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Editorial

New evidence supports multi-modal neuroprognostication after cardiac arrest

Patients in coma after cardiac arrest constitute a major challenge in Intensive Care Units (ICU) where beds and other resources are often limited. Due to improved pre-hospital management, CA-arrest victims have become increasingly common in the ICU and their prognosis on a group level is rather poor. This is particularly true for the substantial fraction of patients who remain comatose after weaning of sedation. Strong indicators of a severe brain injury, such as generalized edema on a head CT, may become apparent already during the first 1−2 days while the patient is still sedated.[1] It is easy to comprehend that clinicians may feel pressured to act on such information and withdraw life-supporting therapy (WLST). Accordingly, early WLST for neurological reasons is seemingly common also for patients who might have done well with prolonged ICU-stay.[2,3]

In the algorithm for neuroprognostication which was included in the 2015 ERC/ESICM-guidelines for post-resuscitation care,[4] information around prognosis is obtained by multiple methods during the first days post-arrest but their use is strictly limited until after 72 or 96 h have passed from the arrest. At 72 h, information from one single modality, i.e. absence of ocular reflexes or somatosensory evoked N20-potentials is sufficient to make a statement that the outcome of the patient is very likely poor. Patients not fulfilling one of these criteria are further evaluated by other methods after an additional 24-h observation. At this stage the ERC/ESECM algorithm turns multi-modal, demanding convergence from at least two diagnostic methods to conclude on a likely poor outcome.

In the current issue of Resuscitation, Dr Scarpino and co-workers challenge the uni-modal element of the current algorithm and provide evidence that a multi-modal approach is safer.[5] They performed post hoc analyses of the ProNECA study[6] and provide us with several interesting results of relevance for future guidelines. In their analyses of this Italian prospective neuroprognostication study, focused on head CT, SSEP and EEG, they found that several patients with absent pupillary light reflexes (PLRs) on day 3 reached a good outcome at 6 months, creating a 7% false positive ratio for the ERC/ESICM-algorithm. An important limitation to this comparison is that PLRs are always considered together with corneal reflexes in the ERC/ESICM-algorithm, only the bilateral absence of both lead to a poor prognosis statement. Nevertheless, along with absent SSEP-N20-potentials, lack of PLRs has for long been considered the most robust predictor of outcome.[4] While this is probably still true, the present study should be taken as a warning that decisions about life and death should never be made without converging evidence from multiple, preferably independent methods. Several other recent studies and a large meta-analysis support the notion that false positive results for PLRs and SSEP-N20-potentials occur in a substantial proportion of patients.[7−10] In similarity with all other methods for neuroprognostication both have their pitfalls, for example the PLRs are sensitive to opioid-induced miosis and the SSEPs to noise from muscle activity. While such sources of error are usually controlled for in a study setting, this is not necessarily the case in clinical practice. Hence, the high rate of false positive PLRs in the current study probably reflect that PLRs were not a primary study objective. It may also reflect the lack of influence from the self-fulfilling prophecy since WLST was not practiced in this study where the majority of survivors had severe brain injuries.[6]

Lack of error in predictions of poor outcome was the overruling priority as the ERC/ESICM algorithm was constructed.[4] It is therefore reassuring that three prior studies on different cohorts have reported a 0% false positive ratio as they validated the algorithm retrospectively.[11−13] However, the other side of the bargain is the limited ability of the algorithm to correctly identify patients with an eventual poor outcome, i.e. a limited sensitivity of 28−39%.[12,13] Currently, a liberal use of all available methodology is probably the best way to improve performance of any local prognostication protocol based on the ERC/ESICM guidelines. Adding serum NSE at 24, 48 and 72 h is, in this authors opinion, a critical step to increase sensitivity.[1] While increased NSE levels can confirm findings from other methods, low levels are equally important to warn that a confounder may have caused another index finding.

In order to raise the sensitivity of future algorithms with preserved specificity, more research on combinations and modifications of methods is needed. Previous results from the ProNECA study have showed that head CT, SSEP and EEG provide additive information.[6] In the current study, Scarpino et al. tested several modifications and were able to show that more liberal SSEP criteria and higher thresholds for CT-GWR lead to increased sensitivity with preserved specificity in a multi-modal context.[5] They also confirmed previous findings from the TTM-trial investigators that a higher GCS-M threshold (≤GCS-M 3) and a more transparent and reproducible EEG-terminology according to the American Clinical Neurophysiology Society (ACNS) improves the prognostic performance further.[12]

Recently, the drafted 2021 ERC/ESICM guidelines for post-resuscitation care were posted for public comments on the ERC homepage (https://cprguidelines.eu/guidelines-public-comment) including a substantially modified and simplified algorithm. This new algorithm is truly multi-modal and it is no longer possible to conclude on a poor prognosis without supporting evidence from at least two methods. Other important modifications are the introduction of the ACNS EEG-terminology and a recommended threshold for serum NSE. Similar to its predecessor, the 2021 algorithm is based on expert opinion. The actual prognostic performance is unknown and new studies are urgently needed to validate this new algorithm and suggest further improvements.

Conflict of interest

No conflicts of interest.

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REFERENCES

1. Cronberg T, Greer DM, Lilja G, Moulaert V, Swindell P, Rossetti AO. Brain injury after cardiac arrest: from prognostication of comatose patients to rehabilitation. Lancet Neurol 2020;19:611–22.
2. Elmer J, Torres C, Aufderheide TP, et al. Association of early withdrawal of life-sustaining therapy for perceived neurological prognosis with mortality after cardiac arrest. Resuscitation 2016;102:127–35.
3. May TL, Ruthazer R, Riker RR, et al. Early withdrawal of life support after resuscitation from cardiac arrest is common and may result in additional deaths. Resuscitation 2019;139:308–13.
4. Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for post-resuscitation care 2015: section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015. Resuscitation 2015;95:202–22.
5. Scarpino M, Francesco L, Giovanni L. Does a combination of $\geq$2 abnormal tests vs. the ERC-ESICM stepwise algorithm improve prediction of poor neurological outcome after cardiac arrest? A post-hoc analysis of the ProNeCA multicentre study. Resuscitation 2021;160:158–67.
6. Scarpino M, Lanzo G, Lolli F, et al. Neurophysiological and neuroradiological multimodal approach for early poor outcome prediction after cardiac arrest. Resuscitation 2018;129:114–20.
7. Amorim E, Ghassemi MM, Lee JW, et al. Estimating the false positive rate of absent somatosensory evoked potentials in cardiac arrest prognostication. Crit Care Med 2018;46:e1213–21.
8. Oddo M, Sandroni C, Citerio G, et al. Quantitative versus standard pupillary light reflex for early prognostication in comatose cardiac arrest patients: an international prospective multicenter double-blinded study. Intensive Care Med 2018;44:2102–11.
9. Dragancea I, Horn J, Kuiper M, et al. Neurological prognostication after cardiac arrest and targeted temperature management 33 degrees C versus 36 degrees C: results from a randomised controlled clinical trial. Resuscitation 2015;93:164–70.
10. Sandroni C, D'Arrigo S, Cacciola S, et al. Prediction of poor neurological outcome in comatose survivors of cardiac arrest: a systematic review. Intensive Care Med 2020;46:1803–51.
11. Bongiovanni F, Romagnosi F, Barbella G, et al. Standardized EEG analysis to reduce the uncertainty of outcome prognostication after cardiac arrest. Intensive Care Med 2020;46:963–72.
12. Moseby-Knappe M, Westhall E, Backman S, et al. Performance of a guideline-recommended algorithm for prognostication of poor neurological outcome after cardiac arrest. Intensive Care Med 2020;46:1852–62.
13. Zhou SE, Maciel CB, Ormseth CH, Beekman R, Gilmore EJ, Greer DM. Distinct predictive values of current neuroprognostic guidelines in post-cardiac arrest patients. Resuscitation 2019;139:343–50.

Tobias Cronberg
Lund University, Faculty of Medicine, Department of Clinical Sciences Lund, Neurology, Lund, Sweden

E-mail address: Tobias.Cronberg@skane.se (T. Cronberg).

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