Conscious Control of Breathing: A Key to Prevention of Sudden Unexpected Death in Epilepsy?

Patients with epilepsy have an increased mortality rate compared to the general population. Increased mortality is related to accidents during seizures, convulsive status epilepticus, and complications of underlying causes of epilepsy. Sudden unexpected death in epilepsy (SUDEP) is the most common cause of death in patients with chronic refractory epilepsy, with incidence estimates per 1,000 patient-years varying from 0.09 to 2.65 in community samples with lower disease severity, and 6 to 9.3 in patients undergoing epilepsy surgery or vagus nerve stimulator implantation.[1]

Pathophysiological mechanisms that may contribute to explaining death include cardiac arrhythmias that may occur during ictal events, airway obstruction followed by central apnea, or a "central shut down,"[1] among others, including deaths that cannot immediately be linked to seizures based on available evidence. Certain risk factors may increase risk of death, such as male gender, younger age, primary generalized epilepsy, number of antiseizure medications, pharmacologically intractable seizures, frequent seizures, noncompliance with antiseizure medication intake, lower antiseizure medication levels, longer duration of epilepsy, alcohol abuse, seizure preceding death, and prone position or being alone or unsupervised, without care at the time of seizure, in bed at night.[1,2]

Impaired respiratory control during and after seizures frequently occurs, and is an essential element in the pathophysiology of SUDEP. An international survey evaluated "incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units," and provided insight into 16 SUDEP cases with recorded clinical physiological parameters, revealing postictal changes in respiratory and cardiac tracings following generalized tonic–clonic seizures, suggesting a sequence of terminal apnea followed by cardiac arrest, and thereby highlighting the central role of apnea in SUDEP.[2]

As polygraphic recordings, including respiratory measurements, become more readily available, identification of ictal apnea is more frequently accomplished. In a recent series of 126 patients, ictal apnea was seen in 51 of 109 patients with focal seizures. Ictal apnea lasting >1 minute led to severe hypoxemia, and was more frequently seen in temporal lobe epilepsy. There was also ictal apnea agnosia, and therefore apnea may go unrecognized or may occur without conscious recognition, unless related respiration is monitored.[3]

Localization of cortical respiration modulation points toward mesial temporal structures, specifically the amygdala. Term infants with hemorrhage or infarction of the temporal lobe, specifically the hippocampus and adjacent mesial and basal temporal cortex regions, presented with seizures and apnea, implying mesial temporal structures in the control of breathing.[4] In a patient with bilateral frontotemporal electrode implantation, central apnea was noted during seizure spread into the amygdala, and localized electrical stimulation reproduced this finding. Patients were not aware of apneas.[5] With the re-emergence of stereo-electroencephalographic recordings in the presurgical epilepsy workup, anatomically precise stimulation of amygdala and hippocampal regions is now feasible. Stimulation of amygdala and hippocampal head elicited central apneas in the expiratory phase in 3 patients,[6] further supporting implications of the amygdala in the control of breathing.

In this issue, Nobis and colleagues provide a milestone in the sparse literature on conscious control of breathing, describing the importance of the central nucleus of the amygdala in this setting, and providing evidence that conscious mouth breathing prior to stimulation may prevent apnea.[7] Furthermore, direct instructions to consciously take a breath could overcome stimulation-induced apnea. Not only do the authors provide evidence regarding central control of breathing, they also add to the sparse information that potentially increasing the level of attention or stimulation of the patient may overcome apnea. These results rekindle hopes that SUDEP during and after seizures is not inevitable in all cases. Of note, even patients with bilateral amygdala resection did not suffer from lethal apnea, suggesting a modulatory function of the amygdala, and not a critical cortical control mechanism similar to the primary language or motor areas.[8]

Improved recognition and understanding of peri-ictal apnea and hypoventilation may offer unique opportunities for intervention. Increasing the level of awareness may be

able to overcome the combination of apnea triggered by electrical discharges in the amygdala and the lack of awareness of apneas, which appears to pose a potentially lethal threat to patients with seizures. As ambulatory seizure monitoring becomes more accessible and affordable, respiratory rate may be calculated from heart rate–related signals, and newer algorithms may be able to derive respiratory rate from a single sensor, such as peripherally recorded heart rate, tentatively allowing more widespread use.[9] Acute seizure care, stimulation and oxygen support, identification of individual risk factor profiles for SUDEP and implementation of individualized monitoring strategies, population-based health strategies utilizing large datasets in combination with artificial and biological intelligence solutions to longitudinally identify patients at risk, and implementation of respective monitoring and intervention solutions tailored to each patient may ultimately assist in reducing SUDEP risk.[10] Some of these monitoring systems now also imply arousing techniques, or allow notification of caretakers to stimulate patients in an attempt to improve level of alertness, or permit a first aid provider to support airway and respiration. The novel findings in this issue[7] provide an additional missing piece of the puzzle of SUDEP pathophysiology, bringing the entire field closer to more comprehensive SUPEP prevention and seizure action plans.

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Potential Conflicts of Interest

Nothing to report.

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