Biomarkers for SUDEP: Are We There Yet?

Postconvulsive Central Apnea as a Biomarker for Sudden Unexpected Death in Epilepsy (SUDEP)

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Objective: To characterize peri-ictal apnea and postictal asystole in generalized convulsive seizures (GCS) of intractable epilepsy. Methods: This was a prospective, multicenter epilepsy monitoring study of autonomic and breathing biomarkers of sudden unexpected death in epilepsy (SUDEP) in patients ≥18 years old with intractable epilepsy and monitored GCS. Video electroencephalography, thoracoabdominal excursions, nasal airflow, capillary oxygen saturation, and electrocardiogram were analyzed. Results: We studied 148 GCS in 87 patients. Nineteen patients had generalized epilepsy, 65 had focal epilepsy, 1 had both, and the epileptogenic zone was unknown in 2. Ictal central apnea (ICA) preceded GCS in 49 (40.4%) of 121 seizures in 23 patients, all with focal epilepsy. Postconvulsive central apnea (PCCA) occurred in 31 (22.1%) of 140 seizures in 22 patients, with generalized, focal, or unknown epileptogenic zones. In 2 patients, PCCA occurred concurrently with asystole (near-SUDEP), with an incidence rate of 10.2 per 1000 patient-years. One patient with PCCA died of probable SUDEP during follow-up, suggesting a SUDEP incidence rate 5.1 per 1000 patient-years. No cases of laryngospasm were detected. Rhythmic muscle artifact synchronous with breathing was present in 75 of 147 seizures and related to stertorous breathing (odds ratio: 3.856, 95% confidence interval: 1.395-10.663, \( P = .009 \)). Conclusions: Postconvulsive central apnea occurred in both focal and generalized epilepsies, suggesting a different pathophysiology from ICA, which occurred only in focal epilepsy. Postconvulsive central apnea was seen in 2 near-SUDEP cases and 1 probable SUDEP case, suggesting that this phenomenon may serve as a clinical biomarker of SUDEP. Larger studies are needed to validate this observation. Rhythmic postictal muscle artifact is suggestive of post-GCS breathing effort rather than a specific biomarker of laryngospasm.

Hyoxemia Following Generalized Convulsive Seizures: Risk Factors and Effect of Oxygen Therapy

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Objective: To analyze the factors that determine the occurrence or severity of postictal hypoxemia in the immediate aftermath of a generalized convulsive seizure (GCS). Methods: We reviewed the video electroencephalography (EEG) recordings of 1006 patients with drug-resistant focal epilepsy included in the REPO2MSE study to identify those with ≥1 GCS and pulse oximetry (SpO2) measurement. Factors determining recovery of SpO2 ≥ 90% were investigated using Cox proportional hazards models. Association between SpO2 nadir and person- or seizure-specific variables was analyzed after correction for individual effects and the varying number of seizures. Results: A total of 107 GCS in 73 patients were analyzed. A transient hypoxemia was observed in 92 (86%) GCS. Rate of GCS with SpO2 < 70% dropped from 40% to 21% when oxygen was administered early (\( P = .046 \)). Early recovery of SpO2 ≥ 90% was associated with early administration of oxygen (\( P = .004 \)), absence of postictal generalized EEG suppression (PGES; \( P = .014 \)), and extratemporal lobe epilepsy (\( P = .001 \)). Lack of early
EEG suppression was present in 71.6% had a longer duration in male patients. Postictal generalized EEG suppression occurred in similar proportions in patients with either generalized or focal epilepsy. In epilepsy, postictal electroencephalography (EEG) suppression has been correlated with respiratory dysfunction,7 and structural imaging studies have revealed volume changes in key structures involved in autonomic and respiratory regulation in patients who have died of, or are at high risk for, SUDEP.8,9

Two recently published reports have characterized the breathing dysfunction and level of hypoxia following GCS in refractory patients who were evaluated in epilepsy monitoring units. Both studies were rigorously conducted, had robust methodologies, and expand our understanding of the cardiorespiratory dysfunction following GCS.

In the first report, Vilella et al present data on breathing biomarkers in a cohort of 87 adults with focal and generalized intractable epilepsy who were evaluated prospectively with video EEG (VEEG). Reliable VEEG recordings were available for 148 seizures, with 48.6% of the seizures occurring during wakefulness and with 3 occurring as a cluster. Capillary oxygen saturation levels, thoracoabdominal excursions, and electrocardiography were measured in all patients, and in a subset of 21, oral and nasal airflow measurements were obtained. Breathing assessments were made continuously from 2 minutes preseizure to 3 minutes postseizure termination. Postconvulsive breathing rates were measured and averaged in 15-second epochs and classified according to deviations from the mean rate. Postictal generalized EEG suppression (PGES) was determined by visual analysis. Postconvulsive central apnea (PCCA) was classified as immediate or delayed.

Ictal central apnea preceded GCS in 40.4% of seizures from 32.4% of patients, all of whom had focal onset epilepsy. Postconvulsive central apnea occurred in similar proportions in patients with either generalized or focal epilepsy. In multivariate analysis, PCCA was more frequently seen in female patients, in focal epilepsy, when PGES was present and had a longer duration in male patients. Postictal generalized EEG suppression was present in 71.6% of seizures and was longer in delayed PCCA. Counterintuitively, PCCA correlated with shorter seizure duration. Stertorous breathing was present in half of all seizures, but no cases of laryngospasm were detected.

Additionally, PCCA occurred in 2 cases of near-SUDEP and in 1 case of probable SUDEP. Because the incidence and severity of PGES was double of what was seen of ICA, the authors suggest that PCCA might serve as a clinical biomarker of SUDEP and speculate that this is driven by brainstem mechanisms rather than a cortical phenomenon. Limitations of this study include the inclusion of only a highly refractory group of patients, making it difficult to extrapolate the possibility of a similar degree of cardiopulmonary dysfunction in less refractory patients, the low number of nasal outflow recordings, and the inability to rule out persistence of intracranial ictal activity in all patients with PCCA.

In the second report, Rheims et al conducted a prospective, multicenter study at 16 French epilepsy monitoring units analyzing factors that determine the occurrence and severity of postictal hypoxemia. The analysis included seizures captured from 114 patients who experienced at least 1 generalized convulsion and had valid pulse oximetry (SpO2) measurements at seizure onset. Clinical characteristics that were analyzed for each seizure included the ictal semiology, duration, prone position at the end of the seizure, and presence or absence of PGES. Different types of oximetry sensors were used across the centers, which in turn influenced the quality of SpO2 data. For each seizure, the evolution of the SpO2 was assessed during the 3 minutes in the preictal state, throughout the seizure, and up to 10 minutes postictally. The primary outcome was the duration of the postictal hypoxemia with respect to seizure cessation using a Kaplan-Meier survival analysis.

Of the 107 seizures with reliable data, the majority arose from temporal lobes during sleep. Transient hypoxemia was observed in 86% of the seizures. The mean delay between the end of the convulsion and recovery of SpO2 ≥ 90% was 59.5 seconds and mean SpO2 nadir was 73.1. Ictal hypoxemia during the focal phase of the seizure was more frequently observed in temporal versus extratemporal seizures. Recovery of SpO2 ≥ 90% was associated with early administration of O2, absence of PGES, and extratemporal seizures. Limitations of this study are the small sample size, the inclusion of only a highly refractory group of patients and the technical difficulties in recording SpO2 during GCS, given that 36% of seizures lacked informative data.

Taken together, these reports add credence to hypothesis of the complex interplay between seizure-induced suppression of cortical and brainstem function, peri-ictal breathing abnormalities, and autonomic dysfunction. These findings also reinforce...
the high frequency of PGES and profound cardiorespiratory
dysfunction seen in 10 monitored cases of SUDEP.4 The sug-
suggestion that PCCA is a more serious condition that could be a
biomarker for SUDEP requires confirmation in larger cohorts
of patients, both with refractory and easy to control epilepsy.
On the other hand, the administration of O2 during the ictus or
within 5 seconds after seizure termination and of O2 during the
focal phase of the GCS in temporal lobe seizures, and use of
disposable flexiform sensors for measuring SpO2 seem clini-
cally sound.

The search for biomarkers of potential cardiorespiratory
dysfunction following convulsive seizures is an important
endeavor but let’s not forget, the best intervention to prevent
SUDEP is the aggressive treatment of refractory epilepsy.

By David King-Stephens

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