The Race is On:

Early Determination of Neuroprognosis after Cardiac Arrest

Running title: Rittenberger et al.; Early Neuroprognosis after Cardiac Arrest

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It is hard to believe that the first descriptions of “brain waves”, later called electroencephalogram (EEG), are older than EKG: both are over one hundred years old. Since then, significant progress has been made in understanding heart and brain functions using novel invasive and non-invasive technologies that allow detailed mapping of structural and functional connections. However, in extreme situations like cardiac arrest, we still rely – at least initially – on these aforementioned “ancient” technologies for a quick diagnosis and guidance for treatment.

EEG in the setting of hypothermia and anoxia has been studied in humans since the 1950s. Specific patterns after cardiac arrest have been associated with prognosis since the 1960s. In early 2000s, therapeutic hypothermia demonstrated improved neurologic outcomes in cardiac arrest patients and quickly became adopted in post-arrest care. Simultaneously, the use of continuous EEG monitoring in critically ill patients increased, which led to the recognition of subclinical seizures occurring in patients after cardiac arrest. As a result of these changes, greater amounts of EEG data were being collected, and the significance of specific patterns is being explored.1

In this issue of Circulation, Oh et al. present data from subjects successfully resuscitated from cardiac arrest receiving hypothermia therapy to 33°C for 24 hours.2 A limited montage amplitude EEG (aEEG) was applied in the Emergency Department at 2-3 hours after return of spontaneous circulation, much faster than in prior cohorts.3,4 Subjects with seizures were treated aggressively and received continuous EEG monitoring thereafter.

Of the 130 subjects in the study, 55 (42%) exhibited a good neurologic outcome at 6 months following resuscitation. All of these had normal EEG within 36 hours of resuscitation. One subject with status epilepticus and one subject with a burst suppression pattern exhibited good outcomes.
The authors suggest that aEEG may be an early method to determine good outcome. They argue that if validated, determination of neurologic outcome could be shortened to 36 hours following resuscitation rather than the greater than 72 hours presently recommended in the Guidelines. These findings are important as they illustrate the need for aggressive cerebral resuscitation in the comatose patient resuscitated from cardiac arrest. Most of post-arrest care focuses on amelioration of underlying pathologies (e.g. coronary artery disease), and prevention of secondary injury (hypotension, hypoxemia). This study provides an additional method to measure the effect of neurocritical care in this population.

There are several strengths that bear mention. First, the authors used one EEG reviewer, blinded to the outcomes, and a standardized scale to interpret aEEG tracings. Subjects received an aggressive and standardized post-arrest care protocol including temperature management to 33°C. A unique aspect of their practice environment is that withdrawal of life sustaining therapies due to poor neurologic function did not occur in any subject, making it markedly less common than seen in the United States, where rapid withdrawal of care from neurologic injury is the norm.6

As with all studies, there are several limitations. The EEG definitions used in this study differ from those recommended by the American Clinical Neurophysiology Society7 with established good inter-rater reliability. Definitions used in this study have not been used extensively beyond this research group.8 Importantly, generalized periodic discharges were considered equivalent to status epilepticus although these are generally considered less severe on the ictal scale.9

Neuromuscular blockade was used in all subjects, making it difficult to determine if any subjects experienced myoclonic status epilepticus rather than a simple burst suppression pattern.
The former has worse outcomes, while the latter is commonly encountered in this cohort receiving anesthetic agents and does not portend as poor an outcome.\textsuperscript{10} Similar to prior work, there are subjects with status epilepticus and burst suppression who enjoy a good outcome and warrant aggressive care.

It is important to note that several subjects with poor outcome achieved a normal EEG trace within 36 hours of resuscitation. Similar to other neuroprognostic tools, aEEG should not be used in isolation.\textsuperscript{11,12}

When the aEEG recording is combined with neurologic assessment, further refinement of prognostic outcome is possible, strengthening the utility of this assessment.\textsuperscript{13} Combining the aEEG data with established biomarkers of neurologic injury\textsuperscript{14} may further improve its prognostication value.

Ischemic insults including cardiac arrest followed by reperfusion result in hemodynamic, neurobehavioral and metabolic impairment, initially called «post-resuscitation disease» by resuscitation pioneer Vladimir Negovsky.\textsuperscript{15} The complex pathophysiological mechanisms operating after cardiac arrest were approximated to «sepsis-like syndrome»,\textsuperscript{16} later defined as «post-cardiac arrest syndrome».\textsuperscript{17} Illness severity following resuscitation from cardiac arrest is heterogenous and highly associated with outcome.\textsuperscript{18,19} While the authors do not have data on the initial cardiac and pulmonary dysfunction, other markers suggest this cohort had significant organ system dysfunction. The rate of death from multiple organ failure (68\%) and death from intractable shock (25\%) is higher than in other studies.\textsuperscript{19,20} Similarly, time to application of aEEG was longer in the poor outcome cohort, suggesting that additional resuscitation measures may have been required in this cohort. Layering both neurologic along with multi-organ dysfunction assessments with the dynamic EEG findings should be a goal for future research.
The results of this work potentially provide us with a new short-term outcome measure. EEG recordings permit evaluation of brain function in real time. While it only provides insight to a small portion of the cerebral cortex, injury in the post-anoxic patient is global and frequently affects the cortex. Unfortunately, the status of subcortical structures remains obscured to this technique. Noninvasive real-time measurements that evaluate cerebral function remain a goal for the resuscitation community. Given the rate of seizures in comatose patients, it should be a goal for any clinician caring for these patients. Invasive CNS monitoring can be used in some patients, but given the high burden of coronary disease and the need for angiography, may not be optimal for many patients resuscitated from cardiac arrest. Strategies incorporating aEEG may permit future studies to compare therapeutic interventions in this population.

It is also important to note that seizures occurred frequently despite two powerful therapeutic strategies used in this study: midazolam infusion and hypothermia. The incidence of seizures in post-arrest patients is high (>20-30%) despite these measures. A recent report showed no difference in long-term outcome from cardiac arrest in patients treated with hypothermia at 33 vs. 36 °C. However, a recent study showed lower incidence of seizures when these patients were cooled to 32 vs. 34 °C. It is possible that 36 °C in fact represents an ultra-mild hypothermia, as suggested by recent findings documenting up-regulation of neuroprotective mechanisms in neuronal cell culture. It could be argued that “every degree matters” at both upper and lower limits of currently endorsed target temperature management.

It should also be noted that this study enrolled all adult resuscitated cardiac arrest victims. The etiologies of cardiac arrest could have been different. There are known differences in outcomes from asphyxial vs. primary cardiac arrest. As the underpinning pathophysiologic mechanisms differ, we can hypothesize that the recovery patterns (including EEG) could also
differ.

Oh et al. provide us a new tool to evaluate the ongoing cerebral resuscitation in the post-arrest patient. It may have promise in other critically ill patients demonstrating coma as well. Like all prognostic tools, it should not be used in isolation and will yield best results when considered as part of the patient’s overall clinical condition.

Considering that EEG was invented in the 19th century, what is its future at the dawn of the 21st century? While this study focused on the value of EEG as a prognostication tool, at the same time it may have identified plausible therapeutic targets. We can easily envision that aEEG will become implemented in a routine care of post-arrest patients in the coming years. More sophisticated neurophysiologic monitoring methods may be tested. On the other hand, continuous EEG may become even more simplified and incorporated into an algorithm that would allow to guide therapy. A precedent could be seen in a processed EEG in anesthesia care where a single number is being considered as a measure of “anesthetic depth”. It is certain that we know more about “the rest of the body” rather than the brain after cardiac arrest. It is time to explore what the brain tells us, and see if we can fix it. To quote another resuscitation science giant, Peter Safar, we need to strive to save “hearts and brains too good to die”.

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**References:**


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