# When Apnea Turns Terminal: When, How, Why?

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**Postictal Death Is Associated with Tonic Phase Apnea in a Mouse Model of Sudden Unexpected Death in Epilepsy**

Wenker IC, Teran FA, Wengert ER, et al. *Ann Neurol.* 2021;89:1023-1035

Objective: Sudden unexpected death in epilepsy (SUDEP) is an unpredictable and devastating comorbidity of epilepsy that is believed to be due to cardiorespiratory failure immediately after generalized convulsive seizures. Methods: We performed cardiorespiratory monitoring of seizure-induced death in mice carrying either a p.Arg1872Trp or p.Asn1768Asp mutation in a single Scn8a allele—mutations identified from patients who died from SUDEP—and of seizure-induced death in pentylenetetrazole-treated wild-type mice. Results: The primary cause of seizure-induced death for all mice was apnea, as (1) apnea began during a seizure and continued for tens of minutes until terminal asystole, and (2) death was prevented by mechanical ventilation. Fatal seizures always included a tonic phase that was coincident with apnea. This tonic phase apnea was not sufficient to produce death, as it also occurred during many nonfatal seizures; however, all seizures that were fatal had tonic phase apnea. We also made the novel observation that continuous tonic diaphragm contraction occurred during tonic phase apnea, which likely contributes to apnea by preventing exhalation, and this was only fatal when breathing did not resume after the tonic phase ended. Finally, recorded seizures from a patient with developmental epileptic encephalopathy with a previously undocumented SCN8A likely pathogenic variant (p.Leu257Val) revealed similarities to those of the mice, namely, an extended tonic phase that was accompanied by apnea. Interpretation: We conclude that apnea coincident with the tonic phase of a seizure, and subsequent failure to resume breathing, are the determining events that cause seizure-induced death in Scn8a mutant mice.

## Commentary

On June 19, 1773, George Washington lost his step daughter Patsy to probable sudden unexpected death in epilepsy (SUDEP), "*She rose from Dinner about four O'clock, in better health & spirits than she appeared to be in for some time; soon after she was seized with one of her usual fits & expired in it, in less than* 2 *minutes without a word, a groan or scarce a Sigh.*"[1] Extensive research indicates that cardiorespiratory failure stands at the core of SUDEP.[2] Ictal and peri-ictal respiratory abnormalities triggered by central and obstructive apnea have been repeatedly observed in both focal and generalized seizures.[3] Ictal central apnea seems to be more common, occurring in over 36% of seizures. It is typically observed in focal epilepsy and suspected to represent a semiological phenomenon of a focal cortical discharge.[4] On the contrary, a postconvulsive central apnea (PCCA) follows an estimated 18% of convulsive seizures and suggests a presence of a brainstem dysfunction.[4] It is linked to the presence of postictal generalized suppression and postictal tonic posturing.[5] Postconvulsive central apnea affects an estimated 22% of patients[4] indicating the possibility of an individual vulnerability to an ictally driven brainstem mediated cardio-respiratory failure. However, it is inherently challenging to interrogate a human brainstem and animal models have proved invaluable in gaining an insight into the complex interactions among seizures, cardio-respiratory functions, and ictally driven mortality. For example, SUDEP modeled in *Kv1.1* deficient mice may result not only from a peripheral autonomic dysfunction owing to the channel localization in the vagus nerve but also due to a suspected central failure given the channel extensive localization in the cardio-respiratory brain regions.[6,7] The investigators found that recurrent seizures seemed to trigger an extensive gliosis in those areas which could be contributory to respiratory abnormalities and premature mortality.[7] Similarly, *Scn1a*$^{R1407X}$ knock-in mice are prone to premature mortality due to ictal and interictal arrhythmias[8] but also due to a respiratory dysfunction.[9] Clinical and experimental evidence has uncovered increase vulnerability to SUDEP due to cardiorespiratory dysfunction also in *SCN8A*-related encephalopathy and its corresponding animal models.

Current work by Wenker et al[10] delivers an important insight into the mechanisms of ictally-driven apnea and pathophysiology of SUDEP through investigation of a *Scn8a* genetic model. The authors performed cardiorespiratory monitoring of convulsive seizures and seizure-induced death in established conditional knock-in mice expressing a gain-of-function

recurrent pathogenic human variant p.Arg1872Trp in the forebrain. Results of this investigation are intriguing as they parallel prior human studies; the authors recorded 52 spontaneous generalized tonic-clonic (Racine scale grade 5) seizures. The majority (56%) were non-lethal clonic, 29% were non-lethal tonic, and 15% were lethal tonic seizures. There was no difference in the ictal duration among the 3 seizure types. However, apnea was only observed in tonic seizures and its duration was proportional to the duration of the tonic phase. Moreover, the monitoring revealed that a tonic muscle contraction prolonged the apnea and coincided with a tonic contraction of the diaphragm that mechanically compromised alveolar ventilation. Interestingly, in non-fatal seizures, tachycardia and tachypnea followed the ictal apnea while fatal tonic seizures were accompanied by ongoing apnea and bradycardia. This finding is reminiscent of the results from the previously published DBA1 model where audiogenic clonic-tonic seizures triggered simultaneous cardio-respiratory depression manifested by bradypnea and bradycardia during a clonic phase and apnea and further bradycardia during the tonic phase. The authors postulated an ictally-driven parallel activation of 2 central nervous system pathways, one inhibiting the respiratory drive and the other cardiac function via vagal efferents.[11] In order to understand a possible temporal window of opportunity for clinical intervention, Wenker et al also modeled convulsive seizures through the administration of an audiogenic stimulus in the *Scn8a* model. Similarly to Shilling et al[11] they found that early administration of mechanical ventilation during the tonic phase prevented apnea from becoming lethal in 7 of 8 animals. Interestingly, the authors observed tonic phase apnea also in a constitutional model for *SCN8A*-related epileptic encephalopathy, the $Scn8a^{Arg1872Trp}$ mouse and in a chemically induced seizure model, pentylenetetrazole-treated wild-type mice. These results are important as they suggest an epilepsy etiology independent common mechanism. They also support the conclusion that apnea is necessary although not sufficient for SUDEP.

There is an interesting link between ictally driven apnea and postictal generalized EEG suppression (PGES). In humans, the occurrence and duration of PGES has been linked to tonic decerebrate posturing. In turn, postictal tonic decerebrate posturing was found to be associated with the presence of PCCA and prolonged hypoxemia, which represent suspected SUDEP biomarkers.[5] Wenker et al therefore evaluated PGES in the *Scn8a* model. However, they did not find difference in the PGES magnitude between the fatal and non-fatal tonic seizures.[10] Nevertheless, PGES duration was not evaluated and the relevance of this EEG marker for SUDEP risk in this model remains uncertain.

Current work by Wenker et al contributes towards further understanding of mechanisms underlying the ictally generated respiratory failure leading up to SUDEP. However, several important questions remain; (1) What mechanisms underlie lethal seizure and terminal apnea? For example, we know that ictally activated brainstem spreading depolarization can lead to apnea and resultant cardio-respiratory collapse.[12] *Scn8a* deficiency can cause wide spread transcriptional alterations[13] and their role in SUDEP risk remains to be elucidated. And the *Kv1.1* model indicates that recurrent seizures may cause structural changes in cardiorespiratory networks[7] as also observed on imaging of SUDEP cases.[14] (2) Are there additional mechanical barriers in lethal vs non-lethal apnea? Experimental evidence indicates that in some cases, ictally driven and brain stem mediated reflex laryngospasm produces severe, prolonged obstructive apnea, causing respiratory arrest. Additional studies across diverse SUDEP models will be informative.[15] (3) Are there therapeutic interventions that might modulate the risk of respiratory arrest? In DBA1 mouse, respiratory arrest and mortality were preventable in a dose dependent manner with the modulation of serotonergic pathways[16,17] It remains to be seen whether this approach will be more broadly effective.

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