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Editorial

Reliable neurological prediction after cardiac arrest — Are we willing to pay the price?

Most patients resuscitated after cardiac arrest remain in coma and are transferred to an intensive care unit. During the ensuing weeks approximately half of them will die, most after a decision to withdraw life-sustaining therapy (WLST) based on a presumed severe brain injury.[1] Survivors, on the other hand, typically have a good outcome and severe neurological disability is not the usual outcome in countries where WLST is practised. This strong link between prognostication, WLST and outcome is exceptional for cardiac arrest, discriminating this condition from stroke or traumatic brain injury, for example.

Prolongation of futile intensive care is considered unethical by many since it may cause the patient and their relatives unnecessary suffering and waste limited intensive care resources. However, clinicians tend to overestimate their ability to prognosticate since WLST typically leads to the death of the patient regardless. This "self-fulfilling prophecy" is also a potential bias in most studies on neuroprognostication. This issue may be compounded by confirmation bias leading the clinician to focus selectively on information supporting their own opinion and neglecting contradictory data.

Guidelines for neurological prognostication has been developed to make estimations of brain injury after cardiac arrest more accurate and the related decisions on WLST safer. In this issue of Resuscitation, the three most commonly cited guidelines are validated for the first time and the results are a strong reminder that further development in this field is necessary. Zhou et al.[2] validated the 2006 guidelines from the American Academy of Neurology (AAN),[3] the 2015 guidelines from the American Heart Association (AHA)[4] and the 2014 European Resuscitation Council (ERC) and European Society of Intensive Care Medicine (ESICM) joint guidelines.[5] Importantly, both the AHA and the ERC/ESICM guidelines were based on a systematic review[6,7] that was adopted by the International Liaison Committee on Resuscitation (ILCOR).

The authors considered each instrument included in the AHA guidelines and the summarised effect of the algorithms included in the texts from AAN and ERC/ESICM. As expected, the AAN guidelines from 2006, which were based on studies performed in the pre-hypothermia era, performed poorly with a false positive rate (FPR) of 8% and 15% at discharge and 3 months respectively. When evaluating the AHA-guidelines, Zhou et al. discovered occasional false predictions of a poor outcome associated with absent pupillary reflexes, early myoclonic status, neuron specific enolase (NSE) $>$ 33 μg/l and diffuse hypoxic injury on head magnetic resonance imaging (MRI). Importantly, several of the patients with good outcome were classified as poor on discharge from hospital but improved by the time of the 6-month evaluation. The ERC/ESICM algorithm, on the other hand, resulted in no false-positive predictions but the sensitivity to detect patients with an ultimately poor neurological outcome was only 26 and 28% at discharge and 6 months respectively. According to the ERC/ESICM guidelines, a Glasgow Motor Score of 1–2 in an unsedated patient is a prerequisite to enter the algorithm. According to this algorithm, absent pupillary and corneal reflexes or bilaterally absent N20 somatosensory evoked potentials (SSEPs) indicate that a poor outcome is 'very likely' (FPR $<$ 5% and narrow 95% confidence intervals (CI)). Otherwise at least two other signs of severe brain injury are required to support a statement of a 'poor outcome likely'. Apparently, this multimodal approach increases the reliability of the prediction, but it comes at the price of more patients remaining with an uncertain prognosis for several days after arrest despite multiple tests being performed. The uncertainty and need for continued treatment of these comatose patients puts considerable strain on families, doctors and nurses. Is this a price we are willing to pay?

A recent international survey found that the majority of the 640 respondents considered 0.1% to be an acceptable FPR for a WLST decision after cardiac arrest.[8] In further support of this cautious attitude, the time to WLST increased in United Kingdom intensive care units (ICUs) during the period 2004–2014.[9] Perhaps controversially, futility has been previously defined as less than 1% chance of a therapy being successful.[10]

In the current study by Zhou et al., electroencephalography (EEG), SSEP and computed tomography (CT) were associated with no false positive predictions of a poor outcome, but this study was limited to 226 patients and the results were based mainly on the combination of clinical examination, EEG and CT, because SSEP, NSE and MRI was used in a minority (19%, 20% and 42% respectively). In a real world setting no method performs without error and therefore the risk of confirmation bias, as physicians seek support for a preconceived poor outcome, needs to be taken seriously. Support from independent methods should always be the standard strategy and favourable signs such as the return of a reactive EEG background and low serum NSE values should be weighed against predictors of poor outcome. In the current study one patient had a good outcome despite having both diffuse anoxic injury on brain MRI and NSE $>$ 33 μg/l. This patient had a Glasgow Motor Score $>$2 which illustrates the importance of giving all patients the benefit of a clinical neurological examination free from the confounding influence of analgosedation.

The present study was retrospective and undertaken at an academic tertiary centre. The high usage (87%) of continuous EEG monitoring

makes the results difficult to generalize since this method is not available in the vast majority of ICUs. A more liberal use of serum NSE might have increased the sensitivity of the ERC/ESICM algorithm but possibly also the FPR. The authors included all patients who were comatose after resuscitation and they did not exclude those who woke up. In another study, 48% of the patients awoke before the planned neuroprognostication 4.5 days after arrest and another 15% died early.[1] This illustrates that formal evaluation of prognosis, and the related risk of incorrect decisions on the level of care may be necessary for only a minority of patients. The rate of WLST reported by Zhou and associates was 52%. Although the timing of these decisions was generally consistent with current guidelines, 11% had early WLST on days 2–3.

In an ideal validation of the guidelines for neuroprognostication all methods in an algorithm would be available to the treating physicians without limitations, data would be collected prospectively from patients in a representative mix of hospitals, and withdrawal of intensive care would be avoided because self-fulfilling prophecy is such a potent confounder. To approach reliable estimates of a 0.1% FPR with narrow 95% CIs much larger sample sizes than the current study are needed. Aside from the financial and organisational challenges, such an approach would likely lead to a severalfold increase in survivors with severe neurological impairment and make it ethically controversial. Small studies from countries where WLST is not practised provide some examples.[11,12] While we await further data, this important study by Zhou et al. gives some reassurance to the users of the conservative ERC/ESICM algorithm and serves as a warning to those relying on a step-by step approach putting too much confidence into single methods. There is no room for error in decisions on WLST.

Conflict of interest

TC and JPN participated in the 2014 ERC/ESICM advisory statement on neuroprognostication after cardiac arrest.

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