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

Joseph P. Mathew, MD; Hilary P. Grocott, MD, FRCPC; Barbara Phillips-Bute, PhD; Mark Stafford-Smith, MD; Daniel T. Laskowitz, MD; Daniel Rossignol, PhD; James A. Blumenthal, PhD; Mark F. Newman, MD; for the Neurologic Outcome Research Group (NORG) and the Cardiothoracic Anesthesiology Research Endeavors (CARE) Investigators of the Duke Heart Center

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.1 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.2–4 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.5 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.6 Furthermore, deterioration in cognitive functioning has negative societal consequences as a result of greater use of critical health-care resources.7

Recent clinical investigations of the extent and duration of cognitive dysfunction after cardiac surgery6,8,9 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 embolization10,11 may be a primary mechanism of cognitive decline, the inflammatory process that follows any initial insult can significantly modulate the extent of injury.12–16 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.17,18 During cardiac surgery, most patients are also exposed to endotoxin,19 the lipopolysaccharide component of the cell wall of Gram-negative bacteria and a major stimulus
for the development of a systemic inflammatory response.\textsuperscript{20} 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-\alpha (TNF-\alpha), interleukin (IL)-1, IL-6, IL-8, and IL-10.\textsuperscript{21} 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.\textsuperscript{22}

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,\textsuperscript{22-24} 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,\textsuperscript{22,23,25} longer hospitalization,\textsuperscript{23} and increased mortality in medical patients with sepsis syndrome.\textsuperscript{26} We therefore hypothesized that reduced endotoxin immunity in CABG patients may be associated with greater postoperative cognitive decline.

\section*{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.

\subsection*{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,\textsuperscript{27} the Wechsler Memory Scale (WMS) Figural Memory Test,\textsuperscript{28} the Digit Symbol subtest of the Wechsler Adult Intelligence Scale–Revised (WAIS-R),\textsuperscript{29} the Trail Making Test (part B),\textsuperscript{30} the Rey Auditory-Verbal Learning Test (AVLT),\textsuperscript{31} and the Digit Span subtest of the WAIS-R examination.\textsuperscript{29}

\subsection*{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 \textsuperscript{-1} m \textsuperscript{-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 (\(\alpha\)-stat), and oxygen partial pressures at 150 to 250 mm Hg.

\subsection*{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 \(-70^\circ\text{C}\) until assayed. Coated

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{Scatterplot of logarithmically transformed EndoCAb values versus the continuous measure of cognitive function, demonstrating the interaction between age and EndoCAb in the raw data.}
\end{figure}

ELISA plates and standard serum containing 165 MU of IgM EndoCAb were obtained from Dr Robin Barclay, Scotland, UK. ELISA assay conditions were as described,\textsuperscript{32,33} with horseradish peroxidase–conjugated anti-IgM antibody (A-6907, Sigma-Aldrich) and tetramethylbenzidine (T-0440, Sigma-Aldrich), except that the phosphate-buffered saline wash buffer contained 0.3% Triton X-100 and sample incubation was performed at 37°C for 60 minutes. Both the conjugate incubation and substrate incubation were performed at room temperature for 30 minutes. All serum standards and samples were diluted (1:100 or more) with ELISA dilution buffer (1% bovine serum albumin, 2.5% adult bovine serum, 0.1 Triton X-100, and 0.1% sodium azide in phosphate-buffered saline).

\subsection*{Statistical Analysis}
To assess cognitive decline over time while minimizing potential redundancy in the cognitive measures, a factor analysis with orthogonal rotation was first performed on the individual baseline cognitive-test scores.\textsuperscript{2} Factor analysis was used to reduce the larger number of correlated scores to a smaller number of uncorrelated variables to be used in the final analysis. The factor weights were based on the entire baseline sample. Patients missing 4 or fewer of the 18 individual scores had missing scores imputed by using a method designed to preserve the observation for analysis without influencing the mean change in that score. Only 133 individual scores (0.8% of the total scores) were imputed in this fashion. Based on patients’ test scores at each time period, weights of each test on each factor were used to construct comparable domain scores at baseline and 6-week follow-up, which produced domains that remained consistent over time.

The 4 resulting factors coherently represent the cognitive domains of: (1) verbal learning, short term and delayed (measured primarily by the Rey test); (2) discourse memory and oral language comprehension, short term and delayed (measured by the Randt test); (3) visuospatial orientation, psychomotor processing speed, and figural memory, short term and delayed (Digit Symbol, Trails B, and Figural Memory); and (4) attention and concentration (Digit Span). A change score for each of the factors was calculated by subtracting baseline from follow-up factor scores. Two summary measures were calculated to represent cognitive function: (1) “cognitive deficit” (the binary outcome) was defined as a decline of 1 standard deviation (SD) or more in performance on at least 1 of the 4 domains. (2) To quantify overall cognitive function and the degree of learning (ie, practice effect from repeated exposure to the testing procedures), a “composite cognitive index” \(\Delta CI\) was first calculated as the sum of the 4 domain scores. A continuous change score \(\Delta CI\) was then calculated by subtracting the baseline from the follow-up cognitive index.

We first investigated the association between EndoCAb level and cognitive dysfunction univariately by using the continuous measure of overall cognitive function. Because the EndoCAb distribution is positively skewed, we performed a logarithmic transformation to achieve a linear fit (Figure 1). A multivariable model was then developed to account for the effects of baseline cognitive function, age, years of education, and significant 2-way interactions of each of these with EndoCAb level. Covariates also considered for inclusion
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 \(0.13 \pm 0.54\). EndoCAb levels ranged from 2.56 to 2490.4 MU, with a median of 67.9 MU (\( Q_1 = 37.9, Q_3 = 123.8 \)).

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 \( (P = 0.005; \text{Figure 3}) \).

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

**TABLE 1. Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<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>
<td>0.005</td>
</tr>
<tr>
<td>Education, y</td>
<td>13.0 (3.3)</td>
<td>11.7 (3.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>35</td>
<td>41</td>
<td>0.22</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>85.5 (19.5)</td>
<td>85.3 (22.7)</td>
<td>0.93</td>
</tr>
<tr>
<td>History of hypertension, %</td>
<td>60</td>
<td>69</td>
<td>0.08</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>31</td>
<td>38</td>
<td>0.16</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>54.5 (11.0)</td>
<td>52.9 (12.4)</td>
<td>0.19</td>
</tr>
<tr>
<td>Duration of cardiopulmonary bypass, min</td>
<td>109.4 (78.1)</td>
<td>120.0 (52.5)</td>
<td>0.14</td>
</tr>
<tr>
<td>Number of grafts</td>
<td>3.0 (0.9)</td>
<td>3.2 (0.8)</td>
<td>0.11</td>
</tr>
<tr>
<td>Baseline cognitive index</td>
<td>0.02 (0.50)</td>
<td>-0.21 (0.52)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Median baseline EndoCAb levels, (( Q_1; Q_3 ))</td>
<td>68.8 (40.4; 125.6)</td>
<td>64.1 (29.2; 106.1)</td>
<td>0.09</td>
</tr>
<tr>
<td>Parsonnet score</td>
<td>8.61 (7.10)</td>
<td>11.08 (7.56)</td>
<td>0.002</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.

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.
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regression model containing the following predictors: log EndoCAb level, baseline cognitive index, age, and the interaction between age and log EndoCAb level. Table 2 presents details of this model with a c index of 0.672. EndoCAb level had a significant interaction with age, indicating that the effect of EndoCAb is different in older and younger patients. For example, in the model, a 40-year-old with an average baseline cognitive index but a reduced EndoCAb level of 20 (normal being 100) has a 16% probability of cognitive deficit. A patient aged 60, however, with the same baseline cognitive index and EndoCAb level of 20 has a probability of 37%. By age 80, an EndoCAb level of 20 raises the risk of cognitive deficit to 65%; an EndoCAb level of 150, however, would lessen this risk to 33%. Increasing the 80-year-old’s EndoCAb level to 600 further lessens the risk to 17%. The interaction between age and the EndoCAb variable is graphically depicted in Figure 4. Without the EndoCAb variable or the age × EndoCAb interaction, the c index is 0.647.

To calculate relative risks, we divided our sample into “high” and “low” age groups based on the median value of 64 years, and we divided the EndoCAb variable into “high” and “low” groups based on the median of 68. For the older age group, the low EndoCAb group had a cognitive deficit incidence rate of 46.9%, compared with the high EndoCAb group, who had an incidence rate of 34.72%, compared with the high EndoCAb group, who had an incidence rate of 32.73%. The relative risk for this group was 1.06.

A multivariable linear regression predicting a change in cognitive index (continuous outcome) shows similar results (Table 3) with an R² of 0.103, indicating that we can account for only slightly >10% of the variability in ΔCI. A model containing only age and baseline index had an R² of 0.076. Thus, the addition of log EndoCAb and the interaction term increased the predictive ability of the model. The linear regression analysis included the following variables as predictors of change in cognitive function: log EndoCAb level, baseline cognitive index, years of education, age > 60 years, and the interaction of age > 60 and log EndoCAb level. Age as a continuous variable was tested and found not to have a linear relation with cognitive index; therefore, age was dichotomized into ≤60 or >60 years.

To test the importance of the nonreturners in our sample, we conducted a secondary analysis in which all nonreturners were assigned a “cognitive deficit.” We still found a significant relation between EndoCAb and cognitive deficit (P = 0.018). Our c index dropped from 0.67 to 0.60 with this change, indicating a less predictive model, likely due to the error produced by overassigning the cognitive deficit.

Discussion

In this study, we investigated the relation between preoperative EndoCAb levels and the occurrence of cognitive decline after CABG. Six-week postoperative cognitive function declined in 36% of patients. Low preoperative IgM EndoCAb levels predicted increased risk of postoperative cognitive decline, particularly among older patients.

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-1B, 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

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Table 2: Multivariable Logistic Regression Model Predicting Cognitive Deficit at 6 Weeks

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta Coefficient</th>
<th>Standard Error</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept*</td>
<td>-1.095</td>
<td>0.64</td>
<td>...</td>
</tr>
<tr>
<td>Log EndoCAb</td>
<td>0.24</td>
<td>0.14</td>
<td>0.08</td>
</tr>
<tr>
<td>Baseline CI</td>
<td>0.25</td>
<td>0.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.03</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Age × log EndoCAb</td>
<td>-0.005</td>
<td>0.002</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Intercept refers to the mathematical constant used in predicting the probability of cognitive deficit.

Table 3: Multivariable Linear Regression Model Predicting Change in Cognitive Index at 6-Week Follow-Up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta Coefficient</th>
<th>Standard Error</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept*</td>
<td>-0.018</td>
<td>0.10</td>
<td>...</td>
</tr>
<tr>
<td>Log EndoCAb</td>
<td>-0.001</td>
<td>0.017</td>
<td>0.95</td>
</tr>
<tr>
<td>Baseline CI</td>
<td>-0.14</td>
<td>0.039</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Years of education</td>
<td>0.016</td>
<td>0.006</td>
<td>0.004</td>
</tr>
<tr>
<td>Age &gt; 60</td>
<td>-0.21</td>
<td>0.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age &gt; 60 × log EndoCAb</td>
<td>0.15</td>
<td>0.05</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*Intercept refers to the mathematical constant used in predicting the probability of change in cognitive index.
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 endotoxemia, 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

Director: Joseph P. Mathew, MD; Co-Director: James A. Blumenthal, PhD; Anesthesiology: Mark J. Bennett, MD, John V. Booth, MD, Fiona M. Clements, MD, Norbert de Bruijn, MD, Katherine Grichnik, MD, Hilary P. Grocott, MD, Steven E. Hill, MD, Mark F. Newman, MD, J.G. Reeves, MD, Debra A. Schwinn, MD, Mark Stafford-Smith, MD, David Warner, MD, Jerry L. Kirchner, BS, Mandy Barnes, RN, BSN, Bonita L. Funk, RN, E.D. Derilus, BS, Jason Hawkins, RN, BSN, I. Lee McClurkin, MA, RN, Terri Moore, BA, Chonna Campbell, BS, Amanda Check, AS, Roger L. Hall, AAS, Tanya Kagarise, BS, Debra L. Whiteheart, BS, Satarah Latiker, BS, Erich Lauff, MA, Charles R. Peters, MA, Debra L. Whiteheart, BS, Regina deLacy, BA, William Hansley, BS, Yvonne M. Connelly, MA, MPH, Meredith Prince, Barbara Phillips-Bute, PhD, and William D. White, MPH; Behavioral Medicine: Michael A. Babyak, PhD; Cardiology: Daniel B. Mark, MD, MPH, and Michael H. Skeich, Jr, MD; Neurology: Carmelo Graffagnino, MD, Daniel T. Laskowitz, MD, John R. Lynch, MD, Ann M. Saunders, PhD, Warren J. Strittmatter, MD, and Kathleen A. Welsh-Bohmer, PhD; Pathology: Ellen Bennett, PhD; Perfusion Services: Ian Shearer, BS, CCP, and Greg Smigla, BS, CCP; Surgery: Robert W. Anderson, MD, Thomas A. D’Amico, MD, R. Duane Davis, MD, Donald D. Glower, MD, David H. Harpole, Jr, MD, James Jaggers, MD, Robert H. Jones, MD, Kevin Landolfi, MD, James E. Lowe, MD, Robert H. Messier, MD, Carmelo Milano, MD, Peter K. Smith, MD, Eric M. Toloza, MD, PhD, and Walter G. Wolfe, MD.

Appendix 2: Cardiothoracic Anesthesia Research Endeavors (CARE) Investigators

Director: Mark Stafford-Smith, MD; Co-Director: Joseph P. Mathew, MD; Mark J. Bennett, MD, John V. Booth, MD, Fiona M. Clements, MD, Norbert de Bruijn, MD, Katherine Grichnik, MD, Hilary P. Grocott, MD, Steven E. Hill, MD, Mark F. Newman, MD, Mihai V. Podgoreanu, MD, J.G. Reeves, MD, Debra A. Schwinn, MD, Madhav Swaminathan, MD, and Ian J. Welsby, MD.

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