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SUPPLEMENT ARTICLE

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Biomarkers of seizure severity derived from wearable devices

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Abstract

Besides triggering alarms, wearable seizure detection devices record a variety of biosignals that represent biomarkers of seizure severity. There is a need for automated seizure characterization, to identify high-risk seizures. Wearable devices can automatically identify seizure types with the highest associated morbidity and mortality (generalized tonic-clonic seizures), quantify their duration and frequency, and provide data on postictal position and immobility, autonomic changes derived from electrocardiography/heart rate variability, electrodermal activity, respiration, and oxygen saturation. In this review, we summarize how these biosignals reflect seizure severity, and how they can be monitored in the ambulatory outpatient setting using wearable devices. Multimodal recording of these biosignals will provide valuable information for individual risk assessment, as well as insights into the mechanisms and prevention of sudden unexpected death in epilepsy.

KEYWORDS

automated analysis, biosignals, monitoring, risk assessment, seizure characterization

1 | INTRODUCTION

Several wearable, noninvasive seizure detection devices have been validated in large scale, phase 2-4 clinical trials.[1,2] The primary aim of these devices was to provide seizure alarms, in order to prevent morbidity and mortality associated with seizures, and to quantify seizure burden.[2] Wearable devices record biosignals for ultralong periods in the ambulatory outpatient setting.[2] Hence, besides alarms, they provide a unique opportunity for objective characterization of seizure severity, using the continuously recorded biomarkers. These data could help clinicians in better risk assessment, provide large datasets for improved understanding of morbidity and mortality associated with seizures, especially sudden unexpected death in epilepsy (SUDEP),[3] and help in selecting high-risk patients for clinical studies aimed at preventing SUDEP.[4]

Seizure severity can be characterized by the type, duration, frequency, and intensity of seizures, as well as by surrogate markers associated with SUDEP, such as postictal generalized electroencephalographic (EEG) suppression (PGES),[5]

postictal immobility,[6] and peri-ictal autonomic changes.[7] Biosignals associated with these features can be readily measured with noninvasive wearable devices. Although most of these biosignals are derived from the ictal and postictal periods, measurements in the preictal and even interictal periods might provide important information for algorithms aimed at prevention of injuries and SUDEP. In this paper, we review how seizure severity can be objectively characterized using biomarkers measurable with noninvasive wearable devices (Figure 1).

Key Points

- Wearable devices monitor various biosignals for ultralong periods in the ambulatory outpatient setting
- Biomarkers of seizure severity can be determined from automated analysis of biosignals
- These include type, frequency, and duration of the seizures, postictal position and immobility, and autonomic changes
- Wearable devices can provide valuable data for individual risk assessment, understanding of the pathophysiology, and prevention of SUDEP

2 | AUTOMATED CHARACTERIZATION OF SEIZURE TYPE AND FREQUENCY

The most severe seizure types are the generalized tonic-clonic seizures (GTCSs), including the focal to bilateral tonic-clonic seizures (formerly known as secondarily generalized tonic-clonic seizures), with the highest morbidity and mortality associated with seizures. Each year, 60% of the patients with GTCSs experience some accidental injury related to a GTCS and 25% experience at least one serious injury, causing incapacitation or requiring hospitalization or surgical intervention.[8] Patients with five or more GTCSs per year had an odds ratio for injuries 3.5 times higher than patients with only one seizure per year.[8] GTCS is the main risk factor of SUDEP. All video-EEG documented cases of SUDEP occurred after a GTCS.[9] Experiencing a GTCS during the preceding year was associated with a 27-fold increased risk of SUDEP, whereas no excess risk was seen in those with exclusively non-GTCS seizures.[10] The combination of not sharing a bedroom and having at least one GTCS per year had a 67-fold increased risk of SUDEP.[10] The SUDEP risk increases in association with increasing frequency of GTCS occurrence.[11]

Patients' and families' reports on GTCS occurrence suffer a number of important limitations, which further justify the development of GTCS-detection devices. First, in patients sleeping alone who are at highest risk for SUDEP, nocturnal GTCSs might remain unnoticed when none of the following inconstant features are observed: urination, tongue biting, and severe post-ictal myalgias. Second, many motor seizures are falsely regarded as GTCSs, including focal bilateral tonic seizures involving the supplementary motor area, the parietal cortex, or the insula. Third, fine analysis of GTCS has revealed different patterns,[12] one of which (type 1), with symmetric bilateral extension of upper limbs during the tonic phase of GTCS, was significantly associated with the occurrence of PGES, a finding confirmed by others.[13]

Phase 3 and 4 clinical validation studies showed that wearable devices detect GTCSs with a high sensitivity (90%-96%), based on accelerometry,[14,15] surface electromyography,[16] or multimodal biosignals.[17] Algorithms specific for GTCSs have been reported, accurately differentiating between GTCSs and convulsive psychogenic nonepileptic seizures.[18,19] However, a significant number of false alarms occur with these devices (0.2-0.7/d).[2] Therefore, the specificity of the detections needs further confirmation for accurate quantification of the GTCS burden. This can be achieved by user interaction (patients or caregivers cancelling false alarms) or by ulterior, visual assessment of the recorded biosignals by experts.[20,21] This hybrid method, consisting in offline, expert evaluation of biosignals recorded during automatically detected events, seems to be a reliable way of quantifying the burden of GTCSs.

Fortunately, only a minority of patients with frequent GTCSs will die of SUDEP.[22] The annual SUDEP risk of patients with ≥3 GTCSs/y, extrapolated from the combination of epidemiology and case-control studies, is estimated to be between 0.5 and 1.8/100 patient-years.[9] Hence, there is a need for recording further biosignals to stratify the more severe (potentially fatal) GTCSs.

3 | POSTICTAL GENERALIZED EEG SUPPRESSION

Postictal cerebral (and possibly brainstem) shutdown is a putative mechanism causing SUDEP.[3] PGES is a hallmark of this phenomenon, and it is defined as the immediate postictal (within 30 seconds) generalized absence of EEG activity >10 μV in amplitude, allowing for muscle, movement, breathing, and electrode artifacts.[5] Prolonged PGES may be an independent risk biomarker for SUDEP.[5] However, another study did not find significant differences in PGES between 17 SUDEP cases and the matched controls,[23] suggesting that additional factors are needed for development of SUDEP. Identification and measurement of PGES requires scalp EEG array, which is not yet feasible for ultralong recordings in the ambulatory outpatient setting. Nevertheless, it

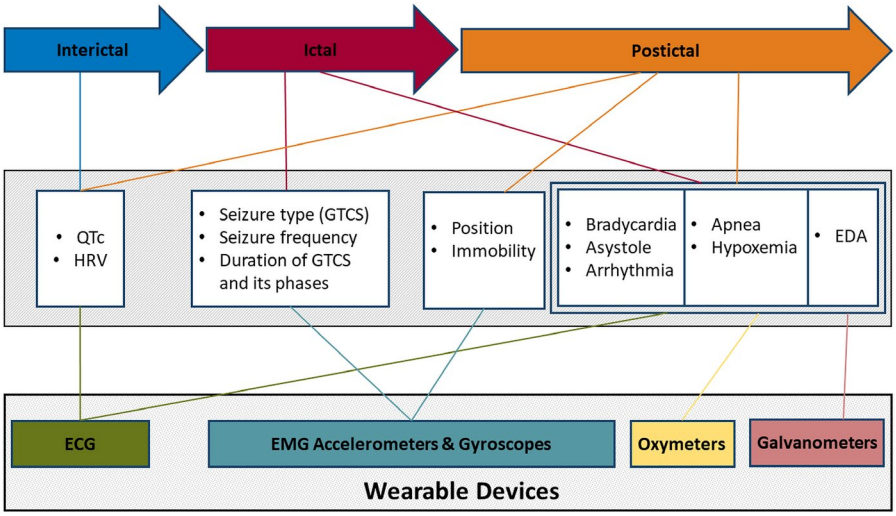

FIGURE 1 Biomarkers of seizure severity recorded with wearable devices. This infographic summarizes the biosignals reflecting seizure severity, measured with wearable devices, during the interictal, ictal, and postictal periods. ECG, electrocardiogram; EDA, electrodermal activity; EMG, electromyographic; GTCS, generalized tonic-clonic seizure; HRV, heart rate variability

can serve as a surrogate marker of seizure severity for investigating associations with biosignals recorded from wearable devices in explorative studies conducted in epilepsy monitoring units (EMUs).

4 | DURATION OF GTCS AND ITS PHASES

The duration of GTCS is also a measure of seizure severity. GTCSs longer than 5 minutes are diagnostic for convulsive status epilepticus, a potentially life-threatening condition.[24] Irreversible neuronal injury may occur after 30 minutes of convulsive seizure activity, as demonstrated by animal and human studies.[24]

GTCS duration can be automatically determined from biosignals recorded with wearable devices by surface electromyography (EMG)[21,25] and accelerometry.[26] Furthermore, EMG-based algorithms can measure duration of the tonic and of the clonic phases[21,25] and parameters derived from the bursts in the clonic phase (durations of the clonic bursts, the silent periods that separate them and the dynamics of their evolution–slope of their development in time).[27] These EMG parameters were significantly correlated with the duration of the PGES, and an EMG-based algorithm identified seizures with prolonged PGES with an accuracy of 85%.[27]

In a recent study, seizures with postictal tonic EMG activity (measured at the EEG electrodes) were associated with longer durations of PGES, as well as a greater severity of respiratory dysfunction, thus being another potential biomarker for SUDEP.[28] Tonic EMG activity following bilateral tonic-clonic seizures is associated with peri-ictal respiratory dysfunction and PGES.[28]

5 | POSTICTAL POSITION AND IMMOBILITY

Among the 16 monitored SUDEP cases in which the position of the patient could be assessed, 14 (87.5%) were in a prone position at the time of the postictal cardiorespiratory arrest.[9] A nationwide case-control population-based cohort study in Sweden showed that 82% of the SUDEP cases were in a prone position.[29] Postictal immobility is believed to play an important role in SUDEP due to the lack of normal arousal mechanisms that prevent the patient from reflex repositioning from a prone position after a GTCS, adding to the already present respiratory dysfunction. Several studies demonstrated that postictal immobility was associated with PGES and with postictal respiratory dysfunctions.[30–33]

Body position sensors are widely used in sleep medicine. Quantification of the mobility can easily be achieved using accelerometers, gyroscopes, EMG, or automated video analysis. Including these modalities into wearable epilepsy monitoring and seizure detection devices could provide valuable information on the postictal prone position and immobility. When present after a GTCS, these would indicate an increased risk of SUDEP.

6 | HEART RATE, ELECTROCARDIOGRAPHY, AND HEART RATE VARIABILITY

Ictal and postictal autonomic changes are well documented. Early postictal cardiorespiratory dysfunctions leading to apnea and cardiac arrest were observed in all monitored SUDEP cases.[9] Although ictal sinus tachycardia is more common,[34]

ictal and postictal bradycardia and asystole (occasionally followed by tachyarrhythmia) seem to be more severe conditions, being observed in patients with SUDEP and near SUDEP.[9,35–37]

Heart rate variability (HRV) measures in patients who later died of SUDEP suggested a significant decrease[38–41] or increase[35,39] in the parasympathetic activity (root mean square of successive differences) during the interictal period. The postictal decrease in parasympathetic activity and increase in sympathetic activity were correlated with PGES.[42–44] Postictal mean heart rate (a combination of sympathetic increase and parasympathetic decrease) was an independent predictor of PGES, suggesting that this could be a useful parameter for monitoring severity in the postictal period.[44] Using automated R-peak detection algorithms,[45] these HRV parameters can be recorded with wearable electrocardiographic (ECG) devices originally designed for seizure detection.[46,47] In addition, ECG monitoring in patients at risk can provide valuable information on cardiac repolarization anomalies (prolonged or shortened QTc interval), which have been suggested to contribute to the development of SUDEP.[35,48]

7 | ELECTRODERMAL ACTIVITY

Electrodermal activity depends on the state of the sweat glands, and it is an indicator of the sympathetic activity. Electrodermal activity (EDA) increases significantly upon seizure onset in 73% of GTCSs and persists for 13 minutes, extending into the postictal period.[26] In a case of SUDEP, an unusual, fast rising, and large postictal EDA was documented, significantly exceeding the values measured during nonfatal GTCSs.[49] The postictal increase in EDA was significantly correlated with PGES.[42,50] EDA can be recorded by wearable wristband seizure detection devices.[26,49,51] EDA provides insight into the autonomic changes during the ictal period of GTCS, when measuring HRV is unreliable due to artifacts. Wearable devices measuring EDA yield valuable information on seizure severity by quantifying the sympathetic changes in the ictal and postictal periods of GTCS.

8 | APNEA AND HYPOXEMIA

Ictal and postictal apnea are associated with severe hypoxemia (SpO2 < 75%).[52] Following the hyperventilation at the end of GTCS, early postictal apnea was documented in all monitored SUDEP case, with onset between 25 and 180 seconds postictally (median = 118 seconds).[9] Terminal apnea always preceded terminal asystole.[9] Hypoxemia was associated with PGES.[53–55] Wearable health devices used for monitoring of physiological changes during various physical activities include those measuring capillary oxygen saturation.[56] Respiration sensors, like the ones used in polysomnography recordings, seem to be less feasible for ultralong-term ambulatory use. However, respiration rate can be estimated from subtle respiration-induced body movements recorded from wristband accelerometer devices.[49] Although this respiration estimator is unreliable during strong movements (ie, ictal period), it works during low-movement postictal periods and it has documented postictal unusually irregular breathing pattern and respiratory cessation in a case of SUDEP.[49] Wearable devices monitoring oxygen saturation and respiration can provide essential information about severe, potentially life-threatening postictal changes.

9 | THE SEVERITY STUDY

Although many wearable biosignals have the potential to characterize the severity of GTCS, it appears desirable to determine a cost-effective solution that would offer maximal relevant information while minimizing redundant data and energy requirements for underlying biosensors. To address this issue, an ongoing multicenter EMU study has been launched (Swiss National Fund "Severity" study #320030_179240) that will capture EEG, arm EMG, arm and body movements, cardiorespiratory functions, and electrodermal activity during GTCS in 75 patients. The collected data shall help us design future wearable devices that will not only detect but also best characterize GTCS severity.

10 | LINKING GTCS SEVERITY TO SUDEP

The intuitive notion that GTCS severity predicts SUDEP has not yet been convincingly demonstrated. Clinically validated wearable devices that reliably detect GTCS may lower SUDEP risk, because a higher incidence of SUDEP was documented in patients with a lower grade of supervision.[57] Ways forward shall include large retrospective case-control studies of SUDEP patients who previously underwent a video-EEG to determine whether currently available biomarkers of GTCS severity are significant predictors. In parallel, data from wearables optimally designed to capture GTCS severity in ambulatory subjects should be correlated to other SUDEP surrogate markers, such as the SUDEP-7 inventory.[38] Eventually, large prospective studies will be needed to demonstrate the potential of wearable devices to provide clinically relevant prediction of SUDEP.

11 | CONCLUSIONS

Wearable devices using noninvasively recorded biosignals (Figure 1) for automated detection of GTCSs are already

available. There is a need for further development of these technologies to characterize seizure severity and to identify seizures with high risk of morbidity and mortality. Several modalities recorded by wearable devices can provide biomarkers of seizure severity, inferred from the type, frequency, and duration of the seizures, postictal position and immobility, autonomic changes derived from ECG/HRV, EDA, respiration, and oxygen saturation. Multimodal wearable devices monitoring these biosignals can potentially provide valuable data for individual risk assessment, as well as a better understanding of the pathophysiology and prevention of SUDEP.

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CONFLICT OF INTEREST

S.B. has served as a scientific consultant for Brain Sentinel. None of the other authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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