

# Wrist sensor reveals sympathetic hyperactivity and hypoventilation before probable SUDEP

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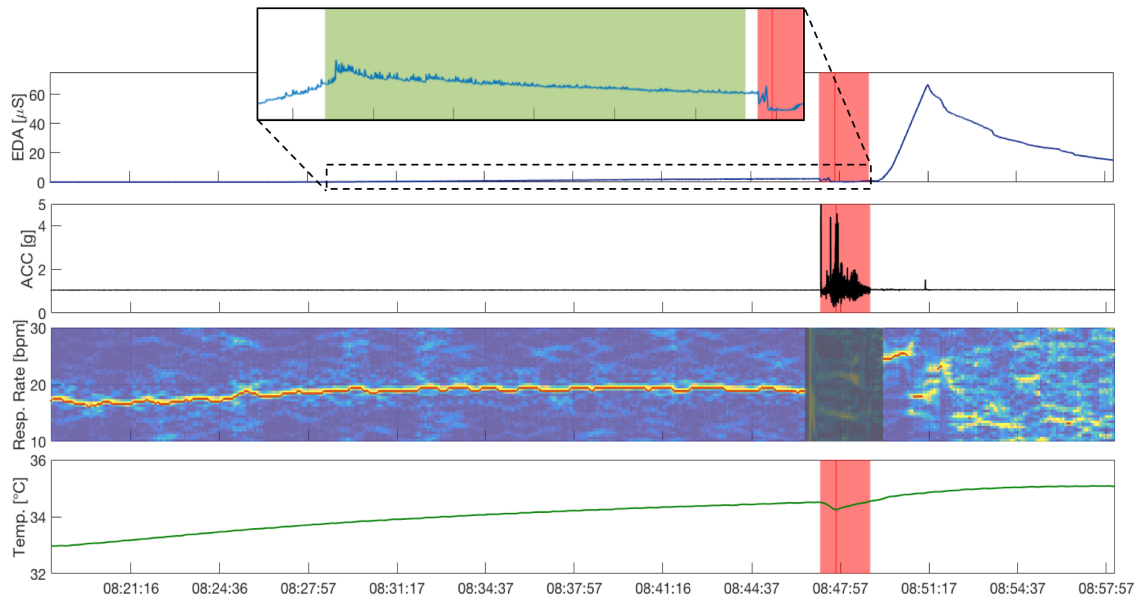
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## Case Report

We report a probable sudden unexpected death in epilepsy (SUDEP) in a 20-year old man wearing a smartwatch that recorded wrist motion via 3-axis accelerometer (ACC) and electrodermal activity (EDA). EDA reflects sympathetic activity without parasympathetic antagonism<sup>1</sup>. The smartwatch (Empatica's Embrace, with CE Medical clearance from the European Union for seizure detection) issued an alert, received by the caregiver at 08:50, indicating a probable convulsive seizure. An adult trained in CPR arrived at 09:05, found him pulseless, prone, face in pillow with mucus in his mouth, and commenced CPR for 15 minutes without recovery. The family declined autopsy.

The patient was diagnosed at age 5 with epilepsy. He had 3-4 generalized tonic-clonic seizures (GTCS) a year, typically during mornings before awakening. More than six antiepileptic medications failed to control seizures. Routine and prolonged EEGs were normal. At the time of death, he was taking lamotrigine twice daily and extended-release oxcarbazepine nightly.



**Figure 1:** From top to bottom, continuous data from the Embrace smartwatch worn on the patient’s wrist, measured before, during, and ten minutes after the terminal seizure: (a) Electrodermal activity (EDA) shows the unusually large EDR; a zoomed subset of exponentially weighted moving averaged EDA shows rapid EDR’s indicating that non-REM sleep was likely present pre-ictal; (b) Physical movement reflected in the magnitude acceleration derived from 3-axis accelerometers (ACC), shows almost no movement after convulsions, except for a very brief spike occurring after the EDA has risen almost to its peak; (c) Estimate of respiration rate derived from ACC, with red traces indicating confident estimation and the grayed region indicating interference from motion. A respiration rhythm seems to continue briefly after the EDA has peaked; (d) Temperature on the surface of the skin. The red highlighted region demarks the time of convulsions with potential motion artifacts for the other channels. The thin vertical red line is when the Embrace watch detected the seizure.

Figure 1 shows the smartwatch data. The red vertical line marks the time of automated seizure detection. Figure 1(a) shows an unusual fast-rising, up to  $1.5\mu\text{S}/\text{sec}$ , and large,  $66.7\mu\text{S}$ , post-ictal electrodermal response (EDR). An inset utilizing exponentially-weighted moving-averages magnifies the pre-ictal period, revealing EDRs typical within non-REM sleep. Figure 1(b) shows the ACC data, indicating convulsive movements lasting 94 seconds, with little or no movement following. Figure 1(c) shows the estimated respiration rate using a validated method<sup>2</sup> that extracts subtle respiration-induced body movements from wrist-ACC in a relatively motionless person. The thin red traces indicate tracking of 18.9 breaths/min before the convulsions, rising to 24.6 breaths/min, and reaching 28.5 breaths/min with the large EDR. After 08:52, despite no detected position-changing movements, a steady respiration signal ceases to be detected. While this respiration estimator does not work with strong movements (grayed region, Fig. 1(c)), it should work during low-movement postictal periods. The inability to identify any regular breathing pattern following 08:52 suggests either an unusually irregular breathing pattern or respiratory cessation. Fig. 1(d) shows the skin surface temperature.

## Discussion

This case obtained continuous EDA 24/7, finding an unusually large ( $66.7\mu\text{S}$ ) EDR preceding death in a probable SUDEP. EDR's during non-terminal GTCS in drug-resistant patients (ages 3-20) showed peaks from  $3.9$  to  $24.3\mu\text{S}$ <sup>4</sup>, which are within ranges occurring with vigorous sports or natural stressors<sup>1</sup>. While this EDR was highly elevated, it is unknown whether EDR changes of this magnitude are a specific SUDEP signature or could occur with other forms of sudden death.

EDRs can be elicited by electrical stimulation of the amygdala, hippocampus, and cingulate gyrus<sup>3</sup>. The physiological basis for post-ictal EDR elevation is not fully understood but may reflect hypothalamic or brainstem centers released from cortical inhibition.

The extremely elevated peri-ictal EDR at the time of death in this case supports autonomic dysfunction and severe post-ictal cerebral dysfunction as SUDEP mechanisms. Sympathetic hyperactivity following GTCS and parasympathetic hyperactivity in animal models of SUDEP suggest that pathological co-activation of opposing systems may contribute to SUDEP<sup>6</sup>. Prolonged post-ictal generalized EEG suppression (PGES; scalp EEG channels  $<10\mu\text{V}$ ), a putative biomarker for SUDEP risk, occurred in 11/11 EEG-monitored SUDEP's immediately after a GTCS<sup>5</sup> and prolonged generalized-EEG suppression was observed before 3/3 SUDEPS without evidence of a seizure<sup>6</sup>. In non-SUDEPS, EDR magnitude accompanying a GTCS correlates with PGES duration; furthermore, all GTCS with EDR amplitude greater  $\geq 15\mu\text{S}$  exhibited prolonged PGES  $> 20\text{s}$ <sup>4</sup>. Thus, finding an unusually large EDR with this terminal GTCS is consistent with profound sympathetic hyperactivity and prolonged PGES before death.

**These data reveal a critical window of postictal autonomic dysregulation**, probably relevant to SUDEP pathophysiology, that is detectable with a wristband sensor. While medical support, even within two minutes of a seizure, does not always prevent SUDEP, evidence supports that SUDEP is less likely to occur when somebody can rapidly stimulate or reposition<sup>7</sup>. Frequent GTCS and long-duration of epilepsy placed this patient at very high risk for SUDEP<sup>7</sup>. Despite having seen six neurologists, the family was never told about the possibility of SUDEP; they expected him to recover from all of his seizures.

**Patients and families should be informed about SUDEP risk and strategies to reduce risk (e.g., medication adherence, sleep hygiene). They should be told that SUDEP can happen in the minutes following a seizure, and if somebody is there to immediately stimulate, reposition, or provide first aid, the patient may have a better chance of survival.** For high risk patients, seizure detection and alert monitors may bring help. As this case illustrates, their utility in preventing SUDEP is predicated on **a helper arriving quickly and providing appropriate aid.**

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Picard is co-founder of Empatica and is a shareholder in Empatica. She serves as (unpaid, part-time) chief scientist and chairman of Empatica's board of directors. She is co-inventor on an MIT-owned patent that relates to this work. She has other disclosures unrelated to this work that can be provided if needed.

Migliorini, Caborni, Regalia, and Onorati are employees of Empatica and hold stock options in Empatica. They have no other disclosures.

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