

ASA BRAIN HEALTH INITIATIVE: *The Science Behind the Scene*

Miles Berger, M.D., Ph.D.

Roderic Eckenhoff, M.D.
Ad Hoc Committee on Brain Health Initiative

The increasing public awareness of postoperative cognitive problems has, in part, led to the ASA Brain Health Initiative. This multi-pronged initiative will include research into definitions of risk factors for and best practices to avoid these disorders. We would like to take this opportunity to tell *ASA Monitor* readers about activities and ongoing discussions in this area.

First, a challenge facing cognitive decline research has been the lack of uniformity or agreement over measurements and definitions.¹ Thus, an international nomenclature group is working on consensus definitions for what has become known as postoperative cognitive decline (POCD). This work is necessary because different research groups have used different criteria to define POCD, and often in different cognitive domains (executive function, memory, etc.).² These divergent definitions have made it difficult to compare results across different studies. Further, just like any other human physiologic trait, human cognitive performance is a continuously distributed trait. Thus, POCD is probably best conceptualized as the tail end of the continuous distribution of cognitive change from before to after anesthesia and surgery,¹ rather than as a dichotomous trait. Moreover, research criteria for POCD rarely include the subjective component – a component that is absolutely required in the neurodegeneration field to diagnose mild cognitive impairment (MCI) or dementia. Nonetheless, having specific testing thresholds for defining

POCD would be extremely helpful for comparing results across research studies and, when ultimately coupled with subjective complaints, to recognize POCD as a real clinical syndrome. These measures would allow inclusion as a diagnosis in the DSM (Diagnostic and Statistical Manual of Mental Disorders) along with related disorders such as delirium, and a diagnosis code in the ICD-10. And to make these diagnoses consistent with the existing cognitive impairment field, a new nomenclature to replace POCD is being considered, which will be described at this year's International Anesthesia Research Society meeting.

In order to gain broad acceptance for any consensus definitions and nomenclature for POCD, the working group includes a multidisciplinary collection of anesthesiologists, surgeons, geriatricians, neuropsychologists, neurologists and psychiatrists. The first position paper from this nomenclature group is expected later this year. In the meantime, those with an interest in the progress of the work on nomenclature and definitions should contact either Lis Evered (lis.evered@svha.org.au) and/or Rod Eckenhoff (roderic.eckenhoff@uphs.upenn.edu).

Second, a broad international group of anesthesiologist-investigators and basic scientists have been holding "Perioperative Neurotoxicity in the Elderly" workshops for the last eight years^{3,4} focused on understanding the multifactorial causes of POCD and delirium, including patient,⁵⁻⁷



Miles Berger, M.D., Ph.D., is Assistant Professor, Neuroanesthesiology Division, Anesthesiology Department, Duke University Medical Center, Durham, North Carolina.



Roderic Eckenhoff, M.D., is Austin Lamont Professor and Vice Chair for Research, Department of Anesthesiology & Critical Care, Perelman School of Medicine, University of Pennsylvania, Philadelphia.



anesthetic^{8,9} and surgical^{10,11} factors. These workshops initially tackled more preclinical, mechanistic topics but have recently started to feature more clinical and translational research. The proceedings of most of these workshops have been published,^{3,4} which provide an opportunity for all anesthesiologists to familiarize themselves with ongoing research in this field. The workshop proceedings also provide evidence on what clinicians can offer to patients about the considerable research effort that is being devoted to ultimately understand the questions many of us have faced from concerned patients, such as “will anesthesia and surgery affect my memory?” or “will I still be able to think straight when I wake up?” Future perioperative neurotoxicity workshops will include presentations on ongoing randomized controlled trials that

seek to define if anesthetic management can optimize postoperative brain health. For example, some studies have suggested that certain techniques, such as total intravenous anesthesia with propofol,¹² or avoidance of burst suppression^{13,14} or “deep anesthesia,”⁸ produce better cognitive outcomes. However, there is conflicting evidence,^{9,15,16} and in most cases we lack level 1 evidence for or against these suggestions. Thus, ongoing trials examining the effect of these¹⁷ and other^{18,19} anesthetic techniques on reducing risk of POCD and delirium will help establish best clinical practices, an important component of the ASA Brain Health Initiative.

Continued on page 14

Third, and in line with a focus on improving cognitive outcomes for patients after surgery, several recent studies have found that preoperative cognitive impairment is a significant risk factor for both POCD⁵ and delirium.²⁰ It is worth noting that the central nervous system (CNS) is the consensus target of nearly every anesthetic drug and that many of the desired clinical endpoints of general anesthesia (such as amnesia, analgesia and unconsciousness) are produced by anesthetic actions on the CNS. It is thus ironic that we rarely test CNS function as part of a routine preoperative anesthetic assessment and that no CNS monitor is part of the ASA standard monitors for anesthetic care. Should anesthesiologists routinely assess cognitive function and status preoperatively? Several studies are now under way to examine different tools to rapidly assess preoperative cognitive function²¹⁻²⁴ and to determine whether this information can help predict postoperative outcomes.^{21,22} As research in this area advances, we expect that implementation of some type of pre-, intra- and even postoperative assessment of CNS function will become an integral and standardized part of the brain health initiative.

Fourth, and again in line with the increasing public awareness of cognitive problems following surgery, there have been discussions over the past year about whether the potential for cognitive dysfunction or delirium should be included as risks on anesthesia and surgical consent forms (since both anesthetics and surgery have been implicated). Although this may seem controversial to some, most anesthesia and surgical consent forms already include other risks that occur much less frequently than either POCD or delirium (such as intraoperative myocardial infarction or death). Given the current literature, we believe the legal risk exposure to be more significant if the possibility of postoperative cognitive problems is not included in consent forms than if it is. Thus, we expect the inclusion of these risks on our consent forms to require additional study and discussion at the ASA level, in conjunction with the American College of Surgeons, and the relevant legal counsel.

Clearly, there is much to be learned about how to classify and define POCD and delirium, what causes these brain disorders and how to predict, prevent and treat them. These issues will continue to be addressed by the international nomenclature consensus group and perioperative neurotoxicity workshops in the hope that we can better assess the brain pre-, intra- and postoperatively, better inform our patients about the risks of anesthesia and surgery, and better promote postoperative cognitive recovery. In doing so, we need to emphasize that causality is not implied: we are not proposing that anesthesia is a primary cause of POCD or delirium.

Rather, we propose that, as anesthesiologists, we know cognitive disorders following surgery can and do occur, and that we are working hard with our colleagues in other fields of medicine to mitigate these disorders and to ensure an optimum postoperative brain recovery for all our patients. In this sense, we are working toward one of medicine's most fundamental tenets: to "first, do no harm."

References:

1. Berger M, Nadler JW, Browndyke J, et al. Postoperative cognitive dysfunction: minding the gaps in our knowledge of a common postoperative complication in the elderly. *Anesthesiol Clin*. 2015;33(3):517-550.
2. Newman MF, Kirchner JL, Phillips-Bute B, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *N Engl J Med*. 2001;344(6):395-402.
3. Baranov D, Bickler PE, Crosby GJ, et al. Consensus statement: First International Workshop on Anesthetics and Alzheimer's Disease. *Anesth Analg*. 2009;108(5):1627-1630.
4. Terrando N, Eriksson LI, Eckenhoff RG. Perioperative neurotoxicity in the elderly: summary of the 4th International Workshop. *Anesth Analg*. 2015;120(3):649-652.
5. Silbert B, Evered L, Scott DA, et al. Preexisting cognitive impairment is associated with postoperative cognitive dysfunction after hip joint replacement surgery. *Anesthesiology*. 2015;122(6):1224-1234.
6. Price CC, Tanner JJ, Schmalfuss I, et al. A pilot study evaluating presurgery neuroanatomical biomarkers for postoperative cognitive decline after total knee arthroplasty in older adults. *Anesthesiology*. 2014;120(3):601-613.
7. Evered L, Silbert B, Scott DA, Ames D, Maruff P, Blennow K. Cerebrospinal fluid biomarker for Alzheimer disease predicts postoperative cognitive dysfunction. *Anesthesiology*. 2016;124(2):353-361.
8. Chan MT, Cheng BC, Lee TM, Gin T; CODA Trial Group. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. *J Neurosurg Anesthesiol*. 2013;25(1):33-42.
9. Radtke FM, Franck M, Lendner J, Kruger S, Wernecke KD, Spies CD. Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. *Br J Anaesth*. 2013;110(suppl 1):i98-i105.
10. Terrando N, Monaco C, Ma D, Foxwell BM, Feldmann M, Maze M. Tumor necrosis factor- α triggers a cytokine cascade yielding postoperative cognitive decline. *Proc Natl Acad Sci U S A*. 2010;107(47):20518-20522.
11. Terrando N, Yang T, Ryu JK, et al. Stimulation of the $\alpha 7$ nicotinic acetylcholine receptor protects against neuroinflammation after tibia fracture and endotoxemia in mice. *Mol Med*. 2015;20:667-675.
12. Cai Y, Hu H, Liu P, et al. Association between the apolipoprotein E4 and postoperative cognitive dysfunction in elderly patients undergoing intravenous anesthesia and inhalation anesthesia. *Anesthesiology*. 2012;116(1):84-93.
13. Fritz BA, Kalarickal PL, Maybrier HR, et al. Intraoperative electroencephalogram suppression predicts postoperative delirium. *Anesth Analg*. 2016;122(1):234-242.
14. Soehle M, Dittmann A, Ellerkmann RK, Baumgarten G, Putensen C, Guenther U. Intraoperative burst suppression is associated with postoperative delirium following cardiac surgery: a prospective, observational study. *BMC Anesthesiol*. 2015;15:61.

For a complete list of references, please refer to the online version of the *ASA Monitor* at asahq.org or email Jamie Reid at j.reid@asahq.org.