Sleep Breathing Varibility as a Potential Biomarker for SUDEP Risk

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Rationale:
Sudden unexpected death in epilepsy (SUDEP) has been shown to occur through a combination of breathing and cardiac dysfunction after generalized convulsive seizures (GCS) in Epilepsy Monitoring Unit (EMU) monitored cases. Terminal apnea usually precedes terminal asystole and so premortem identification of respiratory dysfunction may have biomarker value. Both prolonged ictal central apnea and post-convulsive central apnea are potential biomarkers of SUDEP. A recent study has suggested that increased inter-ictal breathing variability is associated with more severe hypoxemia after GCS in persons with epilepsy. We hypothesized that there would be significant differences in breathing variability between SUDEP patients and matched controls.

Methods:

We used multi-modal electroencephalography (EEG) and cardiorespiratory recordings from 24 SUDEP patients (all with GCS] and age and gender matched low SUDEP risk phenotype controls who had epilepsy but did not suffer GCS. The database of the prospectively recruited cohort in the Center for SUDEP Research was utilized. Five minutes of breathing data were collected from thoraco-abdominal bands during non-rapid eye movement (NREM) sleep during the second night of EMU stay. Breathing data was processed via the Brainstorm suite and imported to MATLAB for further analysis. A custom MATLAB toolbox (BreathMetrics) was used to locate and mark each inhale onset. We then used an in-house tool to extract various biomarkers related to breathing variability. For each subject, we calculated mean, standard deviation, coefficient of variation, root mean square of successive differences (RMSSD), median of the interbreath intervals, the HF/LF ratio, and approximate entropy. To compare metrics between SUDEP patients and low-risk patients, we used the Wilcoxon rank sum test. This non-parametric test was chosen due to the distributions of breathing variability metrics, as both groups did not pass a Kolmogorov-Smirnov test for normality.

Results:

Of all the measured breathing biomarkers, coefficient of variation (CV) was significantly higher in the SUDEP group (P=0.0227) compared to the controls. Standard deviation and the HF/LF ratio tended to significance with p-values of 0.0592 and 0.0650 respectively. The rest of the investigated potential biomarkers, such as RMSS, mean. median and approximate entropy, were not found to be significantly different (P >0.05) between the groups.

Conclusions:

This study suggests significant difference in breathing variability between SUDEP patients and low-risk patients, suggesting that this may a potential premortem biomarker of SUDEP risk. Such premortem identification may help prioritize available preventive strategies and identify patients for preventive trials in the future. It provides additional evidence of abnormal breathing in some patients with intractable epilepsy and GCS, which may reflect impaired central breathing modulation and control due to longstanding seizure induced damage.

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