

reported preliminary findings that tentatively support the conclusion that brief exposure of human infants to anesthesia is associated with increased risk of long-term neurobehavioral disturbances.³⁻⁷ One study did not find an association, but anesthesia exposure was documented only by parental reporting.⁸ These studies and the tentative nature of their conclusions illustrate the difficulty of designing and conducting definitive clinical studies of anesthetic neurotoxicity. While prospective clinical studies are designed and conducted over the next several years, further animal research can provide insights into the mechanisms of anesthetic neurotoxicity and the identification of anesthetic regimens that are not neurotoxic in neonates.

Drs. Mazoit, Roulleau, and Baujard raise an important question: is it possible that the reported findings¹ may be caused by some mechanism other than a direct action of the anesthetic drug? Specifically, they postulate that hypoxia/ischemia, secondary to reduced blood pressure, can explain the neuroapoptosis response in our isoflurane-treated infant monkeys. It is important to recognize that there is no evidence for the claim that reduced blood pressure, even to an extreme degree, can trigger acute neuroapoptosis in the developing brain of any species. In contrast, there are more than 50 published reports from multiple independent laboratories showing that alcohol and anesthetic or anticonvulsant drugs do trigger acute neuroapoptosis in the developing rodent and monkey brain. Moreover, we have shown previously that hypoxia/ischemia causes an acute *excitotoxic* cell death response in the developing rodent brain that is not accompanied in the acute period by any evidence of apoptotic neurodegeneration.⁹⁻¹¹ In contrast, anesthetic drugs cause an acute *apoptotic* cell death response in the developing brain that is not accompanied by any evidence of excitotoxic neurodegeneration.^{1,12-15} Evidence that intentional induction of profound hypoxia/ischemia does not trigger an acute apoptosis response in the developing brain signifies that it is highly unlikely that a decrease in blood pressure to a modest nonischemic degree will trigger acute neuroapoptosis.

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References

1. Brambrink AM, Evers AS, Avidan MS, Farber NB, Smith DJ, Zhang X, Dissen GA, Creeley CE, Olney JW: Isoflurane-induced neuroapoptosis in the neonatal rhesus macaque brain. *ANESTHESIOLOGY* 2010; 112:834-41
2. Creeley CE, Olney JW: The young: Neuroapoptosis induced by anesthetics and what to do about it. *Anesth Analg* 2010; 110:442-8
3. DiMaggio C, Sun LS, Kakavouli A, Byrne MW, Li G: A retrospective cohort study of the association of anesthesia and hernia repair surgery with behavioral and developmental disorders in young children. *J Neurosurg Anesthesiol* 2009; 21:286-91
4. Kalkman CJ, Peelen L, Moons KG, Veenhuizen M, Bruens M, Sinnema G, de Jong T: Behavior and development in

children and age at the time of first anesthetic exposure. *ANESTHESIOLOGY* 2009; 110:805-12

5. Wilder RT, Flick RP, Sprung J, Katusic SK, Barbaresi WJ, Mickelson C, Gleich SJ, Schroeder DR, Weaver AL, Warner DO: Early exposure to anesthesia and learning disabilities in a population-based birth cohort. *ANESTHESIOLOGY* 2009; 110:796-804
6. DiMaggio C, Sun LS, Li G: Early childhood exposure to anesthesia and risk of developmental and behavioral disorders in a birth cohort of 5824 twin pairs (abstract). Presented at: The IARS and SAFEKIDS International Science Symposium: Anesthetic-Induced Neonatal Neuronal Injury, Honolulu, HI, March 20, 2010 (ISS-A1)
7. Thomas JJ, Choi JW, Bayman EO, Kimble KK, Todd MM, Block RI: Does anesthesia exposure in infancy affect academic performance in childhood (abstract ISS-A1)? Presented at: The IARS and SAFEKIDS International Science Symposium: Anesthetic-Induced Neonatal Neuronal Injury, Honolulu, HI, March 20, 2010
8. Bartels M, Althoff RR, Boomsma DI: Anesthesia and cognitive performance in children: No evidence for a causal relationship. *Twin Res Hum Genet* 2009; 12:246-53
9. Ikonomidou C, Price MT, Mosinger JL, Friedrich G, Labruyere J, Shahid Salles KS, Olney JW: Hypobaric-ischemic conditions produce glutamate-like cytopathology in infant rat brain. *J Neurosci* 1989; 9:1693-700
10. Ishimaru MJ, Ikonomidou C, Tenkova TI, Der TC, Dikranian K, Sesma MA, Olney JW: Distinguishing excitotoxic from apoptotic neurodegeneration in the developing rat brain. *J Comp Neurol* 1999; 408:461-76
11. Young C, Tenkova T, Dikranian K, Olney JW: Excitotoxic versus apoptotic mechanisms of neuronal cell death in perinatal hypoxia/ischemia. *Curr Mol Med* 2004; 4:77-85
12. Ikonomidou C, Bittigau P, Ishimaru MJ, Wozniak DF, Koch C, Genz K, Price MT, Stefovskova V, Hörster F, Tenkova T, Dikranian K, Olney JW: Ethanol-induced apoptotic neurodegeneration and fetal alcohol syndrome. *Science* 2000; 287:1056-60
13. Dikranian K, Ishimaru MJ, Tenkova T, Labruyere J, Qin YQ, Ikonomidou C, Olney JW: Apoptosis in the *in vivo* mammalian forebrain. *Neurobiol Dis* 2001; 8:359-79
14. Jevtovic-Todorovic V, Hartman RE, Izumi Y, Benshoff ND, Dikranian K, Zorumski CF, Olney JW, Wozniak DF: Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. *J Neurosci* 2003; 23:876-82
15. Young C, Jevtovic-Todorovic V, Qin YQ, Tenkova T, Wang H, Labruyere J, Olney JW: Potential of ketamine and midazolam, individually or in combination, to induce apoptotic neurodegeneration in the infant mouse brain. *Br J Pharmacol* 2005; 146:189-97

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Postoperative Cognitive Decline: The Unsubstantiated Phenotype

To the Editor:

Correlation of a clinical outcome (phenotype) with a biomarker or genotype requires accurate phenotyping and genotyping. We question the accuracy and reliability of phenotyping (determination of postoperative cognitive dysfunction [POCD] at 1 yr) by McDonagh *et al.*¹ POCD lacks consensus diagnostic criteria, and disparate methods have been employed for its detection.² There are several method-

ological issues pertaining to the approach taken by McDonagh *et al.*¹ that substantially weaken the measurement of POCD: (1) meticulously-matched control groups are imperative if cognitive decline is attributed to anesthetic/surgical events rather than underlying patient comorbidity³ (there was no control group in this study); (2) clinically meaningful, objective outcome measures, such as incident dementia,⁴ are interpretable and comparable across studies, as opposed to the artificial composite cognitive outcome measures used in this study; (3) the arbitrary statistical thresholds for POCD diagnosis employed in this study are likely inappropriate and of questionable clinical relevance;² and (4) preoperative mild dementia should have been assiduously identified, because mild dementia, although difficult to detect, is a potent confounder in relation to POCD.⁵

McDonagh *et al.*¹ reported a 46% 1-yr incidence of POCD and mention that other studies have found different results. However, no studies by other groups have found rates of persistent POCD even remotely approaching the alarming rate found in this study. Some investigators have found little evidence for persistent POCD attributable to a surgical event,^{3,5} whereas others have found rates between 1 and 5%.^{6,7} The investigators suggest that patient, surgical, and anesthetic factors may all be implicated in the causes of POCD.¹ However, they specifically provide evidence against anesthetic factors in showing no difference in POCD between regional and general anesthesia.¹ Could it be that surgery and anesthesia were coincidental and that patient factors alone determined POCD? Might an appropriate control group have shown equivalent cognitive decline?

McDonagh *et al.*¹ employed a principal component analysis to derive four components representing four cognitive domains. No factor loadings on individual tests were reported. Because most principal components contain positive and negative loadings because of the orthogonality requirement, these loadings are important to provide the direction of cognitive score. Furthermore, assuming that a decline in a component score is associated with POCD, McDonagh *et al.*¹ defined POCD as a decline of 1 SD or more in at least one of the four cognitive domains. This definition has two major drawbacks: (1) it depends heavily on the number of principal components and (2) it ignores the time interval after the surgery. By definition, the probability (p) of POCD increases with the number of principal components used. To illustrate this, consider a hypothetical nonsurgical control group. Let q be the probability of individuals in this group not meeting the definition of POCD for a specific cognitive domain (*i.e.*, not declining more than 1 SD). If we assume that the extents of change from baseline for the four cognitive domains follow the same normal distribution and are independent, then the probability in the control group of meeting the definition of POCD would be $1 - q^4$. Even with the relatively conservative assumption that 90% of the hypothetical controls would not meet the diagnostic threshold for POCD on each of the cognitive domains (*i.e.*, $q = 0.9$), the apparent incidence of cognitive decline by the McDonagh *et*

*al.*¹ criteria would still be 34% (*i.e.*, $1 - 0.9^4$) in this hypothetical group. It would therefore be useful if the investigators would clarify what incidence of POCD they expected purely by chance with their model and what their incidence of postoperative cognitive enhancement was, using more than 1 SD improvement in any cognitive domain as a threshold criterion. It would also be helpful to know how the investigators classified patients if they declined by more than 1 SD in one uncorrelated test and improved by more than 1 SD in another.

A further concern is that the reported incidence rate of POCD seems inconsistent with the reported change scores from baseline on the continuous cognitive index, which is the average of four component scores.¹ Among the entire sample, including subjects with and without the APOE4 allele, the 6-week change in cognitive score from baseline had a mean of only 0.05–0.07 (*i.e.*, very mild improvement compared with baseline) with an SD of approximately 0.27–0.28. Given these results, the estimated incidence of a decline of at least -0.5 (the decline in the cognitive index that the authors defined as clinically meaningful) would be roughly 2%, much smaller than the reported 6-week POCD incidence of 54.3%.

For a longitudinally observed function such as cognitive decline, discrete analyses (*i.e.*, incidence of POCD at 6 weeks and 1 yr) might not be optimal. It is crucial to understand the time course of POCD. A longitudinal analysis was not provided but is required to assess the entire longitudinal change from baseline to 6 weeks and then to 1 yr. A simple incidence rate of POCD at each individual time point does not offer much information on those who initially declined fast and then recovered or those who did well initially and then declined fast. The investigators should comment what the extent of overlap was between those who met their POCD diagnostic criteria at 6 weeks and those who met their criteria at 1 yr.

The findings of McDonagh *et al.*¹ could have paradigm-changing implications. If 46% of patients undergoing major elective surgery were really to experience clinically meaningful persistent POCD, it is likely that informed patients would choose to forego many such procedures. If, on the other hand, considerably fewer than 46% were to have persistent POCD, the reported phenotyping would be inaccurate, and correlation with the genotype (APOE4) would be meaningless. Let's hope that the latter is true.

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References

- McDonagh DL, Mathew JP, White WD, Phillips-Bute B, Laskowitz DT, Podgoreanu MV, Newman MF, Neurologic Outcome Research Group: Cognitive function after major noncardiac surgery, apolipoprotein E4 genotype, and biomarkers of brain injury. *ANESTHESIOLOGY* 2010; 112:852-9
- Newman S, Stygal J, Hirani S, Shaefi S, Maze M: Postoperative cognitive dysfunction after noncardiac surgery: A systematic review. *ANESTHESIOLOGY* 2007; 106:572-90

3. Selnes OA, Grega MA, Bailey MM, Pham LD, Zeger SL, Baumgartner WA, McKhann GM: Cognition 6 years after surgical or medical therapy for coronary artery disease. *Ann Neurol* 2008; 63:581-90
4. Ehlenbach WJ, Hough CL, Crane PK, Haneuse SJ, Carson SS, Curtis JR, Larson EB: Association between acute care and critical illness hospitalization and cognitive function in older adults. *JAMA* 2010; 303:763-70
5. Avidan MS, Searleman AC, Storandt M, Barnett K, Vannucci A, Saager L, Xiong C, Grant EA, Kaiser D, Morris JC, Evers AS: Long-term cognitive decline in older subjects was not attributable to noncardiac surgery or major illness. *ANESTHESIOLOGY* 2009; 111:964-70
6. Abildstrom H, Rasmussen LS, Rentow P, Hanning CD, Rasmussen H, Kristensen PA, Moller JT: Cognitive dysfunction 1-2 years after non-cardiac surgery in the elderly. ISPOCD group. International Study of Post-Operative Cognitive Dysfunction. *Acta Anaesthesiol Scand* 2000; 44:1246-51
7. Williams-Russo P, Sharrock NE, Mattis S, Szatrowski TP, Charlson ME: Cognitive effects after epidural vs general anesthesia in older adults. A randomized trial. *JAMA* 1995; 274:44-50

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In Reply:

We thank Avidan *et al.*¹ for their interest in our study and for the opportunity to respond to their concerns, many of which had already been addressed in our article.¹ To begin with, we fully agree that recent studies have highlighted the need for control groups to separate the effects of surgery from aging or underlying disease. Unfortunately, at the time of study inception, a control group was not included, largely as a result of the budgetary limits imposed by the National Institutes of Health. The financial challenges associated with pursuing prospective randomized controlled trials are formidable and frequently mandate other designs, as is evidenced by Dr. Avidan's own *retrospective* work on cognitive dysfunction.² There is also controversy in longitudinal studies as to the appropriate control group and how large it would need to be to minimize crossover. In addition, our primary hypothesis examined the effect of APOE4 genotype upon cognition; therefore, the non-APOE4 subjects were, in effect, the control group. Although the overall rate of cognitive dysfunction may be higher without a "true control group," our finding of no significant effect of APOE4 genotype is still valid.

Second, Avidan *et al.* object to an arbitrary statistical threshold for the diagnosis of postoperative cognitive dysfunction (POCD). Defining POCD as deficit or no-deficit requires specifying a cutoff for amount of decline. In the absence of a criterion standard, any cutoff is arbitrary. We believe a decline of more than 1 SD represents a clinical and noticeable loss in cognitive function. First, in an assessment in which most patients improve over time, any decline is bad. Further, in other samples,

we have seen a significant association between our defined POCD and cognitive difficulty reported by patients themselves in a 39-item assessment of perceived problems in memory, concentration, attention, and psychomotor coordination. The questionnaire includes items such as "I forget errands I planned to do" and "I fail to recognize people I know." A higher score is worse. Patients we classified as having POCD had a mean increase [mean (SD)] of +1.64 (22.1) in difficulties at 6 weeks after surgery, whereas no-POCD patients had a mean decrease of -2.54 (19.4), $P = 0.02$. A trend toward increased mortality at 1 yr in patients with POCD (3.16 vs. 1.25%, $P = 0.23$) was also reported in our article. Thus, our choice of a 1 SD decline does have some clinical relevance. Nevertheless, because any threshold is arbitrary in the absence of a criterion standard, we have also examined a continuous change score, which is calculated by subtracting the baseline from the follow-up cognitive index (mean of the four domain scores). As with the dichotomous outcome, there is no association between APOE4 and cognitive change, once again validating our finding of no significant effect of APOE4 genotype.

Third, the issue of baseline "mild dementia" was raised. As Avidan and colleagues² have demonstrated, baseline mild cognitive impairment or dementia may be confounders when assessing long-term POCD. However, this cognitive impairment can be in single or multiple cognitive domains and can have a variety of clinical manifestations.^{3,4} The International Working Group on Mild Cognitive Impairment published their first efforts toward a consensus in this arena in 2004,³ but only near the completion of our study. Gauthier *et al.*⁴ have more recently highlighted the ongoing uncertainty and debate in this field, noting in particular that "the prognosis in terms of progression to dementia is more heterogeneous in population studies than in the setting of specialized clinics (*such as an Alzheimer's Disease Research Center*) and is driven by the nosological and exclusionary criteria being used in either setting." At the very least, further studies defining and validating the effects of baseline dementia are still needed. In our study focused on shorter-term cognitive dysfunction, we compared postoperative cognition with preoperative baseline values to make each patient his/her own "control" while acknowledging the inherent limitations to this approach.

Fourth, the etiology of POCD remains incompletely ascertained at this time, as Dr. Avidan points out. We do think, however, that it is inappropriate to conclude from our study that anesthetic factors have no effect on POCD because our study was not designed to examine that hypothesis. Thus, we made no conclusions regarding the etiology of POCD. We simply found no association between APOE4 genotype, as well as a panel of serum biomarkers, and postoperative cognitive decline, assessed either as a dichotomous or a continuous measure.

Fifth, Avidan *et al.* requested greater detail on the factor loadings used in our cognitive analyses; these are provided in table 1. We did not publish this table because we believed it would not be meaningful or interpretable to most readers. Trails-Making B scores were reversed to

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