Encephalopathy and Stroke After Coronary Artery Bypass Grafting

Incidence, Consequences, and Prediction

Guy M. McKhann, MD; Maura A. Grega, MSN; Louis M. Borowicz, Jr, MS; Michon Bechamps, MHS; Ola A. Selnes, PhD; William A. Baumgartner, MD; Richard M. Royall, PhD

**Background:** In contrast to perioperative stroke, much less attention has been paid to those with evidence of diffuse brain encephalopathy, presenting as delirium, confusion, coma, and seizures in the immediate postoperative period.

**Objective:** To determine the incidence, consequences, and predictive factors for encephalopathy and stroke following coronary artery bypass grafting.

**Methods:** In a prospective evaluation of 2711 patients operated on between January 1, 1997, and December 31, 2000, preoperative risk factors were obtained before surgery and postoperative outcomes, encephalopathy and stroke, were determined on a daily basis. All strokes were confirmed by neurologic consultation and, in most instances, by imaging. Logistic regression analyses were performed to determine risk factors for these outcomes.

**Results:** The incidence of encephalopathy was 6.9% and of stroke, 2.7%. For patients without either of these outcomes, the average length of stay in the hospital was 6.6 days and the mortality was 1.4%. In contrast, patients with encephalopathy had a length of stay of 15.2 days and a mortality of 7.5%, and those with stroke, a length of stay of 17.5 days and a mortality of 22.0%. Predictive models were developed for encephalopathy involving 5 preoperative factors (age, past stroke, carotid bruit, hypertension, and diabetes) and 1 perioperative factor (time on cardiopulmonary bypass). The model for stroke involved only 3 preoperative risk factors (past stroke, hypertension, and diabetes).

**Conclusions:** Encephalopathy or stroke is associated with significant increases in length of stay and mortality after coronary artery bypass grafting. Patients at higher risk for these outcomes can be identified before surgery.

Arch Neurol. 2002;59:1422-1428

*Original Contribution*

From the Department of Neurology (Drs McKhann and Selnes), Division of Cardiac Surgery, Department of Surgery (Ms Grega and Dr Baumgartner), and Department of Neuroscience (Dr McKhann), Johns Hopkins School of Medicine; the Zanvyl Krieger Mind/Brain Institute (Dr McKhann and Mr Borowicz); and the Department of Biostatistics, The Johns Hopkins University Bloomberg School of Public Health (Dr Royall), The Johns Hopkins University, Baltimore, Md; and the MD Program, Eastern Virginia Medical School, Norfolk (Ms Bechamps).

Considerable attention has been paid to the incidence, consequences, and prediction of stroke associated with coronary artery bypass grafting (CABG). In contrast, much less attention has been paid to patients with evidence of diffuse encephalopathy presenting as delirium, confusion, coma, and seizures in the immediate postoperative period. Only a few studies quantify the risk of encephalopathy after CABG.1,2 This is somewhat surprising because encephalopathy is more common than stroke and, as we demonstrate in this study, is also associated with an increased length of hospital stay (LOS) and a greater mortality. Furthermore, it is not known whether the presence of postoperative encephalopathy is predictive of cognitive declines months or years after CABG.3,4 The ability to predict, before surgery, those likely to have encephalopathy could improve the care of these patients.

In this report, based on the prospective study of 2711 patients undergoing CABG, we describe the incidence, the immediate consequences in terms of LOS and mortality, and predictive factors for each of these 2 postoperative outcomes, encephalopathy and stroke, as well as the aggregate of patients having either outcome.

**Patients and Methods**

**Patients**

Between January 1, 1997, and December 31, 2000, 2711 patients underwent isolated CABG at the Johns Hopkins Medical Institutions, Baltimore, Md. There were 10 intraoperative deaths, and 271 patients had data allowing determinations of postoperative encephalopathy and stroke. Complete information about variables used in the analysis for encephalopathy was available in 2699 patients and for stroke in 2668. Patients with concomitant cardiac procedures, such as valve replacement, repair of a congenital defect, or carotid endarterec-
tomy, were excluded, as were patients undergoing surgery without a bypass pump. The study was approved by the institutional review board of The Johns Hopkins Medical Institutions.

**PREOPERATIVE AND OPERATIVE VARIABLES**

The following data were collected before surgery by members of the study team (M.A.G. and L.M.B.): (1) history of a previous stroke, (2) history of hypertension, (3) history of diabetes mellitus, (4) presence of carotid bruit, and (5) age. With the use of this information, probabilities of encephalopathy, stroke, and the aggregate of either were developed. The only operative variable analyzed was time on cardiopulmonary bypass (CPB). We did not analyze aortic cross-clamping time as a separate variable, because in our data this variable was closely associated with CPB.

**SURGICAL PROCEDURES, ANESTHESIA, AND PERFUSION**

Eight cardiac surgeons were involved in this study. Although there were some individual variations in technique, most procedures were standardized. All patients underwent median sternotomy. Anesthetic technique was standardized and consisted of low- to intermediate-dose narcotics, inhalation agents, and paralytics. Cardiopulmonary bypass was carried out with nonpulsatile flow (in most cases), alpha-stat pH blood gas management, antegrade crystalloid cardioplegia (in most cases) with topical hypothermia, moderate systemic hypothermia (28°C-32°C), and pump flow rates to achieve a mean arterial pressure of 60 to 80 mm Hg. The placement of the aortic cross-clamp varied. Some surgeons used the single clamp technique exclusively, while others used this technique only in certain clinical situations. This variable was not collected as part of this study.

**OUTCOME VARIABLES**

Postoperatively, members of the study team followed up patients in the cardiac surgery care units daily, in collaboration with the medical and nursing staff.

**LOS and Death**

Postoperative LOS referred to the number of days the patient remained in the hospital after surgery either before discharge or before death. Mortality was defined as the deaths of patients that occurred during their postoperative hospital stay.

**Encephalopathy**

The diagnosis of encephalopathy was made by 2 members of the study team (M.A.G. and L.M.B.), who were not aware of the patient’s risk factors at the time of evaluation. We included in the encephalopathy group patients having delirium, coma, or seizures at any time during the postoperative stay, after the first 24 hours following surgery. Neither the duration nor severity of encephalopathy was included in the analysis.

The criteria for delirium were similar to those outlined in *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* and included any of the following: episodes of confusion, agitation, and/or combativeness; alterations and fluctuations in levels of consciousness; acute problems with cognition, including memory; and changes in perception, including hallucinations. The presence of delirium, coma, or seizures was documented by the nursing or medical staff, and the documentation was collected and evaluated daily by study observers.

**Stroke**

A standard clinical examination was used to determine the presence of any neurologic deficit. When patients were suspected of having a focal deficit, a neurology consultation was obtained. Stroke was defined as any persistent focal neurologic deficit lasting 24 hours or more. All stroke outcomes in this study were diagnosed by a neurologist and, in most cases, were localized by imaging studies, either head computed tomography or magnetic resonance imaging. Of note, in this study the diagnoses of stroke and encephalopathy were mutually exclusive.

**STATISTICAL ANALYSES**

**Prediction of Encephalopathy**

Logistic regression analyses were performed to measure the risk of postoperative encephalopathy. Two models were developed: one that used only those 5 variables available preoperatively (age, history of previous stroke, hypertension, diabetes mellitus, and the presence of a carotid bruit) and a second that used these 5 preoperative variables plus CPB time.

**Prediction of Stroke**

In the first set of analyses presented herein, a logistic regression model developed previously for the prediction of stroke using variables available preoperatively was applied to the current patient population. This previously derived model included 5 variables (age, history of previous stroke, hypertension, diabetes mellitus, and the presence of a carotid bruit) that had been selected from a total of 42 variables (26 demographic and medical history variables and 16 intraoperative variables) by a series of univariate and multivariate analyses.

Two stroke risk models were presented in a previously published article, one based on the 5 preoperative variables indicated above and another that included these preoperative variables as well as the operative variable CPB time. With the use of these 5 preoperative variables and the CPB time variable, a revised model was created for the new population. In this analysis, only 3 variables were significant: age, hypertension, and history of previous stroke. Thus, a simplified model for the prediction of stroke was developed.

**Prediction of Encephalopathy or Stroke**

The final logistic regression used the 5 preoperative variables indicated above for prediction of the aggregate outcome “encephalopathy or stroke.” Time on CPB was also combined with these preoperative variables in a second analysis for this outcome.

**RESULTS**

The average age of the patients was 64 years, and the population included 73% men. The incidence of hypertension was 69%; diabetes, 31%; carotid bruit, 10%; and previous stroke, 6%. Encephalopathy occurred in 186 patients in the population (an incidence of 6.9%), and there were 72 episodes of stroke (an incidence of 2.7%). Both of these outcomes, as well as the aggregate of those having either, were associated with longer LOS in the hospital and with greater mortality than in those without these outcomes (Table 1).
When the 5 preoperative variables specified above were used in a logistic regression to predict the development of post-CABG encephalopathy, all were significant (Table 2). With these 5 factors, the probability of postoperative encephalopathy for an individual patient can be calculated, as shown in Figure 1.

**Table 2. Prediction of Encephalopathy**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>SE</th>
<th>P Value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past stroke</td>
<td>2.15</td>
<td>0.52</td>
<td>.002</td>
<td>1.34-3.44</td>
</tr>
<tr>
<td>CB</td>
<td>1.57</td>
<td>0.34</td>
<td>.04</td>
<td>1.03-2.40</td>
</tr>
<tr>
<td>HTN</td>
<td>1.48</td>
<td>0.29</td>
<td>.05</td>
<td>1.01-2.16</td>
</tr>
<tr>
<td>DM</td>
<td>1.48</td>
<td>0.24</td>
<td>.02</td>
<td>1.08-2.04</td>
</tr>
<tr>
<td>Age 1</td>
<td>1.48</td>
<td>0.28</td>
<td>.04</td>
<td>1.02-2.13</td>
</tr>
<tr>
<td>Age 2</td>
<td>2.84</td>
<td>0.56</td>
<td>.001</td>
<td>1.93-4.18</td>
</tr>
</tbody>
</table>

*CB indicates carotid bruit; HTN, hypertension; and DM, diabetes mellitus. For age 1, patients at least 65 but younger than 75 years, the odds in favor of encephalopathy are estimated to be 1.48 times the odds for those younger than 65 years. For age 2, patients at least 75 years of age, the odds in favor of encephalopathy are estimated to be 2.84 times the odds for those younger than 65 years.

**PREDICTION OF STROKE**

When preoperative variables were used to predict the presence of stroke in this current population with the previous model, more than twice as many strokes were predicted than actually occurred (161 vs 71). Moreover, this lack of accuracy was not uniform across levels of risk. In the high-risk group, the model predicted almost 3 times the number of observed strokes (141 vs 50, respectively). In the low-risk group, the model predicted fewer strokes than occurred (8 vs 13, respectively). As a result of the unreliable predictions produced by the model from 1994, we developed a logistic regression model applying the same 5 risk factors to the current population. Two of the variables (presence of carotid bruit and history of diabetes) were no longer significant. Thus, a simpler model, using only 3 variables (age, history of previous stroke, and history of hypertension), was developed. Table 3 presents the odds ratios, significance levels, and confidence intervals for the 3 risk factors in this new model. With this simpler model, the risk of stroke for an individual is indicated in Figure 2.

**PREDICTION OF ENCEPHALOPATHY OR STROKE**

When taken together, 258 patients had either stroke or encephalopathy (incidence of 9.6%). We therefore examined the ability of the logistic regression model to predict the development of either stroke or encephalopathy after CABG. Similar to the model predicting encephalopathy, all 5 preoperative variables were significant (Table 4). Time on CPB was also significant for this outcome.
ASSOCIATION OF TIME ON CPB WITH ENCEPHALOPATHY AND STROKE

Time on CPB was strongly associated with the prediction of postoperative encephalopathy \( (P = .006) \). As indicated in Table 5, for patients without multiple risk factors, there was a 50% increase in the probability of encephalopathy and stroke for each 30 minutes of additional CPB time. For patients with multiple risk factors, the increase in probability was 30% for each additional 30 minutes of CPB time.

In our previous model for prediction of stroke, the only significant operative variable was time on CPB. When this variable was added to the current model for the prediction of stroke, the variable was not significant \( (P = .86) \). Thus, we did not include bypass time in the current model for stroke prediction.

**Table 3. Stroke Risk Model Based on Current Population**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>SE</th>
<th>P Value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past stroke</td>
<td>2.11</td>
<td>0.75</td>
<td>.04</td>
<td>1.05-4.23</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.97</td>
<td>0.63</td>
<td>.04</td>
<td>1.05-3.69</td>
</tr>
<tr>
<td>Age 1</td>
<td>2.39</td>
<td>0.76</td>
<td>.01</td>
<td>1.28-4.45</td>
</tr>
<tr>
<td>Age 2</td>
<td>5.02</td>
<td>1.61</td>
<td>.001</td>
<td>2.68-9.40</td>
</tr>
</tbody>
</table>

*For age 1, patients at least 65 but younger than 75 years, the odds in favor of stroke are estimated to be 2.39 times the odds for those younger than 65 years. For age 2, patients at least 75 years of age, the odds in favor of stroke are estimated to be 5.02 times the odds for those younger than 65 years.*

COMMENT

In this study, we have demonstrated that both postoperative encephalopathy and stroke are associated with significantly longer LOS and greater mortality. Mortality after encephalopathy is 5 times that for patients without encephalopathy or stroke \( (7.5\% \text{ vs } 1.4\%) \). Postoperative stroke has received considerable attention in previous studies, and the effect of a stroke on postoperative morbidity and mortality is well documented, whereas the morbidity and mortality associated with postoperative encephalopathy are not. This may be due to a tendency to ascribe this condition to age, anesthesia, fever, infections, medications, preoperative cognitive status, or a combination of these factors. Our findings suggest, however, that there are specific characteristics of patients undergoing CABG that allow one to predict those at risk for encephalopathy: the patient’s age, cerebrovascular status, and time on the bypass pump. Identification of this subpopulation sets the stage for studying the mechanisms of encephalopathy after CABG and possible approaches to either prevent or treat this outcome.

PREDICTION OF POSTOPERATIVE ENCEPHALOPATHY

In the prediction of encephalopathy, all 5 preoperative factors \( (\text{increasing age, history of stroke, hypertension, diabetes, and the presence of a carotid bruit}) \) were significant. When these preoperative variables were combined with time on CPB, there was a relationship be-

---

Figure 2. Probability of postoperative stroke. To determine a patient’s risk of developing a stroke, ask the following questions and then proceed to the correct part of the flowchart: has the patient had a previous stroke, yes or no; does the patient have a diagnosis of hypertension (HTN), yes or no. Next, determine the patient’s age and proceed to the correct row of age groupings to see the probability for that patient.

- The relationship between bypass time and the odds in favor of postoperative encephalopathy. An additional hour on CPB was associated with an approximate doubling of the probability of postoperative encephalopathy. These findings are consistent with previous studies that suggested that history of a stroke and time on CPB are risk factors for encephalopathy.1,2
- Postoperative delirium after noncardiac surgical procedures has been reported with remarkable variations in incidence \( (0\% \text{ to } 73.5\%) \).9 However, in recent prospective studies of patients undergoing a variety of noncardiac surgical procedures, the incidence of delirium ranged from 9% to 11.4%.10-13 The literature regarding encephalopathy is confusing, in part because different terminology may be used for the same conditions. In some reports, patients with stroke are included in the definition of delirium. Other authors have reported on these patients by using descriptions such as “neurologic complications,”14 “cognitive disorders,”15 and patients with both coma and stroke.15 In this report, we have considered encephalopathy and stroke as separate outcomes.

In attempting to define factors that could be predictive of postoperative encephalopathy, we did not analyze a wide range of preoperative and operative risk factors for postoperative encephalopathy (eg, medical history, physical findings, operative factors other than bypass time, or postoperative factors) but instead focused on the risk factors for cardiovascular disease. In
In addition, we did not have the data to include 2 cardiovascular risk factors: the arteriosclerotic state of the aorta, as indicated by transeosophageal echocardiography,10,11 and the patient's preoperative cardiac function.12 A more comprehensive approach might result in a different predictive model.9

However, in a single hospital setting, the preoperative status, surgical procedures, anesthesia, and postoperative medications are relatively standardized for a given patient population. Nevertheless, postoperative encephalopathy is still a common outcome among the elderly after major surgical procedures other than CABG.10-13 This suggests that there are factors other than those we have listed that are important in the determination of which patients will have encephalopathy. Because cardiovascular risk factors predicted post-CABG encephalopathy, these factors may also be predictive of postoperative encephalopathy in patients undergoing other forms of surgery.

**PREDICTION OF STROKE OR ENCEPHALOPATHY**

In addition to separate predictive models for stroke and encephalopathy, a predictive model for an aggregate of these outcomes was developed. This analysis demonstrated that the same cardiovascular factors, with or without time on CPB, can be used to predict this aggregate. As discussed in the next subsection, this aggregate may, at least in part, represent a continuum of vascular insult to the brain.

**MECHANISMS OF ENCEPHALOPATHY AND STROKE**

The mechanisms underlying postoperative encephalopathy are not entirely clear. There are many possible causes, including medications, cardiac failure, infections, and renal failure.9,10 However, as stated already, in this relatively homogeneous population, medications were used in a standardized way, and the incidence of infection, renal failure, and cardiac failure was quite low. Regardless of these possible precipitating factors, the presence of vascular risk factors predicted postoperative encephalopathy. Diffusion-weighted imaging (DWI) studies indicate multiple small vascular lesions in patients after CABG, some of whom have encephalopathy,24 supporting the role of these factors. In patients with strokes after CABG, DWI also shows numerous small lesions in areas of the brain that are in addition to those involved in the major ischemic stroke. Thus, it is possible that, at least in some patients, postoperative encephalopathy and stroke after CABG represent a continuum of vascular insult to the brain. On the basis of current data, it is clear that patients with risk factors for cerebrovascular disease are at greater risk of these outcomes and associated adverse sequelae, including increased LOS and death.

It has been generally assumed that perioperative stroke is caused by embolic material deposited in larger vessels.25 This hypothesis has been supported by studies with DWI, which indicates new areas of ischemia in the postoperative period.26 These areas of new ischemia are often not detectable with conventional magnetic resonance imaging techniques, because conventional magnetic resonance imaging cannot readily distinguish between new and preexisting small vascular lesions. The prevalence of silent infarcts in populations with coronary artery disease is high, with some studies reporting a 30% rate.26 In candidates for CABG, the prevalence of stroke is estimated to be 1.70 times the odds for those younger than 65 years. For age 2, patients at least 75 years of age, the odds in favor of encephalopathy or stroke are estimated to be 3.61 times the odds for those younger than 65 years.

**Table 4. Prediction of Encephalopathy or Stroke**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>SE</th>
<th>P Value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past stroke</td>
<td>2.28</td>
<td>0.48</td>
<td>.001</td>
<td>1.50-3.45</td>
</tr>
<tr>
<td>CB</td>
<td>1.57</td>
<td>0.30</td>
<td>.02</td>
<td>1.09-2.28</td>
</tr>
<tr>
<td>HTN</td>
<td>1.63</td>
<td>0.28</td>
<td>.004</td>
<td>1.17-2.29</td>
</tr>
<tr>
<td>DM</td>
<td>1.41</td>
<td>0.20</td>
<td>.02</td>
<td>1.07-1.86</td>
</tr>
<tr>
<td>Age 1</td>
<td>1.70</td>
<td>0.28</td>
<td>.002</td>
<td>1.22-2.35</td>
</tr>
<tr>
<td>Age 2</td>
<td>3.61</td>
<td>0.62</td>
<td>.001</td>
<td>2.57-5.06</td>
</tr>
</tbody>
</table>

* CB indicates carotid bruit; HTN, hypertension; and DM, diabetes mellitus. For age 1, patients at least 65 but younger than 75 years, the odds in favor of encephalopathy or stroke are estimated to be 1.70 times the odds for those younger than 65 years. For age 2, patients at least 75 years of age, the odds in favor of encephalopathy or stroke are estimated to be 3.61 times the odds for those younger than 65 years.

**Table 5. Risk of Encephalopathy and Effects of Cardiopulmonary Bypass Time**

<table>
<thead>
<tr>
<th>Cardiopulmonary Bypass Time, min</th>
<th>Probability of Encephalopathy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>High Risk</td>
</tr>
<tr>
<td>60</td>
<td>0.02</td>
</tr>
<tr>
<td>120</td>
<td>0.05</td>
</tr>
</tbody>
</table>

* Low risk indicates younger age without cardiovascular risk factors; high risk, older age with multiple cardiovascular risk factors.
silent infarcts is likely to be even higher. One recent study from Japan reported that 50% of patients undergoing CABG had one or more lacunar infarcts that are shown on their preoperative magnetic resonance images. To our knowledge, careful preoperative and postoperative magnetic resonance imaging and DWI of patients at risk for encephalopathy have not been performed.

The ability to predict outcomes associated with surgery has important implications. First, the added information available to patients, their families, and physicians assists with decisions concerning possible therapies. For patients at higher risk of stroke, interventional cardiology procedures, modification of existing CABG procedures, and alternative surgical procedures, such as surgery without a bypass pump, are possible options.

Our studies indicate that postoperative encephalopathy is associated with increased LOS and mortality. Several studies have indicated that identifying patients at risk of delirium and instigating specific measures can reduce the number of patients requiring to show a definite effect. We base this suggestion on the demonstration that a predictive model for this combined outcome involves cardiovascular risk factors. If correct, the probabilities of an adverse outcome reach remarkably high levels (Figure 3).

Finally, we strongly suggest that encephalopathy after CABG should not be considered an inevitable outcome for elderly patients. The consequences in terms of morbidity and mortality are too high. Careful prospective studies, including postoperative DWI, are indicated to determine which patients have encephalopathy related to vascular insults. As is being done with delirium after other surgical procedures, attempts to understand this phenomenon and to modify its outcome are warranted.

Accepted for publication May 2, 2002.

**Author contributions:** Study concept and design (Drs McKhann, Selnes, and Royall; Ms Grega and Bechamps; and Mr Borowicz); acquisition of data (Ms Grega, Mr Borowicz, and Dr Baumgartner); statistical analysis (Dr Royall); analysis and interpretation of data (Drs McKhann, Selnes, Baumgartner, and Royall; Ms Grega and Bechamps; and Mr Borowicz); drafting of the manuscript (Drs McKhann, Selnes, Baumgartner, and Royall; Ms Grega and Bechamps; and Mr Borowicz); critical revision of the manuscript for important intellectual content (Drs McKhann, Selnes, Baumgartner, and Royall; Ms Grega and Bechamps; and Mr Borowicz); obtaining funding (Drs McKhann and Baumgartner); administrative, technical, and material support (Drs McKhann and Baumgartner); and study supervision (Drs McKhann and Selnes).

This study was supported by grant 5 R01 NS35610-05 from the National Institutes of Health, Bethesda, Md, and by the Charles A. Dana Foundation, New York, NY.

We thank Robert Wityk, MD, and Pamela Talalay, PhD, for helpful comments on analysis, interpretation, and presentation.

Corresponding author and reprints: Guy M. McKhann, MD, Zanvyl Krieger Mind/Brain Institute, The Johns Hopkins University, 338 Krieger Hall, 3400 N Charles St, Baltimore, MD 21218-2685 (e-mail: Guy.Mckhann@jhu.edu).

**REFERENCES**