Stroke and Encephalopathy After Cardiac Surgery
An Update
Guy M. McKhann, MD; Maura A. Grega, RN, MSN; Louis M. Borowicz Jr, MS; William A. Baumgartner, MD; Ola A. Selnes, PhD

Background and Purpose—As a result of advances in surgical, anesthetic, and medical management, cardiac surgery can now be performed on older, sicker patients, some of whom have had prior cardiac interventions. As surgical mortality has declined in recent years, attention has focused on the complications of stroke and encephalopathy after cardiac surgery.

Summary of Review—Patients with preexisting cerebrovascular disease are at increased risk for these untoward neurological outcomes, which are associated with longer lengths of hospital stay, higher costs, and greater mortality. The mechanisms underlying these neurological events may include microemboli and hypoperfusion during surgery, and postoperative atrial fibrillation. Predictive models, based on information available before surgery, allow identification of these “high risk” patients.

Conclusion—Establishing the degree of functionally significant vascular disease of the brain before surgery should be an essential part of the preoperative evaluation, particularly when modifications in surgical technique or novel neuroprotective agents are being evaluated. (Stroke. 2006;37:562-571.)

Key Words: brain injuries ■ cardiovascular surgical procedures ■ cerebrovascular accident ■ coronary artery bypass ■ outcome assessment

The most common cardiac surgical procedure performed in the United States is coronary artery bypass grafting (CABG). In the past 2 decades, there have been significant changes in the population undergoing cardiac surgery. Improvements in surgical procedures have made it possible to operate successfully on older patients with more comorbid disease. Conversely, this population is at higher risk for age-related cerebrovascular disease, which may predispose them to more severe neurological complications, including stroke and encephalopathy, during the immediate postoperative period. This is exemplified in Table 1, in which the risk factor profiles and outcomes for patients at our hospital undergoing CABG in 1994 are compared with those having surgery in 2004. We and others have previously reviewed the neurocognitive complications associated with CABG.1–3 Therefore, this review focuses on 4 main questions regarding neurological problems associated with cardiac surgery: what are the outcomes of patients having stroke or encephalopathy in the postoperative period?; can we predict who is at highest risk?; what are the underlying mechanisms?; and what strategies are available to avoid injury to the brain including possible future pharmacological interventions.

Neurological Outcomes in Cardiac Surgical Patients

Stroke: Incidence
The reported incidence of stroke after cardiac surgery varies depending on the procedure and whether the findings have been obtained prospectively or retrospectively, such as from chart review. For example, the stroke incidence with CABG has been reported from 1.5%4 to 5.2%5 in prospective studies as compared with 0.8% to 3.2% in retrospective studies.6,7 The incidence of encephalopathy and stroke in our prospective studies appears to be increasing, as shown in Table 1. We believe that this increased incidence is because more “high risk” patients currently undergo surgery at our institution than 10 years ago.

Chart reviews may not accurately identify the postoperative timing during which strokes occur. Likosky et al found that 42% of strokes were identified on postoperative day 1 and additional 20% by day 2,8 whereas other investigators, relying solely on chart review, have suggested that the majority of strokes occur several days after surgery.9 We prospectively tracked the incidence (Table 2) and stroke outcomes (Table 3) of CABG and all other types of cardiac surgical procedures at our institution and found that the

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From the Departments of Neurology (G.M.M, O.S.S.) and Surgery (W.A.B., M.A.G.), The Johns Hopkins University, School of Medicine; and The Zanvyl Krieger Mind/Brain Institute (G.M.M., L.M.B.), The Johns Hopkins University, Baltimore, Md.
Correspondence and reprint requests to Dr Guy M. McKhann, 338 Krieger Hall, Johns Hopkins University, 3400 N. Charles Street, Baltimore, MD 21218. E-mail guy.mckhann@jhu.edu
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TABLE 1. The Johns Hopkins Hospital CABG Experience: Comparison of Patients Having Isolated CABG in 1994 and 2004

<table>
<thead>
<tr>
<th>Procedure</th>
<th>CABG in 1994, n=724</th>
<th>CABG in 2004, n=290</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>502 (69%)</td>
<td>230 (80%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Past stroke</td>
<td>51 (7%)</td>
<td>22 (8%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Carotid bruit</td>
<td>107 (15%)</td>
<td>32 (12%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>216 (30%)</td>
<td>107 (37%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Age, y</td>
<td>64.1±10</td>
<td>64.1±10</td>
<td>0.89</td>
</tr>
<tr>
<td>Stroke risk category17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>323 (45%)</td>
<td>130 (45%)</td>
<td></td>
</tr>
<tr>
<td>Medium risk</td>
<td>315 (43%)</td>
<td>104 (36%)</td>
<td>0.008</td>
</tr>
<tr>
<td>High risk</td>
<td>86 (12%)</td>
<td>54 (19%)</td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary bypass time, min</td>
<td>108±35</td>
<td>105±30</td>
<td>0.20</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perioperative stroke</td>
<td>21 (2.9%)</td>
<td>13 (4.5%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>56 (7.7%)</td>
<td>40 (13.8%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Death</td>
<td>21 (2.9%)</td>
<td>5 (1.7%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Postoperative length of stay, d</td>
<td>8.7±9.6</td>
<td>9.2±9.7</td>
<td>0.44</td>
</tr>
</tbody>
</table>

The majority of strokes were detected shortly after surgery (Figure). Importantly, the incidence of stroke is much higher in the setting of combined cardiac procedures (≥2) and in more technically challenging operations, such as aortic aneurysm repairs with the use of hypothermic circulatory arrest. Strokes that were identified after 7 days were more likely to occur in either patients having valve surgery or those with ventricular assist devices. The mechanism for the delayed occurrence of postoperative stroke is not clear. As discussed below, 1 possible mechanism is atrial fibrillation.

TABLE 2. Incidence of Stroke by Cardiac Surgical Procedure (Data From 2001–2004)

<table>
<thead>
<tr>
<th>Cardiac Surgical Procedure</th>
<th>Stroke Rate</th>
<th>Percent of Strokes Identified in the First 2 Days of Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG</td>
<td>4.1%</td>
<td>84%</td>
</tr>
<tr>
<td>Valve</td>
<td>3.1%</td>
<td>65%</td>
</tr>
<tr>
<td>CABG/Valve</td>
<td>7.9%</td>
<td>76%</td>
</tr>
<tr>
<td>CABG/Other</td>
<td>7.2%</td>
<td>80%</td>
</tr>
<tr>
<td>Aortic repair</td>
<td>8.7%</td>
<td>83%</td>
</tr>
<tr>
<td>Other</td>
<td>3.6%</td>
<td>59%</td>
</tr>
</tbody>
</table>

CABG indicates isolated CABG, isolated off-pump CABG, or isolated Redo CABG; VALVE includes any valve replacement, valve repair, Ross procedure, anuloplasty, or valve ring in any valve position (eg, combined with a patent foramen ovale, ventricular septal defect closure, or Maze procedure; CABG/Valve, CABG plus any of the valve procedures listed above; CABG/Other, CABG plus any of the following: patent foramen ovale, surgical ventricular reconstruction, carotid endarterectomy, Maze procedure, ventricular assist device; Aortic procedure, includes Aortic root replacement, or aortic valve replacement composite (eg, combined with CABG); Other, includes ventricular assist device, pericardial window, pericardectomy, attempted surgeries, congenital repairs, transplants.

TABLE 3. Impact of Stroke on Early Outcomes After Cardiac Surgery23

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stroke, (n=214)</th>
<th>No Stroke, (n=5757)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive care unit length of stay, d</td>
<td>7.3</td>
<td>3.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Postoperative hospital length of stay, d</td>
<td>25.2</td>
<td>9.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total hospital charges $60 750 $30 705</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital mortality 41 (19%) 240 (4%)</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Stroke: Outcomes and Predictors of High-Risk Patients

Patients with postoperative stroke have significantly higher mortality rates. Bucerius found that those with stroke had a 6-fold higher mortality (22.2% versus 3.75%; P=<0.001).10 The investigators from the Northern New England Cardiovascular Disease Study Group11 compared survival in those with and without stroke after CABG and found that survival rates at 1 year were 83% versus 94.1%, at 5 years 58.7% versus 83.3% and at 10 years 26.9% versus 61.9%, respectively. These differences were significant and those diagnosed with stroke had a 3-fold greater risk of death during the 10-year follow-up. In addition, in our experience, more than half the patients with strokes require in-patient rehabilitation before returning home.

A number of investigators have developed preoperative predictive models to determine those at higher risk for stroke.12–16 In general, these models use factors associated with systemic vascular disease, such as hypertension, diabetes, peripheral vascular disease, evidence of cerebrovascular disease, and age. The important point of these risk models is that they take into account the additive effect of known risk factors and allows for a stroke probability to be estimated for individual patients. We have developed predictive models for those patients who are at increased risk for perioperative stroke. Our original model was reported in 1997 and then revised in 2002 to account for the changing demographics of our surgical population (see Table 4). Notably, all the components required for this model are available to the physician and the patient before surgery, thus permitting discussion of projected surgical risks to patients and families.
TABLE 4. Risk Model to Predict Stroke in Patients Having CABG

<table>
<thead>
<tr>
<th>Age</th>
<th>HTN</th>
<th>CVA</th>
<th>HTN</th>
<th>CVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65</td>
<td>.01</td>
<td>.02</td>
<td>.01</td>
<td>.03</td>
</tr>
<tr>
<td>65-75</td>
<td>.02</td>
<td>.04</td>
<td>.03</td>
<td>.07</td>
</tr>
<tr>
<td>&gt;75</td>
<td>.04</td>
<td>.07</td>
<td>.07</td>
<td>.13</td>
</tr>
</tbody>
</table>

CVA = history of cerebrovascular accident; HTN = history of hypertension

Example: A 75-year-old patient with no history of previous stroke or hypertension is at lower risk (P=0.04) than a 65-year-old who has reported a previous stroke and has diagnosed hypertension (P=0.07).

As an example of how stroke probabilities can differ, we compare 2 presurgical candidates (see Table 4). The identification of high-risk patients has both intraoperative and postoperative implications that are discussed in the section on protecting the brain.

Stroke: Diagnosis and Treatment

The presence of stroke in the postoperative period may be signaled by the inability of the patient to emerge from anesthesia (follow commands, move all extremities) in the first 6 hours after the operation. Patients suspected of having a stroke should be evaluated by a neurologist immediately and brain imaging obtained. In our experience, brain MRI, specifically diffusion-weighted imaging (DWI), is the most sensitive and accurate neuroimaging technique in this patient population.

DWI can now detect acute ischemic events related to microemboli. This technique reveals significantly more lesions than conventional MRI (T2 and Flair) and is more likely to demonstrate multiple lesions in a “watershed” pattern of distribution. In a recent study of 35 consecutive candidates for CABG, no DWI-positive lesions were found before surgery. This low yield from preoperative imaging suggests that studies using DWI may be able to rely solely on postoperative imaging for the detection of new surgery-related lesions. This study also found that most of the DWI lesions after surgery were small, but 5 patients had multiple lesions. They concluded that patients with preexisting MRI abnormalities were more likely to develop new DWI-positive lesions after surgery. Knipp et al evaluated 29 patients and found that 13 (45%) had new lesions, but these were not associated with impaired neuropsychological performance in their study.

Newer applications of MRI have been introduced to assess, and predict, eventual infarct size using either DWI or cerebral blood flow heterogeneity by dynamic susceptibility contrast MRI. These approaches have yet to be applied to postoperative stroke after CABG, but might be useful in evaluating approaches to preventive therapies.

If DWI is not feasible, because of the presence of metallic implants or surgical metal (temporary epicardial pacing wires), head computed tomography should be obtained. We have previously shown that patients who have a pattern of watershed infarction on brain imaging have worse outcomes. Thus, this may be the most appropriate population to provide interventions that can decrease the penumbral area of brain at risk. Recent studies indicate that stroke patients with hypoperfused brain tissue can be identified by comparing the mismatch between DWI and perfusion-weighted imaging. This postoperative population may benefit from being maintained at higher blood pressure levels.

Encephalopathy: Incidence

In contrast to stroke, less attention has been paid to patients with diffuse brain injury or encephalopathy after cardiac surgery. Encephalopathy has been characterized in the literature using a variety of descriptors, including confusion, delirium, seizures, coma, prolonged alteration in mental status, combativeness, and agitation. The reported incidence of postoperative encephalopathy varies widely from 8.4% to 32%. Some studies have used structured rating/testing scales to define this outcome, whereas others have used clinical documentation. In studies that have used a clinical diagnosis, the incidence is reported as being lower than those with structured interviews. Irrespective of the criteria used to define encephalopathy, patients with this postoperative complication clearly have worse outcomes.

Encephalopathy: Outcomes and Predictors of High-Risk Patients

Like stroke, encephalopathy is also associated with poor inhospital outcomes, with increased length of stay in the hospital, and with higher mortality than in patients without this complication. In our studies, the average length of stay for patients without a complication is 8 days, compared with 14 days for those with encephalopathy, and in-hospital mortality is 7.5% for patients with encephalopathy, which is 3 times the rate of other postoperative patients without this complication. In addition, a proportion of patients with postoperative encephalopathy are not able to return home after discharge from the acute care hospital but require rehabilitation for assistance with activities of daily living. As with stroke, predictive factors have been identified for encephalopathy (see Table 5). The factors that appear important are history of previous stroke, hypertension, diabetes, presence of carotid bruit, and age. Using these 5 risk factors, individual probabilities can be identified before surgery. Several studies have also identified severity of vascular disease and previous cerebrovascular disease as important factors.

Encephalopathy: Diagnosis and Treatment

Because the clinical presentation of encephalopathy tends to be more subtle in the postoperative period, many patients do not get formally diagnosed. Symptoms generally present following extubation, when patients are able to speak, but encephalopathy should be suspected in patients who emerge from anesthesia with persistent agitation or combativeness. These patients can often be identified before extubation, and in some situations, encephalopathy may delay their ability to be removed from ventilatory support.
Although few studies of encephalopathy have included imaging, it is believed that patients with encephalopathy also have evidence of multiple embolic phenomena. Djaiani et al\textsuperscript{33} concluded that atheromatous disease of the ascending aorta is a major contributor to brain injury as seen on diffusion-weighted MRI after surgery. It is likely that patients with postoperative coma, stroke, and encephalopathy represent a continuum of conditions with a similar underlying mechanism: showers of embolic material to the brain.\textsuperscript{34}

**Underlying Pathophysiology of Stroke and Encephalopathy**

**Preexisting Cerebrovascular Disease**

As discussed above, history of previous stroke, as well as hypertension, diabetes, age, and presence of carotid bruit are risk factors that predict which patients are at greatest risk for neurological complications after cardiac surgery. Almost all cardiac surgical candidates are known to have atherosclerotic disease (demonstrated by coronary angiogram). Evidence is also growing that these patients have much more cerebrovascular disease than was previously recognized. Therefore, many patients have potentially compromised cerebrovascular circulation even before they come to surgery.

In the United States, preoperative MRI has been difficult to obtain because of the short time between hospital admission and surgery.\textsuperscript{35} Thus, it has been difficult to demonstrate an association between the degree of preexisting vascular disease and neurological outcomes. However, in a study from Japan in which MRI scans were obtained before surgery in 421 CABG candidates,\textsuperscript{36} 30% of patients had small brain infarctions and 20% had multiple infarctions. Thus, one-half of this sample had evidence of ischemic brain abnormalities before surgery. In addition, these findings of the degree of cerebrovascular disease on MRI were correlated with the occurrence of both postoperative stroke and cognitive change.

In a study that included a combination of MRI and magnetic resonance angiography, an even higher prevalence

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**TABLE 5. Risk Model for Predicting Encephalopathy in CABG Patients**

<table>
<thead>
<tr>
<th>- CVA</th>
<th>- CB</th>
<th>+ CB</th>
</tr>
</thead>
<tbody>
<tr>
<td>- HTN</td>
<td>- DM</td>
<td>+ DM</td>
</tr>
<tr>
<td>&lt;65</td>
<td>.03</td>
<td>.04</td>
</tr>
<tr>
<td>65-75</td>
<td>.04</td>
<td>.06</td>
</tr>
<tr>
<td>&gt;75</td>
<td>.08</td>
<td>.11</td>
</tr>
<tr>
<td>- HTN</td>
<td>+ DM</td>
<td>- DM</td>
</tr>
<tr>
<td>&lt;65</td>
<td>.04</td>
<td>.06</td>
</tr>
<tr>
<td>65-75</td>
<td>.06</td>
<td>.09</td>
</tr>
<tr>
<td>&gt;75</td>
<td>.11</td>
<td>.16</td>
</tr>
<tr>
<td>+ HTN</td>
<td>- DM</td>
<td>+ DM</td>
</tr>
<tr>
<td>&lt;65</td>
<td>.06</td>
<td>.12</td>
</tr>
<tr>
<td>65-75</td>
<td>.08</td>
<td>.12</td>
</tr>
<tr>
<td>&gt;75</td>
<td>.15</td>
<td>.21</td>
</tr>
</tbody>
</table>

CVA indicates history of cerebrovascular accident; CB, presence of carotid bruit; HTN, history of hypertension; DM, history of diabetes mellitus.

Example: a 64-year-old patient with a history of hypertension and diabetes mellitus has twice the risk of developing encephalopathy (0.06) compared to a 64-year-old patient with no risk factors (0.03).
of cerebrovascular disease was found in 39 patients before CABG, with existing cerebral infarction in 97%, internal carotid artery disease in 25%, periventricular hypointensities in 87%, and external carotid artery disease in 41%. Thus, it is important to know the status of the carotid arteries as well. These authors suggest that those patients with evidence of vascular disease on screening MRI should have further follow-up, such as duplex ultrasonography, single-photon emission–computed tomography, or angiography. In a study comparing CABG patients with those undergoing spinal cord stimulation, white matter disease was found in both groups before surgery, but cerebral complications after surgery were higher in the CABG patients who had preexisting white matter lesions.

The finding that candidates for CABG have varying degrees of cerebrovascular disease should not be surprising. Silent brain infarcts are common on MRI in neurologically asymptomatic elderly subjects. In an MRI study of community subjects, white matter brain abnormalities were found in nearly one-third of those with a history of hypertension, diabetes mellitus, peripheral vascular disease, and myocardial infarction (similar to cardiac surgical patients). A possible surrogate marker of preexisting cerebrovascular disease may be poor performance on neuropsychological tests even before surgery. In a sample of 311 patients with diagnosed coronary artery disease, cognitive performance was significantly lower at baseline testing when compared with control subjects with no risk factors for cardiovascular disease. This difference has not been observed in all aspects of cognition, but in those areas affected by chronic cerebrovascular disease, including executive function, and psychomotor and motor speed. This type of cognitive profile is comparable to that seen in prospective studies of patients with MRI-defined subcortical disease. In addition, a recent study involving over 12,000 middle-aged individuals suggested that cognitive test scores below demographic norms predicted subsequent cardiovascular events independently of established cardiovascular risk factors.

**Microemboli**

Although macroembolization is less common during modern cardiac surgery, microembolization remains a problem. The extracorporeal circulatory pump system used during cardiopulmonary bypass creates a unique susceptibility to embolic injury. The internal surface of the pump components and pump tubing is lined with foreign material that creates an interface which is predisposed to the formation of microemboli, even though patients are fully heparinized. While on the cardiopulmonary bypass pump, the pulmonary circulation, which acts as a natural filter between the venous system and the arterial circulation, is removed. Microemboli may be gaseous or particulate, such as thrombus and lipid. Aortic atheromatous debris may be the most common source of cerebral microembolism.

There is an increased risk for cerebral microemboli during the surgery. In addition, transesophageal echocardiography and epiaortic scanning have indicated an association between the degree of atheroma in the ascending aorta and new brain ischemic lesions identified by imaging studies. Thus, the surgical technique was modified to decrease manipulation of the aorta by use of a single aortic clamp instead of the more conventional double clamping technique involving an aortic clamp and a side-biting clamp. In the experience of a single surgeon at our hospital, the single clamp technique was associated with fewer strokes and less neurologic injury/encephalopathy. Another approach is the use of intra-aortic filters to capture particulate emboli. These filters do accomplish this goal. Further, in prospective controlled studies, filters were associated with better neurologic outcomes in high-risk patients.

Studies with transcranial doppler have documented that embolic showers are particularly likely to occur during cannulation and clamping/unclamping of the aorta. These emboli vary in size and composition, and may consist of air or solids. Recently, Abu-Omar compared CABG, off-pump CAB, and open heart surgery patients using a newer transcranial doppler ultrasound technique that purports to distinguish between gaseous and particulate embolic material. The total numbers of emboli varied dramatically between procedures: open heart procedures had the most, CABG next, and off-pump had by far the least. Most emboli were gaseous, but the percentages varied: those with open heart had 20% particulate, CABG 24%, and off-pump 9% particulate.

**Hypoperfusion**

Although there is agreement that prolonged periods of hypoperfusion during cardiac surgery may place the patient at risk for ischemic injury, it is less clear what degree and duration of hypoperfusion can be tolerated intraoperatively. Older patients and those with comorbid disease, such as hypertension and diabetes, may be at greater risk because of alterations in the autoregulation of cerebral blood flow. The optimal level of mean arterial pressure during cardiopulmonary bypass is controversial because there are very few studies with intraoperative blood pressure data to implicate hypoperfusion as a risk factor for stroke and encephalopathy outcomes. Murkin et al showed that even though they were able to demonstrate a 15% increase in cerebral blood flow during surgery with pulsatile flow versus nonpulsatile flow, it did not reduce the incidence of stroke. In one of the few randomized trials, Gold et al assigned 124 patients to a low mean arterial pressure group (50 to 60 mm Hg) and 124 patients to a high mean arterial pressure group (80 to 100 mm Hg) during cardiopulmonary bypass. Those in the high pressure group had fewer combined cardiac and neurological complications (4.8% versus 13%) and fewer strokes (2.4% versus 7.2%). Caplan and Hennerici have suggested that decreased flow may result in reduced washout of microembolic materials from the brain, and that the watershed areas are particularly susceptible to this combination. This latter hypothesis thus brings together two of the putative underlying mechanisms for vascular damage during CABG, suggesting that microembolism in the context of hypoperfusion may be associated with greater risk of ischemic injury.

**Atrial Fibrillation**

It is widely accepted that atrial fibrillation is associated with embolic stroke in the general population. Because atrial
fibrillation occurs at a high rate (30%) in the early cardiac surgical postoperative period, attempts have been made to develop models for predicting postoperative atrial fibrillation. One model, based on data from the Multicenter Study of Perioperative Ischemia Epidemiology II, involved 5436 patients from 70 hospitals and 17 countries. The authors found that atrial fibrillation was associated with a greater incidence of infections, renal dysfunction, and encephalopathy. It is also important to determine the timing of neurological complications and the occurrence of atrial fibrillation. In a retrospective study, Lahtinen attributed 36% of postoperative strokes to the development of atrial fibrillation. They were able to show that, on average, there were 2.5 episodes of atrial fibrillation before the stroke event. In our own studies of DWI in high-risk patients who had a new postoperative DWI lesion, 75% also had postoperative atrial fibrillation.

These and other studies highlight the importance of the prevention of postoperative atrial fibrillation. Zimmer performed a meta-analysis of prospective studies of prophylactic treatment for patients undergoing cardiac surgery. Of 1783 patients reviewed, 1569 (88%) underwent CABG. A variety of treatments were used, which included combinations of 1 or more drugs (Amiodarone, Sotalol, Procainamide), and pacing wires. Overall, there was a 50% decrease in the occurrence of atrial fibrillation, with a 1-day decrease in hospital stay, hospital costs, stroke, and mortality. A review by Crystal et al also reported similar findings. Therefore, preventative treatment strategies in the postoperative period need to be maximized in this population of patients at risk.

**Pathologic Findings in Cardiac Surgical Patients**

Several investigators have attempted to identify pathologic changes in the brains of cardiac surgical patients who died in the postoperative period. In autopsy studies, 1 group found small capillary arterial dilations containing microemboli in the brain; the material in these emboli is most likely lipid. The numbers of small capillary arterial dilations are associated with increasing time on the cardiopulmonary bypass and particularly with heart valve surgery rather than CABG. With increased survival time after surgery (in days), both the number and the size of these emboli decreases.

There are few other studies of the neuropathological changes after CABG, and their interpretation is complicated by the need to distinguish the pathological lesions resulting from the CABG procedure from those of the underlying pathology of vascular disease. Emmrich and colleagues retrospectively examined the brains of 262 patients who came to autopsy shortly after open heart surgery. The majority of these patients survived less than a month after the surgery. Of these patients, 48% had CABG and the remaining patients had valve surgery, combined valve and CABG, or heart transplantation. Forty percent of the CABG patients had large infarcts, and 8% had microinfarcts. Brain hemorrhages were seen in 35% of the CABG autopsy samples. An incidental finding of Alzheimer’s type pathology was observed in 14% of cases, the majority of which were mild abnormalities.

The underlying neuropathology of cerebrovascular disease is complex and includes ischemic brain injury, with multi-infarcts, small vessel disease, leukoaraiosis, and hippocampal sclerosis. Increasingly, the underlying pathology is inferred from imaging studies, primarily MRI. For example, a recent study emphasized the correlation of microbleeds in cerebral cortex, as detected by T2-weighted gradient-echo MRI, and subsequent cognitive dysfunction, particularly on executive function. There are no prospective studies, to our knowledge, that correlate neurologic outcomes after CABG with subsequent neuropathologic findings.

**Stroke After Other Cardiac Interventions**

From the mid 1960’s through the mid 1980’s CABG was essentially the only intervention for coronary artery disease, but in the past 2 decades other procedures have become available: percutaneous coronary intervention or PCI (angioplasty and stent placement) procedures, and an alternative surgical procedure, off-pump coronary artery bypass surgery (“off-pump surgery”). Typical of many cardiac surgery centers around the country, the number of CABG procedures in our hospital declined by nearly 60% from 1994 to 2004 (Table 1). The reported stroke rate after PCI is markedly lower (0.3%) than after CABG in several studies. Whether this is because patient populations under study may have different stroke risks is unclear.

With the introduction of off-pump CABG, it was widely assumed that neurological complications in the immediate postoperative period would be almost eliminated. This surgical procedure, in its early phases, boasted the advantages of no aortic manipulation, no hypothermia, and no use of the cardiopulmonary bypass pump. Theoretically, these differences from conventional CABG would be expected to result in fewer microemboli entering the brain in off-pump versus conventional CABG surgery. We say theoretically because a recent report indicated a similar rate of ischemic lesions, as indicated by postoperative DWI, in off-pump as opposed to on-pump CABG. This finding suggests that factors other than the use of the cardiopulmonary bypass are associated with postoperative ischemic lesions.

With a stroke rate of only 2% to 5% in the CABG group, it takes a study involving a large number of patients to reliably establish the beneficial effects of an alternative procedure, and most studies in the literature have sample sizes too small to show statistical significance. Nevertheless, a large study by Bucerius (n=16 184) found a difference in the incidence of stroke between conventional CABG (3.9%) and off pump group (2.5%), indicating that stroke risk was reduced but not eliminated with this alternative procedure. Further, in a study comparing high risk patients subjected to off-pump CABG versus on-pump CABG, off-pump CABG was associated with improved survival rate.

This same group also compared these 2 surgical populations both in terms of the rate and timing of stroke and found different distributions. On-pump surgery was associated with early stroke (2 days), whereas off-pump was associated with later stroke (4 days). These authors suggest that the mechanisms of stroke might be different in the 2 groups.

As described below, off-pump surgery can be done in multiple ways that can affect the production of emboli. MIDCAB surgery was initially done without aortic manipu-
lution using laparoscopic instruments inserted into the thoracic cavity via small, keyhole incisions. Off-pump surgery has since changed so that patients have a full sternotomy, and in some cases partial occluding aortic clamps are used, whereas others use the “no touch” aortic technique in which the coronary grafts are completed as grafts to an internal mammary artery. In an analysis of 7272 patients, Kapetanakis et al found that those with aortic manipulation were 1.8 times more likely to have had stroke than those without any aortic manipulation. Similar conclusions have been reached by other investigators. Thus, particularly for patients with a diseased aorta, there may be a neurological benefit of off-pump CABG using the “no touch” aortic technique compared with conventional CABG procedures.

Fewer emboli may not be the only advantage of off-pump surgery; there may also be less myocardial damage. However, the issue of stroke after on-pump versus off-pump CABG must be considered in the context of the relative merits of these two procedures by other criteria. A large body of literature on this controversial topic has recently been reviewed in a Scientific Statement from the American Heart Association. This group concluded that excellent outcomes may be achieved with either procedure and that individual outcomes may depend more on patient related variables than on the choice of procedure.

Protecting the Brain During Cardiac Surgery

Strategies for protecting the brain during cardiac surgery can be considered in 2 stages: avoiding injury to the brain, and preventing secondary ischemic damage/promoting recovery. Much research in cardiac surgery has focused on the former. Table 6 summarizes these strategies and suggests ways to implement them.

Methods for preventing secondary ischemic damage and promoting recovery of brain tissue have proven much more challenging. Using a canine model of cardiopulmonary bypass and hypothermic circulatory arrest, work in the laboratory of 1 author (W.A.B.) has yielded several conclusions regarding the pathways of such ischemic brain damage during cardiac surgery. They can be summarized in the following way: glutamate excitotoxicity contributes to injury; inhibition of glutamate excitotoxicity reduces injury; hypothermic circulatory arrest induces nitric oxide; and nerve injury is reduced by inhibition of neuronal nitric oxide synthase. Unfortunately, these therapeutic leads from animal experiments have yet to yield an effective pharmacological neuroprotective agent that can be safely used in patients undergoing cardiac surgery. Indeed, similar problems have plagued neurologists who treat stroke patients in the general population. As newer agents are contemplated, however, we think that patients undergoing cardiac surgery provide a unique clinical opportunity for evaluating such agents. Patients at high risk for stroke and encephalopathy can be identified before surgery; these selected populations can then be randomized prospectively and controlled studies implemented.

Conclusion

From a neurological standpoint, cardiac surgery as currently practiced is a safe and effective procedure for the great majority of patients. Nonetheless, a subset of patients with preexisting risk factors for cerebrovascular disease are at high risk for stroke or encephalopathy. In addition, before surgery, very little is known about the status of not only the vasculature of the brain but also the existence of previous underlying cerebrovascular disease. We suggest that neurologists have a role in assisting their colleagues in cardiology and cardiac surgery to identify those at risk for adverse neurological outcomes. In addition, they need to be involved in evaluating patients after surgery for change in neurological condition, both by examination and interpretation of imaging studies. Most important, neurologists should be involved in the design and interpretation of studies comparing different intervention techniques, modification of existing procedures, and trials of neuroprotective agents.

| TABLE 6. Neuroprotective Strategies to be Used in Cardiac Surgery |
|-----------------|-----------------|-----------------|
| **Time** | **Issue** | **Suggestions** |
| Before Surgery | Identification of patients at high risk using established “risk models” | Alternative surgical procedures (off-pump) |
| | Identification of carotid artery stenosis | Use of PCI therapy |
| | Preexisting cerebrovascular disease and ischemic lesions identified on imaging (MRI) | Use of carotid endarterectomy or stenting |
| | Atrial fibrillation | Alteration of surgical procedures, eg, blood pressure management |
| | | Pretreatment with drug therapy |
| During Surgery | Aortic atheroma | Use of epiaortic/TEE ultrasound to identify ascending and arch aortic disease |
| | Systemic hypoperfusion | Modifications to surgical procedure: minimize aortic manipulation, use of single aortic cross clamp for proximal grafts, no touch aortic technique, altered cannula placement |
| | Brain hyperthermia | Use of higher blood pressures during CPB |
| | Hyperglycemia | Increase hematocrit to 30% |
| | Microemboli | Use of alpha-stat pH management (for adults) |
| | | Prevent rewarming temperatures >37°C |
| | | Prevent hyperglycemia by having a structured glucose management protocol in place |
| | | Use of arterial line filters |
| | | Avoid use of cardiomyopathy suction |
| After Surgery | | Early intervention on arrhythmias |
| | Prevention of atrial fibrillation | Use of diffusion-weighted MRI |
| | Diagnosis and identification of ischemic brain lesions | Early blood pressure interventions to minimize infarction size |
| | Brain perfusion mismatch | Use of diffusion-weighted MRI/Perfusion-weighted imaging |
| | | Early blood pressure interventions to minimize infarction size |
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