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Relationship of Preoperative Antiendotoxin Core Antibodies and Adverse Outcomes Following Cardiac Surgery

[Preliminary Communication]

Bennett-Guerrero, Elliott MD; Ayuso, Liza; Hamilton-Davies, Colin MD; White, William D. MPH; Barclay, G. Robin PhD; Smith, Peter K. MD; King, Sally A. MA; Muhlbaier, Lawrence H. PhD; Newman, Mark F. MD; Mythen, Michael G. MD

From the Department of Anesthesiology, The Mount Sinai Medical Center, New York, NY (Dr Bennett-Guerrero); Harvard Medical School, Boston, Mass (Ms Ayuso); the Department of Anesthesiology, Middlesex Hospital, London, United Kingdom (Dr Hamilton-Davies); the Departments of Anesthesiology (Drs Newman and Mythen and Mr White), Surgery (Dr Smith and Ms King), and Community and Family Medicine (Dr Muhlbaier), Duke Heart Center, Duke University Medical Center, Durham, NC; and the Scottish National Blood Transfusion Service, Edinburgh, United Kingdom (Dr Barclay).

Abstract

Objective: To test the hypothesis that low serum antiendotoxin core antibody (EndoCAb) level is an independent predictor of adverse outcome following cardiac surgery.

Design: Prospective, blinded, cohort study.

Setting: Tertiary care medical center.

Subjects: A total of 301 patients undergoing coronary artery bypass graft surgery and/or valvular heart surgery.

Design: Preoperative serum was assayed for IgM EndoCAb, IgG EndoCAb, total IgM, and total IgG levels. Known preoperative risk factors were assessed, and patients were assigned a risk score using a validated method.

Main Outcome Measure: A major complication, defined as either in-hospital death or

postoperative length of stay greater than 10 days.

Results: Overall, a major complication occurred in 34 patients (11.3%). Lower IgM EndoCAb level independently predicted (P=.002) increased risk of major complication over and above the effects of preoperative risk score (P=.02), total IgG level (P=.07), and all other known perioperative risk factors. In contrast, IgG EndoCAb and total IgM concentrations did not predict outcome. No association existed between risk score and level of IgM EndoCAb.

Conclusion: There is marked preoperative variability in humoral immunity against endotoxin core, which is not accounted for by differences in known preoperative risk factors. In this study, low levels of IgMEndoCAb were an important independent predictor of adverse postoperative outcome, which supports the theory that endotoxemia is a cause of postoperative morbidity.JAMA. 1997;277:646-650

MORE THAN 350 000 cardiac operations are performed in the United States annually. [1] Although the mortality rate for cardiac surgery is low, perioperative complications remain common [2] and include atrial fibrillation, poor ventricular function requiring inotropic agents, and non-cardiac-related etiologies such as infection, gastrointestinal dysfunction, acute lung injury, stroke, and renal dysfunction. A large proportion of non-cardiac-related morbidity may be the manifestation of an exaggerated systemic proinflammatory response seen in many patients following major surgery. [3,4]

It is unclear which factors are pivotal in triggering the systemic inflammatory response in the setting of cardiac surgery. Endotoxin, the lipopolysaccharide component of the cell wall of gram-negative bacteria, is toxic to humans in nanogram quantities [5,6] and may be one of the initiating factors in the activation of this inflammatory cascade. [7-11] Endotoxemia is common in cardiac surgical patients [12-16] and may arise from exogenous sources or from translocation through an impaired gut barrier. [12-20]

In humans, it is unclear whether poor endogenous immunity to endotoxin contributes to complications after heart surgery. Some studies have suggested that poor preoperative immunity against endotoxin may correlate with adverse outcome. [21-23] We therefore tested the hypothesis that reduced preoperative immunity to the highly conserved core region of endotoxin is associated with adverse outcome in patients undergoing heart surgery.

METHODS

Patient Selection

Following institutional review board approval and informed consent, patients undergoing coronary artery bypass graft surgery, valvular heart surgery, or a combination of both were enrolled at the Duke Heart Center, Durham, NC, in a prospective, blinded observational trial from June through October 1995.

Protocol

After oral methadone hydrochloride and benzodiazepine premedication, venous, radial artery, and central venous catheters were inserted. Induction and maintenance of general anesthesia were accomplished with midazolam hydrochloride and fentanyl citrate infusions. Patients underwent standard nonpulsatile hypothermic (28 degrees C to 32 degrees C) cardiopulmonary bypass with a membrane oxygenator. Porcine heparin sodium (Elkins-Sinn,

Inc, Cherry Hill, NJ) was administered as a load of 300 U/kg and supplemented as necessary to maintain an activated clotting time of at least 450 seconds during cardiopulmonary bypass. Following cardiopulmonary bypass, heparin was neutralized with protamine sulfate (Eli Lilly and Co, Indianapolis, Ind). Patients were managed postoperatively according to the standard institutional cardiac surgery "care map" in which patients without significant complications are discharged from the hospital on day 4 or 5.

Blood samples for determination of IgG antiendotoxin core antibody (EndoCAb), IgM EndoCAb, total IgM, and total IgG levels were obtained through an arterial catheter immediately prior to the induction of general anesthesia; samples were collected in glass tubes without additive and centrifuged for 10 minutes at 2000 g, and plasma was stored at -20 degrees C until assayed. IgG EndoCAb and IgM EndoCAb levels were measured using an enzyme-linked immunosorbent assay described previously. [24,25] In brief, incomplete-core rough mutant lipopolysaccharide from each of 4 species of gram-negative bacteria (Escherichia coli, Pseudomonas aeruginosa, Klebsiella aerogenes, and Salmonella typhimurium) were complexed with polymyxin B and coated on polystyrene microplates. IgG EndoCAb and IgM EndoCAb concentrations were determined with alkaline phosphatase-conjugated antibodies specific for human gammaglobulin gamma or micro heavy chains (Zymed Laboratories, Cambridge BioScience, Cambridge, United Kingdom). Test sera were compared in enzyme-linked immunosorbent assay to a reference serum calibrated in EndoCAb median units (MU), where 100 is the median value for 1000 healthy adults' IgG or IgM. [24] Serum was tested for total IgG and IgM concentrations by laser nephelometry. [26] All laboratory measurements were performed on coded samples so as to blind the investigators to the patients' identity and outcome.

Preoperative Risk Scoring and Definitions of Patient Characteristics

Preoperatively, demographic information was collected, and a risk score for mortality and morbidity was assigned according to the validated Parsonnet scoring system. [27] This model sums the assigned values for 19 factors known to increase mortality and morbidity following heart surgery and generates a score between 0 (ie, no risk factors) and 148; most patients in the original series by Parsonnet et al (n=4832) were assigned a score between 0 and 30, with approximately 50% of patients assigned a score between 0 and 9. [27]

Diabetes mellitus was considered present if a patient required oral hypoglycemic or insulin medication preoperatively. Myocardial infarction was defined as electrocardiographic evidence of an old myocardial infarction or previously documented episodes of increased creatine kinase-MB isoenzymes without concurrent electrocardiographic changes. Hypertension was defined as blood pressure greater than 140/90 mm Hg documented on at least 3 occasions or a history of increased blood pressure requiring medication. A history of congestive heart failure required at least 1 documented episode of congestive heart failure diagnosed using standard chest x-ray examination, physical examination, and hemodynamic criteria. History of stroke was defined as the development of a focal neurologic deficit preoperatively. History of atrial fibrillation was defined as any previous episode of atrial fibrillation. Left ventricular ejection fraction was determined from cardiac catheterization data.

Outcomes

Postoperative length of stay was defined as the number of days from the day of operation

(day 0) to hospital discharge or death. Major complication was the primary outcome of this study and was defined as either in-hospital death or postoperative length of stay greater than 10 days. A recent retrospective analysis of 2609 patients undergoing cardiac surgery at Duke University Medical Center demonstrated that the majority of patients with a length of stay greater than 10 days (5 days more than the median) suffered noncardiac morbidity (written communication, Darryl Atwell, MD, Duke University Medical Center, June 1995). Thus, a dramatically prolonged length of stay-greater than 10 days-was chosen as a surrogate for occurrence of significant medical complications, particularly given our written cardiac surgery care map, which provides for patient discharge on day 5. Existing morbidity scoring systems such as the Acute Physiology and Chronic Health Evaluation were not used in this study because they are geared to the intensive care unit setting and thus have limited value in most postoperative patients. [28] All outcome measurements were performed by investigators blinded to the patients' laboratory data.

Statistical Analysis

Given an estimated incidence of 10% for the primary end point (major complication), a sample size of at least 300 was estimated to generate 30 events and allow for a stable logistic regression model to test the study's hypothesis. All statistical calculations and analyses were carried out using the SAS software system (SAS Institute Inc, Cary, NC). Statistical significance was set at alpha=.05. Correlations between continuous variables were tested with linear regression, and associations between categorical variables were tested using the contingency Table chisquared test.

The objective of this study was to test the specific hypothesis that IgM EndoCAb and/or IgG EndoCAb levels are associated with adverse postoperative outcome. The study was not designed to search for predictors of adverse postoperative outcome. We decided prior to the initiation of the study that we would test our specific hypothesis by constructing a multivariable logistic regression model that contained IgM EndoCAb level, IgG EndoCAb level, and Parsonnet risk score. The validated Parsonnet risk score was forced into the model to adjust for the effect of patient comorbidities. This analysis tested the predictive ability of IgM EndoCAb level, IgG EndoCAb level, and Parsonnet risk score independently, after adjusting for the information contributed by the others. The assumption of linearity of fit in the logit was validated against nonlinear transformations and cubic spline fits, and the selected model was validated by a bootstrapping technique. [29,30]

We further tested the validity of this multivariable logistic regression model as follows. We used univariate logistic regression to test the association of perioperative characteristics with major complication. Examples of some of these factors included some variables represented in the preoperative risk score (age, left ventricular ejection fraction) as well as other known risk factors not included in the preoperative risk score (total IgM level, total IgG level, history of stroke, history of atrial fibrillation, history of congestive heart failure, cardiopulmonary bypass duration, aortic cross-clamp duration, and perioperative intraaortic balloon pump insertion). Factors with a significant univariate association ($P<.05$) were tested as a block against the hypothesized model to see whether they would supplant the significance of IgM EndoCAb level. In addition, the relationships between surgeon and IgM EndoCAb as well as outcome were specifically investigated in separate logistic regressions.

RESULTS

A total of 301 patients were enrolled in the study. No patient refused to participate. Preoperative demographics and intraoperative characteristics for the study population are presented in (Table 1). Of the 301 patients, 82% underwent coronary revascularization alone, 8% underwent valvular surgery, and 10% underwent a combination of coronary revascularization and valvular surgery. IgM EndoCAb levels ranged from 1 to 308 MU, with a mean of 85.1 MU (+/-SD of 59.3 MU; median, 72 MU). IgG EndoCAb levels ranged from 16 to 698 MU, with a mean of 197 MU (+/-SD of 133 MU; median, 161 MU). Parsonnet preoperative risk score ranged from 0 to 46, with a mean of 11.6 (+/-SD of 8.2; median, 10). Overall, a major complication occurred in 34 patients (11.3%), as summarized in (Table 2). In patients with a major complication (n=34), IgM EndoCAb levels were lower (mean, 54.4 MU;+/-SD of 42.8 MU; median, 39 MU) compared with patients not having a major complication (n=267) (mean, 89 MU;+/-SD of 60 MU; median, 75 MU). In-hospital death occurred in 10 patients (3.3%), and 28 patients (9.3%) had a postoperative hospital length of stay greater than 10 days. Twenty-four patients (8%) stayed in the hospital for more than 10 days and survived to hospital discharge. Overall, postoperative length of stay ranged from 0 to 45 days, with a mean of 7.0 days (+/-SD of 4.9 days; median, 6 days). Among survivors, length of stay ranged from 3 to 32 days, with a mean of 6.7 days (+/-SD of 3.7 days; median, 6 days).

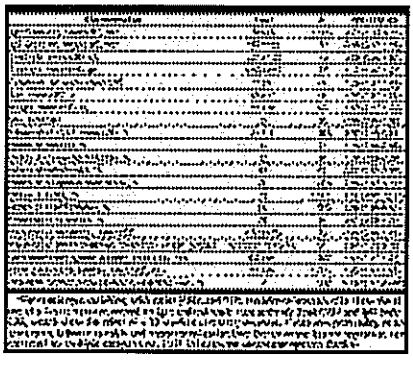

Table 1.-Univariate Associations Between Preoperative and Intraoperative Characteristics and Major Complication*

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Table 2.-Postoperative Diagnoses in 34 Patients With a Major Complication*

Postoperative Diagnosis	No. (%) of Patients
Pulmonary dysfunction†	13 (38)
Infection (nonpulmonary)‡	7 (21)
Renal dysfunction requiring dialysis	2 (5)
Gastrointestinal bleeding requiring transfusion	2 (5)
Neurologic dysfunction§	13 (38)
Cardiac dysfunction‖	19 (56)
Cardiac dysfunction as only diagnosis	5 (15)

*Percentages add up to more than 100% because some patients had more than 1 postoperative diagnosis.

†Pulmonary dysfunction included reintubation of the trachea, tracheostomy, pneumonia, or acute respiratory distress syndrome.

‡Infection (nonpulmonary) included mediastinitis, sternal wound infection, leg wound infection, or positive blood cultures.

§Neurologic dysfunction included stroke, coma, or acute confusion and delirium.

‖Cardiac dysfunction included atrial or ventricular dysrhythmias, cardiac arrest, or ventricular dysfunction requiring vasoactive agents for more than 48 hours postoperatively.

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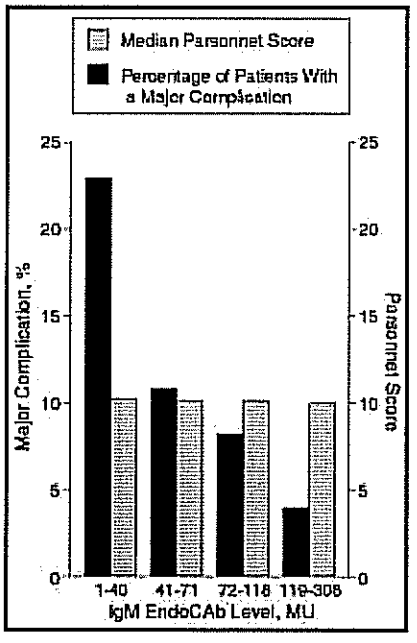
The relationships of Parsonnet risk score with IgM EndoCAb and IgG EndoCAb levels were nonsignificant (P>.50). There was a weak relationship between IgM EndoCAb level and IgG EndoCAb level (Pearson r=0.11, P=.051). Relatively weak but significant Pearson correlations were found between the EndoCAb levels and their respective total levels (IgM, r=0.43, P<.001; IgG, r=0.20, P=.002). In addition, there was no statistically significant association between surgeon and EndoCAb levels or postoperative outcome.

(Figure 1) presents the percentage of patients having a major complication in each quartile of IgM EndoCAb level. Of note, a major complication occurred in only 3.7% of patients in the highest quartile of IgM EndoCAb level. In contrast, 23% of patients in the lowest quartile suffered a major complication. This 6-fold difference in outcome is not explained by known preoperative risk factors, as the median Parsonnet score (10) was the same in each of the IgM EndoCAb level quartiles. The most appropriate statistical test of these relationships in (Figure 1) is the logistic regression described below.

Figure 1. Relationship between preoperative IgM EndoCAb levels by quartile (in median units [MU]) and Parsonnet risk score or percentage of patients having a major complication.



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As stated in the "Statistical Analysis" section, we first tested our specific hypothesis by constructing a multivariable logistic regression model that contained IgM EndoCAb level, IgG EndoCAb level, and Parsonnet risk score. In this model, lower IgM EndoCAb level independently predicted increased risk of major complication over and above the effect of Parsonnet risk score (P=.002; odds ratio [OR]=2.00; 95% confidence interval [CI], 1.29-3.10 for each 50-MU decrease in IgM EndoCAb level). Parsonnet score was also significant in the model, but not as strongly predictive (P=.02; OR=1.05; 95% CI, 1.01-1.09). IgG EndoCAb level was not predictive of outcome (P>.60). Overall model chi squared for covariates (-2 log likelihood) was 18.33 with 2 df (P<.001). Model C index was 0.72. There was no significant interaction between IgM EndoCAb and Parsonnet risk score.

We further tested the validity of this multivariable logistic regression model by determining univariate associations of other potential predictors with major complication. These univariate associations are shown in (Table 1). When tested against our original model, none of the variables from (Table 1) supplanted the significance of IgM EndoCAb level, further confirming the validity of the original model. We also tested the validity of our model using the bootstrapping method. In this test, IgM EndoCAb level was significant in 47 of 50 random subsamples. In contrast, Parsonnet risk score was significant in 26 samples, and total IgG in 24 samples

COMMENT

This is the first large descriptive trial evaluating the association between preoperative antiendotoxin immune status and morbidity in patients following cardiac surgery. We have demonstrated that low preoperative serum IgM EndoCAb concentration is associated with adverse outcome following cardiac surgery and may account for a significant proportion of the variability in outcome seen among patients with identical preoperative risk scores.

Approximately 28 million people undergo surgery annually in the United States, of whom 350 000 undergo cardiac surgical procedures. [1] Postoperative morbidity is poorly characterized; nevertheless, it increases suffering, hospital length of stay, and health care costs. Several preoperative risk scoring systems exist. [27,31-34] Unfortunately, these scoring systems identify patient characteristics (eg, diabetes, age, poor ventricular function) that cannot be altered to improve outcome. Moreover, their ability to predict outcome is limited, suggesting that other factors may be equally or more important.

Many postoperative complications appear to be caused by an exaggerated systemic proinflammatory response to surgical trauma. [3,4] In the most severe form of proinflammatory response, the patient develops systemic inflammatory response syndrome, which may lead to multiple organ dysfunction syndrome and death. [4] Milder forms of a proinflammatory response may be associated with a less severe form of organ dysfunction that does not lead to admission to an intensive care unit but nevertheless increases hospital length of stay and thus cost.

Endotoxin, the lipopolysaccharide component of the cell wall of gram-negative bacteria, has been linked to dysfunction in every organ system of the body and may be one of the initiating factors in the activation of this inflammatory cascade. [7-11] Endotoxemia is common during cardiac surgery. [12-16] Patients may be exposed to endotoxin from translocation through an impaired gut barrier. [17-20] The body's humoral immunity to endotoxin may be limited owing to the numerous serotypes of endotoxin. For example, at least 164 O antigens of E coli and 64 O antigens of salmonellae have been described. [35,36] Serotype-specific antibodies do not recognize the many possible variations of endotoxin O-polysaccharide side chains; however, antibodies directed against the core structure of endotoxin should theoretically be cross-reactive against most enteric lipopolysaccharides. [37,38] In this study, we used an assay that measures the concentration of antibodies that bind to incomplete core rough mutant lipopolysaccharide. [24,25] The plasma concentration of these antibodies has been previously measured in over 1000 human volunteer blood donors and demonstrates marked variability, with some subjects having over 300-fold higher concentrations than others. [24] These antibodies appear to have different binding characteristics and to be more cross-reactive than antibodies induced by lipid A and the extensively studied Rc-like J5 rough mutant lipopolysaccharide of E coli. [25,37-39] These other antibodies may in fact have limited cross-reactivity, which may explain their inability to provide protection consistently in vitro or in animal and human trials. [37-43]

Several studies have suggested that variability in antiendotoxin immunity may be associated with outcome during surgery or illness. [21-23,44] Low concentrations of both IgG EndoCAb and IgM EndoCAb were associated with worse outcome in a study of intensive care unit patients with established sepsis syndrome. [44] A limitation of that study is that true baseline values-ie, prior to injury and endotoxin exposure-were not measured. Thus, it is unknown whether low EndoCAb levels in these patients existed prior to acute illness or were merely a marker for patients who had already sustained a greater disease insult and thus greater endotoxin exposure. In a study of 58 European patients undergoing first-time cardiac valve replacement, low preoperative serum IgM EndoCAb levels were associated with postoperative complications. [21] Another study measured the presence of preoperative antibodies to endotoxin in 86 cardiac surgery patients and found a lower incidence of fever and infections in the 30 patients with antibody. [22] In 86 women undergoing major gynecologic surgery, the presence of preoperative antiendotoxin antibodies was associated with decreased postoperative infections. [23] These 2 studies, [22,23] however, did not quantitate antiendotoxin

antibodies, measure total immunoglobulins, assign risk scores to patients preoperatively, or comment on postoperative length of stay or other complications.

A limitation of all previous studies is the possibility that low antiendotoxin immunity may not be a cause of poor outcome but merely a marker for sicker patients with higher operative risk and poorer general immunity. Our study minimized this possibility by using a validated preoperative risk scoring system to quantify degree of risk and by measuring total immunoglobulin levels. The fact that lower IgM EndoCAb level independently predicted increased risk of major complication over and above the effect of risk score and total immunoglobulin levels supports the theory that poor immunity to endotoxin may be an important cause of postoperative complications. These results are consistent with those from the smaller studies cited above. [21-23] We chose cardiac surgery as a model to study the relationship between EndoCAb levels and adverse outcome given the high incidence of endotoxemia in this population [12-16] as well as the high incidence of postoperative morbidity demonstrated in a review of 2609 patients at Duke University Medical Center. Our study population is representative of cardiac surgery patients at Duke, where the distribution of Parsonnet scores was similar and the incidence of major complication (death or postoperative length of stay greater than 10 days) was 15.7% (mortality alone 3.6%) based on a review of 2609 cases from 1993 to 1995 (written communication, Darryl Atwell, MD, Duke University Medical Center, June 1995).

There are several criticisms of the theory that endotoxemia is an important cause of postoperative morbidity, and they warrant comment in light of our findings. A common criticism relates to the low incidence of culture-proven bacteremia in surgical and intensive care unit patients. [45-48] Endotoxemia, however, is clearly prevalent in these patients [11-16,44,49,50] and usually exists in the setting of negative blood cultures. In fact, studies attempting to detect endotoxemia probably underestimate its incidence given the intermittent nature of endotoxemia. Another criticism against this theory stems from a study using antibiotic-decontaminated rats in which the authors concluded that "shock-induced mucosal permeability and injury appear not to be directly related to the presence of translocating bacteria." [51] Again, an inability to culture live organisms from the blood does not rule out the presence of endotoxemia; therefore, this study's results do not reject the hypothesis that endotoxemia is an important cause of morbidity. The failure of 2 antilipid A monoclonal antibodies (HA-1A, Centocor, Malvern, Pa, and E5, Xoma, Berkeley, Calif) to improve outcome on an intention-to-treat basis in intensive care unit patients with established sepsis has also been used to suggest that endotoxemia is not clinically relevant. [42,43] These monoclonal antibodies, however, were tested in patients with established sepsis and organ failure, which is an entirely different setting than elective surgical patients who are more likely to benefit from prophylaxis with endotoxin-neutralizing drugs. There is also evidence suggesting that these antilipid A monoclonal antibodies may not bind to endotoxin with high affinity, [40] which may explain in part their lack of demonstrable efficacy. [41-43] Results from controlled studies in which endotoxin is selectively neutralized will be necessary to determine the clinical relevance of endotoxemia.

In summary, low preoperative IgM EndoCAb concentration is associated with adverse outcome following cardiac surgery independent of other established risk factors. Our results support the theory that endotoxemia may be an important cause of perioperative morbidity. The preoperative measurement of IgM EndoCAb level may play an important role in risk assessment prior to major elective surgery.

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Reprints: Elliott Bennett-Guerrero, MD, Department of Anesthesiology, Box 1010, The Mount Sinai Medical Center, 1 Gustave L. Levy Pl, New York, NY 10029-6574.

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Antibodies, Antiendotoxin Core; Coronary Artery Bypass; Endotoxemia; Heart Surgery; Postoperative Complications

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