Editors' Note: Responses to this study caution against relying too heavily on neuron-specific enolase (NSE) levels alone to predict death in patients with cardiac arrest (CA) treated with therapeutic hypothermia (TH). Dr. Bazarian writes that the sensitivity of NSE levels in predicting survival may be enhanced by adding a marker of blood–brain barrier permeability. Drs. Freeman and Chiota cite their own data, which showed a cutoff NSE level of 33 $\mu\text{g/L}$ had a false-positive rate of 13% in predicting poor prognosis. The authors of the study reply that they agree that serial NSE levels are best used as an adjunct to traditional prognostic indicators in guiding clinical decision-making.

Megan Alcauskas, MD, and Robert C. Griggs, MD

NEURON-SPECIFIC ENOLASE CORRELATES WITH OTHER PROGNOSTIC MARKERS AFTER CARDIAC ARREST

Jeffrey J. Bazarian, Rochester, NY: Cronberg et al.¹ reported serum NSE levels $>33 \mu\text{g/L}$ to be highly predictive of death after CA treated with hypothermia, and to correlate with abnormal diffusion-weighted imaging (DWI), abnormal somatosensory evoked potentials (SSEP), and postmortem brain histology. The accompanying editorial by Mayer² implied that tests like NSE are needed more than ever because hypothermia has fundamentally changed the way post-CA prognosis is determined. However, while the game may have changed, the rules are still the same.

While hypothermia increases the proportion of patients with CA who regain consciousness, those who do not after 72 hours still have a uniformly poor prognosis. Rather than trying to predict who will die, the more clinically relevant task is to identify the few who are destined to survive. In that case, NSE sensitivity, not its specificity, is the important characteristic to consider. Unfortunately, NSE sensitivity, and its ability to rule out the possibility of death, is considerably less robust. This may be due to variation in the permeability of the blood–brain barrier (BBB) which, when intact, prevents extensive brain injury

from being reflected in the serum. NSE sensitivity can be enhanced by combining it with an independent marker of BBB permeability, such as the CSF/serum albumin ratio³ or serum S100B.⁴ Low NSE in the setting of an open BBB would imply no brain injury and a potentially reversible cause of coma. Low NSE and a closed BBB means the NSE level is not reflective of the degree of brain injury. This strategy provides a more practical adjunct to outcome determination in patients still comatose 72 hours after hypothermia for CA.

William D. Freeman, Nicole A. Chiota, Rochester, MN: Cronberg et al.¹ report that NSE is strongly correlated to other measures of global ischemic brain damage after CA treated with TH. At our center, we reviewed TH-treated patients with CA between November 2006 and April 2010, and identified 35 patients with NSE measured 24–72 hours after CA. Twenty-two had NSE less than 30 $\mu\text{g/L}$, 13 of which had good neurologic outcome (13/22, 59%), as defined by cerebral performance category of 1–2 at discharge. Of the 13 patients with NSE greater than 33 $\mu\text{g/L}$, 2 achieved a good neurologic outcome and followed commands within 72 hours after CA (NSE values of 37 and 41 $\mu\text{g/L}$). Our data suggest that NSE greater than 33 $\mu\text{g/L}$, the cutoff value reported in the 2006 American Academy of Neurology guidelines,⁵ carries a false positive rate of 13% in predicting poor neurologic prognosis in TH-treated patients with CA.⁶ We agree with Cronberg et al. that NSE assists in predicting brain injury in TH-treated patients with CA. We agree that NSE laboratory standardization may contribute to the diverse results in the literature, and until such standardization and validation occurs, a multimodal approach⁷ to prognostication is needed.

Author Response: T. Cronberg, M. Rundgren, E. Westhall, E. Englund, R. Siemund, I. Rosén, H. Widner, H. Friberg, Lund, Sweden : We thank Drs. Freeman, Chiota, and Bazarian for their comments. We agree with the editorialist, Dr. Mayer, that prognostication following cardiac arrest is more complex with hypothermia. However, the NSE 33 $\mu\text{g/L}$ cutoff for poor prognosis could also be questioned without hypothermia.⁸

Rather than discuss cutoff points, we should focus on the potential use of NSE as an adjunct to other methods. That a biomarker, indeed any biomarker, would constitute the foundation of a withdrawal-of-care decision is unrealistic since methodologic problems will always generate outliers. For the same reason, we should not expect to find any biomarker with a 100% specificity for poor prognosis, since cutoff levels will only be gradually raised with increasing data accumulation until the clinical usefulness of the test is lost.

Our experience is that serial measurements of NSE, analyzed on a 24/7 basis, in combination with clinical examinations and amplitude-integrated EEG (aEEG) is a good basis for a continuous neurologic prognostication of cardiac arrest patients.^{1,9} While the patient is still sedated, we find the aEEG and NSE to be valuable tools that help us plan intensive care and communicate with relatives. NSE has become a useful standard laboratory test to evaluate prognosis after cardiac arrest but should be used with realistic expectations.

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1. Cronberg T, Rundgren M, Westhall E, et al. Neuron-specific enolase correlates with other prognostic markers after cardiac arrest. *Neurology* 2011;77:623–630.

2. Mayer SA. Outcome prediction after cardiac arrest: new game, new rules. *Neurology* 2011;77:614–615.
3. Reiber H, Peter JB. Cerebrospinal fluid analysis: disease-related data patterns and evaluation programs. *J Neurol* 2001;184:101–122.
4. Blyth B, Farhavar A, Gee C, et al. Validation of serum markers for blood-brain barrier disruption in traumatic brain injury. *J Neurotrauma* 2009;26:1497–1507.
5. Wijdicks EF, Hijdra A, Young GB, Bassetti CL, Wiebe S. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006;67:203–210.
6. Chiota N, Myers T, Freeman WD. High false positive rate of neuron specific enolase (NSE) in patients treated with hypothermia after cardiac arrest. *Neurocrit Care* 2010;13:S42. Abstract.
7. Rosetti AO, Oddo M, Logroscino G, Kaplan PW. Prognostication after cardiac arrest and hypothermia: a prospective study. *Ann Neurol* 2010;67:301–307.
8. Steffen IG, Hasper D, Ploner CJ, et al. Mild therapeutic hypothermia alters neuron specific enolase as an outcome predictor after resuscitation: 97 prospective hypothermia patients compared to 133 historical non-hypothermia patients. *Crit Care* 2010;14:R69.
9. Rundgren M, Westhall E, Cronberg T, Rosen I, Friberg H. Continuous amplitude-integrated electroencephalogram predicts outcome in hypothermia-treated cardiac arrest patients. *Crit Care Med* 2010;38:1838–1844.

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Jeffrey J. Bazarian, William D. Freeman, T. Cronberg, et al.

Neurology 2011;77;1856-1857

DOI 10.1212/WNL.0b013e31823c1141

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