

Sudden Unexpected Death in Epilepsy (SUDEP)

Current Knowledge and Future Direction

Dr.Yotin Chinvarun M.D. Ph.D.

CEP and Sleep disorder program
PMK hospital

Case

- F 34 yrs old, Briton, housewife, G₂P₂
- Hx of 1st seizure 33 yrs old, CPS, 2GTCS, Rx Trileptal 600mg bid, became seizure-free,
- MRI brain: non-lesion
- EEG occasionally focal epi D/C left fronto-temporal lobe

Case

- FU within 4 yrs, had breakthrough seizure 1-2 per years, most precipitated by poor compliance, very concern about side effects from AEDs
- One month prior death reported had a breakthrough seizure
- Had SUDEP during sleep, informed by her husband found patient died on prone posture in bed early morning
- Autopsy was done, no evidence of toxicology or anatomical causing of death

SUDEP: definition

“Sudden, unexpected, witnessed or un-witnessed, non-traumatic and non-drowning death in a patient with epilepsy where the postmortem examination does not reveal a toxicology or anatomic cause of death, with or without evidence of a seizure and excluding documented status epilepticus”¹

¹ Nashef L, Brown S. Epilepsy and sudden deaths. *Lancet* 1996;348:1324-1325

Epidemiology

- **Epilepsy** – overall mortality 2-3 times that of general population
- **SUDEP**: 2-18% of deaths in patients with epilepsy
- Risk of sudden unexpected death is 24 – 40 times that in the general population, depending on population of epilepsy

Dasheiff

Incidence

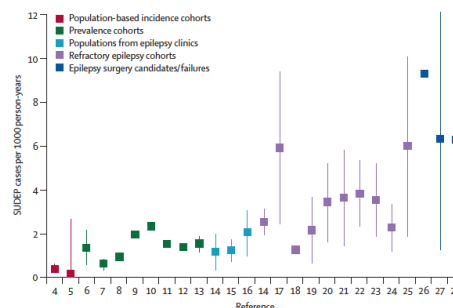
- Relatively rare outcome for epilepsy population in general, but this tragedy is not negligible in person with uncontrolled epilepsy
- Incidence 0.7 to 1.3 per 1,000 patient-years in large cohorts of patients with epilepsy
- About 3.5 to 4.1 per 1,000 patient-years in anticonvulsant drug trials, medical device registries, and epilepsy surgery programs

Incidence

| Series | SUDEP rate | Comments |
|---------------|----------------------|------------------------------|
| Dashieff 1991 | 1/108 person-yrs | Refractory |
| Sperling 1996 | 1/150 person-yrs | Post TL surgery |
| Hennessy 1999 | 1/455 person-yrs | Post TL surgery |
| Walczak 2001 | 1.21/1000 person-yrs | Prospective, epilepsy center |

Dashieff 1991
Sperling 1996
Hennessy 1999
Walczak 2001

Incidence of SUDEP in 26 studies of different epilepsy populations



SUDEP population-based study (Ficker 1998)

- All deaths in persons with epilepsy between 1935-1994 in Rochester, MN
 - SUDEP 1.7% of all deaths (8.6% of deaths in persons 15-44 yrs of age)
- Sudden death rate was 24 times higher than expected

Epilepsy control and risk for SUDEP

- Risk for SUDEP appears to be closely related to seizure control
- Patients with refractory epilepsy are at highest risk for SUDEP
- Patients who become seizure-free after epilepsy surgery reduce their risk for SUDEP (Hennessy 1999, Sperling 1996, Sperling 2005)

Who is at risk?: Age, Sex

- Children to elderly reported
- Most are between 20 – 40 yrs of age
- Men and women affected: No clear male or female predominance

Risk factors

- An earlier review of case-control literature determined that poor seizure control is a major risk
- Hx of GTCS, and frequency of GTCS
 - Nilsson et al. (1999) demonstrated risk of SUDEP nearly four times greater in persons with 3-12 GTCS per year than in persons with 0-2 GTCS per year
- Witnessed SUDEP, about 50-100% of the events have been associated with seizure

SUDEP

- Witnessed SUDEP Langan et al. (2000)
 - 15/135 SUDEP cases were witnessed.
 - 12/15 were associated with a convulsive seizure.
 - One collapse occurred 5 minutes after a GTC seizure and one after an aura.
 - One patient died in a probable postictal state.
 - 12/15 were noted to have experienced respiratory difficulties.
- Suggests that respiratory dysfunction may be an important contributing factor in SUDEP.
- Suggests that positioning or stimulation of respiration may be important in the prevention of SUDEP

SUDEP: risk factor

- Concomitant neurologic illness may influence SUDEP risk
- Structural lesions not associated with SUDEP
- Mental retardation, appears to significant risk factor in a recent analysis
 - Mechanism underlying not known yet.

SUDEP risk factors identified by the literature reviews of case-control studies

- Hx of and number of GTCs
- Frequent seizures
- Subtherapeutic AEDs levels
- Young adult
- Long epilepsy duration; epilepsy onset
- AEDs polytherapy
- Frequent AEDs changes
- IQ < 70

Tellez-Zenteno et al (2005)
Thomson et al. (2005)
So 2006

Possible contributing factors ?

- Positioning – prone position
- Low AEDs
- Seizure in sleep
- Specific AED ?CBZ
- Structural lesions
- Psychotropic drugs
- Lack of stimulation post-ictally

Seizure frequency

| Seizure frequency during last year | Cases | Controls | RR (relative risk) |
|------------------------------------|-------|----------|--------------------|
| 0 - 2 | 5 | 87 | 1.00 |
| 3 - 12 | 16 | 33 | 7.21 |
| 13 - 50 | 15 | 26 | 8.64 |
| > 50 | 9 | 13 | 10.16 |
| Unknown | 12 | 12 | 15.04 |

Adapted from Nilsson, et al., 1999: Increased relative risk of SUDEP with increased seizure frequency (total SUDEP n = 57)

Seizures and risk

- A preceding GTC sz is reported in most witnessed cases of SUDEP
- In many other cases, the patient is found in bed with evidence of a recent seizure (tongue laceration, etc.)
- There are rare reports of SUDEP without a preceding seizure

Other circumstances of death

- 30 – 50% patients are found dead in bed
- Often patients are found in the prone position
- 12/15 witnessed SUDEP cases associated with respiratory difficulties (Langan, 2000)

Case series: SUDEP circumstances

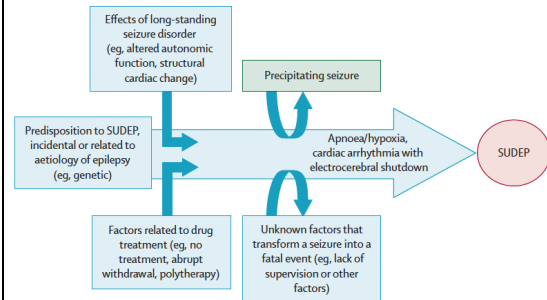
| Age/Sex | Circumstances |
|---------|---|
| 10/F | Found dead in bed in AM |
| 17/F | Found dead at night on bedroom floor |
| 18/F | Found dead in bed |
| 18/F | Found dead at night on floor |
| 20/F | Unconfirmed |
| 20/F | Found dead in morning on floor |
| 23/F | Unconfirmed |
| 25/F | Found dead in bed in AM |
| 28/F | Found dead in bed in AM |
| 28/F | Died after seizure |
| 12/M | Found dead in AM on floor |
| 14/M | Found dead on bathroom floor in AM |
| 16/M | Found dead in bed in AM; vomited/no aspiration, evening |
| 22/M | Found collapsed at home |

Adapted from Nashef, 1995

Types of seizures, timing of seizures

- Generalized tonic-clonic seizures most often associated with higher risk for SUDEP
- ? Nocturnal seizures
- ? Seizure clusters

Interaction between proposed predisposing factors and triggers for SUDEP



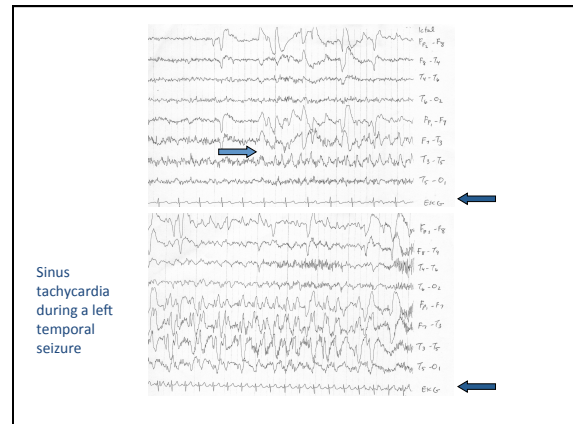
SUDEP: potential mechanism

- Three major domains of potential mechanisms of SUDEP:
 - Cardiac
 - Respiratory
 - Autonomic

Cardiac Data in SUDEP

Epilepsy and cardiac function

- Seizures can affect cardiac rate and rhythm
- Unexplained myocardial injury in epilepsy
- Altered autonomic function in the ictal and interictal states in patients with epilepsy

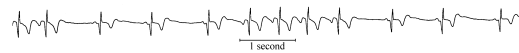


Seizures and cardiac rhythm

- Focal epilepsy:
- Up to 39% of seizures are associated with abnormal cardiac rhythm (Nei 2000, Opherk, 2002)
- Occur in the the ictal and post-ictal periods
- Abnormal rhythm may outlast the seizure duration by minutes to hours (Tigaran,1998)

Common ictal abnormalities

- Atrial premature depolarizations
- Ventricular premature depolarizations
- Marked sinus arrhythmia

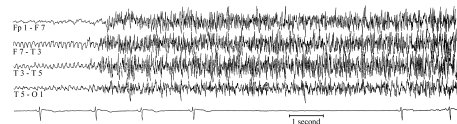


Uncommon ictal abnormalities

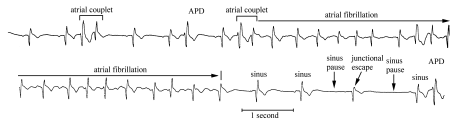
- Atrial fibrillation
- Atrial triplets, couplets
- Ventricular bigeminy
- Supraventricular tachycardia
- Junctional rhythm
- Asystole, bradycardia



Ictal asystole



Uncommon ictal/post-ictal EKG abnormalities



90-110 seconds post-ictal, frequent APD, then atrial fibrillation, sinus rhythm, junctional escape and frequent APD

Cardiac rhythm prior to death in SUDEP

- Junctional rhythm which failed to return to NSR after cardioversion
- Ventricular arrhythmia
- Ventricular fibrillation, then asystole

Potential Cardiac Mechanisms

- Potential cardiac basis of SUDEP preexisting cardiac disease.
 - A postmortem study reported 6 of 15 SUDEP persons had fibrotic changes in deep and subendocardial myocardium
 - However, in another study failed to reveal potentially lethal morphologic abnormalities
- Prime suspect for a SUDEP mechanism: phenomenon of ictal bradycardia or asystole
 - Only 0.4% of patients undergoing VEM had ictal bradycardia or asystole (Rocamora et al., 2003)
 - Approximately two-thirds of patients with ictal bradycardia or asystole have temporal lobe epilepsy, one-third have frontal lobe epilepsy (Tinuper et al., 2001)

EEG: ictal asystole

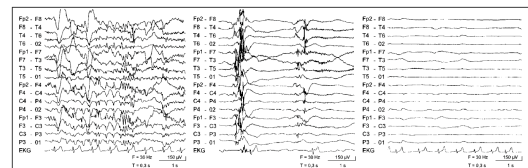


FIG. 1. EEG evolution in patient 1. Left: seizure-onset (SO); center: asystole onset (100 s after SO); right: after 60-s asystole, extremely flattened EEG with almost normalized ECG rhythm.

Potential Cardiac Mechanisms

- Interictal and periictal ECG ?
 - Nei et al. (2004) found 1/3 of 21 persons with definite or probable SUDEP
 - ECG showed rhythm or repolarization abnormalities, including atrial fibrillation, marked sinus arrhythmia, and ST-segment elevation during ictal or immediate postictal period
 - However, these abnormalities similarly observed in 43 control subjects without SUDEP who had intractable epilepsy

Potential Cardiac Mechanisms

Currently reported peri-ictal ECG abnormalities cannot be used to identify persons at high risk of SUDEP

Potential Cardiac Mechanisms

- Initially, low medication levels were noted in autopsied cases, and it was suggested that poor compliance led to seizures and subsequent death
- However, recent studies cast doubt on this explanation
 - Opeskin et al. found no evidence for poor medication compliance or lower levels in patients who died of SUDEP than in case controls
 - SUDEP was not associated with low serum drug levels

Potential Cardiac Mechanisms

- Type of AEDs risk SUDEP ?
 - Carbamazepine and phenytoin rarely associated with atrioventricular block (Stollberger & Finsterer, 2004)
 - Two case-control studies found carbamazepine independent risk factor for SUDEP (Nilsson et al., 2001; Langan et al., 2005)
 - Whereas two other studies did not (Kloster & Engelskjon, 1999; Walczak et al., 2001).

Potential Cardiac Mechanisms

- Type of AEDs risk SUDEP ?
 - Although no specific AED has been proven to cause SUDEP
 - Number of AEDs reported to be a SUDEP risk factor, even after adjusting for seizure frequency (Nilsson et al., 1999; Walczak et al., 2001).
 - In one study, epilepsy patients taking three AEDs had SUDEP risk 8 times higher than patients taking one AED (Nilsson et al., 1999)

Respiratory data

Potential Respiratory Mechanisms

- Increased lung weight, pulmonary congestion, or edema has been frequently observed in postmortem examinations of SUDEP persons
- Prospective autopsy series reported 42 of 52 of SUDEP persons had pulmonary congestion and edema (Leestma et al., 1989)
- Ante mortem observation of pulmonary edema is rare

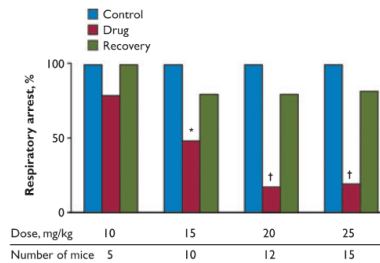
Potential Respiratory Mechanisms

- Pulmonary congestion observed postmortem in SUDEP usually of a degree that is not expected to cause death
- Very rare to observe pulmonary edema occurring with seizure, in contrast, apnea and hypoxia appear frequently during or after seizure episodes (Nashef et al., 1996; Blum et al., 2000)
- Ictal apnea was reported in 10 of 17 patients who were undergoing VEM (Nashef et al., 1996)

Potential Respiratory Mechanisms

- Postictal central apnea documented to be the initiating event in a patient who nearly died of SUDEP (So et al., 2000)
- In animal mouse model, DBA/2 audiogenic seizure mice susceptible to postictal respiratory arrest, respiratory arrest was prevented by administering a selective serotonin reuptake inhibitor (SSRI) fluoxetine

Effect of intraperitoneal injection of a selective serotonin reuptake inhibitor (SSRI), fluoxetine, in reducing the incidence of respiratory arrest



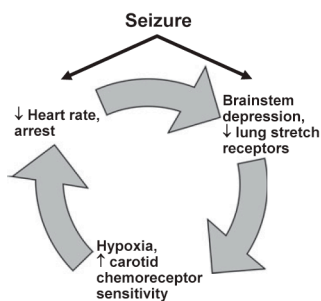
Potential Respiratory Mechanisms

- It is not known why, periictal respiratory arrests are observed, lethal consequences of do not occur frequently in the community or in the hospital
- Brainstem respiratory activity could be suppressed directly by seizure activity or indirectly by hypoxia from ictal cardiac arrest
- This combination of cessation and reduced activity of pulmonary stretch receptors exacerbates bradycardia

Potential Respiratory Mechanisms

- In humans, respiratory arrest could be induced by electrical stimulation of amygdala during expiratory phase (Kaada & Jasper, 1952; Nelson & Ray, 1968)
- The importance role of cardiorespiratory reflex in inducing apnea has been raised (Nashef et al., 1996)
- The magnitude of reflex greater in young adults than in old adults (Weiling, 1992), which may be relevant to higher incidence of SUDEP in young adults

Seizure-induced suppression of brainstem respiratory activity or cardiac arrest



Near-SUDEP central apnea

- 20 yrs woman underwent video-EEG
 - 56 second convulsive seizure
 - Persistent apnea
 - EKG unimpaired for 10 seconds, then gradually slowed and ceased 57 seconds later
 - CPR successful

So, 2000

Potential Autonomic mechanisms

- Most autonomic studies of SUDEP mechanisms involve cardiac rhythm regulation by autonomic system
- Lathers and Schrader (1990) observed in cats; interictal cortical spikes induced by pentylentetrazole were time-locked to cardiac sympathetic and vagal nerve discharges
- Reduced heart-rate variability observed in animal seizure models and in epileptic patients

Potential Autonomic mechanisms

- Reduced heart-rate variability has been observed in animal seizure models and in patients with epilepsy
- Reduced heart-rate variability known associated with increased mortality and sudden death in myocardial infarction and heart failure patients (Kleiger et al., 1987; Takase et al., 1992)
- Reduction of heart-rate variability established in rats during interictal state after seizure induction by maximal electroshock (Naritoku et al., 2003)

Potential Autonomic mechanisms

- Power spectral analysis of heart rate separates bands of frequencies:
 - High-frequency band is associated with parasympathetic activity
 - Low-frequency band is associated with sympathetic activity (Akselrod et al., 1981)

Potential Autonomic mechanisms

- Patients with refractory TLE shown having lower heart-rate variation during normal breathing than control subjects (Ansakorpi et al., 2000)
- They also have significantly less low-frequency band power than control (Tomson et al., 1998)

Potential Autonomic mechanisms

- It is common for SUDEP to occur at night while the patient is in bed (Langan et al., 2005)
- Nei et al.(2004) compared the heart rate during sleep seizures and during wake seizures among 21 SUDEP patients and compared them with those of 43 non-SUDEP patients with refractory epilepsy:
 - SUDEP patients had significantly greater heart-rate increment during sleep seizures than during wake seizures

Potential Autonomic mechanisms

- Carbamazepine Rx with newly diagnosed epilepsy associated with greater reduction in heart rate variability at night than during the day (Persson et al., 2007)
- Withdrawal of carbamazepine Rx shown to improve heart-rate variability (Lossius et al., 2007)
- However, carbamazepine use as a risk factor in series of yielded conflicting results (Kloster & Engelskjon, 1999; Nilsson et al., 2001; Walczak et al., 2001; Langan et al., 2005)

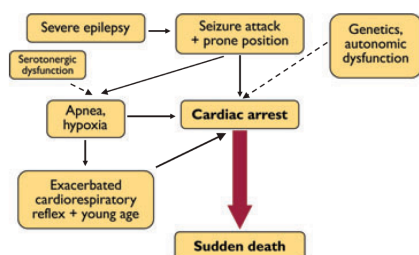
Future direction

- More animal and clinical studies needed to better understand why SUDEP occurs in some epilepsy persons and not in others, even when a condition of frequent seizures exists
- Genetic factors have been considered but not studied much (Nashef et al., 2007).

Future direction

- Multiple factors or mechanisms may be involved in causing SUDEP
- The mechanisms discussed previously may not independent of each other and likely interrelated, possibly in a chain of events that culminates in sudden death

Potentially lethal chain of factors and mechanisms culminating in SUDEP



SUDEP: Can it be prevented?

SUDEP – Prevention

- Best recommendation to reduce SUDEP is to get seizures under control.
- When seizures are not controlled, additional evaluation (e.g., video-EEG) may be valuable in directing correct therapy
- Epilepsy surgery should be considered in appropriate candidates with refractory epilepsy

Potential strategies for preventing SUDEP in high-risk patients

| Risk factor or terminal event | Potential strategy |
|-----------------------------------|--|
| Risk Factor | |
| Uncontrolled epilepsy | Optimize AED treatment, consider epilepsy surgery |
| Generalized tonic-clonic seizures | Optimize AED treatment, consider epilepsy surgery |
| Young adults | Provide prompt medical or surgical treatment |
| Childhood epilepsy onset | Provide prompt medical or surgical treatment |
| Low serum AED concentrations | Improve compliance and monitoring |
| Polytherapy | Reduce AED |
| Frequent AED adjustments | Stabilize regimen |
| Substance abuse | Recommend abstinence |
| Mental retardation | Recommend supervision |
| Unsupervised setting | Recommend supervision |
| Terminal event | |
| Seizure occurrence | Recommend supervision; seizure alarm |
| Pulmonary edema | Recommend recognition and treatment |
| Apnea or hypoxia | Recommend pulse oximetry monitor; stimulation; and oxygenation |
| Asystole | Recommend cardiac monitor; pacemaker |
| Suffocation | Reposition patient; modify environment |

Epilepsy surgery and SUDEP

- 5-years post temporal lobectomy: reduced mortality in seizure-free individuals as compared with those with any seizures, and no SUDEP patients were seizure-free (Sperling, 1996)
- 305 pts post temporal lobectomy: reduced mortality after surgery as compared with SUDEP rate in similar groups of patients with refractory epilepsy who had not undergone epilepsy surgery (Hennessy, 1999)

When to discuss SUDEP with patients ?

- No clear consensus
- Some clinicians and patient advocate groups suggest that the possibility of SUDEP should be discussed with all patients
- Consider in patients with refractory epilepsy; e.g., weighing pros/cons of surgery
- Consider discussing in patients with poor compliance with medical treatment

Discussion with family after SUDEP has occurred

- When a patient dies due to SUDEP, direct communication with the family is important
- A discussion regarding SUDEP is often helpful in family members through the grieving process. They frequently ask, "Could we have prevented this?"

Conclusion

- Recent SUDEP studies mainly reiterate previous findings, and cause of SUDEP still unknown
- Possible SUDEP does not have a single cause, and risk factors vary
- Potential preventive measures must be considered for high-risk patients
- Lack of knowledge about SUDEP indicates that continued and concerted efforts to study phenomenon of SUDEP

Conclusions/Suggestions

- Prospective multicenter studies and studies using animal models of SUDEP needed
- Cardiac evaluation in patients with significant ictal arrhythmias
- Stimulation of patients after seizures may be important
- ?Role of oxygenation during seizures

Conclusion/Suggestions

- Identification of nocturnal seizures may be more important
- Prevention of seizure clusters, particularly when nocturnal - ? Decrease risk of SUDEP
- Role of pacemaker uncertain at this time: May want to consider pacemaker implantation in patients with refractory seizures associated with asystole
- Early expedite surgical evaluation for refractory patients, especially when ictal arrhythmias/prolonged apnea present