Insights of Neurologic Dysfunction After Coronary Artery Bypass Grafting

To the Editor:

We read with great interest the article by Ganushchak and associates (June 2004).1 The authors have investigated the correlation between the combinations of hemodynamic events during cardiopulmonary bypass (CPB) and the development of postoperative neurologic complications. The authors have utilized cluster analysis to review 1,395 perfusion charts, and have concluded that CPB procedures with large fluctuations in hemodynamic parameters have an increased risk for the development of postoperative neurologic complications.

We would like to make a few comments for this important investigation. First, it is well documented that the number of emboli (micro and macro) delivered during CPB has a direct correlation with the postoperative neurologic dysfunction.2,3 The duration of CPB also has an impact on the number of emboli delivered during CPB; the longer the duration, more emboli delivered.4 According to Table 2, the duration of CPB was much longer in one group with postoperative neurologic complications (n = 27) compared to the no-complication group (103 ± 43 min vs 82 ± 33 min, p = 0.01 [± SD]). The only way to quantify the number of microemboli during CPB is to use transcranial Doppler (TCD) monitoring. Did Ganushchak and associates use TCD monitoring during CPB?

Second, the authors have used two different hollow-fiber membrane oxygenators in this investigation. One wonders whether or not there was any significant difference between the oxygenators in 27 patients with postoperative neurologic complications. In 27 patients, did the authors calculate how many times one oxygenator was used vs the other oxygenator? Were there any significant differences between the two oxygenators?

Last, the authors have documented that the majority of patients with postoperative neurologic complications (21 of 27 patients) coincide with postoperative cardiac arrhythmias. It is not clear whether the neurologic complications were secondary to cardiac arrhythmias or not. The cause of postoperative neurologic complications in these 21 patients was probably due to ventricular arrhythmias rather than the CPB procedure.5 We congratulate the authors for applying cluster analysis to this particular patient population, and we also believe that large fluctuations in hemodynamic parameters during CPB has caused significant postoperative neurologic risks.3

Jun Luo, MD, PhD
Akif U¨ ndar, PhD
Penn State College of Medicine
Hershey, PA

Correspondence to: Akif U¨ ndar, PhD, Associate Professor of Pediatrics, Surgery, and Bioengineering, Penn State College of Medicine, Department of Pediatrics-H1085, 500 University Dr. PO Box 850; Hershey, PA 17033-0850; e-mail: aunder@psu.edu

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To the Editor:

First, we thank Drs. Luo and U¨ ndar for their comments on our investigation, and acknowledge them for recognizing the interest and importance of our article. In answer to the first comment, we like to express that we also recognize the fact that the number of emboli (micro and macro) delivered during cardiopulmonary bypass (CPB) could have an impact on the incidence of postoperative neurologic complications. Unfortunately, we were unable to use transcranial Doppler (TCD) routinely in our patients. However, a longer CPB procedure is theoretically accompanied by a higher number of emboli delivered, as was described previously.1,2 Therefore, although we did not use TCD, one could hypothesize that the aforementioned is confirmed by our findings as presented in Table 2. However, the large difference in number of patients in our study (27 patients with postoperative neurologic complications vs 1,368 patients without neurologic complications) made the results of the analysis of variance test suspicious. That is why we used cluster analyses, and in the sequence of these analyses the impact of duration of CPB on the development of postoperative neurologic complications disappeared. Nevertheless, microembolization of cerebral vessels during CPB could be one of the factors explaining the significance of fluctuations in hemodynamic parameters in the increased risk for the development of postoperative neurologic complications. It is well documented that good blood flow through the brain might hasten the clearance of microemboli, and increased perfusion pressure during CPB has been proposed as a means of forcing air bubbles through the cerebral microcirculation.3 It is obvious that fluctuations in perfusion pressure could often provoke the stabilization of an embolus in a cerebral vessel and increase the duration of hypoxia and extend the area of hypoxic damage.

Second, the type of oxygenator indeed could affect the rate of microemboli during CPB4 and, in this way, be related to the incidence of postoperative neurologic complications. The two types of oxygenators used in our patients were used in sequence. Although the influence of oxygenator type on postoperative neurologic complications was beyond the scope of our study, we evaluated whether there was any significant fluctuation in the frequency of neurologic complications during the study period (between May 1996 and January 1999). This appeared not to be the case, and therefore we assumed that the type of oxygenator had no significant impact on the results as described in our article.

Third, in general, causal relations are extremely hard to prove in clinical research. In this retrospective study, we could not distinguish the sequence of events in complications development.

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Vascular Permeability in Active Pulmonary Tuberculosis

To the Editor:

We read with great interest the recent prospective clinical study by Alatas et al1 (June 2004). We would like to add few comments to their work. First of all, we are interested in the wide variance of the serum vascular endothelial growth factor (VEGF) levels in patients with active pulmonary tuberculosis as compared with those in patients with inactive pulmonary tuberculosis or in healthy subjects. In particular, we want to be informed of the detailed profiles of patients with $> 1,000$ pg/mL of VEGF levels. Were there any correlative factors such as clinical symptoms or laboratory data with the high levels of VEGF? As Alatas and colleagues described in the discussion, larger clinical studies are needed to find the factors in close association with VEGF titer.

We also want to introduce another candidate for an indicator of active pulmonary tuberculosis. Metallothionein is a highly conserved, low-molecular-weight, cysteine-rich protein. Metallothionein has been proposed to play an important role in homeostasis and detoxification of heavy metals. Metallothionein can serve as a sacrificial scavenger for hydroxyl radicals in vitro and protects against free radical-induced DNA damage.1-5 Since proinflammatory cytokines, including tumor necrosis factor-$\alpha$, interleukin (IL)-1, IL-6, and interferon-$\gamma$, induce hepatic metallothionein gene expression, the role of metallothionein in inflammatory diseases has been focused. Recently, we have demonstrated that metallothionein-null (-/-) mice were more susceptible than corresponding wild-type mice to lung inflammation, especially to lung edema, which were induced by intratracheal challenge with bacterial endotoxin.6 We confirmed that metallothionein proteins in the lungs were detected in endothelial cells and alveolar epithelial cells of wild-type mice, whereas they were not detected in those of metallothionein (-/-) mice by immunohistochemistry. After endotoxin challenge, metallothionein deficiency enhanced vascular degeneration of pulmonary endothelial cells and type I alveolar epithelial cells, and caused focal loss of the basement membrane without any significant differences in the enhanced local (lung) expression of proinflammatory cytokines and chemokines or in the activation of nuclear factor-$\kappa$B pathway in the lung between the two genotypes. We concluded that endogenous metallothionein is defensive against acute lung injury related to bacterial endotoxin, possibly via the protection of pulmonary vascular integrity.6 Additional researches targeting metallothionein in pulmonary tuberculosis might throw new therapeutic strategies to this persistent infectious disease.

Ken-ichiro Inoue, MD, PhD
Hirohisa Takano, MD, PhD
Rie Yamasita, PhD
National Institute for Environmental Studies
Tsukuba, Japan
Toshikazu Yoshikawa, MD, PhD
Kyoto Prefectural University of Medicine
Kyoto, Japan

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Ken-ichiro Inoue, MD, PhD
Hirohisa Takano, MD, PhD
Rie Yamasita, PhD
National Institute for Environmental Studies
Tsukuba, Japan
Toshikazu Yoshikawa, MD, PhD
Kyoto Prefectural University of Medicine
Kyoto, Japan

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To the Editor:

We thank Dr. Inoue and colleagues for their comments on our recently published article.1 Indeed, the active tuberculosis pa-