A novel blood oximeter for determining and monitoring patients at risk for SUDEP
Kelly Clancy

Executive summary

Sudden Unexpected Death in Epilepsy (SUDEP) is a devastating risk for seizure sufferers, and the leading cause of death in patients with refractory epilepsy. While there is no single underlying cause in all SUDEP cases, several threads have emerged that merit further investigation. Of particular interest is seizure-related hypoxia. While SUDEP events usually go unwitnessed, the majority of documented cases involve a terminal seizure with concomitant respiratory issues (MD et al., 2013). SUDEP most often occurs during sleep, and it has been reported that victims are found in the prone position 70–80% of the time (Kloster & Engelskjon, 1999). These clues strongly implicate breathing problems during sleep as a primary cause in a majority of SUDEP cases, and my proposal is to develop an at-home functional monitor to determine apnea risk in epileptic patients. I propose to monitor patient's nocturnal blood oxygenation levels using a cheap, non-invasive LED-based sensor to detect apnea and seizure-related hypoxia. By functionally identifying patients most likely to be at-risk for SUDEP, we can design more effective clinical studies to identify further molecular or functional markers of SUDEP risk. First I will outline the evidence behind the hypoxia model of SUDEP, discuss the proposed monitor, then suggest its use for identifying patients at high-risk of SUDEP to enroll in further validating studies.

Background

It's increasingly believed that cardio-pulmonary issues underlie a majority of SUDEP cases. In a retrospective study of observed SUDEP cases caught while patients were in-hospital, researchers found that patient breathing ceased before heart failure in all 16 observed events (Rivlin et al., 2013). There is no doubt that SUDEP involves a complex network of effects, but hypoxia may underlie many of the observed abnormalities in SUDEP patients (Giaccia, Simon, & Johnson, 2004). Hypoxia has a profound effect on tissues, from altering the physiology of certain ion channels in the heart and lungs to long-term changes in genetic transcription and vascular remodeling (Kemp & Peers, 2007; Ling et al., 2001; Nei, 2009; Richerson, 2010). Up to 40% of SUDEP cases present cardiac fibrosis in autopsy, which may be a result of chronic intermittent hypoxia (Ling et al., 2001; P-Codrea, Dalager-Pedersen, Baandrup, Dam, & Vesterby-Charles, 2005). Damage was most commonly found in the subendocardial myocardium, which is known to be the heart structure most vulnerable to ischemic damage. SUDEP patients also tend to have had post-ictal cerebral depression, which is also strongly linked with hypoxia (Majkowski, 2004; Takano et al., 2007).

The link between epilepsy and breathing problems is not well understood. In some patients, epileptic activity may affect brain stem circuits controlling breathing. There may be a more fundamental physiological link underlying seizures and breathing: blood acidification, as happens in hypoxic conditions, is anti-convulsive. Thus, the hypoxic response in seizures may not simply be a side effect of seizure, but an evolved mechanism, or one learned by neural circuits, to shut down epileptic activity during otherwise intractable seizures. Regardless of underlying cause, major disruptions in

breathing is a common feature shared in many observed SUDEP cases (MD et al., 2013). Breathing complications have been found to be particularly common during certain phases of sleep, which might explain why so many SUDEP cases happen at night (Hajek & Buchanan, 2016). Epileptic progression in patients could cause a gradual degradation of the neural circuits controlling breathing, as breathing circuits are plastic throughout life, and strongly shaped by hypoxia (So, 2008).

Hypoxia also results in remodeling of the heart. Ischemia tends to be most damaging to the subendocardial myocardium, resulting in the kind of fibrosis often seen in SUDEP victims. Apnea is known to lead to general cardiovascular problems, which may increase patient susceptibility to sudden death. Ischemia in heart tissue results in cellular death, loss of electrical activity, and eletrophysiological and mechanical changes, including reduced heart rate variability (HRV). Low HRV is predictive of increased mortality in heart disease, arrhythmias and sudden cardiac death, and is also found in people with poorly controlled epilepsy, a known risk factor for SUDEP. SUDEP has been associated with a variety of genes implicated in cardiac arrhythmias, as well as several anti-convulsive drugs that make patients prone to arrhythmias (Klassen et al., 2013). However, cardiac abnormalities might not be immediately obvious from patient's cardiograms, being either too subtle even for experts to pick out, or more prominent under non-laboratory conditions. A careful study of these aspects of epilepsy may give important insight to the physiology underlying SUDEP. I therefore propose that patients found to be at-risk for SUDEP using an inexpensive at-home oximeter be enrolled in further studies, with an emphasis on cardiac monitoring, to better understand the relationship between epilepsy and the heart. Cardiac fibrosis may also result in detectible levels of cardiac-remodeling molecules in the blood, and I here suggest that the proposed studies also include blood tests for potential plasma markers of cardiac insult.

Interestingly, SUDEP is more prevalent among males, and males tend to be more sensitive to hypoxia, suffering worse outcomes. This has been found true both in clinical studies and in studies involving multiple animal models (Hill & Fitch, 2012; Mayoral, Omar, & Penn, 2009; Mirza, 2015; Pérez-Crespo et al., 2005). This sexual dimorphism may be due, in part, to the gene G6PD, an X-linked gene related to oxidative stress, which has been implicated in hypoxia-induced damage (Chettimada et al., 2014; Gao, Mejías, Echevarría, & López-Barneo, 2004). Therefore, markers of oxidative stress (and remediation with antioxidants) may play an important role in detecting and preventing SUDEP. Reactive oxygen species generated in hypoxic conditions were found to be partly responsible for apnea-induced changes in the oxygen-sensing carotid body of the heart (Giaccia et al., 2004; Kemp & Peers, 2007; Ling et al., 2001; Lopez-Barneo, 2003; Richerson, 2010). In a rodent model, sleep apnea-induced plasticity of the breathing circuit was normalized with antioxidant treatment, which may similarly show a protective effect in high SUDEP risk patients. Studies with this in mind might help lead to simple interventions for patients deemed at risk, and further refine our understanding of functional and molecular biomarkers of SUDEP.

Determining SUDEP risk may be best served by a functional test until we understand more about it. SUDEP has been associated with a variety of genes implicated in cardiac

arrhythmias, as well as several anti-convulsive drugs that also make patients prone to arrhythmias (Klassen et al., 2013; Omichi, 2014; So, 2008). However, genes do not deterministically dictate SUDEP risk. Given that genetic tests are costly, and only suggestive of susceptibility, a functional measurement of apnea would likely give stronger evidence. There are several other known risk factors that might help identify patients worth testing further: patients with refractory epilepsy, history of poor compliance with medication, family history of cardiac arrythmia, and possibly prenatal nicotine exposure (a known risk for the related disorder, Sudden Infant Death Syndrome (SIDS), as nicotine exposure alters receptor expression in oxygen-sensing neural circuits). While these background factors will be useful for discerning study candidates, the "loaded gun" in SUDEP appears to be sleep-related hypoxia, and I propose a simple, inexpensive and non-invasive device to provide continuous monitoring of sleep-apnea in patients and thereby the functional identification of those most at risk of SUDEP. Rather than require patients stay at the hospital for days or weeks of tests and sleep studies, an at-home monitor could provide low-cost, low-hassle data on the condition that appears to be most strongly linked to SUDEP.

Proposed tests, and suggested studies for hypothesis validation

Blood oxygen level can be monitored by passing red light through tissue and measuring the spectral absorption of circulating hemoglobin, as it is affected by the relative abundance of absorbed oxygen. With new ultrathin LEDs and sensors, such a device can be as non-intrusive as wearing a ring on one's finger. Furthermore, it could interface with apps on smartphone devices for seamless data collection and automated analysis. Epilepsy patients may be asked to wear the device at night for days or weeks to determine their risk for sleep apnea. This device could double both as measurement and intervention device, and be part of the long-term monitoring plan for patients deemed to be at-risk for SUDEP. The device could be set up to alert a patient's caretaker if the patient's blood oxygen levels dip dangerously low while patient is wearing the device.

Arrhythmias, heart rate variability and other cardiac abnormalities are thought to be linked to SUDEP, but such issues can be subtle even for specialists to pick out. I suggest using machine learning techniques to mine large data sets of ECGs and EEGs of past, known SUDEP cases, in case functional differences lend further credence to the proposed hypotheses. This would also serve to improve the design of a proposed monitoring device. Many SUDEP patients, as they tend to be patients with intractable epilepsy, already have extensive EEG and ECG monitoring on file. We can look at a range of factors thought to be implicated in cardiac remodeling (high frequency heat rate variability, hypertension, EEG-heart period correlations) to discover whether any features of the cardiograms cluster out in known SUDEP or high SUDEP risk patients, and whether these features might be continuously studied with a long-term monitoring devices such as the one proposed.

Once identified, at-risk patients could be enrolled in more extensive studies to understand the underlying physiological cascade resulting in SUDEP. Of particular interest in better

understanding the cardiac component would be a panel of cardiac tests, particularly a stress cardiogram, whereby patients are asked to exercise lightly during measurement. This could help uncover whether at-risk patients have abnormal cardiac output in hypoxic conditions. Hypoxia-related changes in the ion channels of the heart may only be obvious in certain physiological states. Hypoxia related plasticity also affects vasodilation, blood pressure, cardiogram shape, heart rate variability, and long-term facilitation (LTF) of the respiratory motor output. LTF is more robust in sleep apnea patients, and stands to reason would also be stronger in patients at risk for SUDEP, who may similarly undergo chronic intermittent hypoxia at night. It should be possible to cluster out patients at risk for SUDEP along a manifold of these various features, and I would hope to be able to translate these findings to a simple, automated risk detection algorithm that could be incorporated in the chronic monitoring device.

Identifying a functionally defined group of patients at risk for SUDEP would help target patients for inclusion in clinical studies of other biomarkers, whether molecular or genetic. In particular, many SUDEP patients are found to have cardiac fibrosis in post-mortem studies. While biopsy is currently the only way to be certain of cardiac fibrosis, studies have begun to show that plasma concentrations of a number of cardiac remodeling biomarkers are increased in heart failure patients. It's possible that epilepsy patients suffering cardiac damage related to sleep apnea might cluster into a similar group. Possible plasma markers worth future testing would include tissue inhibitor of metalloproteinase 1 (TIMP1), tenascin C (TNC), galectin 3 (LGALS3), osteopontin (OPN), and brain natriuretic peptide (BNP). These were found to be significantly elevated in patients near heart failure compared to healthy controls (Mittling et al., 2014; Pitt & Zannad, 2012). Also, markers of oxidative stress may also prove interesting to include in such studies, as they might give insight into the state of the patient's progression along the disease spectrum. As imaging techniques improve, no doubt it will eventually be possible to image cardiac fibroids *in vivo*, but for starters, patients who fit the profile of high SUDEP risk might be tested for these cardiac remodeling markers in order to gain insight into the complex relationship between seizures and heart problems.

Feasibility statement

Red-light sensors are standard in blood oxygenation monitoring, and with new miniaturized LEDs and sensors, such monitors can be made easily and cheaply, while remaining extremely low profile and with little hassle to the patient. While there are already at-home oxygenation monitors, they are clunky and not suited for wearing continuously during sleep. The proposed monitor could be reduced to the size of a ring, and worn around either a finger or toe at night. It could be interfaced with smartphone apps or other measurement devices (e.g. Fitbit, JawBone) to stream and save data while the patient is sleeping and correlate it with ongoing patient activity. Patients who show evidence of sleep apnea should be considered high-SUDEP risk, and should be enrolled in further studies (perhaps including the proposed studies of stress-ECG and plasma-markers of cardiac remodeling). Such a device would be generally useful to medicine for monitoring sleep apnea patients, neonates at risk for SIDS, and other conditions.

To improve the design of such a monitoring device, I would propose a retrospective study to test the prevailing hypotheses that SUDEP is fundamentally cardio-pulmonary related, and to determine whether risk might be automatically inferred from ECG data. As SUDEP patients tend to have intractable epilepsy, hospitals are more likely to have extensive EEG and ECG monitoring already on file. To mine these past datasets, I propose to use open-source deep-learning techniques (such as Google's TensorFlow) to identify physiological features that stand out in the data of SUDEP patients. I have collaborators with neurologists at several university hospitals who would participate in this project by providing access to a large database of EEG and ECG recordings from both SUDEP and control patients. I have previously used machine-learning techniques to automatically detect EEG states, sort neural spikes in electrophysiology data, and automatically detect functional networks in imaged brain activity. We could validate these algorithms with data from known heart-failure patients versus control patients, and determine whether SUDEP patients or suspected high-risk SUDEP patients cluster towards the group with known cardiac insults. By coming up with methods of analyzing functional data in automated, non-subjective way, we might hope to find a testable method for automatically discerning high SUDEP risk patients.

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