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The Deep Breath Before the Plunge: Ictal Apnea and the Amygdala

A Human Amygdala Site That Inhibits Respiration and Elicits Apnea in Pediatric Epilepsy

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Background: Seizure-induced inhibition of respiration plays a critical role in sudden unexpected death in epilepsy (SUDEP). However, the mechanisms underlying seizure-induced central apnea in pediatric epilepsy are unknown. Methods: We studied 8 pediatric patients with intractable epilepsy undergoing intracranial electroencephalography. We recorded respiration during seizures and during electrical stimulation mapping of 174 forebrain sites. A machine learning algorithm was used to delineate brain regions that inhibit respiration. Results: In 2 patients, apnea coincided with seizure spread to the amygdala. Supporting a role for the amygdala in breathing inhibition in children, electrically stimulating the amygdala produced apnea in all 8 patients (3-17 years old). These effects did not depend on epilepsy type and were relatively specific to the amygdala, as no other site affected breathing. Remarkably, patients were unaware that they had stopped breathing, and none reported dyspnea or arousal, findings critical for SUDEP. Finally, a machine learning algorithm based on 45 stimulation sites and 210 stimulation trials identified a focal subregion in the human amygdala that consistently produced apnea. This site, which we refer to as the amygdala inhibition of respiration (AIR) site, includes the medial subregion of the basal nuclei, cortical and medial nuclei, amygdala transition areas, and intercalated neurons. Conclusions: A focal site in the amygdala inhibits respiration and induces apnea (AIR site) when electrically stimulated and during seizures in children with epilepsy. This site may prove valuable for determining those at greatest risk for SUDEP and as a therapeutic target.

Seizure-Related Apneas Have an Inconsistent Linkage to Amygdala Seizure Spread

Park K, Kanth K, Bajwa S, et al. *Epilepsia.* 2020;61(6):1253-1260.

Objective: Sudden unexpected death in epilepsy (SUDEP) is a frequent cause of death in epilepsy. Respiratory dysfunction is implicated as a critical factor in SUDEP pathophysiology. Human studies have shown that electrical stimulation of the amygdala resulted in apnea, indicating that the amygdala has a role in respiration control. Unilateral amygdala stimulation resulted in immediate onset of respiratory dysfunction occurring only during nose breathing. In small numbers of patients, some but not all spontaneous seizures resulted in apnea occurring shortly after seizure spread to the amygdala. With this study, we aimed to determine whether seizure onset or spread to the amygdala was necessary and sufficient to cause apnea. Methods: We investigated the temporal relationship between apnea/hypopnea (AH) onset and initial seizure involvement within the amygdala in patients with implanted depth electrodes. Results: Data from 17 patients (11 female) with 47 seizures were analyzed. With 7 seizures (3 patients), AH preceded amygdala seizure involvement by 2 to 55 seconds. There was no AH with 4 seizures (3 patients) that involved the amygdala. With 8 seizures (4 patients), AH occurred within 2 seconds following amygdala seizure onset. With 28 seizures, AH started >2 seconds after amygdala seizure onset (range: 3-158 seconds). Following seizure onset, there was a significant difference between AH onset time and amygdala seizure onset ($P < .001$). The mean $\pm$ standard deviation AH onset was 27.8 $\pm$ 41.06 seconds, and the mean time to amygdala involvement was 8.83 $\pm$ 20.19 seconds. Significance: There is a wide range of AH onset times relative to amygdala seizure involvement. With some seizures, amygdala seizure involvement occurs without AH. With other seizures, AH precedes amygdala seizures, suggesting that, with spontaneous seizures, involvement of the amygdala may not be crucial to induction of AH with all seizures. Other pathophysiology impacting brain stem respiratory networks may be of greater relevance to seizure-triggered apneas.

Commentary

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Many of us have seen, either as health care professionals, or carers, the dramatic and terrifying cessation of breathing during a seizure. The person turns blue due to cyanosis, often just prior to the descent into convulsion, and it can seem like an eternity before respiration is revived again. This phenomenon is more common than we think, occurring in over one-third of focal seizures.[1]

This often neglected component of seizure semiology (we generally do not measure respiratory effort in the epilepsy monitoring unit) has been addressed by several recent studies.[2-5] In addition, seizure-induced respiratory suppression may be an important element in progression to sudden unexplained death in epilepsy (SUDEP).[6]

Given that central apnea is felt to be pivotal in the evolution of SUDEP, determination of the underlying pathophysiological mechanism and its neuroanatomical correlate (symptomatogenic zone) is of utmost importance.

Interest in cerebral control of respiration, and its role in seizures has its origins in early reports,[7] animal experiments,[8] and Kaada and Jasper's stimulation studies.[9]

The amygdala has been identified as having a possible role in ictal apnea. The amygdala contains several groups of distinct nuclei, each with varied functions and connections. We mostly associate the amygdala with emotions, and the amygdala is located in close proximity to the rest of the limbic system. Although primary centers for respiration lie in the pacemaker pre-Bötzinger cells of the ventrolateral medulla, suprapontine connections can influence patterns of respiration. For example, the hyperventilation seen in excited or emotional states, or breathing variations during speech, or just "holding our breath." There is also a role of the amygdala in response to threat, perhaps an evolutionary survival advantage, overriding automatic control and "holding your breath while the predator is near." Removal or damage to both amydgala in animals and humans leads to reduced autonomic arousal and a docile state, the "Klüver-Bucy syndrome."[10,11]

Increased blood partial pressure of carbon dioxide (pCO2) is a potent stimulus to the medulla to increase respiratory rate and can induce a feeling of panic or dyspnea, probably mediated by the amygdala, and other limbic networks. This subjective emotional component seems to be lost during ictal apnea, so-called apnea agnosia. Conscious instruction to breathe, if the patient is aware, overrides it.[12] When the patient is unaware, the lack of drive to breathe could have devastating consequences.

Both Park et al and Rhone and colleagues utilized invasive extraoperative intracranial recordings to investigate potential sites, particularly the amygdala, for apnea or hypopnea induced by seizure activity, or by electrical stimulation.

Rhone's series adds to Brian Dlouhy's earlier description of apnea with amygdala stimulation.[5] In a beautifully illustrated paper, they looked at 8 pediatric patients who underwent depth electrode evaluation, including the amygdala, as part of their surgical epilepsy workup. None of the patients had a structurally abnormal amygdala, nor had seizure onset from the amygdala. Six patients (2 could not comply with respiratory belts, due to age) had respiratory monitoring with chest/abdominal plethysmography, oral and nasal airflow, and capillary oxyhemoglobin saturation. Apnea was defined as 1 missed breath with flattened airflow trace and absence of chest wall movement with belt or video, for the entire stimulus duration, and transient apnea if normal breathing resumed prior to the end of stimulation. High-density electrodes with 0.88 mm interelectrode distance were used, allowing for a more accurate correlation between the electrophysiology and anatomical imaging. The California Institute of Technology 168 human brain template atlas was used to define amygdala nuclei location. Once a stimulation or contact site was defined as apnea, transient apnea, or no apnea, a support vector machine and probability map, using a machine learning algorithm, was used to identify a potential "amygdalar inhibition of respiration" (AIR) site, in this study located in the medial amygdala. Support vector machine learning can predict a 3D vector's best division (apnea or no apnea) using a set of classifications, in this case, the Montreal Neurological Institute coordinates of each stimulation site.

Park et al looked at 17 adult patients (48 seizures), with depth electrodes in the amygdala. The electrodes were non high density with an interelectrode distance of 5 mm. The exact locations of the electrodes within the amygdala were not detailed. Abdominal movement, nasal airflow, and digital pulse oximetry were used to measure respiration. Apneas were defined as cessation of airflow >5 seconds and hypopneas as a $>50\%$ drop in airflow amplitude >5 seconds. The time of initial seizure involvement in the amygdala on Stereo-electroencephalogrphy (SEEG) was correlated with the onset and duration of apnea. If apnea/hypopnea onset was within 2 seconds of amygdalar involvement, it was deemed to be linked to the amygdala. Three patients (7 seizures) had apnea before amygdalar onset. There was no apnea in 3 patients (4 seizures). In 4 patients (8 seizures) apnea occurred within 2 seconds of amygdalar onset. Twenty-eight seizures occurred >2 seconds after amygdalar onset. Mean apnea duration was 68 ± 50 seconds. Most apneas occurred close in time to amygdalar seizure involvement. They concluded that ictal involvement of the amygdala may not be critical for all ictal apnea events.

So is the amygdala the symptomatogenic zone for seizure-induced apnea? These 2 studies have methodological differences—different definitions of apnea, levels of electrophysiological–anatomical correlation and electroencephalogram (EEG) density, and spatial coverage, as well as patient age groups. Longer duration and higher intensity of stimulation did positively affect apnea response, with a range of 5 to 60 seconds (depending on proximity to the epileptogenic network) and seen mostly at 10 V (15 V in 2 patients).

The Rhone study's use of high-density EEG, and machine learning gives real credence to the presence of an AIR site. However, the concept of a single "AIR" may be too simplistic for some, given the wider network involved as demonstrated by other groups. More recently, the Lhatoo group has expanded ictal apnea

to include a more diffuse area of the limbic network including the hippocampus, anteromesial fusiform gyrus, anterior parahippocampal gyrus, and amygdala. However, the amygdala does seem to play a common role across a number of study groups.[13]

It is likely that while the amygdala plays a role in the suprapontine control of breathing, there is a wider network effect within the limbic system. Ictal apnea may also be useful as a localizing clue as to involvement of limbic symptomatogenic zones.[4] Further research from these groups and others will be welcome, as well as replication of the finding of the AIR site. Further insight into pathways of ictal discharges through subcortical centers and into the brain stem will be possible with modalities such as ictal single-photon emission computed tomography, functional magnetic resonance imaging, and viral vector neural circuit mapping.[14]

Many other questions remain—Is unilateral or bilateral/contralateral spread to both amygdala required for apnea? What are the normal physiological amygdalar-brain stem connectomes as opposed to those with an epileptic limbic system? It must be noted that in the majority of these patients, seizure onset was not in the amygdala itself. The amygdala may play a role in apnea in other conditions, such as breath holding in children,[15] PHOX2B disorders,[16] and in subcortical trauma, stroke, autoimmune encephalitis, or neurodegenerative disorders.

Ideally, we should measure respiration in the epilepsy monitoring unit, although this resource is not always available. An enhanced appreciation of respiratory effort from witnessed observations or on video analysis is an alternative. Until we know more, resuscitation equipment should be close-by, particularly during stimulation of limbic structures. Kaada and Jasper also noted that intraoperative mechanical stimulation or suction of limbic areas in awake patients could induce apnea.[9] Education of caregivers about ictal apnea is important. Smart sensor technology may play a role, particularly given the apnea agnosia; early recognition of seizure-induced apnea and therapeutic intervention can perhaps lead to its termination and mitigate seizure spread to the brain stem. Pharmacological modulation of autonomic brainstem networks such as with serotonin systems holds promise and may reduce SUDEP risks.[17-19] The exact role of ictal apnea or apnea agnosia in SUDEP remains to be fully elucidated.

By Peter Widdess-Walsh

ORCID iD

Peter Widdess-Walsh https://orcid.org/0000-0003-4217-2575

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