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EDITORIAL

Improving the Prognosis: Developing the Right Tool for the Right Patients

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In this issue of Neurocritical Care, researchers from the University of Hawaii, John A. Burns School of Medicine publish data based on methods that merit broader collaboration [1]. Prognostication for patients in coma serves as the foundation for most medical ethics questions in the Neurocritical Care Unit. Investing limited resources in patients who will not recover denies other patients access to specialized healthcare. Patients in coma cannot participate in medical decision making, but their surrogates are most often denied the guidance of a confident assessment of the patient's potential for recovery. Indecision may expose patients to the harm of permanent debilitation, while premature withdrawal of life support eliminates the possibility of an unexpected recovery.

Undeniably, we must guide medical decision making by providing timely assessments of prognostication based on studies whose results are both accurate and reproduced. In the endeavor to meet this essential need, one would expect prognostication after cardiopulmonary arrest (CPA) to stand as an area of relative success. After all, at least 300,000 people suffer out-of-hospital cardiac arrest each year in the United States of America alone [2], and since our arrival in the citizen first-responder era 40 years ago, it has been shown to impose a potentially survivable and stereotypic injury upon its victims [3]. Indeed, beyond supportive care, the dominant clinical approach for patients in coma after cardiac arrest has focused predominantly on early determination of negative prognosis. This approach has enjoyed only limited success. Frustratingly, as the authors correctly note in their introduction, our methods of prognostication leave a large portion of patients in an "indeterminate" category. The PROPAC (Prognosis in PostAnoxic Coma) study group, for instance, primarily sought to investigate the reliability of the somatosensory-evoked potential (SSEP) in accurate prognosis, and indeed, bilaterally absent N20 peaks in SSEPs at 24–72 h had a 0 % false-positive rate for prognosticating poor outcome in comatose patients [4]. Since only 45 % of patients tested had abnormal results on SSEP testing, the results usually do not allow us to address the question foremost on the minds of those we counsel: will our patient awaken? Therefore, over half a century after Stephenson et al. [5] reviewed outcomes for 1,200 patients with cardiac arrest, a well-designed study recruiting patients from almost 40 medical centers leaves over half of the study population with indeterminate prognosis after evaluation. Stated more directly, we leave our patients' surrogate decision makers to their own counsel.

Beyond limited utility, the early negative prognosis approach also confines our management of patients with post-cardiac arrest syndrome to passive observation. The overall approach to brain injury after cardiac arrest has dramatically changed since the introduction of therapeutic hypothermia and the addition of targeted temperature management. In this context, early negative prognostication may well detract from patient care, and encourage withdrawal of life support in patients who could benefit from modern standards of care [6]. Instead, we require reliable indicators of positive prognosis, which identify patients who could benefit from advanced therapy. More importantly, such indicators would allow us to evaluate the

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success of new strategies. Eventually, these indicators would generate hypotheses for an understanding of the pathophysiology involved, yielding new targets for intervention.

Could it be that our methods of prognostication have failed to meet our needs because our methods of assessing the brain depend on incomplete notions of its function? Have we have failed by focusing too narrowly on the manifestations of anoxic injury rather than seeking to understand the intrinsic processes? Key elements of the prognostic paradigm in coma such as cranial nerve reflexes, motor responses, and SSEPs all depend on a stimulus–response model of the brain. However, as Marcus Raichle eloquently argues, the vast majority of brain activity is devoted to functions intrinsic to the organ rather than dependent on stimulation [7]. This interpretation is hardly a new one. Hans Berger, who pioneered EEG in the early twentieth century, had initially sought to quantify psychic energy, the metabolic evidence of conscious thought, but gradually convinced himself that while EEG was the most sensitive method available to evaluate brain activity (compared to caloric and barometric blood flow analyses used before), it revealed a baseline activity without substantial changes attributable to cognitive effort [8]. Positron emission topography (PET) and functional magnetic resonance imaging (fMRI) have further demonstrated that instead of being uniform or generalized, intrinsic activity demonstrates specific, reproducible functional connectivity into a network of regions now known as the default mode network (DMN). We now have a means of evaluating brain function independent of mere responsiveness. For prognostication after cardiac arrest, evaluation of intact DMN in comatose patients could serve as a test for positive prognosis early in the hospital course, an invaluable clinical tool which has thus far eluded us.

Evaluation of the DMN has already changed our understanding of specific clinical conditions. Alzheimer's disease in particular has served as a model to illustrate the role of the DMN in memory formation [9]. Evidence regarding a relationship between disrupted DMN connectivity and cognitive impairment in patients with traumatic brain injury (TBI) also illustrates the utility of evaluating patients during rest [10]. More directly relevant to the post-anoxic syndrome, investigators have published on disrupted functional connectivity in patients with disorders of consciousness (DOC) [11]. As Matthew Koenig and his collaborators note, DMN connectivity in patients with post-cardiac arrest syndrome coma has already been compared to that of healthy controls. This study included all patients in coma regardless of prognostic category. Intriguingly, those investigators found 2 patients with intact DMN connectivity, who awoke while the other 11 without did not [12]. Koenig and colleagues propose a new paradigm for using fMRI and the DMN. Among comatose survivors of cardiac arrest without a definitive negative prognosis by other methods of prognostication, they wish to determine whether preserved DMN connectivity could serve as a marker for positive prognosis.

Unfortunately, the study reported in this edition falls short of this goal. Although patients were comatose as a criterion for enrollment in the study, only six remained so at the time of the fMRI. Of these patients, none had a good outcome as measured by Cerebral Performance Category. One can already deduce the challenges inherent to this research from the high number of patients screened (153) relative to the low number who completed the protocol. Simply transporting a comatose patient in the acute period following cardiopulmonary resuscitation imposes daunting logistical challenges, let alone performing an fMRI. These patients are critically ill, often requiring life support measures with limited compatibility to the MRI environment. In addition, surrogates for informed consent may prove difficult to establish and too emotionally overwhelmed to complete the process. In order to provide consistent results, fMRI must be performed early in the hospital course, and surrogates must agree to a study period before considering limiting life support measures or altering goals of care.

In the realm of academic medical literature, the sentence "these findings require validation in larger cohorts" has become a ceremonial closing rather than an earnest appeal for further effort. This group of researchers, however, recognizes a mandate not from the limitation of their findings but in the potential to meet a fundamental and unmet need in the care of our patients. While the recruitment and logistical challenges outlined above may prove prohibitive at a single center, a coordinated effort with a common research protocol by several centers would very likely yield results that allow for fair examination of this methodology. Modesty in our goals for patients with post-cardiac arrest syndrome will not serve them. An approach restricted to prognostication encourages passivity without gaining piece of mind for our patients' loved ones. It is precisely those patients left in an uncertain state by a retrained approach who would benefit the most from modern, goal-directed therapy. However, proper assessment of these modern approaches requires a means of patient selection and evaluation that gages brain function as a whole instead of relying on stimulus–response tasks, which, while expedient and familiar, fail to discern between patients who are healing from those who will not. While the urge to constantly recalibrate old methods remains, we should strive for therapeutic strategies based on an understanding of the physiologic processes that determine the recovery of consciousness.

Conflict of interest Dr. Puttgen and Dr. Geocadin declare no conflict of interest in relation to this article.

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