

Does B-type Natriuretic Peptide or Its Gene Polymorphism Predict Patient Outcome after Coronary Artery Bypass Graft Surgery?

To the Editor:—We read with great interest the research article by Fox *et al.*¹ on genetic variation within defined regions of the *NPPA/NPPB* and *NPR3* natriuretic peptide system genes as predictors for ventricular dysfunction after coronary artery bypass graft surgery. What concerns us as clinicians is the relation between those biomarkers and postoperative outcome, which can facilitate the preoperative risk evaluation. This article raised a good question: whether B-type natriuretic peptide (BNP) or its gene polymorphism predicts the prognosis in patients undergoing coronary artery bypass graft surgery.

It is well known that a gene's function is mediated by expression of a specific protein. BNP has been established as a prognostic indicator in adults with congestive heart failure² and coronary artery disease,³ whereas single nucleotide polymorphisms (SNPs) in the *NPPB* gene significantly impact BNP levels.⁴ In the article by Dr. Fox *et al.*, there was mention that genetic variation within *NPPA/NPPB* and *NPR3* genes was associated with risk of ventricular dysfunction after adjustment for preoperative BNP level and clinical factors. However, the authors did not directly analyze the relation between SNPs of these BNP genes with BNP level, especially postoperative BNP, whose level was not provided. Previous study has shown that early postoperative BNP levels correlate significantly with the ensuing duration of inotropic support and duration of hospitalization.⁵ Therefore, we considered that SNPs of BNP genes could affect postoperative BNP rather than preoperative BNP and then predicted the prognosis, because expression of those genetic loci could be up- or down-regulated by mechanical stretch, ischemic injury, hypoxia, or even inflammatory mediators during surgery.⁶ And the analysis should include both preoperative and postoperative BNP levels in this study.

We think that the predictive pathway should be: SNPs of BNP-BNP level-clinical prognosis. If this hypothesis is established, it is postoperative BNP rather than SNPs of BNP that directly predicts ventricular dysfunction. Further investigations are still required to elucidate how BNP and its SNPs relate to development of postoperative ventricular dysfunction.

Hai Yu, M.D., Da Zhu, M.D., Bin Liu, M.D.* West China Hospital, Sichuan University, Chengdu, Sichuan, People's Republic of China. benbinliu@hotmail.com

References

1. Fox AA, Collard CD, Shernan SK, Seidman CE, Seidman JG, Liu KY, Muehlschlegel JD, Perry TE, Aranki SF, Lange C, Herman DS, Meitinger T, Lichtner P, Body SC: Natriuretic peptide system gene variants are associated with ventricular dysfunction after coronary artery bypass grafting. *ANESTHESIOLOGY* 2009; 110:738-47
2. Doust JA, Pietrzak E, Dobson A, Glasziou P: How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: Systematic review. *BMJ* 2005; 330:625
3. Kragelund C, Gronning B, Kober L, Hildebrandt P, Steffensen R: N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. *N Engl J Med* 2005; 352:666-75
4. Lanfear DE, Stolk JM, Marsh S, Rich MW, McLeod HL: Genetic variation in the B-type natriuretic peptide pathway affect BNP levels. *Cardiovasc Drugs Ther* 2007; 21:55-62
5. Berry JG, Askovich B, Shaddy RE, Hawkins JA, Cowley CG: Prognostic value of B-type natriuretic peptide in surgical palliation of children with single-ventricle congenital heart disease. *Pediatr Cardiol* 2008; 29:70-5
6. Martinez-Rumayor A, Richards AM, Burnett JC, Januzzi JL Jr: Biology of the natriuretic peptides. *Am J Cardiol* 2008; 101:3-8

(Accepted for publication July 29, 2009.)

In Reply:—We appreciate the interest of Dr. Yu *et al.* in our April 2009 publication in which we describe significant associations between single nucleotide polymorphisms (SNPs) within the natriuretic peptide *NPPA*, *NPPB*, and *NPR3* genes and the occurrence of ventricular dysfunction (VnD) after primary coronary artery bypass graft surgery.¹ We agree that assessing natriuretic peptide system gene SNPs for association with perioperative plasma B-type natriuretic peptide (BNP) levels may improve understanding of the underlying biology linking these SNPs to postoperative VnD, and we are currently conducting these analyses.

Although we agree with Dr. Yu *et al.* that the association between natriuretic peptide SNPs and perioperative BNP concentrations should be assessed, the biologic mechanisms for the association between these SNPs and postoperative VnD may be more complex than the pathway that they propose, *i.e.*, that natriuretic peptide system gene variants predict perioperative plasma BNP levels, which in turn predict postoperative VnD. As Dr. Yu *et al.* rightly point out, increased plasma BNP is an established biomarker for heart failure. Indeed, we have previously reported that postoperative plasma BNP is significantly increased in patients who develop in-hospital VnD after coronary artery bypass graft surgery *versus* those who do not.² Despite the fact that circulating plasma BNP is known to be increased in heart failure, we are aware of at least four studies of outpatient, noncardiac cohorts that report that one or more of the *NPPA/NPPB* SNP alleles that we

found associated with decreased VnD associate with increased plasma BNP levels (approximately 10-pg/ml increase in plasma BNP for each copy of the minor allele).³⁻⁶ One hypothesis to explain the seeming conundrum of why plasma BNP may be modestly increased in ambulatory patients who carry *NPPA/NPPB* SNP alleles that are associated with decreased VnD may be that these SNPs code for qualitative as well as quantitative changes in circulating BNP. Indeed, recent studies have shown that there is functional heterogeneity in circulating forms of plasma BNP, with heart failure patients tending to have higher plasma ratios of biologically inactive precursor pro-BNP compared with subjects without heart failure.^{7,8} Certain natriuretic peptide SNPs may be associated with increased production of biologically inactive BNP. Furthermore, there is evidence that natriuretic peptides have both autocrine and paracrine influences on ventricular myocardium.⁹ Therefore, we can postulate that even though a natriuretic peptide gene SNP may associate with increased BNP levels, the qualitative nature of the BNP produced may mitigate the development of postoperative VnD through its direct effects on the myocardium.

In summary, we appreciate the comments of Dr. Yu *et al.* and fully agree that further study of natriuretic peptide system genes, circulating natriuretic peptides, and natriuretic peptide tissue effects are needed to tease out mechanisms for our observed associations between *NPPA/NPPB* and *NPR3* gene variants and development of VnD after coronary artery bypass graft surgery.

Amanda A. Fox, M.D.,* Charles D. Collard, M.D., Stanton K. Shernan, M.D., Christine E. Seidman, M.D., Jonathan G. Seidman, Ph.D., Kuang-Yu Liu, Ph.D., Jochen D. Muehlschlegel, M.D., Tjorvi E. Perry, M.D., Sary F. Aranki, M.D., Christoph Lange, Ph.D., Daniel S. Herman, Thomas Meitinger, M.D., Peter Lichtner, Ph.D., Simon C. Body, M.B.Ch.B., M.P.H. *Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. afox@partners.org

References

1. Fox AA, Collard CD, Shernan SK, Seidman CE, Seidman JG, Liu KY, Muehlschlegel JD, Perry TE, Aranki SF, Lange C, Herman DS, Meitinger T, Lichtner P, Body SC: Natriuretic peptide system gene variants are associated with ventricular dysfunction after coronary artery bypass grafting. *ANESTHESIOLOGY* 2009; 110:738-47
2. Fox AA, Shernan SK, Collard CD, Liu KY, Aranki SF, DeSantis SM, Jarolim P, Body SC: Preoperative B-type natriuretic peptide is as independent predictor of ventricular dysfunction and mortality after primary coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2008; 136:452-61
3. Newton-Cheh C, Larson MG, Vasan RS, Levy D, Bloch KD, Surti A, Guiducci C, Kathiresan S, Benjamin EJ, Struck J, Morgenthaler NG, Bergmann A, Blankenbreg S, Kee F, Nilsson P, Yin X, Peltonen L, Vartiainen E, Salomaa V, Hirschhorn

JN, Melander O, Wang TJ: Association of common variants in NPPA and NPPB with circulating natriuretic peptides and blood pressure. *Nat Genet* 2009; 41: 348-53

4. Takeishi Y, Toriyama S, Takabatake N, Shibata Y, Konta T, Emi M, Kato T, Kawata S, Kubota I: Linkage disequilibrium analyses of natriuretic peptide precursor B locus reveal risk haplotype conferring high plasma BNP levels. *Biochem Biophys Res Commun* 2007; 362:480-4

5. Lajer M, Tarnow L, Jorsal A, Parving HH: Polymorphisms in the B-type natriuretic peptide (BNP) gene are associated with NT-proBNP levels but not with diabetic nephropathy or mortality in type 1 diabetic patients. *Nephrol Dial Transplant* 2007; 22:3235-9

6. Lanfear DE, Stalker JM, Marsh S, Rich MW, McLeod HL: Genetic variation in the B-type natriuretic peptide pathway affects BNP levels. *Cardiovasc Drugs Ther* 2007; 21:55-62

7. Liang F, O'Rear J, Schellenberger U, Tai L, Lasecki M, Schreiner GF, Apple FS, Maisel AS, Pollitt NS, Protter AA: Evidence for functional heterogeneity of circulating B-type natriuretic peptide. *J Am Coll Cardiol* 2007; 49:1071-8

8. Lam CS, Burnett JC Jr, Costello-Boerrigter L, Rodeheffer RJ, Redfield MM: Alternate circulating pro-B-type natriuretic peptide and B-type natriuretic peptide forms in the general population. *J Am Coll Cardiol* 2007; 49:1193-202

9. D'Souza SP, Davis M, Baxter GF: Autocrine and paracrine actions of natriuretic peptides in the heart. *Pharmacol Ther* 2004; 101:113-29

(Accepted for publication July 29, 2009.)

Anesthesiology 2009; 111:1379

Copyright © 2009, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Learning Disabilities May Be Related to Undetected Hypoxia

To the Editor:—The recent article by Wilder *et al.*¹ presents a concerning correlation between multiple episodes of anesthesia in childhood and later learning disabilities. In the discussion of possible causes for this correlation, they focus on the known neurotoxicity of various anesthetic agents *in vitro* and in animal studies. They identify some possible sources of bias in their study but neglect to mention one of the most significant changes in anesthetic practice, which occurred after the children in the study received their anesthesia.

Pulse oximetry was developed in the 1970s² but only became commonly used in anesthesia at the end of the 1980s and was made a part of the American Society of Anesthesiologists standards for basic anesthetic monitoring. The introduction of a standard for monitoring and the availability of pulse oximetry coincided with a great reduction in the incidence of undetected hypoxia and resultant injury as demonstrated at Harvard at the time.³ Because the children in this study received their anesthesia in the period 1976 through 1986, the possibility that their increased incidence of learning difficulties might have resulted partly from undetected hypoxia brief or mild enough not

to have caused injury that was immediately obvious should not be discounted. A comparison with children who received a more current standard of monitoring after 1990 would be helpful in determining the likely magnitude of this effect.

James A. Mitchell, M.B., B.S., St Vincent's Hospital, Fitzroy, Victoria, Australia. jamesmitchell@mac.com

References

1. 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
2. Severinghaus JW, Honda Y: History of blood gas analysis, VII: Pulse oximetry. *J Clin Monit* 1987; 3:135-8
3. Eichhorn JH: Prevention of intraoperative anesthesia accidents and related severe injury through safety monitoring. *ANESTHESIOLOGY* 1989; 70:572-7

(Accepted for publication July 31, 2009.)

Anesthesiology 2009; 111:1379-80

Copyright © 2009, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Learning Disability and Repeated Anesthetics: Drugs or Airway Management Issues?

To the Editor:—Regarding the article by Wilder *et al.*,¹ this research is an important step in the right direction to either prove or disprove the association of learning disabilities with multiple exposures to anesthesia in the early years of life possibly caused by anesthetic agent-induced neuroapoptosis. The authors are to be congratulated for making a stab at this complex issue, and not connecting the dots directly but rightfully pointing out that many factors might contribute to their findings that are unrelated to anesthesia. However, one important factor that seems to have been overlooked is that the majority of these children were likely anesthetized before the routine use of pulse oximetry and capnography (1976-1982) became our standard of care. We do not know what happens to a child who

is excessively ventilated for prolonged periods of time, resulting in severe hypocapnia and possibly reduced areas of cerebral perfusion. Nor do we know how many of these children experienced prolonged or repeated short episodes of hypoxemia that were either unrecognized or only recognized late in the event, when the child developed bradycardia that could have resulted in subtle neurologic insults. In the early years when capnography was first being advocated but not yet a standard of care, in a prospective study of 331 children, we found an 11% incidence of hypocapnia (expired carbon dioxide value ≤ 30 mmHg) in intubated children, with a very high incidence in children younger than 1 yr.² Likewise, in two randomized blinded studies involving 554 children, we found 94

Anesthesiology, V 111, No 6, Dec 2009

major desaturation events (oxygen saturation measured by pulse oximetry $\leq 85\%$ for 30 s or longer) in 67 children with a higher incidence by a factor of 2 in those whose anesthesiologist did not have the oximeter data available. These studies suggested that the oximeter allowed early recognition and intervention, thus preventing a minor desaturation event from progressing to a major desaturation event.^{3,4} We also found a higher incidence of these major desaturation events in children younger than 2 yr. I do not know whether it is possible for Wilder *et al.* to go back and examine the anesthesia records from the 144 children in their cohort who had two or more anesthetic exposures to determine whether hypoxic events were recorded, but it might be a useful endeavor. I suggest that we need to look at other issues beyond simple exposure to anesthetic agents as possible contributory factors and look forward to more wonderful work from the Mayo group.

Charles J. Coté, M.D., Harvard Medical School, Mass General Hospital for Children, Massachusetts General Hospital, Boston, Massachusetts. cjcote@partners.org

References

1. 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
2. Coté CJ, Liu LM, Szyfelbein SK, Firestone S, Goudsouzian NG, Welch JP, Daniels AL: Intraoperative events diagnosed by expired carbon dioxide monitoring in children. *Can Anaesth Soc J* 1986; 33:315–20
3. Coté CJ, Goldstein EA, Coté MA, Hoaglin DC, Ryan JF: A single-blind study of pulse oximetry in children. *ANESTHESIOLOGY* 1988; 68:184–8
4. Coté CJ, Rolf N, Liu LM, Goudsouzian NG, Ryan JF, Zaslavsky A, Gore R, Todres ID, Vassallo S, Polaner D, Alifimoff JK: A single-blind study of combined pulse oximetry and capnography in children. *ANESTHESIOLOGY* 1991; 74:980–7

(Accepted for publication July 31, 2009.)

Anesthesiology 2009; 111:1380

Copyright © 2009, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

The Elephant in the Room

To the Editor:—The conclusion reached by Wilder *et al.*¹ that exposure to multiple anesthetics is a significant risk factor in the development of learning difficulties is a headline-grabbing statement with far-reaching consequences for all providers of children's services. However, we believe there has been an insufficient attempt to draw attention to the elephant in the room: that children who require multiple operations usually have significant medical diagnoses, and/or syndromes with associated morbidities, that in turn are associated with a higher incidence of learning disorders than the general population has. Though this information on diagnoses is essential to interpret the data, it is only accessible on-line, and there is no information at all on the actual surgical procedures involved. Further analysis of the on-line data reveals that 22 of the 45 patients with multiple exposure to anesthesia have severe comorbidity or congenital anomalies that are frequently associated with learning difficulties. It should come as no surprise that children with cerebral palsy, Sturge-Weber syndrome, a history of meningitis, or cleft lip and palate have a higher incidence of learning difficulties than the general population.² Of the remaining 23 patients, 13 have serous otitis media. Even such isolated "minor" conditions are known to be associated with an increased incidence of educational delay.³

An attempt has been made to adjust statistically for neonatal factors but not for the effect of comorbidity. Though the inability to adjust for comorbidity is referred to in the text, we believe this omission is so significant that it invalidates any conclusion from this study. We are therefore afraid that this study does not contribute sensibly to the important discussion about potential anesthetic neurotoxicity in the immature human brain.

G. Suren Arul, F.R.C.S., Karl-Christian Thies, D.E.A.A.* Birmingham Children's Hospital, Birmingham, United Kingdom. kcthies@hotmail.com

References

1. 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
2. Broder HL, Richman LC, Matheson PB: Learning disability, school achievement, and grade retention among children with cleft: A two-center study. *Cleft Palate Craniofac J* 1998; 35:127–31
3. Reichman J, Healey WC: Learning disabilities and conductive hearing loss involving otitis media. *J Learn Disabil* 1983; 16:272–8

(Accepted for publication July 31, 2009.)

Anesthesiology 2009; 111:1380–1

Copyright © 2009, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

"If the Odds Are a Million to One Against Something Occurring, Chances Are 50–50 It Will"*

To the Editor:—Given the potential ramifications of findings linking early anesthesia exposure to the later development of learning disabilities (LDs), we expectantly read the article by Wilder *et al.*¹ titled "Early Exposure to Anesthesia and Learning Disabilities in a Population-based Birth Cohort." This topic was not only of interest to the medical community, but also garnered significant attention from the lay media. However, despite the authors' interesting and thought-provoking conclusion that multiple anesthetic exposure in children before age 4 yr increased the risk of developing a subsequent LD, we caution against the overinterpretation of associations without investigation of potentially important medical, psychological, and psychosocial confounders.

For example, Wilder *et al.* used a less stringent, study-defined definition of LD, as opposed to that of the *Diagnostic and Statistical Manual of Mental Disorders* published by the American Psychiatric Association.^{1,2} Included in the *Diagnostic and Statistical Manual of Mental Disorders* criteria is the following caveat: "If a sensory deficit is present, the learning difficulties must be in excess of those usually associated with the deficit."² This *Diagnostic and Statistical Manual of Mental Disorders* provision to the diagnosis of an LD is particularly relevant to the authors' study, which included multiple children with known medical diagnoses associated with sensory deficits. Similarly, many of the patients in the study cohort who received multiple anesthetics and were subsequently diagnosed with a LD also had medical diagnoses that may have contributed to their low achievement and led

* —Anonymous.

to their inclusion in a broadly study-defined LD group. For example, 2 children who were subsequently diagnosed with an LD had Sturge-Weber syndrome, and another child had cerebral palsy. It thus seems reasonable to question whether the LDs in these children are really "in excess" of those usually associated with these medical conditions.

Furthermore, the authors report an incidence of LDs in the Olmsted County, Minnesota general population as 20.0% for children not receiving an anesthetic, and 20.4% and 35.1% in children receiving one or multiple anesthetics, respectively. This is significant because the inclusion criteria used for the diagnosis of an LD in the authors' study resulted in an incidence more than double that reported in the 2007 Summary Health Statistics for U.S. Children: National Health Interview Survey, which reported an LD incidence of 8% in children aged 3–17 yr.³ In addition, the LD prevalence reported in the *Diagnostic and Statistical Manual of Mental Disorders* ranges from 2% to 10%, depending on the diagnostic criteria used.² Finally, in examining the authors' previous publications based on the same population cohort, the "low achievement criteria" diagnosed reading disability (11.8% vs. 5.3%) and math disability (13.8% vs. 5.9%) at more than double the rate of the criteria used by the Minnesota Department of Education, and significantly higher than the other diagnostic criteria used in the current study.^{4,5} Indeed, it would be interesting to view the results obtained when each diagnostic criterion used in the current study was displayed individually (similar to the authors' previous studies of this same population).

The study of anesthetic effects on childhood neurodevelopment is both timely and clinically relevant, and the authors are to be commended for attempting the difficult task of translating animal research findings into humans. However, more rigorous clinical evaluations of

the effects of anesthetics on the developing human brain, including controlling for potential confounders (e.g., medical diagnoses, type of surgery, prenatal history) using a multivariate model and propensity scoring are needed before drawing a link between anesthetic use in children and the subsequent development of LDs. As suggested by the title, the lay media is all too quick to jump on such an extremely controversial and sensitive topic, while at the same time preying on parents' worst fears.

Daniel A. Tolpin, M.D., Charles D. Collard, M.D.† †Baylor College of Medicine and Texas Heart Institute, St. Luke's Episcopal Hospital, Houston, Texas. ccollard@bcm.tmc.edu

References

1. 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
2. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision. Washington, DC, American Psychiatric Association, 2000, pp 49–56
3. Bloom B, Cohen RA: Summary health statistics for U.S. children: National Health Interview Survey, 2007. National Center for Health Statistics. No. 239. *Vital Health Stat* 10 2009; 1567
4. Katusic SK, Colligan RC, Barbaresi WJ, Schaid DJ, Jacobsen SJ: Incidence of reading disability in a population-based birth cohort, 1976–1982, Rochester, Minn. *Mayo Clin Proc* 2001; 76:1081–92
5. Barbaresi WJ, Katusic SK, Colligan RC, Weaver AL, Jacobsen SJ: Math learning disorder: Incidence in a population-based birth cohort 1976–82, Rochester, Minn. *Ambul Pediatr* 2005; 5:281–9

(Accepted for publication July 31, 2009.)

Anesthesiology 2009; 111:1381–2

Copyright © 2009, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Anesthesia in Infancy Linked to Later Disabilities: Causation, Association, or Coincidence?

To the Editor:—"Anesthesia in Infancy Linked to Later Disabilities" is a provocative, if not sensational headline published by *Time* magazine Tuesday, March 24, 2009,¹ regarding the findings of a retrospective cohort study of anesthetic exposure and learning disabilities between 1967 and 1982 by Dr. Wilder *et al.*² The articles in the April 2009 issue of *ANESTHESIOLOGY* regarding anesthesia and the developing brain are of great interest to practitioners of pediatric anesthesia. The alarms are ever increasing regarding the risk of anesthesia for the developing human brain. But the significance of the animal studies to clinical practice is uncertain, and there is little to support a causal link between anesthesia and learning disabilities. There does seem to be an association between anesthetic exposures and learning disabilities, but a similar correlation undoubtedly exists between hospital admission, intravenous fluid administration, and repeated invasive and/or noninvasive hemodynamic monitoring and these same learning disabilities. A few comments regarding both the animal research and the retrospective studies will, I hope, provide some perspective on the issue of anesthetic neurotoxicity.

Previous animal studies do not evaluate anesthetic effect in the presence of surgical or medical stressors. The tail clamp model of Stratmann *et al.*³ more closely resembles the response to surgery, and they are to be applauded for detailing the effects of hypercapnia and acidosis on outcome.⁴ However, they report a mortality of 25%, including deaths in the animals exposed to "only" 2 h of anesthesia. Although the phrase "clinically relevant doses of anesthetics" is now commonly used, I would remind readers that the life expectancy of a rat is only 9 months. One might ask what a comparable anesthetic exposure in humans is. Simple mathematics would suggest that 4 h in the life of a rat might represent as many as 16 days for humans with a

life expectancy of 75 yr. Interestingly, in an early study, Jevtovic-Todorovic *et al.*⁵ demonstrated a threshold response to cerebrocortical injury and reported that inclusion of isoflurane (1%), halothane, pentobarbital, and diazepam all prevented neurotoxic reactions in adult rats during a 3-h exposure to nitrous oxide and/or ketamine. These specimens demonstrated histologically normal neurons. It is unclear why subsequent studies of anesthetic neurotoxicity in rodent pups subjected the animals to longer exposures when a threshold effect was seen with various anesthetic agents. Perhaps an animal model with mortality statistics that resemble outcomes in anesthetized neonates would be more appropriate for evaluating the long-term effects of anesthesia on the developing brain. One must also be aware that exposure of the developing brain to increased oxygen concentrations produces similar neuropathologic changes.⁶

As the parent of a 17 year old with moderately severe learning disabilities and a history of multiple anesthetic exposures before the age of 4 yr, I found the article by Dr. Wilder *et al.* linking early exposure to anesthesia and learning disabilities both intriguing and troubling. They do provide some interesting data, most of which they do not address in the discussion. To their credit, they admit that one cannot determine whether the results reflect exposure to anesthesia or the need for anesthesia. However, in the discussion, despite controlling for birth weight, sex, and gestational age, they do not address the confounders cited, including prolonged labor and hemorrhagic complications of pregnancy. They do not speak to the comorbidities of children presenting to the operating room for multiple procedures. One would expect this information to be available in their hospital database. Certainly, one should analyze the data for the effects of factors such as perioperative hemorrhage, sepsis, seizure disorders,

severe lung disease and its associated episodes of hypoxemia and prolonged ventilation, neurologic malformations, and cerebral palsy. I would suggest that the complex medical history of my own son is representative of the learning disabled who have had multiple anesthetic exposures. His American Society of Anesthesiologists physical status never exceeded II during his four anesthetics as a young child, despite the fact that during that critical period of development, he experienced neonatal sepsis, disseminated osteomyelitis, hepatic insufficiency with attendant coagulopathy, postfebrile partial complex seizure disorder, perioperative hemorrhage, and postoperative anemia. I have searched for explanations for his learning disabilities, but not once in 17 yr have I thought to attribute them to his anesthetic exposures.

A rational understanding of the potential neurotoxicity of anesthetic and sedative agents in the developing brain requires an animal model that closely mimics the clinical reality of serious illness and surgical stress requiring intervention. Clinical reviews, both retrospective and prospective, that address the association of anesthetic exposure and compromised neurodevelopment in young children are critical to our understanding. A threshold toxic dose should be sought and the possibility of a biphasic response of the developing brain should be considered, much like oxygen exposure where both hypoxia and hyperoxia result in permanent deficits. Paracelsus stated that "Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy." His observation is as relevant today as it was nearly 500 yr ago.

Susan P. Taylor, M.D., M.P.H., Children's Hospital of Wisconsin, Medical College of Wisconsin, Milwaukee, Wisconsin. sutaylor@mcw.edu

References

1. Park A: Anesthesia in infancy linked to later disabilities. *Time*. March 24, 2009
2. 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
3. Stratmann G, Sall J, May L, Bell J, Magnusson K, Rau V, Visrodia K, Alvi R, Ku B, Lee M, Dai R: Isoflurane differentially affects neurogenesis and long-term neurocognitive function in 60-day-old and 7-day-old rats. *ANESTHESIOLOGY* 2009; 100:834-48
4. Stratmann G, May L, Sall J, Alvi R, Bell J, Ormerod B, Rau V, Hilton J, Dai R, Lee M, Visrodia K, Ku B, Zusmer E, Guggenheim Firouzaian A: Effect of hypercarbia and isoflurane on brain cell death and neurocognitive dysfunction in 7-day-old rats. *ANESTHESIOLOGY* 2009; 110:849-61
5. Jevtovic-Todorovic V, Benshoff N, Olney J: Ketamine potentiates cerebrocortical damage induced by the common anaesthetic agent nitrous oxide in adult rats. *Br J Pharmacol* 2000; 130:1692-8
6. Yiş U, Kurul SH, Kumral A, Cilaker S, Tuğyan K, Genç S, Yilmaz O: Hyperoxic exposure leads to cell death in the developing brain. *Brain Dev* 2008; 30:556-62

(Accepted for publication July 31, 2009.)

Anesthesiology 2009; 111:1382

Copyright © 2009, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Surgical Diagnosis Is an Important Variable to Consider in Postanesthesia Exposure-associated Learning Disabilities

To the Editor:—We commend Dr. Wilder *et al.*¹ for their work titled "Early Exposure to Anesthesia and Learning Disabilities in a Population-based Birth Cohort." In their article, they report that patients younger than 4 yr, with two or more exposures to general anesthesia, had a greater proportion of learning disabilities (LDs) compared with children who had one or no exposure to general anesthesia. This represents a clinically important epidemiologic correlate to compliment the worrying animal observations demonstrating the detrimental effects of general anesthesia on the developing brain.

A primary assumption in cohort analyses is that the groups observed are the same before exposure. However, children requiring anesthesia for surgical treatment may be inherently different from those who do not; these differences may present unique factors that predispose to LDs independent of anesthesia *per se*. In particular, we are concerned that a subpopulation at risk for learning disabilities—children undergoing ears, nose, and throat surgery—is overrepresented. Typical ears, nose, and throat surgeries in this age group include adenotonsillectomy and bilateral myringotomy with tympanostomy tube placement. The former is associated with obstructive sleep apnea, which can result in neurocognitive defects²; the latter may be associated with otitis media with effusions, which can yield poor performance in expressive speech and math testing in younger children.³

These coexisting conditions may have skewed the diagnosis of LD in this population. This is relevant because children tested within a short period of time from their ears, nose, and throat surgery may not have had sufficient time to "catch up" with their peers in terms of testing, should the surgery have improved their condition. Furthermore, given the frequency of achievement tests administered to the cohort population, is it possible to find children who no longer met LD definitions at some time point during follow-up testing? This

would be of particular interest for those children undergoing ears, nose, and throat surgeries.

In addition, we are concerned that the third definition of LD included patients in the low-average IQ range *versus* average intelligence. Moreover, using a cutoff of 1.75 SDs below their predicted standard score, as opposed to the conventional 2 SDs, might be an oversensitive method of identifying patients with LDs.

We are interested to know whether the authors could remove patients who underwent adenotonsillectomy and bilateral myringotomy with tympanostomy tube surgeries from the analysis and apply conventional definitions of LD to determine whether a relation between general anesthesia and LD persists.

Christopher L. Pysyk, M.D., Kimmo Murto, M.D., F.R.C.P.C., Sally Kuehn, Ph.D., Dermot R. Doherty, M.B., B.Ch., F.C.A.R.C.S.I.* *Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, Ontario, Canada. ddoherty@cheo.on.ca

References

1. Wilder RT, 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
2. Giordani B, Hodges EK, Guire KE, Ruzicka DL, Dillon JE, Weatherly RA, Garetz SL, Chervin RD: Neuropsychological and behavioral functioning in children with and without obstructive sleep apnea referred for tonsillectomy. *J Int Neuropsychol Soc* 2008; 14:571-81
3. Roberts JE, Burchinal MR, Zeisel SA: Otitis media in early childhood in relation to children's school-age language and academic skills. *Pediatrics* 2002; 110:696-706

(Accepted for publication July 31, 2009.)

Anesthesiology 2009; 111:1383

Copyright © 2009, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

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 Sun³ 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 Saugstad⁷ 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.

Vincent J. Kopp, M.D., University of North Carolina at Chapel Hill, Chapel Hill, North Carolina. vkopp@aims.unc.edu

The author thanks Nicole Chenault, B.A. (Administrative Support Associate, Department of Anesthesiology, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina), for manuscript preparation assistance.

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, Kerner 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-Slechta 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

(Accepted for publication July 31, 2009.)

Anesthesiology 2009; 111:1383–4

Copyright © 2009, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

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 prematurity² and on bronchopulmonary dysplasia³ 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 (FiO_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 FiO_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 (Po_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 Po_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 neurons¹⁶ 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.

Brian P. Head, Ph.D., Piyush M. Patel, M.D.* *VA San Diego Healthcare System, San Diego, California. ppatel@ucsd.edu

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. Klingler 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, Siffringer M, Jarosz B, Korobowicz E, Mahler L, Piening T, Moysich A, Grune T, Thor F, Heumann R, Buhner C, Ikonomidou C: Oxygen causes cell death in the developing brain. *Neurobiol Dis* 2004; 17:273-82
11. Jevtic-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, Siffringer M, Zabel C, Nebrich G, Wacker MA, Felderhoff-Mueser U, Endesfelder S, von der Klagen M, Stefowska 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

(Accepted for publication July 31, 2009.)

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 ex-

pressed 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-

priate (Pysyk *et al.*, Tolpin and Collard); (3) hypoxia or hyperoxia may be responsible for the observed effects (Coté, Mitchell, Kopp); and (4) the underlying relevant animal data are flawed (Taylor). As to number 4, we did not participate in the many animal studies, and given that the animal data have been recently reviewed by Loepke and others,²⁻⁷ we will simply refer the reader to those studies, reviews, and editorials.

Clearly, we share the concern expressed by several of the authors for the need to control or adjust for comorbidity. However, we also recognize the difficulty of doing so in retrospective studies (or even in prospective studies) involving children. Arul and Thies suggest that comorbidity is the “elephant in the room.” We completely agree and extensively discussed this clear limitation of our data in our article. A cautionary sentence appears in the abstract, and this limitation is discussed at length in the body of the article, most clearly as follows: “These data cannot reveal whether exposure to anesthesia itself may contribute to the pathogenesis of LD, or whether the need for anesthesia is a marker for other unidentified confounding factors that contribute to LD.” We also chose not to include the positive findings in the article’s title.

We appreciate similar concerns expressed by Pysyk *et al.* regarding the difficulty of determining whether the effect observed in our study was the result of the surgical indication rather than the exposure to anesthesia *per se*. In our cohort, as would be true in any community-based sample, otolaryngologic procedures are the majority of the total, and children requiring myringotomy or tonsillectomy may indeed be predisposed to the adverse effects of sleep disturbance and/or hearing deficiency on learning. However, if surgical treatment of these conditions is efficacious and results in catch-up growth and development in those undergoing surgery, and if not all children receive surgical treatment, those *not* undergoing the procedure may be at greatest risk for the neurocognitive and speech problems described by Pysyk *et al.*,^{8,9} which would bias against the observed effect of multiple surgeries on learning abilities. Also, the relation between this (and many other) condition(s) and the development of learning disabilities is not always clear. Arul and Thies cite a 1983 article that suggests that minor conditions such as otitis media are known to be associated with educational delay. The cited review of the existing literature of that time concluded that, “children who have been medically managed [with otitis media] have minimal deficits.” A subsequent article failed to demonstrate an increase in LD among children who were surgically managed for recurrent otitis media.¹⁰ A recent Cochrane review suggests that it is uncertain that otitis media represents a risk for language or speech delay, and as a consequence, surgical treatment is of unclear benefit. Other studies have demonstrated that among children with language delay of unclear etiology, the only factors of significance were those controlled for in our analysis, *e.g.*, hearing abnormalities were not found to be predictive.¹¹

Ideally, extensive information regarding comorbid conditions would be available in a sample of children large enough to allow the subanalysis suggested by Pysyk *et al.* Realistically, however, controlling for comorbidity is much more difficult than may be appreciated. Unfortunately, no uniformly recognized measure of burden of illness exists for children, requiring that we rely on measures such as the American Society of Anesthesiologists (ASA) physical status (PS) score. Arul and Thies point out that many of those children with multiple exposures had comorbid conditions that may predispose them to LD. LD was not, however, clustered among those with the greatest burden of illness as measured by the ASA PS. In fact, among the 144 children with multiple exposures, only 11% (2 of 19) with an ASA PS of greater than 2 had LD, whereas among those with an ASA PS of 2 or less, 34% (43 of 125) had LD. Therefore, it is by no means clear that the burden of comorbidity, as reflected by ASA PS, is associated with an increased risk of LD. Like Taylor, we also recognize the problems associated with the use of the ASA PS in this setting but also appreciate that no alternative measure is available. Similarly, we could not, as she suggests, control for comorbidity in the exposed group and not do so in the comparison group. To do so would have required that we individually abstract the complete medical records of more than 5,000 children. In an ongoing analysis

using the same cohort, we, in partnership with the U.S. Food and Drug Administration, are in the process of examining, in a case-control design, the comorbid conditions of both cases and controls in an attempt to better control for both medical and surgical diagnosis. We hope that this will provide more insight into the concerns expressed.

The definitions used to determine LD in the birth cohort were those used for the original incidence (not prevalence) studies performed using the Rochester Epidemiology Project. Those studies used four methods to determine the incidence of various types of LD. For the study by Wilder *et al.*, one method (Shaywitz) was eliminated because it was deemed to be redundant. The rates quoted by Tolpin and Collard from our group’s previous publications are for the incidence of the individual types of LD (math, reading, *etc.*). The higher rate that we reported was because our outcome was the development of one or more types of LD. As described in the article, we chose this as an outcome because (1) we had no data to suggest that one type of LD (math, reading, *etc.*) is more likely in this setting and (2) to examine a single type of LD would have dramatically reduced the statistical power of the study. For the same reason, we were not able to perform subanalyses to determine whether the observed effect was concentrated in one or more types of LD, but agree that this would be a fruitful topic for future investigations of sufficient power to conduct this analysis. In addition, LD as determined by the National Health Interview Survey and the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision*, are measures of prevalence rather than incidence and therefore cannot be directly compared with the incidence rates found in the Rochester Schools. Furthermore, the definition of prevalence found in the National Health Interview Survey is based on questionnaire responses to “Ever told sample child had a learning disability” rather than specific testing as was used in our cohort. The observation by Pysyk *et al.* regarding our use of a cutoff of 1.75 SDs rather than the conventional 2 SDs is correct. This was chosen because it was the criterion in use by the state of Minnesota at that time.

Mitchell and Coté raise an issue that we did not discuss, positing unrecognized hypoxia as an explanation for the increase in LD observed in our cohort. The studies by Coté do not address the issue of cognitive impairment but do suggest that unrecognized hypoxia frequently occurred before the widespread adoption of pulse oximetry. Likewise, the presence of brief modest hypocapnia (a finding that occurred in only 9 of 260 total events and may have been as brief as 60 s in his study) is suggested as a potential confounder.¹² To our knowledge, brief hypocapnia has not been linked to subsequent deficits in learning, although among preterm neonates sustained profound hypocapnia has been suggested as a cause of periventricular leukomalacia, a pathology that is highly unlikely to have contributed to our findings. Interestingly, studies of hyperoxia in neonates have examined the effect of the prolonged oxygen saturations as low as 70% on the incidence and severity of retinopathy of prematurity. Those studies have failed to show an adverse neurocognitive effect in follow up as long as 18 months,^{13,14} suggesting that even prolonged periods of hypoxia may be relatively well tolerated in children. Conversely, Kopp suggests that hyperoxia could lead to LD, observing that virtually all children in our cohort received a 30:70 mixture of oxygen and nitrous oxide. The degree of hyperoxia that could result from this mixture is modest. Furthermore, we are not aware of studies that link LD to oxygen exposure in young children, nor were studies cited that associate hyperoxia with abnormalities in memory, cognition, and learning in animals. The studies previously mentioned examining hyperoxia and its relation to retinopathy of prematurity do not show an increase in cerebral palsy or cognitive dysfunction. Therefore, although oxygenation state and hypocapnia are factors that could conceivably contribute to LD after anesthesia, experimental support for this possibility is not robust, although future animal studies could evaluate this possibility.

We appreciate the opportunity to respond to the thoughtful concerns and criticism contained in the accompanying letters. Each of the authors has provided additional food for thought as this issue moves forward. What unifies all is the clear need for larger, more extensive

prospective and retrospective studies that would allow for the control of comorbidity and variations in anesthetic management, the examination of effects according to surgical procedure, the determination of effect by LD type, and more comprehensive measures of academic achievement, cognitive/memory functions, and quality of life. This study represents an initial attempt at unraveling this complex and difficult issue. Other studies planned and currently under way will, no doubt, add to the slowly accumulating body of clinical data that we hope will help to resolve this important and difficult issue.

Randall P. Flick, M.D., M.P.H., Robert T. Wilder, M.D., Ph.D., Juraj Sprung, M.D., Ph.D.,* Slavica K. Katusic, M.D., Robert Voigt, M.D., Robert Colligan, M.D., Darrell R. Schroeder, M.S., Amy L. Weaver, M.S., David O. Warner, M.D. *Mayo Clinic, Rochester, Minnesota. sprung.juraj@mayo.edu

References

1. 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
2. Loepke AW, McGowan FX Jr, Soriano SG: Con: The toxic effects of anesthetics in the developing brain—The clinical perspective. *Anesth Analg* 2008; 106:1664-9
3. Jevtovic-Todorovic V, Olney JW: Pro: Anesthesia-induced developmental neuroapoptosis—Status of the evidence. *Anesth Analg* 2008; 106:1659-63

4. Sun L: Anesthesia and neurodevelopment in children: Time for an answer. *ANESTHESIOLOGY* 2008; 109:5
5. Soriano SG, Anand KJ, Rovnaghi CR, Hickey PR: Of mice and men: Should we extrapolate rodent experimental data to the care of human neonates? (letter). *ANESTHESIOLOGY* 2005; 102:866-8, reply 868-9
6. Olney JW, Young C, Wozniak DF, Ikonomidou C, Jevtovic-Todorovic V: Anesthesia-induced developmental neuroapoptosis. Does it happen in humans? *ANESTHESIOLOGY* 2004; 101:273-5
7. Hansen TG, Danish Registry Study Group, Flick R, Mayo Clinic Pediatric Anesthesia and Learning Disabilities Study Group: Anesthetic effects on the developing brain: Insights from epidemiology. *ANESTHESIOLOGY* 2009; 110:1-3
8. Mitchell RB, Kelly J: Behavior, neurocognition and quality-of-life in children with sleep-disordered breathing. *Int J Pediatr Otorhinolaryngol* 2006; 70:395-406
9. Mitchell RB: Adenotonsillectomy for obstructive sleep apnea in children: Outcome evaluated by pre- and postoperative polysomnography. *Laryngoscope* 2007; 117:1844-54
10. Hutton JB: Incidence of learning problems among children with middle ear pathology. *J Learn Disabil* 1984; 17:41-2
11. Campbell TF, Dollaghan CA, Rockette HE, Paradise JL, Feldman HM, Shriberg LD, Sabo DLL, Kurs-Lasky M: Risk factors for speech delay of unknown origin in 3-year-old children. *Child Dev* 2003; 74:346-57
12. Cote CJ, Rolf N, Liu LM, Goudsouzian NG, Ryan JF, Zaslavsky A, Gore R, Todres TD, Vassallo S, Polaner D, Alifimoff JK: A single-blind study of combined pulse oximetry and capnography in children. *ANESTHESIOLOGY* 1991; 74:980-7
13. 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
14. Tin W, Milligan DW, Pennefather P, Hey E: Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed* 2001; 84:F106-10

(Accepted for publication July 31, 2009.)

Anesthesiology 2009; 111:1386

Copyright © 2009, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

The Need for Perspective

To the Editor:—We were disappointed that *ANESTHESIOLOGY* chose to publish the articles by Kalkman *et al.*¹ and Wilder *et al.*² without an accompanying cautionary editorial. Kalkman *et al.*¹ state, “children undergoing urologic surgery at age less than 24 months showed more behavioral disturbances . . . although the results were not statistically significant.” We disagree with this statement; namely, because statistical significance was not achieved, more behavioral disturbances were *not* observed. Furthermore, they go on to perform a sample size calculation to determine the number of patients that would be required to detect a statistically significant effect of the effect size they found. Their estimate for such a potential association between anesthesia and behavioral problems could be explained by chance alone, and using such an estimate to guide future studies is misleading. Wilder *et al.*² were unable to separate out the effects of multiple anesthetics from the effects of the underlying clinical problems requiring multiple procedures. By publishing these two studies as part of a larger series including several animal models, *ANESTHESIOLOGY* seems to send the message that two independent teams reported similar findings in humans. At a minimum, a cautionary editorial putting these studies into context was warranted. Studies such as these, reported on by the lay

media, may cause an already wary public much alarm and put pediatric anesthesiologists in an impossible position. Parental concerns regarding the possible deleterious effects of anesthesia will not be assuaged by statistical explanations. *ANESTHESIOLOGY* has an obligation beyond merely reporting interesting studies. We are sure that, like us, other readers are looking for perspective.

Karthik Raghunathan, M.D., M.P.H.,* Donald A. Schwartz, M.D., Neil Roy Connelly, M.D. *Tufts University School of Medicine, Baystate Medical Center, Springfield, Massachusetts. karthik.raghunathan@bhs.org

References

1. 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
2. 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

(Accepted for publication August 7, 2009.)

Anesthesiology 2009; 111:1386-7

Copyright © 2009, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

In Reply:—We thank Dr. Raghunathan *et al.* for their letter regarding their disappointment that we did not publish a cautionary editorial regarding the reports by Wilder *et al.*¹ and Kalkman *et al.*² in the April issue of *ANESTHESIOLOGY*. These clinical articles, which were published with laboratory work presented at the *ANESTHESIOLOGY*/Foundation for Anesthesia Education and Research session at the 2008 Annual Meeting of the American Society of Anesthesiologists, were accompanied by an editorial by Drs. Patel and Sun,³ thought leaders in research regarding

the mechanisms and clinical relevance of neurodevelopment after exposure to anesthetics. Regarding the clinical article, they concluded in their editorial, “Although two retrospective studies herein suggest that a correlation between anesthetic exposure early in life is associated with learning and behavioral abnormalities later in life, the data cannot be considered to be evidence of the existence of anesthetic neurotoxicity in humans. The absence of rigorously conducted prospective randomized trials precludes recommendations on clinical

practice.”³ In our opinion, this statement expresses appropriate and adequate express caution regarding the application of these data to clinical practice.

We would also like to comment regarding the statistical analysis and presentation in the article by Kalkman *et al.*,² as questioned by Dr. Raghunathan *et al.* Their study focused on effect sizes and not on statistical significance judgments. This was a prudent choice because of the pilot nature and goals of the effort. This clear focus on effect sizes is made abundantly clear by the fact that in the article by Kalkman *et al.*² there is not a single *P* value reported. Instead, Kalkman *et al.*² referenced the size of the observed effects throughout. For a properly powered study, making a claim about an effect that is not statistically significant is, indeed, anathema. However, in this clearly defined pilot study, reminding a reader that an observed effect size did not reach statistical significance is actually a responsible practice. The uncovered effect sizes in a pilot study are estimates of their population values, but as Kalkman *et al.*² overtly stated, these estimates are in the context of very wide confidence intervals.

We strongly believe that there is a place for small *n* research in ANESTHESIOLOGY. Small *n* research is tricky to report. We have a sophisticated community of researchers (mostly bench scientists) who successfully add to our knowledge base while using studies that are not optimally powered. Again, this reinforces the importance of clear effect size reporting (as in the two mentioned studies), *a priori* power analyses to overtly report assumptions, and exact *P* value reporting to arm a reader with enough information to properly interpret experimental effects.

Regarding their statement on *post hoc* power analyses, Raghunathan *et al.* are wise to be concerned about power calculations that are based on observed *P* values. We agree with this sentiment, articulately voiced by Hoenig and Heisey,⁴ and for that reason actively discourage such

power calculations. The provided power calculation, though, was clearly presented as the primary aim of the study, and posits that the observed risks are the population values, and to reject a null hypothesis of no added risk (under a traditional set of inference assumptions), a future prospective study would need to study 2,268 children (thus making it similar to power analyses conducted throughout the research world; this one is simply in print). There is a difference between stating “These differences would be statistically significant with *n* patients” *versus* “If these differences are population values, we need *n* patients to reject a null hypothesis in our next study.” In that regard, Kalkman *et al.*² have succeeded in providing a context for interpreting their study.

Timothy T. Houle, Ph.D.,* James C. Eisenach, M.D.† *Statistical Editor, ANESTHESIOLOGY, Wake Forest University School of Medicine, Winston-Salem, North Carolina. thoule@wfubmc.edu. †Editor-In-Chief, ANESTHESIOLOGY, Wake Forest University School of Medicine.

References

1. Wilder RT, Flick RP, Sprung J, Slavica K, 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
2. 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
3. Patel P, Sun L: Update on neonatal anesthetic toxicity: Insight into molecular mechanisms and relevance to humans. *ANESTHESIOLOGY* 2009; 110:703–8
4. Hoenig JM, Heisey DM: The abuse of power: The pervasive fallacy of power calculations for data analysis. *Am Stat* 2001; 55:19–24

(Accepted for publication August 7, 2009.)

Anesthesiology 2009; 111:1387

Copyright © 2009, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

“Innocent Prattle” and the Quality of Scientific Discourse

To the Editor:—We read with interest the editorial titled “Innocent Prattle” by Dr. Lagasse¹ that accompanied our article on anesthesia mortality.² As we described, the recent 10th revision of the *International Classification of Diseases* (ICD-10) codes now includes extensive data on anesthesia complications. Its adoption by the United States to classify death certificate data offers both the opportunity and the obligation for researchers to engage in thoughtful analyses of these data. Our study was the first to accept that challenge. As stated in our article,² our objectives were “to develop a comprehensive set of anesthesia safety indicators based on the latest version of the ICD and to apply these indicators to a national data system for understanding the epidemiology of anesthesia-related mortality.” By any measure, we have achieved these objectives despite Dr. Lagasse’s critique. It is well recognized and extensively discussed in our article that administrative data, such as those from ICD-coded, multiple-cause-of-death files, may underestimate the true incidence of adverse outcomes of medical care. It has been estimated, for example, that adverse drug effects reported to the US Food and Drug Administration account for substantially less (< 20%) than the true incidence.³ However, such data can and have been crucial in detecting trends, identifying safety problems, and defining strategies to improve drug safety. In addition, thoughtful analyses will allow further granularity to be either detected from the current data or built into future ICD editions. Dr. Lagasse seems to disagree with our view that the opportunity should not be lost to

analyze the ICD-10-coded mortality data as presented in our article and seems to view such analyses as “innocent prattle.”

Although vigorous argument, discussion, and even disagreement are essential and useful parts of the scientific process, derogatory comments about colleagues’ work are not. It would be a pity if learned publications fall into the trap of adopting the headline style of some popular tabloid newspapers. A deeper reading of the message of Hans Christian Andersen might be that substance and reality (read: scientific data) trump posturing and belief regardless of one’s perceived status. We will look forward to the application and validation by the scientific community of the techniques described in our article to monitor anesthesia safety and improve patient outcomes in the future.

Guohua Li, M.D., Dr.P.H.,* Lena S. Sun, M.D. *Columbia University College of Physicians and Surgeons, New York, New York. GL2240@columbia.edu

References

1. Lagasse RS: Innocent prattle. *ANESTHESIOLOGY* 2009; 110:698–9
2. Li G, Warner M, Lang BH, Lin H, Sun LS: Epidemiology of anesthesia-related mortality in the United States, 1999–2005. *ANESTHESIOLOGY* 2009; 110:759–65
3. McAdams M, Staffa J, Dal Pan G: Estimating the extent of reporting to FDA: A case study of statin-associated rhabdomyolysis. *Pharmacoepidemiol Drug Saf* 2008; 17:229–39

(Accepted for publication August 24, 2009.)

Supported in part by grants R01AG13642 and R01AA09963 from the National Institutes of Health, Bethesda, Maryland.

Anesthesiology, V 111, No 6, Dec 2009

Anesthesiology 2009; 111:1388

Copyright © 2009, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

In Reply:—The recent editorial titled “Innocent Prattle”¹ congratulated Dr. Li *et al.* for introducing new methodology to examine the epidemiologic patterns of anesthesia-related deaths at the national level. Specifically, they used *International Classification of Diseases*, 10th Revision (ICD-10) codes to identify anesthesia-related deaths from the multiple-cause-of-death data files maintained by the National Center for Health Statistics for the years 1999–2005. They then calculated death rates from anesthesia complications based on population data and hospital surgical discharge data. Using their innovative methodology, the authors found that the number of anesthesia-related deaths averaged 316 per year and the number of deaths with an anesthesia complication as the underlying cause averaged 34 per year,² for an estimated 30 million anesthetics annually. I also look forward to the application and validation by the scientific community of their techniques to monitor anesthesia safety in the future, but until such time, it is difficult to accept their claims that the United States has experienced a 97% decrease in the anesthesia-related death rate since the late 1940s and that 46.6% of anesthesia-related deaths are attributable to overdose of anesthetics and 42.5% are attributable to adverse effects of anesthetics in therapeutic use.²

It is incredible claims of improved anesthesia safety that previously led to my analogy to *The Emperor's New Clothes* by Hans Christian Andersen.³ Some of our anesthesia community, like the townspeople in the fable, want to believe that we are somehow special, so they blindly accept these claims of improved anesthesia safety. In my analogy, I play the role of the child who is accused of “innocent prattle” by challenging the claims of Dr. Li *et al.* in an editorial of the same name. I apologize to Dr. Li *et al.* if my editorial led them to believe that their work was accused of being prattle. That was certainly not my intention. In fact, I see their role in my analogy as being much more noble.

Robert S. Lagasse, M.D., Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York. boblage@yahoo.com

References

1. Lagasse RS: Innocent prattle. *ANESTHESIOLOGY* 2009; 110:698–9
2. Li G, Warner M, Lang BH, Lin H, Sun LS: Epidemiology of anesthesia-related mortality in the United States, 1999–2005. *ANESTHESIOLOGY* 2009; 110:759–65
3. Lagasse R: Anesthesia safety: Model or myth? A review of the published literature and analysis of current original data. *ANESTHESIOLOGY* 2002; 97:1609–17

(Accepted for publication August 24, 2009.)

Anesthesiology 2009; 111:1388

Copyright © 2009, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Outpatients Do Not Need to Void after Short Neuraxial Blocks

To the Editor:—Baldini *et al.*¹ are to be congratulated for their excellent review of the problem of postoperative urinary retention. It reflects the growing role of the anesthesiologist in perioperative management and enhances our awareness of the impact of our anesthetic techniques on postoperative outcomes. Their description of the anatomy, physiology, and pharmacology of this phenomenon will serve as a reference source for many practitioners.

As an anesthesiologist in the ambulatory setting, however, I have a concern about their generalizations in their concluding page about the requirement for voiding in outpatients after neuraxial blockade. The authors correctly identify in earlier references that the potential for urinary retention is proportional to the duration of the blockade, which they discuss both in their section on the duration of surgery and in their review of spinal anesthetics.^{2–5} They cite our own prospective study that specifically addressed the issue of discharge without a voiding requirement.⁶ These references support the principle that otherwise low-risk outpatients have no greater risk of retention after short duration neuraxial blockade than those receiving general anesthesia, and requiring voiding before discharge may represent an unnecessary delay. Therefore, it is unfortunate that the discussion of outpatient requirements refers only to the policy by Pavlin *et al.*, that spinal and epidural blockade are inherent risk factors for urinary retention.

That conclusion was based on previous publication from Pavlin's group, which demonstrated delayed discharge after spinal anesthetics performed with bupivacaine and lidocaine plus epinephrine.⁷ In their subsequent study of voiding in outpatients, 26 patients received neuraxial blockade: 22 were given either bupivacaine or lidocaine plus epinephrine.⁸ Therefore, their conclusions are consistent with their experience and data, and previous reports regarding long-duration blockade. The publications mentioned above, however, demonstrate that the use of short-duration local anesthetics for outpatient spinal

blockade are not associated with an increased risk of urinary retention for low-risk patients, and thus do not necessarily mandate voiding before discharge. Further work is obviously indicated, but it seems that neuraxial anesthesia alone (with a short-acting drug in a low-risk patient) is not a risk factor for postoperative retention.

Michael F. Mulroy, M.D. Virginia Mason Medical Center, Seattle, Washington. michael.mulroy@vmc.org

References

1. Baldini G, Bagry H, Aprikian A, Carli F: Postoperative urinary retention: Anesthetic and perioperative considerations. *ANESTHESIOLOGY* 2009; 110:1139–57
2. Pawlowski J, Sukhani R, Pappas AL, Kim KM, Lurie J, Gunnerson H, Corsino A, Frey K, Tonino P: The anesthetic and recovery profile of two doses (60 and 80 mg) of plain mepivacaine for ambulatory spinal anesthesia. *Anesth Analg* 2000; 91:580–4
3. Gupta A, Axelsson K, Thörn SE, Matthiessen P, Larsson LG, Holmström B, Wattwil M: Low-dose bupivacaine plus fentanyl for spinal anesthesia during ambulatory inguinal herniorrhaphy: A comparison between 6 mg and 7.5 mg of bupivacaine. *Acta Anaesthesiol Scand* 2003; 47:13–9
4. Liu SS, Ware PD, Allen HW, Neal JM, Pollock JE: Dose-response characteristics of spinal bupivacaine in volunteers: Clinical implications for ambulatory anesthesia. *ANESTHESIOLOGY* 1996; 85:729–36
5. Ben-David B, Levin H, Solomon E, Admoni H, Vaida S: Spinal bupivacaine in ambulatory surgery: The effect of saline dilution. *Anesth Analg* 1996; 83:716–20
6. Mulroy MF, Salinas FV, Larkin KL, Polissar NL: Ambulatory surgery patients may be discharged before voiding after short-acting spinal and epidural anesthesia. *ANESTHESIOLOGY* 2002; 97:315–9
7. Pavlin DJ, Rapp SE, Polissar NL, Malmgren JA, Koerschgen M, Keyes H: Factors affecting discharge time in adult outpatients. *Anesth Analg* 1998; 87:816–26
8. Pavlin DJ, Pavlin EG, Gunn HC, Taraday JK, Koerschgen ME: Voiding in patients managed with or without ultrasound monitoring of bladder volume after outpatient surgery. *Anesth Analg* 1999; 89:90–7

(Accepted for publication August 25, 2009.)

Anesthesiology 2009; 111:1389

Copyright © 2009, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

In Reply:—We thank Dr. Mulroy for his comments on voiding requirement in outpatients receiving neuraxial blockade with short-acting local anesthetic. We would like to take the opportunity to clarify some issues raised by Dr. Mulroy.

In our review,¹ we identified several risk factors for postoperative urinary retention (POUR), such as type and duration of surgery, patient comorbidities, intraoperative fluid management, and choice of anesthetic and analgesic technique.

In the setting of ambulatory surgery, we proposed an algorithm based in part on two previous studies by Pavlin *et al.*^{2,3} In the first study, patients were stratified before surgery in high and low risk for POUR. Patients who had a past history of urinary retention and those who underwent anorectal and inguinal hernia repair surgery were considered at high risk, even if they did not receive either spinal or epidural anesthesia. In the second study,³ 27% of the patients who received neuraxial anesthesia with local anesthetic (bupivacaine or lidocaine \pm epinephrine) were unable to void and had a bladder volume greater than 600 ml, thus requiring in-and-out bladder catheterization. These patients were identified by Pavlin *et al.* as high risk only because they received neuraxial anesthesia. However, in our opinion, the high incidence of POUR in this group was not caused by the use of spinal-epidural anesthesia *per se*, but by the use of long-acting local anesthetics. Mulroy *et al.*,⁴ in contrast, studied 46 patients without risk factors for POUR who received spinal or epidural anesthesia with short-acting local anesthetic with or without intrathecal fentanyl and who were discharged without voiding. None of them returned to the hospital because of POUR.

The aim of our review was to bring to the attention of anesthesiologists the perioperative risk factors for POUR, and propose an algorithm on how to manage urinary retention judiciously. We agree with Dr. Mulroy that in outpatients with no risk factors for POUR, neuraxial anesthesia with short-acting local anesthetic does not increase the risk of POUR, and patients can be discharged home without voiding. However, in patients with preoperative risk factors for POUR, neuraxial anesthesia with short-acting local anesthetic may or may not further increase the risk, but the availability of a perioperative algorithm that includes the use of a bladder scan could facilitate the management of this potential complication.

Gabriele Baldini, M.D., Hema Bagry, M.D., F.R.C.A., Armen Aprikian, M.D., Franco Carli, M.D., M.Phil., F.R.C.A., F.R.C.P.C.* *McGill University Health Centre, Montreal, Canada. franco.carli@mcgill.ca

References

1. Baldini G, Bagry H, Aprikian A, Carli F: Postoperative urinary retention: Anesthetic and perioperative considerations. *ANESTHESIOLOGY* 2009; 110:1139–57
2. Pavlin DJ, Pavlin EG, Fitzgibbon DR, Koerschgen ME, Plitt TM: Management of bladder function after outpatient surgery. *ANESTHESIOLOGY* 1999; 91:42–50
3. Pavlin DJ, Pavlin EG, Gunn HC, Taraday JK, Koerschgen ME: Voiding in patients managed with or without ultrasound monitoring of bladder volume after outpatient surgery. *Anesth Analg* 1999; 89:90–7
4. Mulroy MF, Salinas FV, Larkin KL, Polissar NL: Ambulatory surgery patients may be discharged before voiding after short-acting spinal and epidural anesthesia. *ANESTHESIOLOGY* 2002; 97:315–9

(Accepted for publication August 25, 2009.)

Anesthesiology 2009; 111:1389–90

Copyright © 2009, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

High Positive End-expiratory Pressure and Mortality in Acute Respiratory Distress Syndrome

To the Editor:—In acute lung injury and acute respiratory distress syndrome (ARDS), the aim of positive end-expiratory pressure (PEEP) is to recruit lung tissue preventing the cyclic opening and closing of alveoli (atelectrauma).¹ However, PEEP is associated to deleterious pulmonary (overdistension of healthy tissue) and hemodynamic (decreased venous return, abnormalities in organ blood flow) effects.^{2–4} In recent years, several studies have attempted to answer the question of which PEEP should be used in acute lung injury and ARDS. Two strategies may be used: the setting of a “low” PEEP to minimize its secondary effects or a “high” PEEP to maximize lung recruitment and gas exchange (open lung strategy). In their recent meta-analysis, Phoenix *et al.*⁵ observed that, in ARDS patients, the use of a high-PEEP strategy showed a trend toward improved mortality and increased risk of barotrauma, although these changes were not statistically significant. However, the authors stated that “the benefits [of this strategy] far outweigh potential risks” and considered that “current evidence supports the use of high PEEP in unselected groups of patients.”

A major limitation in these studies is the lack of definition of high PEEP. Protocols include two strategies in which one of the groups is randomly assigned to receive a higher level of PEEP than the other. The selection of the PEEP level is rather arbitrary, based on oxygenation criteria, and always limiting the plateau pressure. The PEEP is never individualized according to the primary cause (pulmonary *vs.* extrapulmonary) or severity of ARDS. Results are not conclusive, because every group includes patients who require different levels of PEEP. Therefore, the potential benefits of a specific strategy in some of the patients

in a group are likely neutralized by the deleterious effects on the rest of the patients. Another reason that may explain the lack of conclusive results is the limitation of the plateau pressure in all patients, which plays a major role in outcome and may be more important than the level of PEEP in unselected cases.

The results from the meta-analysis are in accord with recent literature questioning the decrease in mortality in ARDS in the past decade despite the implementation of new ventilatory strategies.^{6–8} In the ARDSNet trial,⁹ a significant reduction in mortality was observed when a “protective strategy,” based on a low tidal volume (6 ml/kg), was used. But we may speculate that patients were actually being protected from an “aggressive strategy” (tidal volume 12 ml/kg in the control arm). It is likely that the application of a high PEEP in the initial phase of severe ARDS, with an expected important lung edema and inflammation, is justified.¹⁰ Even accepting this approach, it remains unanswered for how long the PEEP should be “high.” The lack of clear benefits in unselected patients is probably related to the absence of objective tests that help in the individual titration of the ventilatory parameters. Several techniques have been proposed, such as the plotting of pressure-volume curves,¹¹ the stress index¹² (actually a sort of dynamic pressure-volume curve), or the electrical impedance tomography.¹³ Interestingly, in the three smaller studies included in the meta-analysis by Phoenix *et al.*⁵ but finally excluded for the conclusions, PEEP was set according to the pressure-volume curve. Of note is the apparent major benefit observed with a high PEEP level in these studies. Until recruitment/derecruitment and hyperinflation are not estimated repeatedly in individual ARDS patients as their lung injury

evolves, it is unlikely that any attempt to demonstrate the superiority of a ventilatory strategy will be conclusive.

David Pestaña, Ph.D., Servicio de Anestesia-Reanimación, Residencia General, Hospital Universitario La Paz, Madrid, Spain. dpeñana.hulp@salud.madrid.org

References

1. Rouby JJ, Lu Q, Goldstein I: Selecting the right level of positive end-expiratory pressure in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2002; 165:1182-6
2. Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, Russo S, Patroniti N, Cornejo R, Bugedo G: Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med* 2006; 354:1775-86
3. Manny J, Justice R, Hechtman HB: Abnormalities in organ blood flow and its distribution during positive end-expiratory pressure. *Surgery* 1979; 85:425-32
4. Fujita Y: Effects of PEEP on splanchnic hemodynamics and blood volume. *Acta Anaesthesiol Scand* 1993; 37:427-31
5. Phoenix SI, Paravastu S, Columb M, Vincent J-L, Nirmalan M: Does a higher positive end expiratory pressure decrease mortality in acute respiratory distress syndrome? A systematic review and meta-analysis. *ANESTHESIOLOGY* 2009; 110: 1098-105
6. Phua J, Badia JR, Adhikari NK, Friedrich JO, Fowler RA, Singh JM, Scales DC, Stather DR, Li A, Jones A, Gattas DJ, Hallett D, Tomlinson G, Stewart TE, Ferguson

ND: Has mortality from acute respiratory distress syndrome decreased over time? A systematic review. *Am J Respir Crit Care Med* 2009; 179:220-7

7. Zamboni M, Vincent J-L: Mortality rates for patients with acute lung injury/ARDS have decreased over time. *Chest* 2008; 133:1120-7

8. Esteban A, Ferguson N, Meade M, Frutos-Vivar F, Apezteguia C, Brochard L, Raymondos K, Nin N, Hurtado J, Tomacic V, González M, Elizalde J, Nightingale P, Abroug F, Pelosi P, Arabi Y, Moreno R, Jibaja M, D'Empaire G, Sandi F, Matamis D, Montañez AM, Anzueto A: Evolution of mechanical ventilation in response to clinical research. *Am J Respir Crit Care Med* 2008; 177:170-7

9. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342:1301-8

10. Caironi Gattinoni L: Refining ventilatory treatment for acute lung injury and acute respiratory distress syndrome. *JAMA* 2008; 299:691-3

11. Pestaña D, Hernández-Gancedo C, Royo C, Pérez-Chrzanowska H, Criado A: Pressure-volume curve variations after a recruitment manoeuvre in acute lung injury/ARDS patients: Implications for the understanding of the inflection points of the curve. *Eur J Anaesthesiol* 2005; 22:175-80

12. Grasso S, Terragni P, Mascia L, Fanelli V, Quintel M, Herrmann P, Hedenstierna G, Slutsky AS, Ranieri VM: Airway pressure-time curve profile (stress index) detects tidal recruitment/hyperinflation in experimental acute lung injury. *Crit Care Med* 2004; 32:1018-27

13. Kunst PWA, Vazquez de Anda G, Böhm SH, Faes TJC, Lachmann B, Postmus PE, de Vries PMJM: Monitoring of recruitment and derecruitment by electrical impedance tomography in a model of acute lung injury. *Crit Care Med* 2000; 28:3891-5

(Accepted for publication September 1, 2009.)

Anesthesiology 2009; 111:1390-1

Copyright © 2009, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

In Reply:—Thank you for giving us the opportunity to respond to the communication by Dr. David Pestaña. The author is correct in his assertion that most of the studies do not define the terms *high positive end-expiratory pressure (PEEP)* and *low PEEP* and that the appropriate level of PEEP has been selected on the basis of oxygenation and peak/plateau airway pressures.¹⁻³ This reflects the practical difficulties inherent in recruiting large numbers of patients into clinical trials using highly individualized criteria. We are therefore left with the mean values recoded in each of the groups to infer the threshold values for “low” and “high” PEEP. Nevertheless, the underlying physiologic principles are clear and suggest that there are several biologic benefits associated with selecting PEEP levels between 10 and 15 cm H₂O in patients with severe acute lung injury. This is particularly so during the early stages of the illness, when lung edema is maximal and therefore the tendency for cyclical opening and collapse of alveolar units is maximal.¹⁻⁵ The author is also correct in stating that the most appropriate level of PEEP in a given patient can only be determined through an individualized titration protocol. He raises a pertinent point in his final statement that “it is unlikely that any attempt to demonstrate the superiority of a ventilatory strategy will be conclusive.” We agree entirely and would like to pose the question of whether the current emphasis on the need to demonstrate significant improvements in final outcome-based endpoints (mortality, duration of stay, duration of mechanical ventilation, and so forth) is appropriate for evaluating new ventilation strategies.

Ventilation is a supportive measure needed in the management of other systemic illnesses such as sepsis, acute lung injury/acute respiratory distress syndrome, systemic inflammatory response syndrome, and heart failure. Clinical outcome in such patients is usually a manifestation of the underlying disease process itself or the “mediator variables.” Ventilation, in this context, is best seen as a “moderator variable” that alters the quantitative relation between disease severity and its consequence (mortality and or morbidity). Improvements in ventilation strategies can, therefore, have only a modest impact on disease specific mortality. As iatrogenic contributions to mortality (such as excess sedation, barotrauma/volutrauma, and ventilator-induced lung injury) are recognized and rectified, it becomes inevitable that further improvements in ventilator technology will require an

unrealistic sample size to demonstrate mortality/morbidity benefits based on the basic principles of diminishing returns.⁵ Such large numbers cannot be recruited within a geographically, culturally, and economically homogeneous area or during a reasonable time period during which clinical practices remain comparable across several other domains. More importantly, it is well recognized that interactions between organ systems in humans are nonlinear, and the importance of such nonlinearity in critical illness was highlighted elegantly by Buchman⁶ and Rixen *et al.*⁷ If we agree on the most fundamental premise that the initial manifestations and subsequent development of a disease state are governed by nonlinear interactions between the severity of the initial insult (the mediator variables), host's physiologic responses, and other moderator variables (such as ventilation, secondary infections, iatrogenic complications, and nutritional status), it follows that each patient would follow a unique trajectory as dictated by nonlinear dynamics. In such nonlinear systems, the final clinical outcome (survival, death, or prolonged morbidity) is unpredictable and is sensitively dependant on the initial conditions (the mediator variables) and subsequent modulator variables. It does not follow simple rules based on linear assumptions. That is, a “small change” in one of the moderator variable does not always lead to a “small change” in the final outcome. Such “unpredictable” events occurring (in the control or treatment arms) in clinical trials involving moderator variables, with a relatively modest influence on the overall disease process, will necessarily lead to conclusions that are difficult to reproduce and at times erroneous. Therefore, the current emphasis placed on clinical outcome alone reflects a mind-set (promoted by the business world) that is rooted in cost-benefit analysis and aims to identify and support only those interventions with a relatively large effect size. This approach, if adopted blindly and dogmatically, is likely to lead to the abandonment of several interventions that may be beneficial to individual patients.

Estimating the qualitative and quantitative improvements to patient care that can be achieved by refining moderator variables (such as ventilation), in our view, requires the adoption of more dynamic models as suggested by Dr. Pestaña, rather than the final clinical outcome alone.

Susan I. Phoenix, Mahesh Nirmalan, M.D., F.R.C.A., Ph.D.*
 *Manchester Royal Infirmary and Manchester Academic Health Sciences
 Centre, Manchester, United Kingdom. m.nirmalan@manchester.ac.uk

References

1. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT: Higher *versus* lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004; 351:327-36
2. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, Davies AR, Hand LE, Zhou Q, Thabane L, Austin P, Lapinsky S, Baxter A, Russell J, Skrobik Y, Ronco JJ, Stewart TE: Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2008; 299:637-45

3. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, Lefrant JY, Prat G, Richecoeur J, Nieszkowska A, Gervais C, Baudot J, Bouadma L, Brochard L: Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2008; 299:646-55
4. Gattinoni L, Caironi P: Refining ventilatory treatment for acute lung injury and acute respiratory distress syndrome. *JAMA* 2008; 299:691-3
5. Phoenix SI, Paravastu S, Columb M, Vincent JL, Nirmalan M: Does a higher positive end expiratory pressure decrease mortality in acute respiratory distress syndrome? A systematic review and meta-analysis. *ANESTHESIOLOGY* 2009; 110:1098-105
6. Buchman TG: Physiologic stability and physiologic state. *J Trauma* 1996; 41:599-605
7. Rixen D, Siegel JH, Friedman HP: "Sepsis/SIRS," physiologic classification, severity stratification, relation to cytokine elaboration and outcome prediction in posttrauma critical illness. *J Trauma* 1996; 41:581-98

(Accepted for publication September 1, 2009.)

Anesthesiology 2009; 111:1391

Copyright © 2009, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Is It Time for a Glidescope Letter?

To the Editor:—I am the Vice-President of a large anesthesia practice based in Massachusetts. Our group provides services to a number of community hospitals, surgery centers, and an academic medical center. During the past 3 yr, our practice has acquired a number of Glidescopes (Verathon Medical, Bothell, WA), and we are using them with increasing frequency. It is now common for the Glidescope to be used as the first-attempt intubation device in patients who clinically present as a potential difficult airway. This is very much the case for patients undergoing bariatric surgery. A number of studies have shown that the Glidescope and other video airway devices, such as the Airway Scope (Pentax, Tokyo, Japan) and the Airtraq (King Systems, Noblesville, IN), have a higher successful intubation rate than that of direct laryngoscopy,¹⁻³ so our approach is founded on the principle that securing the airway in the shortest time, with minimal instrumentation, is in the best interest of the patient and represents good clinical care. In addition, there are also occasions when the Glidescope may be used as the first-line airway instrument for teaching purposes in both easy and difficult airways. This practice, though, is making me increasingly uncomfortable because of the implications for those patients in whom no attempt has been made at conventional laryngoscopy who may present for surgery, possibly emergent, at another institution that does not have a Glidescope. We are currently not telling all of our patients whether a Glidescope was used unless it was in the context of a failed

conventional laryngoscopy. These patients could present to other facilities and may indeed seem to be a potentially difficult intubation, only to have the anesthesiologist falsely reassured by a report of a prior "uneventful" anesthetic. The question, therefore, is should all patients in whom a Glidescope is used be given a letter indicating such, regardless of circumstance, and/or should all patients have one attempt made at conventional laryngoscopy, before elective Glidescope use, to document the airway classification for future reference?

I think this is an increasingly important clinical issue, with definite patient safety implications, and I would like to bring it to the attention of your readers for further contemplation and discussion.

Glynn D. Stanley, M.B., Ch.B., F.R.C.A. North Shore Medical Center, Salem, Massachusetts, and Anaesthesia Associates of Massachusetts, Westwood, Massachusetts. gdstanley@comcast.net

References

1. Nouruzi-Sedeh P, Schumann M, Groeben H: Laryngoscopy *via* Macintosh blade *versus* Glidescope: Success rate and time for endotracheal intubation in untrained medical personnel. *ANESTHESIOLOGY* 2009; 110:32-7
2. Maharaj CH, Costello JF, Harte BH, Laffey JG: Evaluation of the Airtraq and Macintosh laryngoscopes in patients at increased risk for difficult tracheal intubation. *Anaesthesia* 2008; 63:182-8
3. Asai T, Liu EH, Matsumoto S, Hirabayashi Y, Seo N, Suzuki A, Toi T, Yasumoto K, Okuda Y: Use of the Pentax-AWS in 293 patients with difficult airways. *ANESTHESIOLOGY* 2009; 110:898-904

(Accepted for publication August 28, 2009.)

Support was provided solely from institutional and/or departmental sources.