Breathing New Life into the Fight against Sudden Death in Epilepsy

Ictal Hypoxemia in Localization-Related Epilepsy: Analysis of Incidence, Severity and Risk Factors. Bateman LM, Li CS, Seyal M. *Brain* 2008;131(Pt 12):3239–3245. Ictal hypoxemia has been reported in small series of cases and may contribute to sudden unexpected death in epilepsy (SUDEP). We sought to determine the incidence and severity of ictal hypoxemia in patients with localization-related epilepsy undergoing in-patient video-EEG telemetry. We examined whether seizure-associated oxygen desaturation was a consequence of hypoventilation and whether factors such as seizure localization and lateralization, seizure duration, contralateral spread of seizures, patient position at seizure onset and body mass index influenced ictal-related hypoxemia. A total of 304 seizures with accompanying oxygen saturation data were recorded in 56 consecutive patients with intractable localization-related epilepsy; 51 of 304 seizures progressed to generalized convulsions. Pulse oximetry showed oxygen desaturations below 90% in 101 (33.2%) of all seizures with or without secondary generalization, with 31 (10.2%) seizures accompanied by desaturations below 80% and 11 (3.6%) seizures below 70%. The mean duration of desaturation below 90% was 69.2 ± 65.2 s (47; 6–327). The mean oxygen saturation nadir following secondary generalization was 75.4% ± 11.4% (77%; 42–100%). Desaturations below 90% were significantly correlated with seizure localization [$p = 0.005$; odds ratio (OR) of temporal versus extratemporal = 5.202; 95% CI = (1.665, 16.257)], seizure lateralization [$p = 0.001$; OR of right versus left = 2.098; 95% CI = (1.078, 4.085)], contralateral spread of seizures [$p = 0.028$; OR of contralateral spread versus no spread = 2.591; 95% CI = (1.112, 6.039)] and gender [$p = 0.048$; OR of female versus male = 0.422; 95% CI = (0.179, 0.994)]. In the subset of 253 partial seizures without secondary generalized convulsions, 34.8% of seizures had desaturations below 90%, 31.8% had desaturations below 80% and 12.5% had desaturations below 70%. The degree of desaturation was significantly correlated with seizure duration ($p = 0.001$) and with electrographic evidence of seizure spread to the contralateral hemisphere ($p = 0.003$). Central apnoeas or hypopnoeas occurred with 50% of 100 seizures. Mixed or obstructive apnoeas occurred with 9% of these seizures. End-tidal carbon dioxide (ETCO2) was recorded in seven patients (19 seizures). The mean increase in ETCO2 from preictal baseline was 18.6 ± 17.7 mm Hg (13.2; 2.8–77.8). In these 19 seizures, all oxygen desaturations below 85% were accompanied by an increase in ETCO2. Ictal hypoxemia occurs often in patients with localization-related epilepsy and may be pronounced and prolonged; even with seizures that do not progress to generalized convulsions. Oxygen desaturations are accompanied by increases in ETCO2, supporting the assumption that ictal oxygen desaturation is a consequence of hypoventilation. Ictal hypoxemia and hypercapnia may contribute to SUDEP.

COMMENTARY

Sudden unexpected (or unexplained) death in epilepsy (SUDEP) occurs at a rate of approximately 1 in 1,000 person-years, when combining all epilepsy types and severities, and increases to 1 in 150 person-years for those with refractory epilepsy (1,2). The vast majority of SUDEP deaths are associated with seizures. Young adults with uncontrolled convulsive seizures constitute the highest risk group, though SUDEP occurs in many other patient populations. Leading theories of the cause of SUDEP include ictal or postictal cardiac arrhythmias, apnea (central apnea is more commonly invoked than obstructive apnea, though both might play a role), and cerebral shutdown, with flattening of the EEG that never recovers (1,3,4). Although there have been many publications on the cardiac effects of seizures, effects on oxygenation and respiration have received minimal investigation. Yet, among six cases of SUDEP or near-SUDEP (i.e., cardiopulmonary arrest with successful resuscitation) that occurred during EEG monitoring, arrhythmia was only documented in one patient and that patient had a prior myocardial infarction (1). Three of the other five cases were felt to be due to "central nervous system shutdown," one to central apnea, and one to obstructive apnea, possibly laryngeal spasm. Of note, none of these cases had oxygen saturation or respirations monitored, as such monitoring is not standard in most epilepsy video-EEG monitoring units—at least not yet.

In the current study by Bateman et al., continuous digital oxygen saturation was monitored during seizures in an epilepsy monitoring unit, with the results recorded second-by-second and incorporated into the video-EEG record. The investigators also continuously recorded respirations as measured by nasal airflow, respiratory effort as measured by abdominal excursions, and heart rate in 10-second epochs. The findings demonstrated conclusively that complex partial seizures, with or without generalization, commonly lead to significant and prolonged oxygen desaturation. In a subgroup of 7 patients with 19 seizures, the authors further showed that the desaturation was indeed due to hypoventilation, rather than peripheral vasoconstriction, by identifying elevated end-tidal carbon dioxide ($ETCO_2$), as averaged over 4 breaths and recorded every 4 seconds. Desaturations typically lasted more than a minute.

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In some patients, hypoventilation (i.e., elevated $ETCO_2$) persisted despite increases in ventilatory rate. Overall, hypoventilation was far more commonly found to be central than obstructive. Risk factors for ictal hypoxemia included temporal lobe onset, male gender, bilateral spread, longer seizure duration, and right hemisphere onset. It is important to point out that desaturations were just as common and significant in complex partial seizures that did not progress to secondary generalized convulsions; in fact, saturation dropped below 80% in about one-third of these seizures and below 70% in one-eighth. Although this is not the first investigation documenting ictal desaturation, it is the largest and most carefully conducted study on ictal hypoventilation and hypoxemia to date.

Pertinent factors that were not associated with the risk of ictal hypoxemia included patient position at the onset of the seizure (i.e., supine, prone, sitting), antiepileptic drug load, and the degree of increase in heart rate during the seizure. An interesting observation was that O_2 saturation never dropped below 90% except in the periictal setting. This finding suggests that oximetry may be useful as a seizure detector with few false positives (high specificity, but not necessarily high sensitivity), which could be useful in both the inpatient setting and perhaps even at home or elsewhere.

As these authors and others have reviewed, respiration can be inhibited by electrical stimulation of multiple portions of the limbic system, including the hippocampus (5). In addition, stimulation of the hippocampus has been reported to entrain the respiratory rhythm, and hippocampal activity increases just before resumption of breathing after apnea. Thus, there is some rationale for the theories that ictal activity during temporal lobe seizures can lead to apnea and that postictal limbic dysfunction might inhibit resumption of breathing. Notably, the degree of hypercarbia seen in these patients also is sufficient to affect cardiac conduction.

Bateman and colleagues found that patients with seizure-related desaturation below 85% were highly likely to have similar desaturations with subsequent seizures. It remains to be seen if these patients are at higher risk of SUDEP and if preventing their periictal desaturations might prevent SUDEP. Animal models suggest that preventing hypoventilation or desaturation can prevent seizure-related death. For example, one study reported three strains of mice with audiogenic seizures and seizure-related sudden death in which supplying supplemental oxygen completely prevented sudden death, without affecting the seizure activity itself (6). In addition, in a particular strain of mice (DBA/2) that have audiogenic seizures with respiratory arrest, increasing serotonin levels (via fluoxetine) prevented the ictal apnea, and most mice survived (7). In the potentially related condition of sudden infant death syndrome (SIDS), postmortem studies have found that a large proportion of cases—perhaps even the majority—have an abnormality in the brainstem serotonergic system (8,9). This medullary 5-hydroxytryptamine system is believed to be important in arousal as well as for respiratory effort and gasping, including in response to hypoxemia or hypercarbia, although several other neurotransmitters are also involved. Infants who subsequently suffer from SIDS or near-SIDS, have impaired sighs, gasps, and arousal mechanisms (9,10). These arousal and respiratory measures have not been studied in relation to SUDEP, though they can be easily assessed. Exposure to smoking, especially during early development, is a major risk factor for SIDS and may affect development of these arousal/respiratory pathways. Whether or not perinatal exposure to smoking is a risk factor for SUDEP is also unknown.

Investigations into respiratory drive, such as the studies of animal models or people with epilepsy discussed here, show great promise for providing clinically relevant information related to SUDEP (and SIDS), as do recent advances in the understanding of basic respiratory physiology. Programs that teach up-to-date specifics on the neuroanatomy and neurophysiology of respiration to neurologists and epileptologists would be useful as well. For example, most neurologists are not overly familiar with the pre-Botzinger complex, a component of the ventral respiratory column in the lower brainstem (11). It is now known that the pre-Botzinger complex is critical for generating inspiration and lesioning it leads to breathing cessation (10). Perhaps, via careful periictal monitoring of cardiac and respiratory physiology, it will soon be possible to better identify those patients at highest risk for SUDEP, the most likely mechanism(s) for it in a given individual, and a means of prevention. The potential for development of devices that can both monitor and treat the most likely mechanisms (all now technically feasible) adds further grounds for optimism in the fight against SUDEP.

Although previously SUDEP was a largely neglected condition, it is now beginning to receive the attention it deserves. The American Epilepsy Society and Epilepsy Foundation recently published a report of their Joint Task Force on SUDEP (2). The task force recommendations led to a multidisciplinary SUDEP conference, sponsored by the National Institutes of Health's National Institute of Neurological Disorders and Stroke, in which experts in cardiac death, SIDS, animal models, epidemiology, genetics, and other related disciplines participated. Whether or not the ictal hypoxemia described in this study is a major contributor to SUDEP (which it certainly might be), the collaborative approach and increased interest (and presumably, funding) points to the great potential for ultimately defining the pathophysiology of SUDEP and how to prevent it.

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