Oxidative Stress Response and Delirium after Cardiac Surgery

Can Circulating Biomarkers Refine New Therapeutic Paradigms?

Mihai V. Podgoreanu, M.D., Michael J. Devinney Jr., M.D., Ph.D., Joseph P. Mathew, M.D., M.H.Sc., M.B.A.

Although postoperative delirium afflicts as many as half of cardiac surgery patients[1] and is associated with prolonged hospitalization, long-term cognitive decline, and mortality, we know little of the pathophysiologic mechanisms that subtend this common neurobehavioral syndrome. Delirium is an acute confusional state, generally viewed as a marker of increased brain vulnerability and an aberrant response to stress. As such, its neuropathogenesis depends on complex interrelationships between predisposing and precipitating factors, with a number of overlapping mechanistic theories involving neuronal aging, neuroinflammation, oxidative stress, neurotransmitter deficiency, neuroendocrine activation, circadian dysregulation, and breakdown in brain network connectivity.[2] While anesthesia/surgery are clearly inciting factors for delirium, *intraoperative* strategies to reduce it are sorely lacking. This is in part because prevailing theories have focused on preoperative (older age, frailty, medical comorbidities, and preexisting cognitive impairment) and postoperative recovery factors (disrupted sleep, altered sensorium, pain, and sedating medication use/polypharmacy) as drivers of postoperative delirium.

"While anesthesia/surgery are clearly inciting factors for delirium, *intraoperative* strategies to reduce it are sorely lacking."

In this issue of Anesthesiology, Lopez *et al.*[3] refocus our attention on *intraoperative* factors associated with delirium—namely, oxidative stress and blood–brain barrier breakdown. They report results from a subset of patients (n = 400) enrolled in a single-center randomized controlled trial of statin therapy to reduce acute kidney injury and delirium following cardiac surgery. The primary trial results revealed no statin effects on incident postoperative acute kidney injury as well as incidence or duration of postoperative delirium.[4] Here, in a prespecified secondary analysis, the authors performed mass spectrometry–based plasma quantification of oxidative stress indicators F2-isoprostanes and isofurans, demonstrating clear associations with incident postoperative delirium. They also found that postoperative elevations of a putative marker of blood–brain barrier breakdown, S100 calcium-binding protein, are associated with delirium. Oxidative stress and blood–brain barrier breakdown markers were both associated with increases in ubiquitin carboxyl-terminal hydrolase isozyme L1, a plasma marker of neuronal injury, and the strength of the association between oxidative damage and neuronal injury was higher in patients with biomarker evidence of blood–brain barrier disruption. Overall, this biologically plausible triangle of elegant consecutive correlations between surrogate circulating biomarkers and delirium adds evidence in support of the oxidative stress hypothesis, which proposes that pathologic insults such as hypoxia and ischemia-reperfusion may lead to reduced cerebral oxidative metabolism and associated cognitive and behavioral symptoms of delirium.[2]

Readers might consider several factors in interpreting the potentially wide-ranging clinical and translational relevance of the study by Lopez *et al.*[3] The first promising translational implication is the use of circulating biomarkers to predict, monitor, and assess therapeutic effectiveness for postoperative delirium. The Institute of Medicine has outlined a clear

Image: ©gettyimages.

This editorial accompanies the article on p. 551.

Accepted for publication November 13, 2019. Published online first on January 7, 2020. From the Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina.

 Anesthesiology 2020; 132:418–20. DOI: 10.1097/ALN.0000000000003097

three-step framework for evaluating putative biomarkers of disease, consisting of analytical validation (analytical performance of an assay), qualification (associations between the biomarker and disease states, including effects of interventions on both the biomarker and clinical outcomes), and utilization (contextual analysis based on proposed specific use and applicability of available evidence). The authors are to be congratulated for providing evidence in support of analytical validity and associations between the panel of plasma markers investigated and delirium. However, fulfilling the qualification step also requires evidence that interventions targeting the biomarkers in question impact the clinical endpoints of interest, and this is where the study has some limitations. First, the analysis was conducted in the context of a pharmacologic intervention to reduce delirium (high-dose statin therapy), and although biomarker associations with delirium were adjusted for statin use, the actual effects of statin treatment on markers of oxidative damage, blood–brain barrier disruption, and neuronal injury are not reported. Statins are known for their pleiotropic cholesterol-independent activities, including both reduced and paradoxical increases in oxidative stress, linked to a number of organ toxicities. Despite lacking clinical effect on delirium in the primary trial, a significant effect of statins on the biomarkers investigated would alter the interpretability and translational relevance of these findings.

Second, there is no concomitant assessment of antioxidant defense systems. Previous studies found lower preoperative concentrations of the antioxidant enzyme catalase in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) who developed delirium, compared to those without delirium.[5] The intraoperative increase in plasma F2-isoprostanes reported by Lopez *et al.* is consistent with previous findings.[6] Importantly, these previous studies also reported a concomitant gradual intraoperative increase in circulating antioxidants α- and γ-tocopherol. This suggests that an adaptive upregulation of antioxidant counterregulatory response to the oxidative injury associated with CPB is at play. In interpreting the role of oxidative stress in the pathobiology of postoperative delirium, factors driving biomarkers of oxidative injury should be jointly assessed with those modulating endogenous antioxidant capacity and redox resilience, as both are equally important targets for therapeutic interventions (*e.g.,* prehabilitation). Given the paucity of properly conducted trials of perioperative antioxidant supplementation, all with debatable results and mainly focused on postoperative atrial fibrillation (none on postoperative delirium), such integrated biomarker analysis of redox state may serve as quantitative intermediate phenotypes to assess the efficacy of multicomponent nonpharmacologic intervention programs, integral to clinical consensus for delirium management in at-risk older adults.

Third, the standardized anesthetic and surgical management in the study by Lopez *et al.* omits, for practical reasons, parameters related to intraoperative systemic and cerebral oxygenation, especially during conduct of and separation from CPB. Most published data correlate poor oxygenation with cerebral dysfunction and delirium.[7] However, as reported by the same investigative group and others in previous observational studies, hyperoxia during reperfusion is equally detrimental and is associated with delirium.[8] This is perhaps the most tangible potential clinical implication of this study for future anesthesiologist-implemented *intraoperative* interventions to reduce delirium. To this end, we are awaiting the results of two ongoing randomized controlled trials evaluating the effectiveness of preventing hyperoxia during cardiac surgery in reducing intraoperative oxidative stress, neuronal injury, and delirium (ClinicalTrials.gov ID NCT02591589 and NCT02361944).

An important finding by Lopez *et al.* is that blood–brain barrier breakdown modified the association between markers of oxidative stress and neuronal injury. Thus, blood–brain barrier "health" might be a defense from neurologic injury in the face of oxidative stress. The incidence of blood–brain barrier disruption after CPB, assessed by dynamic contrast enhancement magnetic resonance imaging, is as high as 71%, primarily in the frontal lobes, and correlates with cognitive changes in attention and executive functions.[9] However, little is known about blood–brain barrier disruption during off-pump surgery. Although a *post hoc* sensitivity analysis reported by Lopez *et al.* revealed no differences in biomarker associations with delirium between the subgroup of patients who underwent on-CPB surgery (70%) and the total cohort, the study would have been bolstered by directly comparing on-CPB *versus* off-pump biomarker concentrations. Serial perioperative magnetic resonance imaging studies after cardiac operations are a *tour de force*, thus identifying a specific circulating biomarker of blood–brain barrier disruption would aid assessment of much needed pharmacologic and nonpharmacological interventions to improve blood–brain barrier function preoperatively—potentially by optimizing preoperative sleep (such as treating sleep apnea) and vascular disease (such as treating hypertension).

A strength of the study is that standardized preoperative cognitive assessment (Mini-Mental State Exam and Trail Making Test) together with twice-daily postoperative assessments (Confusion Assessment Method for the Intensive Care Unit) were conducted by trained investigators to minimize risk of misclassification bias and detect transitions to delirium, which should become part of clinical consensus. Unfortunately, the study did not attempt to determine specific associations with severity or subtype (hyperactive *versus* hypoactive *versus* mixed) of delirium. Expert opinions state that the hypoactive form is frequently missed when using established diagnostic tools, and future implementation of biomarkers in assessment tools could be especially useful. The field would further benefit from shifting the current dichotomized endpoint definition of delirium, based on Confusion Assessment Method for the Intensive Care Unit assessment, to a deep phenotyping of delirium, including quantitative neurophysiological and neuroimaging information.[10]

In conclusion, Lopez *et al.* provide us with valuable data suggesting that *intraoperative* oxidative brain injury

may contribute to delirium, refocusing important clinical research questions related to intraoperative interventions to reduce brain injury and postoperative delirium. Irrespective of a possible causal relationship between oxidative injury, blood–brain barrier disruption, neuronal injury, and postoperative delirium, if independently validated in other cohorts, the circulating markers reported by Lopez *et al*. may become part of a molecular signature used to predict, monitor, and modify a patient's perioperative cognitive trajectory.

Research Support

Supported by National Institutes of Health grant No. R01HL130443 (Bethesda, Maryland; to Dr. Mathew); a Duke Pepper Older Americans Independence Center (NIA P30AG028716) and a Duke Health Scholars award (Durham, North Carolina; to Dr. Podgoreanu); and a Foundation for Anesthesia Education and Research award (Schaumburg, Illinois; to Dr. Devinney).

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Podgoreanu: mihai.podgoreanu@duke.edu

References

1. Rudolph JL, Jones RN, Levkoff SE, Rockett C, Inouye SK, Sellke FW, Khuri SF, Lipsitz LA, Ramlawi B, Levitsky S, Marcantonio ER: Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. Circulation 2009; 119:229–36
2. Maldonado JR: Neuropathogenesis of delirium: review of current etiologic theories and common pathways. Am J Geriatr Psychiatry 2013; 21:1190–222
3. Lopez MG, Hughes CG, DeMatteo A, O'Neal JB, McNeil JB, Shotwell MS, Morse J, Petracek MR, Shah AS, Brown NJ, Billings FT: Intraoperative oxidative damage and delirium after cardiac surgery. Anesthesiology 2020; 132:551–61
4. Billings FT IV, Hendricks PA, Schildcrout JS, Shi Y, Petracek MR, Byrne JG, Brown NJ: High-Dose perioperative atorvastatin and acute kidney injury following cardiac surgery: A randomized clinical trial. JAMA 2016; 315:877–88
5. Karlidag R, Unal S, Sezer OH, Bay Karabulut A, Battaloğlu B, But A, Ozcan C: The role of oxidative stress in postoperative delirium. Gen Hosp Psychiatry 2006; 28:418–23
6. Ulus AT, Aksoyek A, Ozkan M, Katircioglu SF, Vessby B, Basu S: Oxidative stress and changes in alpha- and gamma-tocopherol levels during coronary artery bypass grafting. Ann N Y Acad Sci 2004; 1031:352–6
7. Schoen J, Meyerrose J, Paarmann H, Heringlake M, Hueppe M, Berger KU: Preoperative regional cerebral oxygen saturation is a predictor of postoperative delirium in on-pump cardiac surgery patients: A prospective observational trial. Crit Care 2011; 15:R218
8. Lopez MG, Pandharipande P, Morse J, Shotwell MS, Milne GL, Pretorius M, Shaw AD, Roberts LJ 2nd, Billings FT IV: Intraoperative cerebral oxygenation, oxidative injury, and delirium following cardiac surgery. Free Radic Biol Med 2017; 103:192–8
9. Abrahamov D, Levran O, Naparstek S, Refaeli Y, Kaptson S, Abu Salah M, Ishai Y, Sahar G: Blood-Brain barrier disruption after cardiopulmonary bypass: Diagnosis and correlation to cognition. Ann Thorac Surg 2017; 104:161–9
10. Sun H, Kimchi E, Akeju O, Nagaraj SB, McClain LM, Zhou DW, Boyle E, Zheng WL, Ge W, Westover MB: Automated tracking of level of consciousness and delirium in critical illness using deep learning. NPJ Digit Med 2019; 2:89