

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.

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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.

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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.

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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 \leq 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

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