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Hyperoxia in Pediatric Anesthesia: Time for Reconsideration?

To the Editor:—Kalkman *et al.*[1] link anesthesia to clinically deviant behaviors in children anesthetized for urologic procedures before age 2 yr but make no mention of intraoperative oxygen measurement in their study cohort. Wilder *et al.*[2] link multiple pediatric anesthetic exposures to learning disabilities using a sophisticated database, albeit one built before pulse oximetry was in wide use. Editorially, Patel and Sun[3] provide a review of molecular mechanisms with "relevance" to human development that overlooks the current state of data pertaining to oxygen's neurotoxic effects in cell and animal models. Although all exemplify Engle's proposition that scientists and clinicians must account for how submolecular or molecular actions ramify through a "continuum of natural systems" to produce events at higher systems levels—persons, families, communities, cultures, the biosphere—none acknowledge that early and multiple anesthetic exposure is also a marker for early and multiple oxygen exposure.[4,5]

Anesthesiologists and the anesthesia literature, by and large, tend to discount supplemental oxygen effects in patient care in the absence of ischemia–reperfusion injury.[6] Others have more balanced views. Maltepe and Saugstad[7] note that evolution equips humans with numerous hypoxemia defense responses; hyperoxia, however, always iatrogenic, is not as easily defended against, biologically speaking. Neonatologists know hyperoxia is not always beneficial in neonatal resuscitation.[8] Supplemental oxygen use for 3 min or more at birth shows a vexing connection to an increased cancer incidence for children younger than 8 yr.[9] The now well established association of retinopathy of prematurity with supplemental oxygen use was incorrectly overlooked for decades.[10]

Degos *et al.*[11] list hypoxia-induced oxidative stress reduction among potential targets for neuroprotective efforts. But significant hypoxemia may be less common than intentional hyperoxia in pediatric anesthesia practice. Even with the classic 70% nitrous oxide–30% oxygen plus volatile anesthetic inhalational induction sequence, hyperoxia exists. Recent bench research using cell cultures and animal models shows that hyperoxia alters cell ultrastructure and function across multiple organelle and neuronal action sites: mitochondria, membrane surfaces, cell nuclei, and progenitor cell lines.[12–14] Reactive oxygen species, with other mechanisms, are a source of submolecular injury where hyperoxia is induced experimentally. Such data suggest that neurocidal/neurotoxic potential effects research must account for hyperoxia's submolecular effects, too—effects Engle's model predicts will express at higher levels of biopsychosocial organization.

Endeavors such as Safety of Key Inhaled and Intravenous Drugs in Pediatrics (SAFEKIDS) and General Anesthesia for Effects on Neurodevelopmental Outcome and Apnea in infants (GAS) are much needed.[15] Should protocols in future clinical studies include control anesthetics administered at atmospheric or "capped" oxygen partial pressures? Controlled for, hyperoxic effects—known and unknown—might be reasonably addressed as answers emerge to the question, Do anesthetics damage the developing human brain? How else can we gain certainty that iatrogenic hyperoxia does not also play a role in the human developmental adverse outcomes we are now tempted to attribute predominantly to anesthetic agents? Sound science dictates that any known factors that might contribute to pediatric behavioral problems, such as lead, iron, and mercury levels—not just anesthetic exposure—should be taken into account.[16] Iatrogenic hyperoxia, sadly, might need to be investigated, too.

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References

1. Kalkman CJ, Peelen L, Moons KG, Veenhuizen M, Bruens M, Sinnema G, de Jong TP: Behavior and development in children and the age at the first anesthetic exposure. ANESTHESIOLOGY 2009; 110:805–12
2. Wilder RT, Flick RP, Sprung J, Katusic SK, Barabresi 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
3. Patel P, Sun L: Update on neonatal anesthetic neurotoxicity: Insight into molecular mechanisms and relevance to humans. ANESTHESIOLOGY 2009; 110: 703–7
4. Engel GL: The need for a new medical model: A challenge for biomedicine. Science 1977; 196:129–36
5. Engle GL: The clinical application of the biopsychosocial model. Am J Psychiatry 1980; 137:535–44
6. Forkner IF, Piantidosi CA, Scafetta N, Moon RE: Hyperoxia-induced tissue hypoxia: A danger? ANESTHESIOLOGY 2007; 106:1051–5
7. Maltepe E, Saugstad OD: Oxygen in health and disease: Regulation of oxygen homeostasis—Clinical implications. Pediatr Res 2009; 65:261–8
8. Vento M, Asensi M, Sastre J, García-Sala F, Pallardó FV, Viña J: Resuscitation with room air instead of 100% oxygen prevents oxidative stress in moderately asphyxiated term neonates. Pediatrics 2001; 107:642–7
9. Spector LG, Klebanoff MA, Feusner JH, Georgieff MK, Ross JA: Childhood cancer following neonatal oxygen supplementation. J Pediatr 2005; 147:27–31
10. Jacobson RM, Feinstein AR: Oxygen as a cause of blindness in premature infants: "Autopsy" of a decade of errors in clinical epidemiologic research. J Clin Epidemiol 1992; 45:1265–87
11. Degos V, Loron G, Mantz J, Gressens P: Neuroprotective strategies for the neonatal brain. Anesth Analg 2008; 106:1670–80
12. D'Agostino DP, Olson JE, Dean JB: Acute hyperoxia increases lipid peroxidation and induces plasma membrane blebbing in human U87 glioblastoma cells. Neuroscience 2009; 159:1011–22
13. Chang E, Hornick K, Fritz KI, Mishra OP, Delivoria-Papadopoulos M: Effect of hyperoxia on cortical neuronal nuclear function and programmed cell death mechanisms. Neurochem Res 2007; 32:1142–9
14. Koch JD, Miles DK, Gilley JA, Yang CP, Kernie SG: Brief exposure to hyperoxia depletes the glial progenitor pool and impairs functional recovery after hypoxic-ischemic brain injury. J Cereb Blood Flow Metab 2008; 28:1294–306
15. FDA to study anesthetic risks in pediatrics. Anesthesiol News 2009; 35:5
16. Canfield RL, Henderson CR Jr, Cory-Slecht DA, Cox C, Jusko TA, Lanphear BP: Intellectual impairment in children with blood lead concentrations below 10 μg per deciliter. N Engl J Med 2003; 348:1517–26

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In Reply:—We read with considerable interest the critical commentary of Kopp with respect to our editorial in the April issue of ANESTHESIOLOGY.[1] That editorial presented a brief introduction to the research articles that were presented at the ANESTHESIOLOGY/Foundation for Anesthesia Education and Research Symposium on Anesthetics and the Developing Brain; the intent was to summarize current research in anesthetic neurotoxicity with an emphasis on the molecular mechanisms that underlie the adverse impact of anesthetics. The central concern expressed by Kopp is the potential toxicity of oxygen. Given that oxygen administration is a routine practice in the clinical practice

of anesthesia, it is highly probable that a state of hyperoxemia is induced in subjects undergoing anesthesia and surgery. Kopp suggests that it is this hyperoxemia that can injure the brain, and in particular the developing brain.

There is growing evidence that the administration of oxygen in concentrations that produce hyperoxemia is associated cellular injury. The adverse impact of high concentrations of oxygen on retinopathy of prematurity[2] and on bronchopulmonary dysplasia[3] has long been recognized. In susceptible neonates, the incidence of cerebral palsy is increased in association with hyperoxemia.[4] More recent evidence also indicates that resuscitation of premature neonates with a high fraction of inspired oxygen (F_{IO_2}) is associated with greater mortality and worse outcomes.[5] Indeed, the authors of a recent metaanalysis concluded that the available data support the use of room air for resuscitation of asphyxiated neonates in place of 100% oxygen.[5] Importantly, the use of room air for this purpose does not seem to be associated with worse cognitive outcomes.[6] Preclinical studies in adult animals also suggest that resuscitation from global ischemia with high F_{IO_2} leads to greater neurologic injury.[7]

In the investigations of Kalkman *et al.*[8] and Wilder *et al.*,[9] the concentration of oxygen that was administered is not clear. It is reasonable to assume, based on the current standard of practice, that supplemental oxygen was administered and some degree of hyperoxemia did occur. Could the association between anesthetic exposure and adverse outcomes be explained by oxygen toxicity rather than anesthetics? Although Kopp's contention is feasible, it is difficult to separate the effects of oxygen from those of the patients' primary disease, anesthetics, surgery, postsurgical inflammation, and use of analgesics. The question of whether oxygen can injure the otherwise normal developing brain is best answered in the laboratory.

Of significant interest are the observations of Felderhoff-Mueser *et al.*,[10] who demonstrated oxygen toxicity in the developing brain. An inspired concentration of oxygen of 80% resulted in widespread neurodegeneration; toxicity was apparent with as little as 2 h of exposure. The pattern of injury was similar to that produced by anesthetics. Moreover, the period of vulnerability, as with anesthetics, was approximately postnatal day 7, with little injury seen at postnatal day 14. By contrast, injury was not observed with the administration of 40% oxygen for as long as 12 h. This begs the question of whether anesthetic toxicity observed in previously published studies might be due to oxygen.

In published studies to date, the reported inspired concentrations of oxygen were 30%,[11] 50%,[12,13] and 21%.[14,15] The duration of exposure ranged from 4 to 6 h. In these studies, injury produced with anesthesia was significantly greater than that in control nonanesthetized animals. With the exception of the studies of Stratmann *et al.*,[12,13] the concentration of oxygen used was well below the level that has been shown to produce injury to the developing brain. Furthermore, the duration of exposure is well below the 12-h exposure to 40% oxygen in the study of Felderhoff-Mueser *et al.*[10] in which injury was not observed. The available data indicate, therefore, that in experimental models, the toxicity produced by anesthetic exposure is not due to oxygen administration but due to anesthetics.

There is a remote possibility that there might be a *relative* increase in brain tissue partial pressure of oxygen (P_{O_2}) during anesthesia, even with the administration of air. Anesthetics decrease the cerebral metabolic rate for oxygen substantially and, depending on the inspired concentration of inhaled agents, cerebral blood flow may increase. Whether this relative increase in tissue P_{O_2} is detrimental in the developing brain is not clear. However, it is not outside of the realm of possibility that relative tissue hyperoxia might reduce the antioxidant defenses of neurons[16] and thereby make them more vulnerable to anesthetic neurotoxicity. This question will have to be addressed experimentally. We therefore invite Dr. Kopp to join us in our efforts to more definitely characterize anesthetic (and oxygen) toxicity in the developing brain and to develop the means and practices by which this toxicity can be prevented. This would, to paraphrase Kopp, allow us to bring more balance to the discussion.

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References

1. Patel P, Sun L: Update on neonatal anesthetic neurotoxicity: Insight into molecular mechanisms and relevance to humans. ANESTHESIOLOGY 2009; 110:703–8
2. Vanderveen DK, Mansfield TA, Eichenwald EC: Lower oxygen saturation alarm limits decrease the severity of retinopathy of prematurity. J AAPOS 2006; 10:445–8
3. Tin W, Gupta S: Optimum oxygen therapy in preterm babies. Arch Dis Child Fetal Neonatal Ed 2007; 92:F143–7
4. Klinger G, Beyene J, Shah P, Perlman M: Do hyperoxaemia and hypocapnia add to the risk of brain injury after intrapartum asphyxia? Arch Dis Child Fetal Neonatal Ed 2005; 90:F49–52
5. Rabi Y, Rabi D, Yee W: Room air resuscitation of the depressed newborn: A systematic review and meta-analysis. Resuscitation 2007; 72:353–63
6. Deulofeut R, Critz A, Adams-Chapman I, Sola A: Avoiding hyperoxia in infants < or = 1250 g is associated with improved short- and long-term outcomes. J Perinatol 2006; 26:700–5
7. Balan IS, Fiskum G, Hazelton J, Cotto-Cumba C, Rosenthal RE: Oximetry-guided reoxygenation improves neurological outcome after experimental cardiac arrest. Stroke 2006; 37:3008–13
8. Kalkman CJ, Peelen L, Moons KG, Veenhuizen M, Bruens M, Sinnema G, de Jong TP: Behavior and development in children and age at the time of first anesthetic exposure. ANESTHESIOLOGY 2009; 110:805–12
9. 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
10. Felderhoff-Mueser U, Bittigau P, Sifringer M, Jarosz B, Korobowicz E, Mahler L, Piening T, Moysich A, Grune T, Thor F, Heumann R, Buhrer C, Ikonomidou C: Oxygen causes cell death in the developing brain. Neurobiol Dis 2004; 17:273–82
11. 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
12. Stratmann G, May LD, Sall JW, Alvi RS, Bell JS, Ormerod BK, Rau V, Hilton JF, Dai R, Lee MT, Visrodia KH, Ku B, Zusmer EJ, Guggenheim J, Firouzian A: Effect of hypercarbia and isoflurane on brain cell death and neurocognitive dysfunction in 7-day-old rats. ANESTHESIOLOGY 2009; 110:849–61
13. Stratmann G, Sall JW, May LD, Bell JS, Magnusson KR, Rau V, Visrodia KH, Alvi RS, Ku B, Lee MT, Dai R: Isoflurane differentially affects neurogenesis and long-term neurocognitive function in 60-day-old and 7-day-old rats. ANESTHESIOLOGY 2009; 110:834–48
14. Head BP, Patel HH, Niesman IR, Drummond JC, Roth DM, Patel PM: Inhibition of p75 neurotrophin receptor attenuates isoflurane-mediated neuronal apoptosis in the neonatal central nervous system. ANESTHESIOLOGY 2009; 110:813–25
15. Johnson SA, Young C, Olney JW: Isoflurane-induced neuroapoptosis in the developing brain of nonhypoglycemic mice. J Neurosurg Anesthesiol 2008; 20:21–8
16. Kaindl AM, Sifringer M, Zabel C, Nebrich G, Wacker MA, Felderhoff-Mueser U, Endesfelder S, von der Hagen M, Stefovska V, Klose J, Ikonomidou C: Acute and long-term proteome changes induced by oxidative stress in the developing brain. Cell Death Differ 2006; 13:1097–109

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In Reply:—We are gratified by the interest generated by the publication of our recent article.[1] The accompanying letters raise important issues and questions relevant to our article and to the question of anesthetic neurotoxicity as it applies to children. The concerns expressed by the various authors can be categorized as follows: (1) The observed effect may reflect comorbidity or other unidentified factors rather than the effects of anesthesia *per se* (Arul and Thies, Pysyk *et al.*, Taylor); (2) the definitions for learning disability (LD) were inappro-