Central Nervous System Complications of Coronary Artery Bypass Graft Surgery: Prospective Analysis of 421 Patients

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SUMMARY A prospective analysis of 421 patients undergoing coronary artery bypass graft (CABG) surgery as the sole cardiac procedure was carried out to assess the frequency of central nervous system (CNS) complications. In all, 451 variables were assessed in each patient. Stroke occurred in 5.2% but was severe in only 2%. Prolonged encephalopathy occurred in 11.6% but usually resolved before discharge. No statistically significant pre- or intraoperative risk variables for CNS complications were found; specifically, age or pump times in excess of two hours were not significant factors. Postoperative use of an intraaortic balloon pump and pressor agents were significantly correlated with prolonged encephalopathy. The frequency of CNS injury in CABG surgery is similar to that in other forms of open heart surgery, and there has been little change in the frequency of CNS complications over the past seven years. Possible mechanisms of CNS damage during CABG surgery are discussed.

IN THE United States over 137,000 patients undergo coronary artery bypass graft (CABG) surgery annually and this number is steadily increasing. Neurologic complications during CABG surgery are infrequent but represent a major source of morbidity and occasional mortality. While there is considerable literature concerning neurologic complications in patients undergoing various mixtures of open heart procedures and cardiac transplantation, there is little information on the neurologic difficulties encountered in patients undergoing myocardial revascularization as the sole heart procedure. The extensive experience with myocardial revascularization at the Cleveland Clinic (over 2,000 procedures are performed annually) afforded us an opportunity to study a consecutive series of patients undergoing CABG surgery. The results of this computer-assisted prospective analysis with reference to central nervous system (CNS) complications form the subject of this report. Peripheral nervous system complications are reported elsewhere.

Methods

A consecutive series of 421 patients undergoing CABG surgery between January 1 and December 31, 1980 by two cardiothoracic surgeons were evaluated by a team of four neurologists. The patients underwent various combinations of saphenous vein and internal mammary artery grafting via median sternotomy utilizing left ventricular venting as a standard operating procedure. Cardiac valve, ventricular aneurysm, and congenital heart defect surgical procedures were excluded.

Patients were premedicated prior to surgery with scopolamine 0.4 mg and morphine sulfate 0.15 mg/kg. Anesthesia was induced by a sleeping dose of sodium thiopental, up to 250 mg intravenously (IV), to which was added inhalation of a 50% oxygen/50% nitrous oxide mixture and increasing concentrations of up to 4% Halothane or Enfuran. Muscle relaxation was achieved by administration of pancuronium bromide.

Arterial systolic, diastolic, and mean pressure, as well as pump pressure and central venous pressure, were monitored using continuous digital display. Hypertension (mean arterial or pump pressure >110 mm Hg lasting >3 minutes) was treated with IV boluses of nitroglycerine (0.2 mg). Hypotension (mean arterial or pump pressure >60 mm Hg lasting >3 minutes) was treated with volume expansion, Trendelenburg positioning, or small IV doses of neosynephrine. Anesthesia was maintained with inhalation of 50% oxygen/50% nitrous oxide containing 0.5–2% Halothane (342 patients) or 0.5–2% Enfuran (79 patients). Hypothermia was used in 132 patients with systemic cooling to 28 ± 2°C monitored by esophageal and rectal thermistor probes.

A disposable Travenol Bubble Oxygenator with an Extracorporeal Intercept 20 micron arterial line filter was used in 52 patients. In 369 patients, a disposable Travenol Membrane Oxygenator without arterial line filtration was used. In all cases, a Harvey Cardiomiomy Reservoir with integral microaggregate filtration was a standard part of the extracorporeal bypass pump system. The pump oxygenator was routinely primed with a balanced electrolyte solution, and one or two units of the patient’s blood were drawn off through the venous lines. Normovolemic anemia with hematocrit of 20 ± 4% resulted.

Each patient underwent a detailed neurologic history and examination prior to surgery and one or more times afterward beginning on the fourth postoperative
day. The mental status examination included assessment of alertness; orientation to time, place, person; language function; recent memory; simple calculation ability; right-left orientation; and the ability to identify fingers. Formal psychological test batteries were not employed. Patients with a history of recent transient ischemic attack (TIA) or who were found to have an asymptomatic carotid bruit underwent four-vessel cerebral angiography or carotid compression tonography prior to surgery. In the postoperative period, neurolologic tests such as computed tomography (CT) of the brain and electroencephalography were performed only on patients with CNS complications.

Data from each patient was logged on a 55-page computer protocol. Hard copy output of the raw data was edited for all values falling outside programmed check limits as means of insuring accuracy of data transfer. Information was processed by computer, and multiple cell Chi Square analysis was conducted looking for statistically significant risk variable correlations in patients with neurologic complications. In all, 451 preoperative, intraoperative, and postoperative variables were assessed in each patient. An abbreviated list of these variables is shown in table 1. Because of the large number of variables recorded in this study, statistically significant relationships were viewed with caution and every effort made to interpret their meaning in the total context of the study. Patients who suffered cerebral infarction were followed up six months to one year later by telephone interview and/or return visit to the clinic.

Results

There were 361 men (86%) and 60 women (14%) with the following age distribution: 36–45 years, 36 (9%); 46–55 years, 139 (33%); 56–65 years, 186 (44%); 66–75 years, 58 (14%); 76–85 years, 2 (1%). There were 279 patients (66%) in New York Heart Association Class I or II, and 142 patients (34%) in Class III or IV. Using 50% stenosis of a coronary artery on arteriography as a criterion of significant vessel disease, 50 patients (12%) had one-vessel, 136 (32%) had two-vessel, and 235 (56%) had three-vessel disease. In all, 379 patients (90%) underwent CABG for the first time and 42 patients (10%) for a second time.

One-third of the patients had an abnormality on the preoperative neurologic examination. In most cases the finding was relatively minor such as a missing reflex, hearing loss, a Horner’s syndrome, or a peripheral polyneuropathy. However, a visual field loss was discovered in one patient and an abnormal mental status in another, underscoring the importance of the prospective approach in determining the frequency of new CNS deficits after CABG surgery.

CNS Infarction

Twenty-four CNS infarcts occurred in 22 patients (5.2%) (table 2). In eight patients (2%) the infarction resulted in major functional disability and one of these patients died as a result of the infarct. Clinical details of the patients suffering CNS infarction are summarized in table 3.

No significant pre-, intra-, or postoperative risk factors for stroke were found. Among six patients with a prior history of stroke, two suffered a new cerebral infarct, but these numbers are too small to draw definitive conclusions.

Thirty-one patients had a carotid bruit preoperatively (21 with ipsilateral anterior circulation symptoms and 10 without) and 22 underwent cerebral angiography. Five of these patients had more than 70% internal carotid artery stenosis and all five underwent combined carotid endarterectomy and myocardial revascularization. One patient undergoing the combined procedure suffered a retinal infarct ipsilateral to the carotid endarterectomy. Of the other 26 patients with carotid bruits who did not have their carotid arteries operated on, one suffered CNS infarction ipsilateral to the bruit at the time of his CABG surgery. Another five patients had anterior circulation TIsAs with no carotid bruits, three of these had cerebral angiograms, and none subsequently underwent carotid endarterectomy. One of these patients suffered a perioperative retinal infarct contralateral to the preoperative symptoms. The frequency of CNS infarctions in these subsets of patients was thus too low to draw definitive conclusions regarding the risk significance of carotid bruits and/or anterior circulation symptoms for stroke in this setting.

A detailed review of the chart of each stroke victim disclosed a possible cause for the stroke in half the patients, but these possible causes were present in many other patients who had no CNS event and, therefore, have no statistical significance. Possible causes for stroke identified in 11 patients included air in the left ventricle (2), cross-clamping a very brittle aorta...
TABLE 2 CNS Complications in 421 CABG Patients Studied Prospectively

<table>
<thead>
<tr>
<th>Frequency:</th>
<th>Stroke</th>
<th>Prolonged encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>22/421 (5.2%)</td>
<td>49/421 (11.6%)</td>
<td></td>
</tr>
</tbody>
</table>

Significant risk factors

| preop: | none | none |
| intraop: | none | none |
| postop: | none | pressor agents \( p < .05 \) |

Clinical outcome

<table>
<thead>
<tr>
<th>(6-12 month follow-up)</th>
<th>Stroke</th>
<th>Prolonged encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>(at discharge)</td>
<td>6</td>
<td>resolved 39/49 (80%)</td>
</tr>
<tr>
<td>mild residua</td>
<td>9</td>
<td>not fully resolved 10/49 (20%)</td>
</tr>
<tr>
<td>disabled</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

IABP = intra-aortic balloon pump.

(1), inadvertent puncture of a carotid artery while attempting internal jugular vein cannulation (1), postoperative cardiac arrhythmia (4), postoperative hypotension (2), and a combination of the above (1). Follow-up results are summarized in table 2.

Prolonged Encephalopathy

Forty-nine patients (11.6%) were encephalopathic at postoperative day four. We attributed mild confusion prior to postoperative day four to general anesthesia and intraoperative medication. The 49 patients who were encephalopathic at day four were confused and disoriented in varying degrees. Focal neurologic deficits were not evident in these patients.

While no statistically significant pre- or intraoperative risk factors for prolonged encephalopathy emerged, two postoperative variables did correlate significantly with confusion. These were use of an intraaortic balloon pump \( p < 0.02 \) and use of pressor drug \( p < 0.05 \), both markers for patients with severe hypotension.

Review of the charts of encephalopathic patients revealed other possible causes for the abnormal mental status in 47 patients (96%). In two patients no apparent cause could be identified; in eight patients one possible cause was found; in 39 patients two or more (up to 5) possible factors, any one of which could have accounted for the encephalopathy, were detected. These possible causes included hypoxia in 12, medications in 11, fever/sepsis in four, air in the left ventricular cannula in three, reoperation within 24 hours in two, renal failure in two, ethanol withdrawal in one, and hyperosmolar state in one.

Thirty-nine (80%) of these patients had a normal mental status by the time of discharge. In the remaining 10 (20%) mental status abnormalities persisted at the time of discharge. These abnormalities included such findings as partial disorientation (errors in naming 10 (20%) mental status abnormalities persisted at postoperative day four. We attributed mild confusion with crossed-body commands — all of which were present to one degree or another in each of these patients. There were no localizing mental status examination findings in this group to suggest a focal lesion and CT head scanning was not routinely carried out.

Ninety-eight percent of all patients in the study had elevated levels of the "brain" isoenzyme of creatine phosphokinase (BB-CPK) in blood drawn when the patient reached the recovery room. The average total CPK level immediately postoperatively in our patients was 575 ± 210 I.U. and average BB-CPK 2.0 ± 1.3%. Eight hours later the average total CPK had fallen to 463 ± 195 I.U. and BB-CPK to 0.08 ± 0.04%. There was no correlation between BB-CPK levels and the occurrence of prolonged encephalopathy or stroke.

Discussion

The frequencies of CNS infarction (5.2%), severe CNS infarction (2%), and prolonged encephalopathy (11.6%) in this prospective study are similar to previously reported frequencies as summarized in table 4. Current CNS complication rates are lower than those of 10 years ago which can be partially attributed to the development of finer mesh blood filters in the extracorporeal bypass pump system. However, there has been

<table>
<thead>
<tr>
<th>Patient Age</th>
<th>Sex</th>
<th>Infarct location</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46</td>
<td>R cerebral hemisphere</td>
<td>mild</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>R cerebral hemisphere</td>
<td>mild</td>
</tr>
<tr>
<td>3</td>
<td>56</td>
<td>R cerebral hemisphere</td>
<td>mild</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>R cerebral hemisphere</td>
<td>moderate</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>R cerebral hemisphere</td>
<td>moderate</td>
</tr>
<tr>
<td>6</td>
<td>59</td>
<td>R cerebral hemisphere</td>
<td>severe</td>
</tr>
<tr>
<td>7</td>
<td>64</td>
<td>R cerebral hemisphere</td>
<td>severe</td>
</tr>
<tr>
<td>8</td>
<td>44</td>
<td>L cerebral hemisphere</td>
<td>mild</td>
</tr>
<tr>
<td>9</td>
<td>52</td>
<td>L cerebral hemisphere</td>
<td>mild</td>
</tr>
<tr>
<td>10</td>
<td>64</td>
<td>L cerebral hemisphere</td>
<td>severe</td>
</tr>
<tr>
<td>11</td>
<td>64</td>
<td>L cerebral hemisphere</td>
<td>severe</td>
</tr>
<tr>
<td>12</td>
<td>65</td>
<td>L cerebral hemisphere</td>
<td>severe</td>
</tr>
<tr>
<td>13</td>
<td>55</td>
<td>brainstem</td>
<td>mild</td>
</tr>
<tr>
<td>14</td>
<td>55</td>
<td>brainstem</td>
<td>mild</td>
</tr>
<tr>
<td>15</td>
<td>49</td>
<td>brainstem</td>
<td>moderate</td>
</tr>
<tr>
<td>16</td>
<td>70</td>
<td>brainstem</td>
<td>moderate</td>
</tr>
<tr>
<td>17</td>
<td>60</td>
<td>brainstem</td>
<td>severe</td>
</tr>
<tr>
<td>18</td>
<td>39</td>
<td>retina</td>
<td>mild</td>
</tr>
<tr>
<td>19</td>
<td>53</td>
<td>retina</td>
<td>mild</td>
</tr>
<tr>
<td>20</td>
<td>64</td>
<td>retina</td>
<td>mild</td>
</tr>
<tr>
<td>10</td>
<td>64</td>
<td>retina</td>
<td>moderate</td>
</tr>
<tr>
<td>21</td>
<td>61</td>
<td>optic nerve</td>
<td>severe</td>
</tr>
<tr>
<td>22</td>
<td>63</td>
<td>optic nerve</td>
<td>severe</td>
</tr>
</tbody>
</table>
### Table 4: Summary of Recent Data on CNS Complications of Open Heart Surgery

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year*</th>
<th>Study design</th>
<th>Type of OHS</th>
<th>Number of patients</th>
<th>% with CNS deficit</th>
<th>Method of ascertainment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hill JD et al.</td>
<td>1968</td>
<td>pathologic analysis autopsy cases</td>
<td>mixture</td>
<td>133</td>
<td>focal infarct: † encephalopathy: ‡</td>
<td>pathological analysis of brains (fat embolii in 62% brains, non-fat embolii in 31% brains)</td>
</tr>
<tr>
<td>2. Heller SS et al.</td>
<td>1969</td>
<td>prospective</td>
<td>mixture</td>
<td>100</td>
<td>†</td>
<td>psychiatric interview psychologic testing (24% had post-operative delirium)</td>
</tr>
<tr>
<td>3. Javid H et al.</td>
<td>1969</td>
<td>prospective</td>
<td>mixture</td>
<td>100</td>
<td>13 + %</td>
<td>clinical exam psychologic testing</td>
</tr>
<tr>
<td>4. Tufo HM et al.</td>
<td>1969</td>
<td>prospective</td>
<td>mixture</td>
<td>100</td>
<td>13 + %</td>
<td>clinical exam psychologic testing</td>
</tr>
<tr>
<td>5. Branthwaite MA</td>
<td>1970</td>
<td>retrospective</td>
<td>mixture</td>
<td>417</td>
<td>9.4%</td>
<td>chart review clinical exam</td>
</tr>
<tr>
<td>6. Hansotia PL et al.</td>
<td>1972</td>
<td>prospective</td>
<td>mixture</td>
<td>177</td>
<td>†</td>
<td>serial EEG (51% with persistently abnormal EEG at discharge. Includes 11 patients who died.)</td>
</tr>
<tr>
<td>7. Cannon DS et al.</td>
<td>1972</td>
<td>retrospective</td>
<td>mixture</td>
<td>400</td>
<td>1% †</td>
<td>chart review</td>
</tr>
<tr>
<td>8. Hutchinson JE et al.</td>
<td>1972</td>
<td>retrospective</td>
<td>CABG alone</td>
<td>376</td>
<td>0.3% †</td>
<td>chart review</td>
</tr>
<tr>
<td>9. Branthwaite MA</td>
<td>1973</td>
<td>prospective</td>
<td>mixture</td>
<td>140</td>
<td>†</td>
<td>intra-operative use of cerebral function monitor (7.1% had clinical neurologic damage)</td>
</tr>
<tr>
<td>10. Branthwaite MA</td>
<td>1973</td>
<td>retrospective</td>
<td>mixture</td>
<td>538</td>
<td>3%</td>
<td>chart review</td>
</tr>
<tr>
<td>11. Hodgman JR et al.</td>
<td>1974</td>
<td>retrospective</td>
<td>mixture</td>
<td>100</td>
<td>†</td>
<td>chart review (20% had minor psychiatric problems)</td>
</tr>
<tr>
<td>12. Kolka R et al.</td>
<td>1977</td>
<td>prospective</td>
<td>mixture</td>
<td>204</td>
<td>2.9%</td>
<td>clinical exam</td>
</tr>
<tr>
<td>13. Lee MC et al.</td>
<td>1978</td>
<td>retrospective</td>
<td>mixture</td>
<td>943</td>
<td>0.7%</td>
<td>chart review</td>
</tr>
<tr>
<td>14. Gonzalez-Sacramo F et al.</td>
<td>1978</td>
<td>retrospective</td>
<td>CABG alone</td>
<td>1427</td>
<td>1%</td>
<td>chart review</td>
</tr>
<tr>
<td>15. Loop FD et al.</td>
<td>1978</td>
<td>retrospective</td>
<td>CABG alone</td>
<td>8741</td>
<td>1.3%–2%</td>
<td>chart review computerized cardiovascular information registry</td>
</tr>
<tr>
<td>16. Muraoka R et al.</td>
<td>1979</td>
<td>prospective</td>
<td>congenital heart disease</td>
<td>57</td>
<td>0%</td>
<td>chart review (10.5% had persistent CT scan changes)</td>
</tr>
<tr>
<td>17. Turnipseed WD et al.</td>
<td>1979</td>
<td>prospective</td>
<td>CABG alone</td>
<td>170</td>
<td>4.7%</td>
<td>clinical exam</td>
</tr>
<tr>
<td>18. Breuer AC et al.</td>
<td>(present study)</td>
<td>prospective</td>
<td>CABG alone</td>
<td>421</td>
<td>5.2% (total) 2% (severe)</td>
<td>clinical exam</td>
</tr>
</tbody>
</table>

*Latest year patients in study underwent surgery reflecting technology of that time (i.e. not year study published).
†These retrospective studies are largely devoted to analyses of non-neurologic issues and complications and mention CNS dysfunction.
‡No clinical examination data available.

Little change in the complication rates over the past seven years. The frequency of neurologic complications detected is directly influenced by the study design, the method of ascertainment, the personnel conducting the neurologic assessment, the types of heart procedures being evaluated, and differences in patient selection and surgical technique in different institutions, among other factors. The pitfalls of retrospective studies in particular have been pointed out.

No statistically significant pre- or intraoperative risk factors were found for either stroke or encephalopathy. Contrary to previous reports, age was not a factor, as CNS complications in 60 patients 65 years or older in our study were no more frequent than in patients under 65 years of age. Pump time in excess of two hours was not associated with an increased frequency of CNS complications in the 36 patients in our study who underwent prolonged bypass, in contradistinction to reports of 12 years ago and seven years ago. Improved blood filtration technology and continuous monitoring by digital display of hemodynamic parameters in more recent years may account in part for these differences.

Use of pressor agents and an intra-aortic balloon pump, both markers for hypotensive and severely ill patients, did correlate with prolonged postoperative
encephalopathy. This suggests that global hypoperfusion of the brain may have occurred in some of these patients. These findings are of little practical clinical utility, however, as postoperative hypotension requiring this form of treatment could not be predicted in any given patient.

While BB-CPK isoenzyme levels have been reported elevated in patients with acute cerebrovascular accidents, no correlation was found between isoenzyme levels and CNS complications in this study. Normally, no BB-CPK is found in human serum. This "brain" isoenzyme of CPK is also found in a number of other human tissues including stomach, colon, ileum, urinary bladder, prostate, uterus, lung, and thyroid, and one or more of these organs may have been the source of the isoenzyme levels detected.

The incidence of carotid bruits 31/421 (7.3%) in our patients was lower than the 14% incidence in patients undergoing a variety of elective surgical procedures but within the range of bruit frequency (4 to 27%) found in other studies. The frequency of retinal or optic nerve infarcts 7/24 (29%) was, however, higher than that seen in a spontaneous stroke population. We have addressed this issue in detail elsewhere. Multiple factors including hyperthermia with its effect on blood viscosity, and extracorporeal bypass triggered release of C4A, a smooth muscle vasoconstrictive spasmon, may be involved.

Since no single pre- or intraoperative factor proved significant for risk prediction, stroke and encephalopathy in this setting may be of multifactorial cause. Both Halothane and Ethrane may produce alterations in neuronal microtubules and thereby alter axonal transport. Ethrane may produce occult seizures, un witnessed during general anesthesia, resulting in a prolonged postictal encephalopathy in some patients. Complement activation during bypass, complement-induced granulocyte aggregation, or altered thromboxane synthesis with effects on platelet function during extracorporeal circulation may also play a role in producing some CNS dysfunction. However, since all patients undergo anesthesia and all have their blood exposed to the surfaces of the disposable plastic extracorporeal tubing, yet only a few develop CNS dysfunction, other factors must be involved.

The efficacy of blood filters has been documented, yet aggregates less than 20 micrometers in diameter may still pass through these filters and obstruct brain capillaries. Cross-clamping of the ascending aorta, necessary for the anastomosing of the proximal end of a vein graft, or aortotomy alone may liberate cholesterol and/or calcific plaque debris to produce cerebral infarction as has been documented on at least one occasion. Yellow plaque areas are frequently seen in the aorta in these patients and regions of the aortic stiffness can be palpated by the surgeon in many cases. At times an audible crunch is heard as the cross-clamp is applied. It may be prudent to avoid vein grafting to an aorta heavily involved with atherosclerosis and to use internal mammary artery grafting instead when feasible.

Large left ventricular clots may be another source of emboli. In a separate study from this institution, the stroke rate in 155 patients with left ventricular clot was 10%; twice the stroke rate in the present study. This raises the possibility of embolic stroke from small ventricular clots beneath the resolving power of ventriculography and echocardiography in coronary artery disease patients, many of whom have had an old myocardial infarction. Intraoperative manipulation of the heart during suturing of the distal vein graft anastomoses, particularly with left circumflex artery grafting where the heart is lifted upward to achieve adequate exposure, may be a contributing factor in such cases.

Since an increased risk cannot be predicted preoperatively, strategies to resolve the problem of CNS damage during myocardial revascularization should include an effort to detect when strokes occur during surgery using intraoperative EEG or other monitoring techniques. If the insult could be quickly identified then the cause might be more apparent and treatment might be instituted in an attempt to limit the extent of brain injury. If our 2% serious stroke rate is applied to the national figure of 137,000 bypass graft patients per year, 2,740 strokes per year occur in this setting in the U.S. alone, each in a patient surrounded by physicians with multiple venous and arterial access routes for drug administration, analysis, and study. Surely, there is an opportunity to further understand and remedy a problem that has remained unchanged for several years.

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