Lower Endotoxin Immunity Predicts Increased Cognitive Dysfunction in Elderly Patients After Cardiac Surgery

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Background and Purpose—Although coronary artery bypass graft surgery (CABG) improves the quality of life and functional capacity for numerous patients, many also exhibit impairment in cognitive function immediately after surgery. Although the etiology of this cognitive decline is multifactorial, the inflammatory response to the primary insult may modulate the extent of dysfunction. Patients with low preoperative levels of anti-endotoxin core antibody (EndoCAb) are more likely to experience adverse outcomes, suggesting that decreased immunity to endotoxin causes a heightened release of inflammatory mediators. We therefore sought to determine the association of decreased EndoCAb and the incidence of postoperative cognitive decline.

Methods—EndoCAb levels were measured before surgery in 460 patients undergoing elective CABG. Cognitive function was measured preoperatively and 6 weeks postoperatively. Multivariable analysis accounted for the effects of age, Parsonnet score, sex, body mass index, baseline cognition, years of education, history of hypertension, bypass time, cross-clamp time, and number of grafts.

Results—At 6-week follow-up, 122 patients (36%) showed cognitive decline. Lower preoperative EndoCAb levels were associated with a greater incidence and severity of postoperative cognitive decline. The elderly with decreased endotoxin immunity are particularly susceptible to this decline (relative risk = 1.97 for age > 64).

Conclusions—Reduced preoperative endotoxin immunity is a predictor of increased postoperative cognitive dysfunction in patients undergoing CABG, particularly in those > 60 years old. Interventions that increase IgM EndoCAb levels might improve cognitive function after cardiac surgery. (Stroke. 2003;34:508-513.)

Key Words: cognitive disorders ▪ coronary artery bypass surgery ▪ endotoxemia

Advances in perioperative anesthetic and surgical techniques have substantially reduced mortality for patients undergoing cardiac surgery. Although elderly patients with multiple health problems now undergo surgical procedures with less fear of loss of life, they are at increased risk of cognitive dysfunction after surgery. Although many complications associated with cardiac surgery have been minimized, little progress has been made in reducing cognitive decline, which occurs in as many as 80% of patients immediately after surgery and in 30% after 6 months. Cognitive dysfunction is also associated with reduced quality of life for patients who expect that postoperative improvements in physical status will generally improve their lives. Furthermore, deterioration in cognitive functioning has negative societal consequences as a result of greater use of critical health-care resources. This is of particular concern for elderly patients, who are at increased risk of cognitive decline after cardiac surgery. Recent clinical investigations of the extent and duration of cognitive dysfunction after cardiac surgery have helped to identify patients who may be at increased risk of postoperative impairment; however, many etiological factors underlying the process of cognitive injury remain to be identified. Although cerebral embolization may be a primary mechanism of cognitive decline, the inflammatory process that follows any initial insult can significantly modulate the extent of injury.

Coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB) is associated with ischemia/reperfusion injury, inducing a complex inflammatory response that affects not only the heart but also the lungs, kidneys, gut, and brain. During cardiac surgery, most patients are also exposed to endotoxin, the lipopolysaccharide component of the cell wall of Gram-negative bacteria and a major stimulus for the release of inflammatory mediators. Reduced preoperative endotoxin immunity is a predictor of increased postoperative cognitive dysfunction in patients undergoing CABG, particularly in those > 60 years old. Interventions that increase IgM EndoCAb levels might improve cognitive function after cardiac surgery.
for the development of a systemic inflammatory response. Endotoxins do not elicit their toxic effects by directly killing host cells or inhibiting cellular functions. Rather, they interact with a variety of host cell types—including mononuclear cells, polymorphonuclear granulocytes, thrombocytes, and macrophages—to produce bioactive lipids, reactive oxygen species, and peptide mediators such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1, IL-6, IL-8, and IL-10. Although the origin of exposure to endotoxin during surgery remains unconfirmed, current theories suggest that high levels of circulating endotoxins during CPB are caused by gut hyperperfusion with translocation of bacteria from the intestinal mucosa.

Interestingly, patients with low preoperative levels (<100 median units [MU]/mL) of IgG and IgM anti-endotoxin core antibody (EndoCAB) are more likely to experience adverse outcomes, suggesting that decreased immunity to endotoxin may result in a heightened release of inflammatory mediators. Decreased EndoCAB concentrations have also been associated with prolonged ventilator dependence, longer hospitalization, and increased mortality in medical patients with sepsis syndrome. We therefore hypothesized that reduced endotoxin immunity in CABG patients may be associated with greater postoperative cognitive decline.

Subjects and Methods

After institutional review-board approval and written, informed consent were obtained, 460 patients undergoing elective CABG at Duke University Medical Center from October 1997 to November 2000 were enrolled. Patients were excluded who had a history of cerebrovascular disease with residual deficit, psychiatric illness, renal disease (creatinine >2 mg/dL), active liver disease, <7 years of formal education, or an inability to read.

Measurement of Cognitive Function

Experienced psychometricians blinded to the patient’s EndoCAB level examined the patients with a well-validated battery of 6 cognitive tests on the day before surgery (baseline) and again at 6 weeks. Instruments included the short story module of the Randt Memory Test, the Wechsler Memory Scale (WMS) Figural Memory Test, the Digit Symbol subtest of the Wechsler Adult Intelligence Scale—Revised (WAIS-R), the Trail Making Test (part B), the Rey Auditory-Verbal Learning Test (AVLT), and the Digit Span subtest of the WAIS-R examination.

Patient Management

Anesthesia was induced and maintained with midazolam, fentanyl, and isoflurane with muscle relaxation provided by pancuronium. All patients underwent nonpulsatile hypothermic (30°C to 32°C) CPB. The perfusion apparatus consisted of the Cobe CML membrane oxygenator (COBE Chem Labs), the Sarns 7000 MDX pump (3M Inc), and the Pall SP3840 arterial line filter (Pall Biomedical Products Co). Perfusion was maintained at pump flow rates of 2 to 2.4 L · min⁻¹ · m⁻² throughout CPB. The pump was primed with crystalloid, and serial hematocrit levels were kept at ≥0.18 with packed red blood cell transfusions as necessary. Arterial blood gases were followed every 15 to 30 minutes to maintain arterial carbon dioxide partial pressures at 35 to 40 mm Hg, unadjusted for temperature (α-stat), and oxygen partial pressures at 150 to 250 mm Hg.

EndoCAB Level Determination

Blood samples were obtained through a radial artery catheter immediately before induction of general anesthesia. Samples were collected in glass tubes without additive and centrifuged for 10 minutes at 2000g; plasma was stored at −70°C until assayed. Coated

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in the model were Parsonnet score, bypass time, cross-clamp time, number of grafts, hypertension, body mass index, and sex. The best predictive model was achieved by starting with all covariables and iteratively removing nonsignificant terms until only significant terms remained. A multivariable logistic regression was used to assess the relation between log EndoCAb and cognitive deficit, defined as the binary outcome. \( P < 0.05 \) was considered significant. All analyses were performed with SAS, version 8.02 software.

**Results**

The baseline sample consisted of 460 patients, ranging in age from 23 to 87 years old, for whom EndoCAb data had been collected and for whom we had sufficient cognitive function data. At 6-week follow-up, 343 patients (75\%) had sufficient cognitive function data to be included in the analysis. Characteristics of the baseline population are shown in Table 1.

Not included in the analysis were 26 patients who returned for follow-up but were unable to complete neuropsychological testing; an additional 91 did not return at 6 weeks. Reasons for loss to follow-up included health problems (\( n = 19 \)), lack of interest (\( n = 20 \)), inability to contact (\( n = 23 \)), travel difficulties (\( n = 9 \)), death (\( n = 11 \)), and other miscellaneous reasons (\( n = 9 \)). Patients who did not return for follow-up testing differed from those who did in that they were older, had less education, a lower baseline cognitive index, and a higher Parsonnet score.

According to the criterion of a 1-SD decline on at least 1 of the 4 cognitive factors, 36\% (122/343) of patients experienced cognitive decline. However, the cognitive index score (ΔCI) for the entire patient sample showed a small positive change from the baseline mean of \( -0.04 (\pm 0.51) \) to the 6-week follow-up mean of 0.13 (±0.54). EndoCAb levels ranged from 2.56 to 2490.4 MU, with a median of 67.9 MU (Q₁ = 37.9, Q₃ = 123.8).

For the binary-outcome measure, a univariable logistic regression demonstrated a significant relation between log EndoCAb level and cognitive deficit at 6 weeks (\( P = 0.03 \)). Figure 2 illustrates the relation between EndoCAb and the probability of cognitive deficit. As a univariate predictor, the EndoCAb variable has a c index of 0.563 (\( P = 0.03 \)). For the continuous-outcome measure, a univariable linear regression model also demonstrated a significant relation between log EndoCAb level and a change in cognitive index at 6 weeks (\( P = 0.005 \); Figure 3).

The best predictive model of cognitive deficit (binary outcome) at 6 weeks was found to be a multivariable logistic

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**TABLE 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Completed Follow-Up (n=343)</th>
<th>Lost to Follow-Up (n=117)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.8 (11.5)</td>
<td>65.3 (11.1)</td>
</tr>
<tr>
<td>Education, y</td>
<td>13.0 (3.3)</td>
<td>11.7 (3.4)</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>35</td>
<td>41</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>85.5 (19.5)</td>
<td>85.3 (22.7)</td>
</tr>
<tr>
<td>History of hypertension, %</td>
<td>60</td>
<td>69</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>31</td>
<td>38</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>54.5 (11.0)</td>
<td>52.9 (12.4)</td>
</tr>
<tr>
<td>Duration of cardiopulmonary bypass, min</td>
<td>109.4 (78.1)</td>
<td>120.0 (52.5)</td>
</tr>
<tr>
<td>Number of grafts</td>
<td>3.0 (0.9)</td>
<td>3.2 (0.8)</td>
</tr>
<tr>
<td>Baseline cognitive index</td>
<td>0.02 (0.50)</td>
<td>-0.21 (0.52)</td>
</tr>
<tr>
<td>Median baseline EndoCAb levels, (Q₁; Q₃)</td>
<td>68.8 (40.4; 125.6)</td>
<td>64.1 (29.2; 106.1)</td>
</tr>
<tr>
<td>Parsonnet score</td>
<td>8.61 (7.10)</td>
<td>11.08 (7.56)</td>
</tr>
</tbody>
</table>

*Values are expressed as percentages or mean (SD); continuous variables were compared with t tests; categorical variables were compared with chi-square tests.

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Figure 2. Univariable relation between EndoCAb and predicted probability of cognitive deficit is shown with 95\% confidence intervals. The logarithmically transformed antibody variable has been exponentiated to illustrate the logarithmic relation with cognitive deficit. The horizontal axis is truncated at antibody levels of 600 to focus on the antibody range of greatest interest.

Figure 3. Univariable relation between EndoCAb levels and change in cognitive index is shown with 95\% confidence intervals. The logarithmically transformed antibody variable has been exponentiated to illustrate the logarithmic relation with change in cognitive index. The horizontal axis has been truncated at 600 to best illustrate the range of values of greatest interest.
Endotoxins of Gram-negative bacteria are composed of lipopolysaccharides consisting of an O-specific chain, a core oligosaccharide, and a lipid component termed lipid A. Lipid A confers the toxic and immunomodulatory properties of endotoxin. Endotoxin is recognized as a major stimulus for the development of the systemic inflammatory response syndrome. After intravenous administration of endotoxin, cytokines are released in a characteristic pattern, initiated by peaks in TNF levels and followed within 3 hours by rises in IL-1β, IL-6, and IL-8. Endotoxin exposure is also associated with complement, plasminogen, and neutrophil activation; initiation of coagulation; and generation of bradykinin. The association between increased endotoxin or decreased EndoCAb levels and an exaggerated inflammatory response may shed light on the mechanisms underlying cognitive decline in older patients.
is supported by a study that evaluated the relation between EndoCAb levels and cytokine release in 100 patients who underwent CABG with CPB. Rothenberger et al demonstrated that lower preoperative EndoCAb levels were associated with a greater rise in endotoxin as well as IL-8 release. Similarly, in a smaller study of 26 patients, higher EndoCAb levels contributed to the prevention of endotoxin-induced contact activation and neutrophil degranulation.

Endotoxiaemia, which is common during cardiac surgery, generally results from gut mucosal hypoperfusion. Intraoperative EndoCAb depletion occurs through its consumption during endotoxia, adherence to CPB tubing, and decreased production. Low EndoCAb concentrations have been associated with a higher incidence of postsurgical death and major-organ failure, requirement for intra-aortic balloon counterpulsation, and greater ventilation time and postoperative hospitalization. Similar adverse outcomes were also predicted by low concentrations of EndoCAb during noncardiac surgery. Finally, in medical patients with sepsis syndrome, low EndoCAb levels were associated with increased mortality.

The association of endotoxin immunity and cognitive function is dependent on patient age; in elderly patients, especially those patients >60 years, the association between low endotoxin immunity and cognitive dysfunction is more pronounced. An age-associated decline in immune function may play an important role in the pathogenesis of cognitive dysfunction. CPB produces a profound alteration in the pool of circulating lymphocytes and monocytes, with older patients showing consistently lower lymphocyte numbers. Aging has also been associated with substantial dysregulation of the inflammatory process. Baseline elevation of serum cytokines, as well as white blood cell release of proinflammatory cytokines in response to stimulus, substantially increases with age. This chronic inflammation has been associated with reduced wound-healing ability, susceptibility to infection, and possibly cognitive dysfunction.

Our study is limited by the fact that 25% of our baseline population did not return for follow-up testing. Nonreturning patients were older, sicker, and had lower educational levels and baseline cognitive function scores than did returnees. However, both groups had similar EndoCAb levels. Second, we found slightly different models that described our continuous and our binary outcomes; these outcomes differed in that the continuous variable measures the effect of learning. Though not identical, both models confirm a detrimental effect of low EndoCAb levels on cognitive function. Third, it is possible that low EndoCAb levels are simply a surrogate for a generally debilitated or mildly immunocompromised state. However, the association of low EndoCAb levels and cognitive dysfunction independent of Parsonnet score demonstrates that presurgical health was not a significant factor. Finally, we examined only the effect of baseline EndoCAb levels on cognitive decline. Further decline during and/or after CPB may be of equal or greater importance. Nevertheless, this study is the first to report an association between low preoperative endotoxin immunity and increased cognitive decline.

Our study confirms and expands earlier reports that demonstrated an association between low preoperative endogenous EndoCAb and increased postoperative complications. Reduced preoperative endotoxin immunity predicts increased postoperative cognitive dysfunction in patients who undergo CABG, particularly the elderly. Among patients who undergo cardiac surgery, low endotoxin immunity may exacerbate the inflammatory response typically associated with CPB and cause greater cognitive dysfunction. Therefore, interventions that increase IgM EndoCAb levels or reduce the inflammatory response to endotoxin might improve cognitive function after cardiac surgery.

**Appendix 1: Neurologic Outcome Research Group (NORG) of the Duke Heart Center**

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