Biomarkers for SUDEP: Are We There Yet?

Epilepsy Currents
2019, Vol. 19(4) 231-233

DOI: 10.1177/1535759719855948
journals.sagepub.com/home/epi
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Postconvulsive Central Apnea as a Biomarker for Sudden Unexpected Death in Epilepsy (SUDEP)

Laura Vilella, MD, Nuria Lacuey, MD, Johnson P. Hampson, MSBME, M. R. Sandhya Rani, PhD, Rup K. Sainju, MBBS, Daniel Friedman, MD, Maromi Nei, MD, Kingman Strohl, MD, Catherine Scott, MPhil, Brian K. Gehlbach, MD, Bilal Zonjy, MD, Norma J. Hupp, Anita Zaremba, BA, Nassim Shafiabadi, MD, Xiuhe Zhao, MD, Victoria Reick-Mitrisin, MS, Stephan Schuele, MD, MPH, Jennifer Ogren, PhD, Ronald M. Harper, PhD, Beate Diehl, MD, PhD, FRCP, Lisa Bateman, MD, Orrin Devinsky, MD, George B. Richerson, MD, PhD, Philippe Ryvlin, MD, PhD, and Samden D. Lhatoo, MD, FRCP. *Neurology*. 2019;92:e171-e182.

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 $\geq$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.

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

Sylvain Rheims, MD, PhD, Blanca Mercedes Alvarez, MD, Veriano Alexandre, MD, PhD, Jonathan Curot, MD, Louis Maillard, MD, PhD, Fabrice Bartolomei, MD, PhD, Philippe Derambure, MD, PhD, Edouard Hirsch, MD, PhD, Véronique Michel, MD, Francine Chassoux, MD, PhD, Didier Tourniaire, MD, Arielle Crespel, MD, Arnaud Biraben, MD, Vincent Navarro, MD, PhD, Philippe Kahane, MD, PhD, Bertrand De Toffol, MD, PhD, Pierre Thomas, MD, PhD, Sarah Rosenberg, MD, PhD, Luc Valton, MD, PhD, Laurent Bezin, PhD, and Philippe Ryvlin, MD, PhD, on behalf of the REPO2MSE Study Group. *Neurology*. 2019;92:e183-e193.

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 $\geq$1 GCS and pulse oximetry (SpO_2) measurement. Factors determining recovery of $SpO_2 \geq 90\%$ were investigated using Cox proportional hazards models. Association between SpO_2 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 $SpO_2 < 70\%$ dropped from 40% to 21% when oxygen was administered early ($P = .046$). Early recovery of $SpO_2 \geq 90\%$ 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

administration of O_2 ($P = .003$), occurrence of PGES ($P = .018$), and occurrence of ictal hypoxemia during the focal phase ($P = .022$) were associated with lower SpO_2 nadir. Conclusion: Postictal hypoxemia was observed in the immediate aftermath of nearly all GCS, but administration of oxygen had a strong preventive effect. Severity of postictal hypoxemia was greater in temporal lobe epilepsy and when hypoxemia was already observed before the onset of secondary GCS.

Commentary

Sudden unexpected death in epilepsy (SUDEP), with an incidence of approximately 0.5% per year,[1] is a leading cause of premature death in patients with epilepsy. Sudden unexpected death in epilepsy, which is primarily seen in refractory epilepsy, has been linked to cardiorespiratory dysfunction in the immediate postictal state after generalized convulsive seizures (GCS). The exact pathophysiology is not known, but experimental and clinical data suggest that in most cases, postictal central respiratory dysfunction, progressing to terminal apnea, is followed by cardiac arrest.[2-4] Postictal apnea and bradycardia resulting in death has been described in animal and human SUDEP.[5,6] 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 recorded 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 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 (SpO_2) 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 SpO_2 data. For each seizure, the evolution of the SpO_2 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 $SpO_2 \geq 90\%$ was 59.5 seconds and mean SpO_2 nadir was 73.1. Ictal hypoxemia during the focal phase of the seizure was more frequently observed in temporal versus extratemporal seizures. Recovery of $SpO_2 \geq 90\%$ was associated with early administration of O_2, 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 SpO_2 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 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 O_2 during the ictus or within 5 seconds after seizure termination and of O_2 during the focal phase of the GCS in temporal lobe seizures, and use of disposable flexiform sensors for measuring SpO_2 seem clinically 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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