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, Blankenberg 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, Stolker 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

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 1970s[2] 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

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