Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study.

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Sudden unexpected death in epilepsy (SUDEP) is a significant cause of non-accidental death in young adults with epilepsy, generally drug-resistant epilepsy, with a cumulative risk of 12% over 40yrs for this population. At the time of this study, the pathophysiology inherent to SUDEP remained largely unclear, though peri-ictal cardiorespiratory dysfunction was felt to be a primary driver. For this reason, the main goal of this study was to better understand the physiologic and/or neurologic mechanisms underlying SUDEP, by analyzing video EEG (VEEG) data from patients who died unexpectedly during VEEG monitoring in participating EMUs.

Experimental design and statistics: This was a retrospective study using data from several EMUs internationally, in which VEEGs occurred for >24hrs in the admitted patients. Census data for the study ran from Jan 1968 through Dec 2007. The data collected was used to understand both the mechanisms underlying SUDEP as well as the epidemiologic factors inherent to SUDEP in these EMUs. The primary data collected included that related to cardiorespiratory arrest during SUDEP (i.e., periods of apnea, respiratory rate, rhythm strip data on EKGs during VEEG)[1], in addition to primary VEEG data surrounding the time of SUDEP. VEEG data was assessed for the presence of post-ictal generalized suppression (absence of EEG activity >10uV in amplitude), and more generally for the sequence of ictal events leading up to cardiorespiratory arrest. Cardiorespiratory arrests were then classified as either definite or probable SUDEP, near SUDEP (fatal or non-fatal), or non-SUDEP (see Panel 1)[2]. Statistically, data were analyzed for the incidence of SUDEP in the evaluated EMUs via an estimation of total patient-years spent in the units, with sub-group analyses based on clinical indication for VEEG (pre-surgical vs. other). Where appropriate, two investigators conducted independent analyses, and their outcomes were compared for inter-rater reliability.

Results: A total of 160 EMUs were invited to participate in the study, of which 147 completed the surveys provided. 49% of the VEEG data was from patients undergoing a pre-surgical evaluation in participating EMUs. In terms of the primary outcome, a total of 29 cardiorespiratory arrests were reported by 27 of the participating EMUs over the census period (8 definite SUDEP, 8 probable SUDEP). This data suggested an incidence of definite or probable SUDEP of 7.5 per 1000 person-years in those undergoing VEEG for pre-surgical evaluation, and 1.2 per 1000 person-years in those undergoing VEEG for other purposes (**Table 3**). Of the SUDEP or near-SUDEP cases, 64% had epileptic foci within the temporal lobe, 8% were found within the insula, and 20% had bilateral or generalized-onset seizures; most had undergone tapering of their AEDs prior to their arrest (**Table 1**). In all assessable cases, a seizure occurred immediately prior to the documented arrest, and all were GTC-type seizures. SUDEP was monitored in 11 of the patients documented, and in all such cases, four consistent features were seen: 1) immediate post-ictal tachypnea with HR variability, 2) post-ictal generalized EEG suppression, 3) early cardiorespiratory dysfunction (bradycardia, asystole, or apnea) in the first 3min postictally, and 4) terminal apnea always preceding terminal asystole (**Figs 1 – 3**). Two patterns of evolution were also

[1] Apnea: defined as a recording segment >10s w/o respiratory movement, with respirations assessed by video inspection

[2] Non-fatal near SUDEP: sudden cardiorespiratory arrest in a patient with epilepsy, no structural cause, with or without a seizure, and with the patient surviving resuscitation >1hr post-arrest. Fatal near SUDEP: an arrest was responsible for irreversible and major brain damage directly leading to death, but >1hr post arrest

seen, with one characterized by early, post-ictal terminal arrest and the other by a brief period of spontaneous arrest reversal (2.5 – 11min) before a terminal arrest.

Conclusions: Overall, this study effectively described a consistent pattern of cardiorespiratory compromise that contributed to the development of SUDEP, even if a relatively rare occurrence. All cases of SUDEP in this study cohort were triggered by a GTC-seizure and were characterized by early cardiorespiratory dysfunction, EEG suppression, then apnea progressing to asystole. The authors proposed that a potential mechanism leading to this pattern is the development of a neurovegetative state induced by the significant neuronal excitation inherent to GTC-type seizures. EEG suppression was also proposed to occur *after* respiratory dysfunction, suggesting a sequence of peri-ictal hypoxemia from cortical network dysfunction, subsequent respiratory compromise, and then EEG suppression at the nadir of oxygen desaturation. Finally, it is worth noting that all cases of SUDEP in this cohort occurred at night (1930 – 0600), not only suggesting a circadian pattern to SUDEP, but also strongly supporting the need for constant supervision (especially overnight) of all patients admitted to the EMU. Ultimately, despite some limitations related to the retrospective design of this study, it was among the first to identify a more clear, physiologic mechanism inherent to SUDEP.

Summary created by Elaine Sinclair, D.O.