

## **A novel, prognostic EEG signal during cardiac arrest with therapeutic potential**

Cardiac arrest (CA) afflicts >500,000 individuals in the USA annually with survival rates of 5-17% after cardiopulmonary resuscitation (CPR). Among survivors, ~80-90% emerge in a coma with severe neurological damage as the primary cause of morbidity. Neurologic outcome after CPR is poor due to devastating hypoxic-ischemic brain damage. While research on focal ischemia (i.e. the common “stroke”) has progressed, including clot-busting agents, little to no progress has been made towards improving outcome after global ischemia, such as with CA. Thus, there is a large unmet need to develop treatments for post-CA care.

Our translational laboratory includes a rodent model of asphyxial CA and cardiopulmonary resuscitation (CPR) that closely mimics the hospital setting. During our CA+CPR experiments, we conduct multimodal brain monitoring: electroencephalogram (EEG), blood pressure (BP) and electrocardiogram (ECG). Upon resuscitation, rodents enter a comatose state similar to humans.

While monitoring EEG activity during CA and CPR, we have noticed an intriguing phenomenon. As expected, wide-band EEG activity (i.e. filtered at 1-150Hz), highly active in living animals, reaches electrocerebral silence (i.e., “flat-line”) within 30-50 seconds of asphyxia, signifying a loss of the brain’s electrical activity (see Fig. 1a, an EEG from a single epidural electrode implanted in the left frontal lobe of a representative rat entering CA after initiation of asphyxia at t=0). Following the onset of 8 minutes of asphyxia, the BP steadily drops, eventually reaching the threshold for CA, defined by our lab as systolic blood pressure (SBP) < 30mmHg, at t~2.5 min. **During this asphyxia period, when**

**filtering out all EEG signals >1Hz signals, a very noticeable ultra-slow wave EEG signal emerges, lasting for ~1 min (see Fig 1b).** We then discovered that the onset of this wave correlates strongly (Fig 2) with neurological recovery 48 hours after successful CPR, as measured by a neurologic deficit scale (NDS) ranging from 0 (dead) to 70 (normal). **This ultra-slow wave EEG and its onset appears to be the earliest prognostic marker of CA that we know of.** Essentially, within 2-3 minutes after the onset of a CA-inducing insult, we can predict the neurological outcome of a rat, assuming all resuscitative efforts and post-CA care are the same for all animals.

*To add translational value that our rodent data is relevant to humans, we found a similar ultra-slow wave EEG in 2 patients hospitalized at the UC Irvine Medical Center’s Neuro-ICU who suffered CA while under EEG surveillance.* While we are fascinated by the prognostic value of this slow wave EEG in our rodent model of CA, we are far more interested in investigating this phenomenon as a **potential therapeutic measure to modify outcome during and after CA since this ultra-slow wave appears to be an endogenous neuroprotective wave.** To undertake this long-term goal, *we first have to understand the origin and mechanisms of this ultra-slow wave.*

We hypothesize that the mechanism underlying the ultra-slow wave is cortical spreading depression (CSD), a massive depolarization of neurons known to occur in humans that can propagate slowly to adjacent tissue, resulting in a wave-like phenomenon. CSD is also closely linked to hypoxic events, termed “anoxic depolarization” or “hypoxia-induced spreading depression”. **To our knowledge, no studies have been conducted to directly evaluate the role of CSD during CA.** If our hypothesis holds, this would suggest that CSD occurs during CA and serves not only as the earliest prognostic marker for outcome, but more importantly, may have potential therapeutic implications in future CA studies.

**Aim 1a: Measure 2 hallmark features of CSD (DC potential and extracellular K<sup>+</sup> concentration) during our CA experiments**

**Aim 1b: Trigger CSD earlier *in vivo* during CA and assess for possible neuroprotection.**

**Aim 1c: Block CSD pharmacologically *in vivo* during CA and assess for worse neurological recovery.**

This proposed one-year pilot study will help elucidate the molecular mechanisms behind the ultra-slow EEG wave that we detect during CA with the wave onset time strongly correlating with subsequent neurological recovery after CPR. After this pilot study, we hope to submit an Early-Stage Investigator R01 grant proposal to test for 1) detection of the ultra-slow EEG wave in humans at-risk of CA and correlation with neurological outcome. 2) a closed loop system to trigger CSD earlier during CA by using established outpatient techniques known to trigger CSD that are safe and already used in humans (e.g. transcranial magnetic stimulation) to provide neuroprotection and improved outcome after CA+CPR.

Fig 1

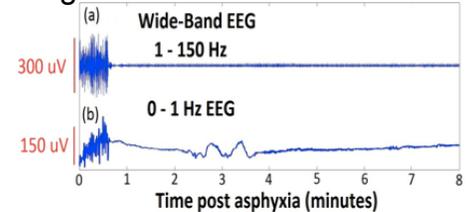


Fig 2

