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EEG Reactivity in Coma After Cardiac Arrest: Is it Enough to Wake Up the Dead?

EEG Reactivity as Predictor of Neurological Outcome in Postanoxic Coma: A Multicenter Prospective Cohort Study

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Objective: Outcome prediction in patients after cardiac arrest (CA) is challenging. Electroencephalogram reactivity (EEG-R) might be a reliable predictor. We aimed to determine the prognostic value of EEG-R using a standardized assessment. Methods: In a prospective cohort study, a strictly defined EEG-R assessment protocol was executed twice a day in adult patients after CA. The EEG-R was classified as "present" or "absent" by 3 EEG readers, blinded for patient characteristics. Uncertain reactivity was classified as "present." Primary outcome was best Cerebral Performance Category (CPC) in 6 months after CA, dichotomized as "good" (CPC 1-2) or "poor" (CPC 3-5). The EEG-R was considered reliable for predicting poor outcome if specificity was $\geq$95%. For good outcome prediction, a specificity of $\geq$80% was used. Added value of EEG-R was the increase in specificity when combined with EEG background, neurological examination, and somatosensory evoked potentials (SSEP). Results: Of 160 patients enrolled, 149 were available for analyses. The absence of EEG-R for poor outcome prediction had specificity of 82% and sensitivity of 73%. For good outcome prediction, specificity was 73% and sensitivity was 82%. Specificity for poor outcome prediction increased from 98% to 99% when EEG-R was added to a multimodal model. For good outcome prediction, specificity increased from 70% to 89%. Interpretation: The EEG-R testing in itself is not sufficiently reliable for outcome prediction in patients after CA. For poor outcome prediction, it has no substantial added value to EEG background, neurological examination, and SSEP. For prediction of good outcome, EEG-R seems to have added value. This article is protected by copyright. All rights reserved.

Commentary

A variety of tools have been developed to aid in the prognosis of comatose patients after cardiac arrest (CA), particularly since the advent of targeted temperature management, which has rendered clinical examination less predictive than in the past. Among the most promising and widely used is electroencephalogram reactivity, defined as change in electroencephalogram (EEG) frequency or amplitude in response to an external stimulus; the absence of reactivity 72 hours after CA as a poor prognostic marker is included in the American Heart Association Guidelines for post-CA care.[1] However, there are no definite standards for delivering or assessing EEG reactivity, there have been concerns for substantial interrater disagreement,[2] and there are marked variations in practice across institutions.[3]

A rigorous multicenter assessment of this important diagnostic tool is therefore welcomed, conducted by this experienced Dutch group that prospectively studied 160 patients from 3 Dutch centers. Their protocol entailed increasingly noxious stimuli consisting of clapping/calling name, passive eye opening, nasal tickle, and sternal rub, each performed for 5 seconds and applied 3 times in a row. Stimuli were discontinued if the patient showed any sign of arousal. This was done twice a day for the duration of EEG monitoring. Electroencephalogram reactivity was then evaluated by 3 blinded readers to determine whether stimuli resulted in a change in EEG amplitude or frequency and whether they felt certain or uncertain. If there was disagreement, a majority vote was used. One EEG assessment per patient was used for analysis, either the first reactive or, if thought to be unreactive, the one obtained with the lowest dose of sedation, with selection by majority vote of 3 raters.

Their first main finding was that in determining poor outcome, as measured by Cerebral Performance Category scale at 6 months, the sensitivity of absent EEG reactivity was 82% and specificity was 73% (this is identical to stating that for good outcome, the presence of EEG reactivity has sensitivity of 73% and specificity of 82%). In contrast, previous studies report specificity of absence of reactivity for poor outcome as 98% to 100% and the presence of reactivity, particularly early in the

course, for good outcome as 62% to 94%.[4-9] One study did note that 6 of the 27 patients with good outcome had absence of reactivity on the first day of monitoring, resulting in a specificity for poor outcome of 78%.[9] The most alarming finding in the current study is the low specificity rate (73%) for poor outcome (eg, the high false-positive rate). A difference between 73% and 98% to 100% is enormous in this context and particularly problematic if reactivity is integral to decision-making regarding withdrawal of care.

There may be several explanations for this finding. The current study appears to have been more cautious in determining what constituted reactivity than other studies. Reactivity was present in only 53% of all tested patients, which is lower than previous studies—and especially striking in the context of a cohort with a relatively high proportion of good outcomes (>50%). Previous studies have reported the presence of reactivity in over 70% of patients.[6] Whether this study was too conservative or other studies were not sufficiently stringent remains debatable. I do wonder whether this study was overly conservative; to my surprise, their published example of an EEG that was considered an uncertain pattern appeared reactive to me as several other qualified electroencephalographers I have asked. Although uncertain patterns were, for the purpose of analysis, considered reactive in this study, it is still potentially indicative of overly conservative reactivity evaluations. Other factors behind differences in rates of reactivity may be due to lack of video-EEG use, and avoidance of nipple pinch as a noxious stimulus—while it is the most effective reactivity-inducing stimulus,[10] it is generally not practiced due to ethical concerns.[3]

On the other hand, this was an extremely well executed, blinded study; its methodical precision really unmatched, and its results robust. There may be factors leading to other studies potentially overcalling reactivity. There is fear of the dreaded self-fulfilling prophecy (a negative test will necessarily lead to withdrawal of care), thus a natural desire to avoid it, even at the cost of decreasing sensitivity. This may lead to a bias to call a questionable rhythm reactive. What is apparent, though, is that even advanced practitioners find reactivity testing difficult—in fact, this study found that their intrarater reliability was lower than their interrater reliability. Quantitative methods may be needed to address this issue.[2]

Next, the authors determined the additional value of EEG reactivity to other multimodal, baseline prediction algorithm. Their "baseline" model for poor outcome includes highly malignant EEG findings at 24 hours, absent brainstem reflexes, or absent somatosensory evoked potential N20 peaks. As practitioners of CA prognosticators will know, these tests will result in an extremely high specificity but just moderate sensitivity, and indeed that is what they find here, with a specificity of 98% and a sensitivity of 54%. They find that a new model (baseline model and EEG reactivity absent) did little to improve specificity (99%) and decreased sensitivity to 51%.

They then evaluated whether the contribution of reactivity was useful to determining good outcome. The authors choose an entirely different baseline model; the presence of benign EEG at 12 hours or intact brainstem reflexes. Even the individual components are not calculated identically; the absence of brainstem reflexes (absent of both reflexes) was not considered the inverse of the presence of brainstem reflexes (presumably only one of them needs to be present). The authors find that their "baseline" model has a specificity of 70% and a sensitivity of 79%. Adding the EEG reactivity (baseline model and reactivity present) increases specificity to 89% and decreases sensitivity to 66%. Thus, they conclude that EEG reactivity does not add value in determining poor outcome and that it might be of added value in determining good outcome.

In my view, this conclusion is unwarranted. This will be obvious if one takes the hypothetical example of a theoretically perfect (or near perfect) classifier of outcome in this population. As compared to their baseline model for predicting poor outcome, constructing a new model with criteria (baseline and perfect classifier) as the authors have done cannot really do much better than a specificity of 98%; adding the perfect classifier will drive it up to 100%. At the same time, adding the perfect classifier will keep sensitivity at 54%; anything but perfection will arithmetically decrease sensitivity (and perhaps not manage to push the specificity up to 100%). So, with the way the authors performed the analysis of determining whether reactivity was useful, even the perfect classifier would be declared as adding no value for determining poor outcome—which arithmetically (and by common sense) points to a serious problem with this methodology. Certainly, there must be more reasonable methods to assess the added value of EEG reactivity, perhaps by determining which combination of predictors results in the most accurate model.

So, what should we conclude from this study? Despite the concern that EEG reactivity may have been assessed overly conservatively, I am inclined to believe the conclusion that specificity of reactivity for poor outcome may potentially be problematic in the way reactivity is currently practiced, especially in a nonideal clinical environment where reactivity may have to be tested while sedative medications are still lingering in patients, video correlation is not available, time does not permit testing multiple modalities multiple times, and most vigorous stimulation methods are not practiced. However, I believe that the analysis for determining whether EEG reactivity adds value is problematic and that there is value in EEG reactivity in assessing outcomes.

By Jong Woo Lee

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