Association of prone position with sudden unexpected death in epilepsy

ABSTRACT

Objective: To examine the association between prone position and sudden unexpected death in epilepsy (SUDEP).

Methods: We conducted a systematic review and meta-analysis based on a literature search from databases PubMed, Web of Science, and Scopus, using keywords “SUDEP” or “sudden unexpected death in epilepsy” or “sudden unexplained death syndromes in epilepsy.” Twenty-five publications met the inclusion and exclusion criteria and were enrolled in this study.

Results: Body positions were documented in 253 cases of SUDEP. Of these patients, 73.3% (95% confidence interval [CI] = 65.7%, 80.9%) died in the prone position, whereas 26.7% (95% CI = 16.3%, 37.1%) died in nonprone positions. Binary random-effects analysis showed that prone position is significantly associated with SUDEP, as compared with nonprone position (p < 0.001). In addition, the prone position was reported in all 11 cases of video-EEG-monitored SUDEP. Moreover, in a subgroup of 88 cases of SUDEP in which demographics and circumstances of death were documented, the prone position was observed in 85.7% (95% CI = 74.6%, 93.3%) of patients aged 40 years or younger, but in only 60% (95% CI = 38.7%, 78.9%) of patients older than 40 years. Statistical analysis confirmed that the prone position was significantly more prevalent in the younger patient group, as compared with the older patient group (odds ratio 3.9; 95% CI = 1.4%, 11.4%; p = 0.009).

Conclusion: There is a significant association between prone position and SUDEP, which suggests that prone position is a major risk factor for SUDEP, particularly in patients aged 40 years and younger. As such, SUDEP may share mechanisms similar to sudden infant death syndrome.

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GLOSSARY

CI = confidence interval; GTCS = generalized tonic-clonic seizure; OR = odds ratio; PGES = postictal generalized EEG suppression; SIDS = sudden infant death syndrome; SUDEP = sudden unexpected death in epilepsy.

Sudden unexpected death in epilepsy (SUDEP) is the most common cause of death associated with chronic uncontrolled epilepsy.1 The risk factors for SUDEP include generalized tonic-clonic seizures (GTCS), early-onset and chronic refractory epilepsy, a young adult age (20–40 years), antiepileptic drug polytherapy, poor compliance with antiepileptic drugs,2 and nocturnal seizures.3

Although peri-ictal cardiorespiratory dysfunction is frequently considered to be a likely culprit, the mechanisms of SUDEP are largely unknown. It is known that SUDEP usually occurs during sleep, in bed, and as an unwitnessed event. Patients are frequently found in the prone position.4 These circumstances of SUDEP are remarkably similar to those of sudden infant death syndrome (SIDS). The prone position is considered to be a minor risk factor by some authors, and it was observed in only a minority (42%–46%) of SUDEP cases in some series.5 However, a large majority (71%–81%) of SUDEP patients were found in the prone position in other case series.4 Unfortunately, the prevalence of the prone body position in cases of SUDEP has not been determined in a large series.

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the author, if any, are provided at the end of the article.
Therefore, we performed a systematic review and meta-analysis to determine specifically the prevalence of the prone position in a large cohort of published SUDEP cases in which body positions were documented at the time of death.

**METHODS** A systematic review and meta-analysis were conducted via a comprehensive literature search from databases PubMed, Web of Science, and Scopus, using keywords “SUDEP” or “sudden unexpected death in epilepsy” or “sudden unexplained death syndromes in epilepsy.” We searched all the available publications up to October 23, 2013. The search strategy for each database is detailed in appendix e-1 on the Neurology® Web site at Neurology.org. Hand review of all the references of the enrolled studies was also performed. The searching methods and strategies were formulated under guidance of the medical reference service in the John Crerar Library at the University of Chicago.

Study inclusion criteria were as follows: (1) study of one or more possible, probable, and definite SUDEP cases published in the English language; (2) in order to minimize publication bias, the total number of SUDEP patients found in various body positions must be documented; (3) the number of SUDEP patients found in the prone position was documented. Eligible studies had to meet all inclusion criteria. Study exclusion criteria included small case reports meeting inclusion criteria, which were later included in a larger series. SUDEP was defined as sudden, unexpected death in patients with epilepsy, which is witnessed or unwitnessed, nontraumatic and nondrowning, excluding status epilepticus or an identifiable cause of death at autopsy. SUDEP was considered definite when autopsy revealed no alternative cause of death, whereas it was considered probable when an autopsy was not performed. When there was an alternative cause of death, SUDEP was considered possible.

Two reviewers conducted the search together and reviewed the abstracts and full text articles in duplicates. The differences in data extraction were resolved by consensus. SUDEP cases with documented body positions were identified from enrolled studies. Additional information was also obtained from a subgroup of SUDEP cases, including demographics and circumstances of death, such as age, sex, and whether SUDEP occurred during sleep or wakefulness. We adopted the previously published criteria for sleep and wakefulness SUDEP. In unwitnessed cases, SUDEP was considered to occur during sleep if the patient was found in bed or at bedside on the floor. In unwitnessed cases, SUDEP was considered to occur during wakefulness if death occurred outside of the bed or bedroom. If circumstances of death were unknown, the cases were excluded from analysis. Authors were contacted when there were uncertainties in their data.

Statistical analysis was performed in the Department of Public Health at the University of Chicago. Study heterogeneity (I²) of the enrolled studies was assessed. Forest plot was constructed by calculating the proportion of patients in the prone position in each study and its 95% confidence interval (CI) using a weighted random-effects model. Binary random-effects analysis was performed to assess the significance of association between prone position and SUDEP, as compared with nonprone position. Chi-square tests were used to compare the difference of prone position at death among the different age groups (<20, 20–40, and >40 years), between the sexes, and between SUDEP during sleep vs during wakefulness. Odds ratios (ORs) with 95% CIs were calculated to assess the relative risk associated with the prone position.

**RESULTS** This database search resulted in 1,106 publications after excluding duplicates. Review of the abstract was conducted in all publications, and a full-text review was conducted in approximately 80% of them. One thousand seventy-five publications without documenting body position in SUDEP patients were excluded. Two publications without documentation of the total number of patients with known body position were excluded. Twenty-nine publications met the inclusion criteria from database searching. In addition, a video-EEG–recorded SUDEP case was enrolled by hand searching the references of enrolled studies. As such, a total of 30 publications met the inclusion criteria. Four small case studies were further excluded, because they were later included in a large cases series. Another case report was also excluded, because it was followed by a larger case series from the same authors. This brought the total number of enrolled studies to 25, including 14 single case reports and 11 case series (figure 1).

Statistical heterogeneity (I²) was examined. I² indicates the percentage of variance contributed by study
heterogeneity. Its values of 25%, 50%, and 75% are thought to reflect low, moderate, and high heterogeneity.\textsuperscript{29} \(I^2 = 41\%\) in this study, which indicated the presence of a low to moderate heterogeneity. For this reason, we adopted a weighted random-effects model to provide a more conservative effect in assessing the proportion of the prone position and its 95% CI (figure 2).

The body positions at death of SUDEP patients were categorized as prone, supine, lateral, or sitting. In a small portion of SUDEP patients, body positions were reported only as prone and nonprone or “other” (i.e., supine, lateral, or sitting) by the authors. We arbitrarily designated the undifferentiated, nonprone body position as undefined. A total of 413 cases of SUDEP were reported in the 25 studies, and body position was documented in 253 patients. On comparing the body positions in these 253 SUDEP cases, 73.3% (95% CI = 65.7%, 80.9%) of patients were found in the prone position, whereas 26.7% (95% CI = 16.3%, 37.1%) of patients were found in nonprone positions (table 1). Binary random-effects analysis showed that prone position is significantly associated with SUDEP, as compared with nonprone position (\(p < 0.001\)).

In 11 of the 253 cases, SUDEP occurred during video-EEG monitoring.\textsuperscript{9,15,28} These cases were published over a period of 25 years. Of note, prone position was observed during SUDEP in all 11 patients. Four of the 11 patients were sleeping prone before the terminal seizure onset, whereas 3 of the 11 patients turned to a prone position during versive seizures. Both GTCS and postictal generalized EEG suppression (PGES) were also observed in all 11 cases recorded by video-EEG (table 2). A total of 14 cases of SUDEP during video-EEG monitoring have been published. These 3 additional cases were not enrolled in this study, because either the body position was not documented by the authors or the patients were not on camera.

Moreover, in a subgroup of 88 SUDEP patients, whose demographics and circumstances of death were documented (table e-1), we determined the occurrence of the prone position as a function of age in

![Figure 2 Forest plot of the proportion of patients in the prone position and its 95% CI](image)

Of the 253 cases of sudden unexpected death in epilepsy with known body positions, 73.3% of patients were found in prone position. A weighted random-effects model was used for the calculation. CI = confidence interval.
years: <20, 20–40, and >40. Of the 14 patients younger than 20 years, 85.7% (95% CI = 57.2%, 98.2%) died in the prone position. Of the 49 patients between age 20 and 40 years, 85.7% (95% CI = 70.9%, 90.9%) of patients were found in a prone position. Of the 21 cases of SUDEP that occurred during wakefulness, 61.9% (95% CI = 38.4%, 81.9%) of patients were found in this manner. This difference was not statistically significant (OR 2.9; 95% CI = 0.9%, 8.6%; p = 0.055) (figure 3).

DISCUSSION

This systematic review and meta-analysis enrolled a large cohort of 253 SUDEP cases with documented body position to determine the prevalence of a terminal prone position. It was found in 73.3% of SUDEP patients, whereas nonprone positions were found in 26.7%. Of note, all 11 cases of SUDEP that occurred during video-EEG monitoring were documented in a terminal face-down body position. These findings demonstrate that there is a significant association between the prone position and SUDEP. In addition, prone position was statistically more prevalent in patients younger than 40 years, as compared with those older. Why prone position represents such a significant risk factor for younger individuals is unclear. It may be related to the fact that they are more likely to be single and thus alone without peri-ictal supervision, particularly during sleep. A terminal prone position was more common with SUDEP during sleep than during wakefulness. This difference, however, was not statistically significant. Therefore, risks for SUDEP during sleep may be multifactorial.

We believe that our findings have significant implications regarding the mechanism and prevention of SUDEP. It has become increasingly clear that SUDEP is a heterogeneous disorder. Seizures frequently induce prominent peri-ictal cardiovascular and respiratory dysfunctions. It is likely that some cases of SUDEP primarily resulted from fatal cardiac arrhythmias, while others primarily resulted from respiratory depression and central apnea. However, SUDEP related to seizure-induced primary cardiorespiratory failures does not reconcile with the high prevalence of a terminal prone position found in our study. Video-EEG–monitored SUDEP cases have provided us with the most valuable insights into the mechanism of SUDEP. In a recent study of SUDEP cases recorded in epilepsy monitoring units, SUDEP was suggested to be primarily a result of GTCS-induced early postictal, neurovegetative

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*a* Reference numbers refer to the cited references in this study.  
*b* Undefined body position refers to the body positions other than prone position, such as supine, lateral, and sitting.
breakdown, which could lead to immediate death or a short period of partially restored cardiorespiratory function followed by terminal apnea and cardiac arrest. However, the exact cause of death remains uncertain in these patients because of a lack of O$_2$ and CO$_2$ monitoring. The initial postictal tachycardia and tachypnea observed in these SUDEP-related GTCS are also frequently observed in other non–life-threatening GTCS. Therefore, what could be a differentiating factor is unclear. Nevertheless, striking similarities were observed in all monitored SUDEP cases, namely, GTCS, PGES, and a terminal prone position. Given that these monitored SUDEP cases have been randomly reported over a period of 25 years, these commonalities cannot be simply a matter of chance. Instead, they likely reflect a common mechanism.

GTCS, as the utmost risk factor for SUDEP, is highlighted by these SUDEP cases monitored in epilepsy monitoring units. PGES is a postictal EEG pattern that is nearly unique to GTCS. It is rarely seen in patients with partial-onset seizures. PGES has also been proposed as an EEG marker for SUDEP, because it is thought to reflect primary electrocerebral shutdown that can subsequently cause cardiorespiratory failure. In a study comparing 10 people who later died of SUDEP with 30 controls, the duration of PGES was significantly prolonged in SUDEP compared with non-SUDEP patients. However, these findings were not replicated in a subsequent study of 17 SUDEP patients contrasted with 17 matched controls. Meanwhile, in a study of 13 patients with PGES, these patients were significantly more likely to be motionless. These findings were further confirmed in another case cohort of 64 patients, in which nearly all patients with PGES were comatose and unresponsive to verbal and physical stimulations for the duration of the PGES. Accordingly, PGES is a likely EEG marker for impaired arousal in postictal patients.

The role of impaired arousal in the pathogenesis of SUDEP is unclear, and it has seldom been previously

### Table 2 Video-EEG–recorded SUDEP cases with known body position

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<tr>
<th>Cases</th>
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<th>Seizure type</th>
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Abbreviations: GTCS = generalized tonic-clonic seizure; NA = not available; NVB = neurovegetative breakdown; PGES = postictal generalized EEG suppression; SUDEP = sudden unexpected death in epilepsy.
stem regulate both respiration and arousal in response to fluctuations of blood CO2 and maintain pH homeostasis. In SIDS patients, impaired arousal secondary to serotonin deficiency can suppress autonomic mechanisms and prevent them from lifting or turning their heads when their airway is obstructed by soft bedding in a prone position. As such, positioning susceptible children on their backs at bedtime, as in the “Back-to-Sleep” campaign, has been highly successful for the prevention of SIDS.

Similar to SIDS patients, impaired arousal is also frequently observed in postictal patients, particularly after a GTCS. The impaired arousal in postictal patients may also compromise the brainstem autonomic mechanisms and prevent them from lifting or turning their heads, while their airway is obstructed by soft bedding. Given the high prevalence of prone position that was observed in many SUDEP patients in our study, we propose that this body position may be a significant component in a peri-ictal SUDEP cascade. The cardinal features of this cascade are GTCS, PGES, and the prone position. Convergence of these 3 in a patient is likely to have a major role in many patients who experience SUDEP. Therefore, SUDEP likely shares mechanisms similar to those of SIDS.

In addition, our study highlights the importance of peri-ictal surveillance for the prevention of SUDEP. Compared with other possible causes of SUDEP, such as cardiac arrhythmia and central apnea, remaining in the prone position after a GTCS can be prevented by peri-ictal supervision and intervention by a lay person. In fact, early peri-ictal nursing intervention was associated with reduced duration of respiratory distress and reduced duration of PGES. As such, simple measures, such as stimulating the patient or turning a postictal prone patient to a lateral position to allow recovery of ventilation after a convulsive seizure, or advising against the prone sleep position, may effectively prevent SUDEP. Devices for seizure detection such as wrist watch and bed alarms may also be helpful.

There are several study limitations, which may affect the outcomes in this study. First, the search strategy was limited by searching only English articles, and the key words used for database search may not identify all SUDEP publications. Second, publication bias of reporting prone position in SUDEP patients may be present in SUDEP publications. Such bias was mitigated by the inclusion criteria 2. In addition, prone position has not been considered to be a major risk factor for SUDEP in the literature. Among the enrolled 25 studies in this meta-analysis, the prone position was considered to be a risk factor of SUDEP only by the authors of 3 studies. Therefore, the publication bias was likely insignificant in this study, because it was reflected by the relatively symmetrical forest plot. Third, the body position of the patients before sleep-related SUDEP was not known in most subjects. Whether they were sleeping in the prone position before the terminal seizure or turned to prone position during the terminal seizure can only be determined in a few monitored cases. Fourth, actual airway obstruction in patients who were prone cannot be unequivocally determined even in video-EEG–monitored cases. Finally, oxygen, carbon dioxide, and respiratory effort were not monitored in nearly all cases. Therefore, it remains unclear whether hypoxia, secondary to airway obstruction, was the primary cause for cardiorespiratory arrests in these SUDEP cases. Additional studies are warranted to further delineate implications of the prone position in the mechanisms of SUDEP and thereby develop effective measures for SUDEP prevention. We recommend including the information related to patients’ body position in all further SUDEP case reports.

**AUTHOR CONTRIBUTIONS**
Jennifer Liebenthal: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. Shasha Wu: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval. Sandra Rose: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval. James X. Tao: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. Shasha Wu: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval. John S. Ebersole: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data. James X. Tao: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. Jennifer Liebenthal: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, statistical analysis, study supervision.

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