lobe and the level of desaturation is found to be dependent on the duration of the seizure, the contralateral spread of the seizure and the younger age in a pediatric population.*
6. *Patients monitored during a seizure and available data offers little evidence concerning the respiratory function through a complete cardiorespiratory monitoring with an evaluation of pO2 and pCO2.*
7. *There are few data to determine whether or not the respiratory mechanism contributes with other mechanisms to cause SUDEP and there is no evidence concerning the presence in patients with pulmonary comorbidities who died of SUDEP.*

Postictal generalized EEG suppression (cerebral electrical shutdown)

The third mechanism, which is thought to be involved in the SUDEP, is the prolonged postictal generalized EEG suppression (PGES). Lhatoo (208) defined this condition as a generalized reduction of the cerebral EEG activity which goes below 10 uV in amplitude and whose observation is not affected by muscle, movement, respiratory or electrode artifacts. The author remarked, while evaluating retrospectively the EEG parameters of the patients who died of SUDEP, that these had a significantly longer PGES than the control group (208).
PGES was found in a series of case-reports and studies on monitored SUDEP and near-SUDEP (192, 206, 208-215) and it was shown that the risk of SUDEP would increase by 1.7% with every second of increase of PGES (208).
PGES has been associated with generalized tonic-clonic seizures rather than complex partial seizures (208, 212-216) and is positively correlated with the duration of the seizure (208), especially in its tonic phase which has been identified as an independent predictor of PGES (214).
Some authors pointed out some correlations with postictal arousal deficit (214, 217) and the level of desaturation and hypercapnia during the seizure, but not with disturbances of the respiratory rate. This confirms the hypothesis that PGES is related to a specific pulmonary dysfunction rather than to an inhibition of the bulbar respiratory centers (213).
The mechanisms which trigger PGES are not well defined;suppression EEG activity directly related to hypercapnia and acutely generated hypoxia has been impheated (218-221) or to cortical spreading depression phenomenon (222, 223).
The role that PGES plays in SUDEP needs to be confirmed. It is uncertain whether postictal arousal deficit, found in some patients, can be related to the duration of PGES or whether PGES, associated with a deficit of serotoninergic systems which are responsible for the arousal, can have a role in causing SUDEP.

Cerebral Electrical Shutdown (CES)
1. *CES is the prolonged postictal generalized EEG suppression (PGES) below 10 uV in amplitude and whose observation is not affected by muscle, movement, respiratory or electrode artifacts.*
2. *Post-ictal generalized EEG suppression has been associated with generalized tonic-clonic seizures rather than complex partial seizures and is positively correlated with the duration of the seizure, especially in its tonic phase which has been identified as an independent predictor.*
3. *The mechanisms which trigger PGES are not well defined and its role in SUDEP needs to be confirmed.*

How to prevent SUDEP

Shankar et al. (224) wrote an evidence based safety checklist in which some risk factors could be modified in order to prevent SUDEP events: severity of seizures, number of AEDs, compliance with treatment, frequent AED prescribing changes, sub-therapeutic AED levels, use of lamotrigine and/or carbamazepine, alcohol addiction, treatment for depression and anxiolytic medications (modifiable factors), no surveillance at night, prone position, failed assessment for epilepsy surgery (moderate risk-modifiable factors), high seizure frequency with special reference to tonic-clonic seizures (established risk-modifiable factors) (224).
Verma and Kumar (225) wrote about possible preventive measures (see the box below).

1. *Minimize the risk of generalized tonic-clonic seizures (GTCS) with optimal medical management and patient education.*
2. *Reduce the risk of GTCS-induced postictal respiratory distress by use of lattice pillow, provide nocturnal supervision, reinforce interictal serotonergic tone, and lower opiate- or adenosine-induced postictal brainstem depression.*
3. *Patients at high risk must be supervised during the night through attendance or use of alarms.*
4. *After a tonic-clonic seizure continuous attendance until full consciousness is restored and call emergency services for high-risk seizures are recommended.*
5. *Identify and avoid trigger factors for seizures.*

6. *Full adherence with and avoidance of sudden changes in the taking of medication.*
7. *Improve seizure control and possibly avoid polytherapy.*
8. *Epilepsy surgery, vagal nerve stimulation, and dietary management (e.g., ketogenic diet and omega-3 supplementation) to be considered.*
9. *Owing a pet.*
10. *Monitoring devices that claim to detect seizure-like movement in bed or changes in breathing, heart rate or blood oxygen levels, to trigger an alarm.*
11 *Based on data from a mice model, treatment with antidepressants of the selective serotonin-reuptake inhibitor type could reduce the risk of SUDEP by prevention of postictal respiratory arrest* (225).

To prevent or modify these 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 (226), but further research is needed. In this study, 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, nonclinical reasons, ethical or deontological issues (226). Also for Kruja and Vyshka (227) disclosing the risk of SUDEP is necessary; however, the action should be personalized and situation-related, using a more helpful and psychologically acceptable step-by-step approach (227).
In the U.S. and Canadian survey of Friedman et al. (228), neurologists rarely discuss SUDEP with patients or caregivers. More experienced neurologists encounter less negative reactions and they could minimize patient/caregiver distress (228). A UK study (229) 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 diagnosis (74%) or when seizures were poorly controlled (16%); the remaining parents were not sure about receiving information or they did not want to know about SUDEP (229). The Authors concluded that the best way to provide SUDEP information is through discussion with the parents followed by giving an information leaflet.
Brodie and Holmes (230) had different positions about SUDEP discussion: the first Author wrote that all patients and their families have the right to know about the risk of epilepsy and the reasons for treatment;the second believed in a more individualized approach that it is not necessary to discuss about SUDEP with all patients but only with those at higher risk. This issue is still unsettled.

Conclusions

SUDEP is a rare event, not always observed by witnesses and poorly monitored with reference to respiratory, cardiac and electrophysiological activities, and it represents the effect of disease-related factors in subjects genetically predisposed to cardiac defects. In line with the reports on the incidence of SUDEP, young age, disease severity (GTCS), symptomatic etiology and response to AEDs are negative predictors. Seizures and epilepsy can affect the 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. 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, a safety checklist was written, but the discussion about SUDEP with patients and families remains an unsolved issue.

Conflict of interest

Dr. La Neve has nothing to disclose.
Dr. Giussani has nothing to disclose.
Dr. Beghi has received personal fees for board membership by VIROPHARMA and GSK;has received funding for travel and speaker honoraria from UCB-Pharma and GSK, for educational presentations from GSK;has received grants for research activities from the Italian Drug Agency, Italian Ministry of Health, EISAI and the American ALS Association.

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