

NEUROLOGICAL AND NEUROBEHAVIORAL
COMPLICATIONS OF CORONARY ARTERY BYPASS SURGERY

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INTRODUCTION

Successful management of coronary artery disease with surgical coronary revascularization is often frustrated by serious neurological outcomes, such as stroke. Coronary artery bypass surgery (CABG) for myocardial revascularization remains a fundamental component of successful therapy for coronary artery disease, and is the most common cardiac surgery performed. Well over 250,000 aortocoronary bypass graft surgeries are performed annually in the U.S. alone (91). Over the past decade, research has focused on causes of, and risk factors for, perioperative neurological dysfunction—primarily ischemic neurological dysfunction—and resultant implications for neural protection perioperatively. This article will mainly review these topics pertaining to perioperative central nervous system dysfunction, stroke, and their sequelae. Perioperative peripheral nerve complications will also be addressed briefly.

PERIOPERATIVE STROKE AND NEUROPSYCHOLOGICAL DEFICIT

The incidence and severity of central nervous system dysfunction and stroke are greater in patients undergoing CABG than in matched patients undergoing non-cardiac surgery (113). The incidence of adverse central neurological complications in patients undergoing CABG was reported by Roach et al in 1996(114) to be 6.1% of 2,108 patients in a multi-center study; these complications

included stroke, prolonged encephalopathy, seizures, or stupor. The incidence of frank stroke in this study was approximately 2%. In other studies, the reported incidence of postoperative cerebral dysfunction has ranged from 0.4% to 53%% (64, 147).

Postoperative ischemic stroke and neuropsychological dysfunction are often difficult to differentiate, since strokes may cause psychological, behavioral, cognitive, and memory disturbances. Furthermore, as is the case with postoperative stroke, cerebral embolism is the major cause of postoperative neuropsychological change (5, 19, 21, 92, 93, 94, 96, 97, 108). Nevertheless, cerebral complications of CABG are broadly categorized as either stroke, or neuropsychological deficit.

Postoperative Stroke: Risk factors

The most accepted and widely reported incidence rates for postoperative stroke after CABG range between approximately 1 and 6% (64, 66, 69, 70, 89, 106, 114). Risk factors for postoperative stroke include advanced age, diabetes, female gender, hypertension, prior history of cerebrovascular disease, markers of atherosclerosis including carotid bruits, renal failure, aortic and carotid atherosclerotic disease, peripheral vascular disease, cigarette smoking, low ejection fraction, and left ventricular mural thrombi (64, 66, 89, 106). Other variables which affect the risk of postoperative stroke include urgent or emergent need for surgery, duration of cardiopulmonary bypass, and perioperative hypotension requiring pressure support—variables which are often a reflection of the degree of disease that the patient brings to the case—and the development of postoperative atrial fibrillation (66, 70, 83, 89, 106). A history of pulmonary disease—emphysema, chronic bronchitis, restrictive lung disease, or asthma—was found to be a significant predictor of both postoperative stroke and neurobehavioral changes after CABG in a prospective study of 2108 patients as reported by Roach et al (114). Theories proffered by these investigators included probable retained carbon dioxide impacting cerebral vascular activity, and the higher requirement in these patients for prolonged mechanical ventilation which might also affect cerebral perfusion and reflect less adequate cerebral oxygenation. Other concomitant cardiac procedures, such as valve replacement in addition to CABG, also confer a higher risk of perioperative stroke (89). Additionally, patients undergoing redo heart surgery have a higher risk of perioperative stroke (76). The majority of perioperative strokes in association with CABG are felt to be

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embolic: the presumed mechanism of stroke being undetermined in 33%, aortic embolism in 32% (from manipulation of the aorta, for example), cardiogenic embolism in 12%, hypotension in 12%, and concomitant cerebrovascular disease in 11% (76).

Advanced Age

Most studies identify advancing age as the single most important determinant of perioperative stroke. This is attributed to the relationship between age and the progression of atherosclerosis (64, 69, 89). In one series reported by Almassi et al (89), patients <60 years of age had a 1.6% incidence of stroke that increased to 5.25% for patients above the age of 70. Many other series similarly show a two to five-fold increase in the incidence of stroke comparing patients younger than 60 with patients over the age of 70 or 75 (66, 69, 89). A contradictory implication of the series of 465 patients undergoing CABG reported by McKhann et al, is that age in isolation should not be used to determine stroke risk (69). In their series, a 70-year old patient without other risk factors was considered to be at a low risk for postoperative stroke. Since age has been reported as an independent variable for predicting postoperative stroke in larger series (64, 89), including the series of 10,860 patients reported by Puskas et al, the finding by McKhann et al that age alone was not an independent predictor of postoperative stroke should be viewed with skepticism. This issue is significant given the increasingly older populations undergoing CABG: in the CASS (Coronary Artery Surgery Study) Registry data reported in 1992, 2.45% of patients were older than 70 years, as compared to 31.5% patients older than 70 in a series of 4,969 patients reported by Almassi et al in 1999 (89).

Atherosclerotic disease of the ascending aorta

Atherosclerotic disease of the ascending aorta is a particularly significant independent risk factor for postoperative stroke (64, 106) in patients undergoing CABG. It is well recognized that the atherosclerotic ascending aorta is an important source of cerebral emboli intraoperatively. Aortic atheroma have been shown to increase dramatically with increasing age, particularly in patients over the age of 70 (74). Correlation between aortic atheromatosis and stroke in patients undergoing CABG has been shown at necropsy in a study of 221 patients; atheroemboli were present in 46 of 123 patients (37%) with severe disease of the ascending aorta, but in only 2 of 98 patients (2%) without significant ascending aortic disease (117). Studies utilizing transcranial doppler (TCD)

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have correlated large releases of embolic particles in association with manipulation of the aorta, such as with aortic clamp release, and with aortic cannulation during coronary bypass surgery (5, 74, 78). In a prospective TCD study of 127 patients (78), Clark et al reported neurologic complications (stroke, coma, delirium, aberrant behavior) in 7 of 20 patients (35%) with large numbers of emboli compared with 2 of 83 patients (2.4%) with small numbers of emboli. Interestingly, the embolic particles associated with surgical events, such as aortic manipulation, rather than perfusion alone, were correlated with neurological outcome. Similar findings were seen in the smaller series of 41 patients studied intraoperatively with TCD by Sylivris et al (5), and further reinforce the particularly pathogenic nature of microembolization from the aorta as compared with the pathogenicity of the emboli attributed to perfusion only. The usage of epiaortic ultrasound intraoperatively—rather than direct aortic palpation—to assess the ascending aorta in selection of appropriate sites for aortic cannulation and clamping is increasingly advocated (71, 74). Goto et al (71) reported that, out of 121 patients undergoing CABG, 13 had moderate or severe atherosclerosis in the ascending aorta, and were considered to be at increased risk of embolization; in those patients, utilizing epiaortic echocardiography, the standard operative procedure was modified to avoid manipulation of the diseased aortic segments. In their small series of patients, they subsequently found no postoperative stroke in any of the patients with significant atherosclerotic disease of the aorta. Further larger studies would be helpful in confirming these findings.

Atherosclerotic Carotid Artery Disease

Atherosclerotic carotid artery disease is another strong predictor of postoperative stroke, and the management of coexistent carotid artery and coronary artery disease is not yet fully resolved. The risk of perioperative stroke has been shown to be significantly higher in patients undergoing CABG with carotid stenosis; in some series the incidence of stroke increased threefold or more in patients undergoing CABG who possess carotid stenosis, in comparison to those who do not. In a retrospective analysis, Brener et al noted a 9.2% incidence of TIA/stroke when asymptomatic carotid lesions ($\geq 50\%$) were present in patients undergoing CABG, as compared to 1.9% in those without such lesions (119). A stroke rate of 8.9% in CABG patients with angiographically documented carotid stenosis ($>70\%$) has been reported, compared with 1.3% in patients without carotid stenosis (120). Another retrospective study disclosed increased

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perioperative stroke risk in patients with asymptomatic carotid disease only if the stenosis exceeded 90% (121). There is some evidence that many of the strokes associated with carotid stenosis in patients undergoing CABG are delayed, occurring often 24 hours or more after CABG (76). A relatively benign postoperative course for young patients with unilateral carotid occlusion undergoing CABG has been reported (44).

Results of Combined CEA/CABG

The issue of how to surgically approach combined coronary artery and carotid artery disease remains unsettled. Investigators reporting on results of their experience with either combined carotid endarterectomy (CEA)/CABG or staged procedures for patients with combined disease have disparate results. Experience at the Mayo Clinic with combined CEA/CABG was discouraging, with investigators concluding that combined surgery should only be done for patients with symptomatic carotid artery stenosis and unstable angina (118); even this subgroup of patients fared poorly, with mortality at 3 to 4 year follow-up being 36%. Bass et al (124) in 1992 reported an overall 25% neurological complication rate, including an 11% incidence of stroke ipsilateral to the side of carotid artery surgery; in this small group of 99 patients, most of the patients (79%) had asymptomatic carotid artery stenosis of 80% or greater. Coyle et al (125) in 1995 reported a series of 110 patients undergoing either simultaneous CEA/CABG, or staged CEA preceding CABG during the same hospitalization. The former group (simultaneous procedures) suffered a combined stroke/death rate of 26.2% within 30 days, whereas that of the latter group (CEA followed by CABG within the same hospitalization) suffered a 6.6% combined stroke/death rate.

Conversely, in 1989, Cambria et al (62) reported a series of 51 patients with carotid stenosis $\geq 75\%$ (69% of these patients were neurologically asymptomatic) undergoing combined CEA/CABG in comparison to patients undergoing CABG alone. There was no difference in operative mortality (2.0% as compared to 2.2%) or perioperative stroke (2.0% as compared to 0.6%). Darling et al (126) in 1998 reported a prospective series of 470 simultaneous CEA/CABG surgeries. Permanent neurological deficits occurred in five patients (1%), and six (1.7%) of the patients had a transient neurological deficit that improved prior to discharge. Operative mortality was 2.4%, with 90% of these patients dying from cardiac complications postoperatively, and one patient dying from a stroke.

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Characteristics of this patient population included an average age of 69 years, 62% were male, 15% were diabetic, and 38% were smokers. Sixty patients (13%) presented with TIA's, 22 (5%) with amaurosis fugax, 16 (3.4%) with a prior history of stroke, and 372 (70%) were asymptomatic. Jahangiri et al (44) in 1997 reported a series of 64 patients undergoing combined CEA/CABG. Retrospective analysis disclosed that myocardial revascularization was successful in all 64 patients with no perioperative myocardial infarcts; a new neurological deficit occurred in three patients postoperatively (4.7%), with two of these three patients recovering fully prior to hospital discharge. In this study, the criteria for CEA in combination with CABG were 1) unilateral carotid stenosis $>70\%$, 2) bilateral carotid stenosis $> 50\%$, or, 3) unilateral carotid stenosis $> 50\%$ with contra lateral occlusion. Sixty percent of patients presented with symptoms of TIA or stroke, and thus 40% of the patients in this study had carotid disease, which was asymptomatic. Donatelli et al (143) in 1998 reported their series of 70 patients undergoing CEA immediately preceding cardiopulmonary bypass for cardiac surgery in whom there were no perioperative strokes. There were seven perioperative deaths, all related to cardiac events. CEA was performed on patients with carotid stenosis $>70\%$, unilateral stenosis $>50\%$ with ulcerated plaque or bilateral stenosis $>50\%$ (this latter group also included patients with unilateral occlusion). Cardiac surgeries in these patients included 69 coronary artery bypass grafts, four left ventricular aneurysmectomies, three aortic valve replacements and surgery on two mitral valves.

Evolving Consensus in Management of Coexisting Carotid Stenosis and Coronary Artery Disease

Although randomized prospective trials addressing the issue of how to approach coexistent carotid artery disease and coronary artery disease are not available, there is broad consensus among investigators on some points. Firstly, investigators agree that combined CEA/CABG should be performed in patients who possess both unstable coronary artery disease and unstable carotid artery disease wherein neurological symptoms correlate to carotid stenosis which is $\geq 70\%$ (44, 47, 62, 118). Additionally, investigators agree that when both CABG and CEA are indicated in stable patients, CEA should be performed first. Hertzler et al compared 58 "reversed-staged" procedures with 71 combined operations (126). The mortality and stroke rates in the "reversed-staged" operations were 5.2% and 14% respectively. The combined procedures resulted in a mortality of 4.2% and stroke rate of 2.8%.

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When CEA is not combined with CABG, but is staged to occur prior to CABG, the optimal time interval between procedures is not established.

What constitutes an indication for CEA either prior to, or combined with, CABG is not fully settled. Certainly the NASCET (North American Symptomatic Carotid Surgery Trial) and the ECST (European Carotid Surgery Trial) provide at least a rational basis for either staged or simultaneous CEA in combination with CABG for patients with symptomatic greater than 70% carotid artery stenosis (127, 128). The prophylactic benefit of CEA prior to, or simultaneous with, CABG in patients with asymptomatic carotid artery disease is not established, but asymptomatic $\geq 90\%$ carotid artery stenosis represents a circumstance where prophylactic CEA is recommended (118, 129, 130,131). Clinical scenarios of special concern where prophylactic CEA is considered are circumstances of asymptomatic or symptomatic bilateral carotid stenosis $>50\%$, or unilateral occlusion with contra lateral asymptomatic or symptomatic carotid stenosis of $>50\%$. Lewis et al (75) assessed the stroke risk of 582 patients undergoing cardiopulmonary bypass with reference to the presence or absence of significant asymptomatic carotid stenosis. Patients without carotid stenosis had a stroke rate of 0.34% and with significant stenosis, 3.8%. Within the latter group, risk of hemispheric stroke was 5.3% (4 of 75 patients) in those with $>80\%$ stenosis, bilateral stenosis of 50-99%, or unilateral occlusion with contra lateral stenosis of $\geq 50\%$. No strokes occurred in the patients with unilateral 50% to 79% stenosis (n=52). Hill et al (131) found that patients undergoing cardiac surgery with asymptomatic carotid stenosis 50% to 90% and 80%-90% had, respectively, a 5.2-fold and 24.3-fold increase in ipsilateral hemispheric stroke risk within 30 days following surgery. Thus, asymptomatic carotid artery stenosis between 80-90% was found to be an independent risk factor for ipsilateral hemispheric stroke.

The prophylactic benefit of CEA for patients with asymptomatic carotid stenosis, such as in the ACAS (Asymptomatic Carotid Atherosclerosis Study) study, does not predict the prophylactic benefit of CEA for patients with asymptomatic carotid stenosis undergoing CABG in terms of reducing postoperative stroke within the first 30 days after surgery. In the former situation, in which one is undergoing the surgical risk of CEA for asymptomatic carotid stenosis in order to prevent future stroke, the benefit is seen as accrued over a period of years, so that one is willing to face a certain risk of perioperative stroke in the immediate future in

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order to garner a lower overall future stroke risk over time. However, in the latter case, the distant future is less important, and the immediate surgical risk of postoperative stroke (within 30 days of surgery) from CEA in combination with CABG becomes a more important variable.

Another critical point is surgical risk of CEA. The centers performing CEA should have a high level of expertise, and a low incidence of postoperative major complications. The NASCET investigators, for example, reported a 2.1% incidence of major stroke and death (122). With a higher incidence of major stroke and death, the benefit of carotid endarterectomy diminishes, and vanishes with an incidence of major stroke and death of 10% (122). The issue of low surgical risk is greater in asymptomatic carotid stenosis when considering CEA, as exemplified particularly by the ACAS study wherein, the absolute risk reduction of stroke projected over five years was 5.8% as compared to the absolute risk reduction of stroke in the NASCET study of 17%. This absolute risk reduction was entirely dependent upon the low operative complications as the surgical benefit incorporated a perioperative stroke and death rate of 2.3% including a permanent arteriographic complication rate of 1.2% (124).

Carotid angioplasty and stenting may alter the landscape of future decision-making for those patients afflicted with dual coronary artery and carotid artery disease who require CABG. The data accumulated has not yet established prophylactic benefit of carotid angioplasty and stenting in patients with symptomatic carotid stenosis or asymptomatic critical stenosis.

Past History of Cerebrovascular Disease

A past history of stroke or TIA is another important risk factor for postoperative stroke and neurobehavioral abnormalities after CABG. Redmond et al reported their findings from a prospective analysis of 1000 patients, of which 71 patients had previously documented stroke (79). Two control patients with no history of stroke were selected for each of these study patients. There were no other significant differences between the study and control groups with respect to other established risk factors for neurological complications of CABG, including asymptomatic or symptomatic carotid artery disease or ascending aortic arch disease. Compared with controls, study patients took longer to awaken, longer to extubate, had a greater incidence of reintubation and postoperative confusion. There was an increased incidence of

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neurologic deficit among these study patients as well: 31 of 71 patients suffered postoperative neurologic deficits in contrast to 2 of 142 patients in the control group. These deficits included new stroke in 6 of 71 patients, reappearance of old deficits in 19 of 71 patients, or worsening of previous deficits in 6 of 71 patients. The deficits were noted soon after extubation in 22 of the 31 patients, and in the remaining 9 patients, the deficit became clinically apparent between 24 and 48 hours after surgery. Study patients with neurological deficits had longer cardiopulmonary bypass times than did those without deficit; and the 30-day mortality was greater than in the control patients. It is worth noting that in the 19 patients who had completely recovered from their original stroke before CABG, the postoperative deficit closely resembled their previous stroke and there were no new ischemic lesions seen on CT scans postoperatively, nor in MRI scanning in three of the patients. Near complete recovery was achieved in 14 of these patients by discharge and 17 were at their preoperative baseline by 6 months. Younger patients with prior strokes did better than patients who experienced their prior stroke at an older age. Some investigators postulate that impaired cerebral autoregulation conferred by a prior stroke is a factor in worsening of the deficit postoperatively. Another study disclosed that a stroke occurring more than 3 months prior to surgery eliminated the risk of perioperative exacerbation of the prior deficit (89).

What is the optimal time interval to wait after a patient has suffered a stroke before proceeding with CABG in a patient with coronary artery disease? Each case has unique circumstances, which mandate individualized recommendations, including the size of the stroke and extent of neurological injury or recovery, the severity or stability of the patient's coronary artery disease, and other concomitant medical problems. Time intervals of between three weeks to three months are generally accepted.

Postoperative Atrial Fibrillation

Atrial fibrillation is another important cause of delayed postoperative stroke. In one prospective study of 4,941 patients undergoing cardiac surgery, atrial fibrillation occurred in 30% of patients with stroke versus 5.7% of patients without stroke; in this study the rate of stroke in patients with atrial fibrillation was 5.9% versus 2.5% in those who did not develop this rhythm disturbance (83, 89). Other studies cite the higher incidence of stroke in patients who suffer post-operative atrial fibrillation (70). Such a strong relationship between post-operative atrial fibrillation and

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stroke should prompt immediate therapeutic intervention to terminate this rhythm disturbance and to consider prophylactic anticoagulation unless contraindicated.

Cardiopulmonary Bypass

Increased length of cardiopulmonary bypass is a risk factor for perioperative stroke, and for the related but more diffuse findings of cognitive impairment after CABG. Other measurable parameters of cardiopulmonary bypass may predict the risk of perioperative stroke or cognitive decline. These include embolic phenomena associated with cardiopulmonary bypass, and abnormal perfusion pressures (2).

Embolization During Cardiopulmonary Bypass

Emboli during cardiopulmonary bypass may be particulate or gaseous. Gaseous microemboli may originate from the oxygenator, reservoirs, pumps, or the cardiac chambers. The latter source is more significant usually in such open heart procedures where CABG is accompanied by additional procedures such as valve replacement or repair of septal defects. Particulate micro-emboli may originate from the oxygenator, the residua of destroyed red cells, white cells and platelets, serum lipids, fibrin, and fibrin degradation products. Microparticles of plastic and other material from the disposable components of the oxygenator may also circulate. Larger particulate emboli may originate from atherosclerotic areas of the aorta, debris from valves, or clot from the left ventricle or left atrium in patients with impaired wall motion or chronic atrial fibrillation. As previously stated, current evidence indicates that particulate emboli, which result from manipulation of the aorta or heart, such as with cross clamping and clamp-release of the aorta, and valve procedures, are the most pathogenic emboli for postoperative neurological or neurobehavioral deficits (47). Epi-aortic ultrasound may aid in localizing the best sites for aortic cross clamping, thus reducing the rate of aortic embolism during cardiopulmonary bypass (5, 6, 47, 108).

Is Hypothermia Effective as a Neuroprotective Strategy?

Hypothermia versus normothermia during cardiopulmonary bypass is a controversial issue. Modest hypothermia during cardiopulmonary bypass as a neuroprotective strategy has been shown to be successful in the laboratory, but proof of efficacy in clinical studies with patients undergoing CABG is inconclusive (39). Investigators at Emory observed a stroke rate of 3.1% in the

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“warm” group as opposed to a stroke rate of 1.0% in the “cold” group, in a prospective study of 1,001 patients undergoing cardiac surgery. This study has been criticized for the fact that other factors might have influenced the higher stroke rate in the warm group, such as aggressive rewarming leading to hyperthermia, and the more frequent use of retrograde cardioplegia (39). The “Warm Heart Investigators” studied 1,732 patients and found stroke rates of 1.6% in the warm group and 1.5% in the cold group. Other investigators have sought to measure postoperative cognitive decline, rather than stroke, as a more sensitive surrogate measure of putative neuroprotection against ischemic brain injury of hypothermia during cardiopulmonary bypass. Thus, there have been conflicting findings regarding a beneficial effect of hypothermia. The most serious potential adverse effects of perioperative hypothermia include bleeding, infection, and cardiovascular complications (39).

The Systemic Inflammatory Response

A systemic inflammatory response evoked by cardiopulmonary bypass may affect the potential for stroke, cognitive impairment and systemic organ dysfunction (3, 6, 7). During cardiopulmonary bypass, the interaction of blood with nonbiological surfaces can result in activation of humoral cascades such as bradykinin and kallikrein (enzymes which can effect changes in microvascular permeability resulting in cerebral edema), coagulation, fibrinolysis, and complement, as well as activation of cells including neutrophils, platelets, and endothelial cells which can lead to Coagulopathy and a systemic inflammatory response. In a pilot study of 6 patients, Taylor reported pre- and post-operative MRI scanning at 60 minutes and 24 hours after uneventful CABG. All six patients showed acute swelling of the brain at 1 hour after bypass, with 5 of the 6 patients demonstrating resolution of the brain edema at the time of the subsequent postoperative imaging study at 24 hours postoperatively. An inflammatory response in the brain was proposed by Taylor to explain these striking findings (6). Other investigators have postulated that MRI findings of diffuse postoperative brain edema might be related to diffuse microembolization, or due to the lack of arterial pulsations during cardiopulmonary bypass (15). Aprotinin, a serine protease inhibitor well-known for its antifibrinolytic actions might also blunt the release of TNF-alpha occurring during cardiopulmonary bypass, and may have other anti-inflammatory properties. It has been found to inhibit enzymatic intermediaries involved in the generalized inflammatory response to cardiopulmonary bypass

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(92). It is also an inhibitor of plasmin, which is the likely mediator of aprotinin's effect on the observed decrease in blood loss and in transfusion requirements. Belgium investigators reported that cytokine release and neutrophil activation were not attenuated by the use of heparin-coated circuits or by the administration of aprotinin; nor were there additive effects on these measurable endpoints with the combined usage of heparin-coated circuits and aprotinin administration (3). However, aprotinin was found in two other studies to significantly lower incidences of perioperative stroke (92).

Biochemical Markers of CNS Injury in Patients Undergoing Cardiopulmonary Bypass

Biochemical markers have been correlated with postoperative neuropsychological deficit after CABG. These biochemical markers include the measurement of neuron-specific enolase (NSE) and S-100 protein (16). NSE is a glycolytic enzyme localized in neurons and is regarded as brain specific. It is predominantly used as a tumor marker for small-cell lung cancer, neuroblastoma, and other malignancies of neuroendocrine origin and is not therefore entirely brain specific. However, it has been shown to be increased in CSF but not in serum after epileptic seizures (16). The half-life of NSE is about 20 to 48 hours (16). Problems interpreting NSE levels can arise because NSE is also present in platelets and erythrocytes; therefore even limited hemolysis can substantially add to the NSE value in plasma. This is a theoretical limit for its use as a marker of CNS injury during and shortly after cardiopulmonary bypass. The S-100 protein's name is derived from its solubility in 100% saturated ammonium sulphate at neutral pH. It is a small cytosolic protein, which exists in various forms, predominantly the beta/beta form and the alpha/beta form. The beta/beta form is found primarily in astroglial and Schwann cells and the alpha/beta form in astroglial cells. S-100 is metabolized in the kidney and excreted in the urine, with a biologic half-life of 113 minutes. Both CSF and serum S-100 levels have been used to detect and characterize brain damage from stroke, subarachnoid hemorrhage and traumatic brain injury. In one study of 35 patients undergoing cardiopulmonary bypass, eight patients demonstrated postoperative CNS dysfunction. Of these, 7 had elevated levels of NSE and S-100 (16). There were four patients with elevated levels in which no overt neurologic complications were encountered. Two of these were examined with a neuropsychologic test battery, and through comparison of postoperative test results to preoperative test results, there was evidence of cognitive deterioration (16).

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Although S-100 has only just recently been applied to studying CNS damage in patients undergoing cardiopulmonary bypass, it has the potential to become very useful as a sensitive and specific marker of CNS dysfunction (16).

Perioperative Hypotension

Perioperative hypotension requiring pressors or intra-aortic balloon pump support is also a risk factor for perioperative stroke or the diffuse findings of cognitive decline and delirium. The regions at greatest risk of ischemic injury from hypotension are the watershed regions of the brain, which are between the anterior, middle, and posterior cerebral arterial vascular territories. In severe cases, the radiographic findings of watershed infarcts are very distinctive, with the appearance of bilateral, linear border zone parieto-occipital infarcts.

Postoperative Stroke: Clinical Assessment

Neurological Examination in the Intensive Care Unit

The neurologic examination in the intensive care unit can be left neither to nurses nor to technological studies. Some nurses are superbly trained but any fault in judgment exposes both the physician and the patient to diagnostic and treatment errors, which are less likely when a well-trained physician examines the patient postoperatively. CT scans of the brain may be normal in the presence of severe pathology; EEG's may be normal despite an acute cerebral infarct, especially if deeply subcortical, and may not reflect epileptiform activity even in the aftermath of a seizure. A brief review of the neurologic exam in the ICU patient and its rationale is appropriate at this point.

The aim of the neurologic examination in the intensive care unit is to discover the presence of peripheral and central nervous system pathology. If there is central nervous system involvement, focal disease must be differentiated from global dysfunction. Serial neurological evaluations alone may be the only diagnostic measure feasible when the patient is too unstable to be moved for CNS imaging studies. Evaluation of the patient's neurologic status after extubation following cardiac surgery can be perfunctory and inadequate or organized and precise. Yet the difference in time consumed between these approaches may be little. The presence of aphasia, visual field deficits, and eye movement disorders, and unilateral facial or body weakness or sensory deficit are examples

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of focal deficits which are sought during the course of the neurological examination. Impaired mentation is a nonlocalizing finding. Before assuming the presence of confusion, it is essential to establish that the patient is not aphasic. Many acutely aphasic patients are agitated and have no other obvious findings to easily establish focal brain involvement. An added obstacle occurs when these patients are intubated and therefore may be assumed to be encephalopathic. Nonconvulsive status epilepticus, a well-recognized treatable phenomenon, is often caused by embolic stroke. It might be mistaken for encephalopathy as overt focal motor manifestations are not apparent apart from abnormal eye movements such as ocular deviation or nystagmoid jerks.

The Intubated Patient

Neurological evaluation of patients who are intubated can be thorough and includes cognitive testing. The patient need only nod yes or no to specific questions. First it is essential to establish accuracy of the responses. Patients who are aphasic or confused may nod yes in a seemingly appropriate manner. "Yes" responses to questions such as "do you understand what we are about to do," "will you follow the nurse's instructions," "are you feeling better now" have no meaning if a patient cannot recognize his own name from three names given to him. In the same manner, one might ask the patient to nod his head yes or no correctly when given the names of three hospitals, three months, and three years to choose from when testing orientation. Can the patient follow simple commands such as "raise your hand," a 2-step command such as "raise your right hand," a 3-step command such as "raise your right hand and touch your nose," or a 4-step command such as "raise your left hand and touch your right ear." Comprehension is most accurately assessed in this manner. If comprehension is deficient the patient may have diffuse pathology or may be aphasic.

Examination of the cranial nerves in an intubated patient can be surprisingly detailed, when focusing on vision, pupils, eye movement and facial movement. Patients may easily respond to fingers shown in either visual field by imitating the examiner with the same number of their own fingers. Otherwise, visual threat may be required to check for eye blink from either field of vision. Pupillary asymmetry is routinely searched for and indicates either sympathetic (Horner's Syndrome) or parasympathetic involvement (3rd nerve) involvement. A small pupil suggests an ipsilateral Horner's Syndrome, which may occur due to lesions of the hypothalamus, brainstem (medulla), spinal cord, superior cervical

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ganglia, or internal carotid artery. A large poorly reactive pupil indicating an ipsilateral third nerve lesion is rare in this clinical setting but may be indicative of mass effect with incipient uncal herniation. Eye deviation or gaze paresis must be sought, whether by oculocephalic maneuver (doll's eyes maneuver), by simple observation, or by noting the patient's ability to follow commands to gaze in all four directions. A vertical gaze paresis may indicate an upper brainstem lesion (midbrain). A horizontal gaze paresis is immediately indicative of either a cerebral hemispheric lesion or a mid-brainstem lesion (pons). Unilateral ophthalmoplegia or ophthalmoparesis (for example only one eye deviated down and out indicative of a third nerve brainstem lesion) is a helpful clue to the presence of a brainstem lesion. The presence of conjugate (both eyes are deviated horizontally or vertically) gaze deviation is an extremely helpful clue in localization of pathology in the intubated patient. For example, conjugate eye deviation to the right indicates either a right cerebral hemispheric lesion or a left pontine brainstem lesion. To then accurately distinguish whether the lesion is in the right cerebral hemisphere or in the left brainstem, one has only to look for a few other clues. If the patient has a left hemiparesis with eyes deviated to the right, the lesion is in the right hemisphere. If the patient has right eye deviation and right hemiparesis, the lesion has to be in the left brainstem. Very simply, eye deviation or gaze preference is toward the side of the cerebral lesion and is away from the side of the pontine lesion.

Facial asymmetry is best appraised by examining the eyes (orbicularis oculi) in an intubated patient. The weak side usually has a wider palpebral fissure because of weak eye closure. A droopy lid is often inaccurately diagnosed as being abnormal when actually the droopy lid is the normal one, and the eye that is wider open is the abnormal side, as there is weakness of eye closure. Weakness of eye closure represents a facial weakness. In this setting, the reason for facial weakness is most often a contralateral central 7th nerve lesion, not a peripheral nerve lesion. Asymmetry of the nasolabial fold must also be noted in determining whether a facial weakness is present. Flattening of the nasolabial fold in conjunction with ipsilateral weakness of eye closure clinches 7th cranial nerve involvement, central or peripheral. However, accurate assessment of the nasolabial fold in an intubated patient may not be possible. The corneal reflex may be diminished with ipsilateral brainstem or contralateral subcortical lesions. Endotracheal and nasogastric tubes ordinarily interfere with assessment of the gag reflex and direction of tongue protrusion.

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The most sensitive method of ascertaining motor dysfunction in an intubated ICU patient is examining dexterity such as rapid finger tapping and foot tapping and checking for arm drift. Vigorous detailed strength testing is often not possible and may be misleading for a variety of reasons including pain and local factors such as peripheral and central IV's, and chest tubes. Strength of hand grasp is frequently preserved in patients with an acute stroke, or even with brachial plexus lesions. Ataxia on finger to nose and heel to shin testing usually indicates ipsilateral cerebellar system involvement either in the brainstem or cerebellum.

Reflex examination should emphasize symmetry and abnormal reflexes, particularly Babinski signs and clonus. The sensory exam may be limited to pin prick stimulation and double simultaneous stimulation. The latter can be particularly helpful in identifying unilateral particularly right-sided cerebral hemispheric lesions. If the patient, with eyes open readily perceives pinprick on both sides of his body, but with eyes closed, only feels stimulation on one arm when both arms are being simultaneously stimulated, then a cerebral lesion contralateral to the ignored stimulus is present. Assessment of position and vibration sense may be possible in the alert cognitively normal patient. Hemisensory loss to pin is best checked by testing the patient on the suspected involved side and slowly crossing over the midline on the trunk. A slight wince or hand movement to the stimulus may be discerned as soon as the midline is approached.

Neurologic Assessment After Extubation

After the patient has been extubated, a detailed mental status testing should be performed. A brief assessment should include orientation to person, place, month, and year. What procedure was just performed? Can the patient speak fluently without word substitution and name objects or body parts? If questions are raised about the patient's cognitive status by the patient's appearance and performance during the physician's examination, or by nurses or family, additional tests are indicated such as giving the patient three simple words to remember, asking him to repeat them immediately and again at 5 minutes. The patient should be requested to follow commands as described in the above paragraphs as well as do simple addition such as 14 + 16 and spell 5-letter words forward and backward. The remainder of the examination is as described under the examination of the

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intubated patient except that the palate and tongue can also be assessed.

Murkin et al, (53) outlined the Western Perioperative Neurological Scale to be used preoperatively, at 7 days and 2 months postoperatively. This scale has some defects such as lumping cerebellar and sensory sections together as well as using a separate category for primitive reflexes. Primitive reflex assessment—aside from Babinski testing—is an unreliable indicator of acute cerebral pathology and probably should be omitted. The scale is still a reasonable method of quantifying the degree of neurological dysfunction.

Postoperative Stroke: Clinical Management

Identification of acute stroke or TIA in the patient who has undergone CABG prompts immediate clinical intervention. The mortality rate in patients undergoing CABG who have suffered a postoperative stroke is approximately 20% compared to a perioperative death rate of 2-4% without stroke (64, 134). The immediate concern is to determine whether the stroke is ischemic or hemorrhagic. Intracranial hemorrhage in the setting of the postoperative CABG patient is infrequent. While computerized tomography is very sensitive for excluding hemorrhage, newer brain imaging techniques, such as diffusion-weighted magnetic resonance imaging, are more sensitive for demonstrating ischemic infarctions than is computed tomography; additionally, perfusion-weighted magnetic resonance imaging may demonstrate areas of relative cerebral hypoperfusion which guide medical management, such as lowering of anti-hypertensive medications to increase cerebral hypoperfusion, which result in clinical improvement (128).

The cause of the stroke/TIA must be ascertained as quickly as possible so that appropriate measures may be instituted. Is the stroke of embolic origin associated with a ventricular or atrial thrombus, atrial fibrillation, or valvular embolism. Is the stroke due to acute thrombus at the site of carotid stenosis or carotid endarterectomy that was just performed? When a patient with acute stroke has just undergone CABG, intra-arterial thrombolysis is contraindicated. Emergent carotid endarterectomy for acute thrombosis at the site of carotid stenosis or carotid endarterectomy is an option. Other therapeutic measures include conversion of atrial fibrillation, correction of hypotension or hypertension, minimizing fever and hyperglycemia, and ensuring that hypoglycemia is not present. Should cardiogenic embolism be

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considered likely, heparin should be administered if not contraindicated because of just completed surgery, hemorrhagic complications, coagulopathy, or concern over potential hemorrhagic transformation of a large ischemic stroke.

If the ischemic stroke is due to extra- or intracranial arterial disease, then treatment of the patient with anti-platelet agents should be considered. Aspirin and clopidogrel are options. Patients may be administered a 375 milligram loading dose of clopidogrel, which has been shown to induce the same degree of platelet inhibition within hours of administration as is seen after five days of clopidogrel therapy at 75 milligrams a day with no loading dose (125). Ticlopidine is another consideration but has been associated with fatal blood dyscrasias. Clopidogrel, a compound structurally related to ticlopidine, rarely causes blood dyscrasias. Aggrenox (dipyridamole/aspirin) is another option; there is a theoretical contraindication in patients with coronary artery disease, with a concern over the possibility of inducing angina, but the clinical veracity of this is not proven.

Assessment of swallowing should be specifically evaluated in some patients with acute stroke by a competent professional trained to assess swallowing and to make recommendations regarding aspiration prevention. The patient's head is ideally elevated in the face of acute stroke as part of routine aspiration precautions. However, if there is an issue of hypotension, hemodynamically significant carotid or basilar artery stenosis or occlusion, it can be important to keep the patient supine, as this may preserve optimal brain perfusion. Care in an ICU or stroke unit is recommended for patients who have recently undergone CABG who have suffered postoperative stroke. The etiology of the stroke should be determined, and the patient's neurological status closely monitored for any evidence of worsening, which might indicate extension of the patient's infarct, recurrent infarct, hemorrhagic conversion of infarct, or systemic illness which is causing the patient's neurologic deficit to appear to have worsened. Common examples of the latter circumstance include sepsis and aspiration pneumonia. Deep venous thrombosis should be sought daily in the patient with limb weakness or immobility for any reason, and preventative measures for DVT should be instituted.

Postoperative Neuropsychological Deficit: Risk Factors

Postoperative neuropsychological deficits after surgical myocardial revascularization have received increasing attention over the past

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several years. Newman et al (147), recently reported in February of 2001 rather surprising data regarding the incidence of neuropsychological syndromes in their series of 261 patients undergoing CABG. They found the incidence of cognitive decline was 53% at discharge, 36% at six weeks, 24% at six months, and 42% at five years. They found that patients with cognitive decline at five years after surgery were predicted by their prior levels of cognitive decline at discharge five years earlier. In other words, there seemed to be a biphasic pattern among those with cognitive decline at discharge: a pattern of early improvement followed by a later decline that was predicted by the earlier presence of postoperative decline at discharge after surgery. Correlative ApoE allele data, or longer follow-up to determine if the patients who demonstrated this biphasic pattern ultimately had a higher incidence of Alzheimer's Disease would be very interesting and relevant. A recent study by Selnes et al, (130), did not demonstrate any correlation between ApoE allele status and cognitive decline between 1 and 5 years postoperatively after CABG in their cohort of 102 patients.

Selnes and McKhann recently (148) organized the neuropsychological syndromes seen after coronary bypass into four basic categories: stroke, postoperative delirium, short-term cognitive changes, and long-term cognitive changes. Postoperative cognitive deficits most commonly include memory loss, visuospatial disturbances, confusion, attention/concentration difficulties, depression, executive difficulties such as planning complex actions, difficulty following directions, difficulty with arithmetic, and decreased ability to withstand frustration (97, 99, 147, 148). Patients with delirium may often have the above features but will often also manifest sleep disturbance, disorientation, psychotic manifestations such as hallucinations and/or delusions, depressed level of consciousness, and/or agitation. The reported incidence of postoperative cognitive impairment persisting at three to sixth months following CABG has been reported as high as 10%-30% (118, 134, 147,148).

Risk factors for neuropsychological syndromes following CABG are much the same as for postoperative stroke, perhaps reflecting the fact that an ischemic etiology underlies many post-CABG neuropsychological syndromes. These include increasing age, diabetes, atherosclerotic disease (particularly of the aorta), poor education, increased cerebral emboli released during cardiopulmonary bypass (134), longer duration of cardiopulmonary bypass (92,107), changes in arterial carbon dioxide tension

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secondary to acid-base regulation during cardiopulmonary bypass (27), the need for hypothermic circulatory arrest, and history of stroke (107). Perioperative hypotension may cause hypoperfusion in the watershed regions between major arterial territories. The findings of Rolfson et al (146) in 1999 underlined the importance of prior stroke and longer duration of cardiopulmonary bypass as risk factors for postoperative delirium. They reported that, in their series of 75 patients undergoing coronary artery bypass grafting, three died and one was comatose and remained comatose at follow-up. Of the remaining 71 patients, 23 (32%) were found to have delirium postoperatively. Those with delirium were more likely to have had a previous history of stroke (21% versus 4%) and to have had a longer duration of cardiopulmonary bypass (113 minutes versus 95 minutes). Additional postulated concerns include the effects of the systemic inflammatory response resulting from cardiopulmonary bypass during CABG, and patients who carry the apolipoprotein e4 allele (97, 131, 134). It is not unexpected for patients with a known antecedent cognitive disturbance, such as patients with established early Alzheimer's Disease, to have a higher incidence of postoperative neuropsychological syndromes including delirium or accelerated cognitive decline. Preoperative findings of brain atrophy have also been associated with worse neurological outcomes (118).

Specific evidence of an ischemic etiology for postoperative neuropsychological syndromes following CABG include the study as already described, demonstrating elevated levels of S-100 protein and neuron-specific enolase after cardiopulmonary bypass in patients subsequently found to have delirium or cognitive deficits on neuropsychological testing (16). Moody et al (21) demonstrated the presence of microvascular obstruction in the brains of patients dying after undergoing CABG with cardiopulmonary bypass or extensive invasive manipulation of the arterial circulation but not in patient's undergoing other types of surgery. In a study of 167 patients undergoing intra-operative transcranial doppler monitoring while undergoing CABG, patients with neuropsychological deficits averaged nearly twice the number of emboli compared with those without deficits (94). Another study of 94 patients undergoing transcranial doppler monitoring during CABG and subsequent neuropsychological assessment at 8 weeks post-op demonstrated similar findings: when the microemboli count (recorded from the middle cerebral artery during surgery) was less than 200, 5/58 patients (8.6%) were seen to have a deficit at 8 weeks; when the count was more than 1,000, 3/7 (43%) patients were seen to have a deficit at 8 weeks (155).

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Additional evidence for an ischemic etiology for postoperative neuropsychological syndromes following CABG comes from SPECT studies of patients with neuropsychological deficits. One Turkish (99) study reported a series of 25 patients undergoing CABG. Eight of these patients suffered neuropsychological deficits postoperatively including cognitive deterioration and depressed mood in 5 patients; agitation, confusion and disorientation occurred in two patients, and visual hallucinations in one patient. No patient had focal deficits or CT abnormalities consistent with stroke. SPECT scans disclosed frontal hypoperfusion in all five patients with cognitive deterioration (memory, concentration and attentional difficulties). At the fifth postoperative month, two of these patients were rescanned; the perfusion abnormalities were no longer present and their symptoms had resolved. In the patient with visual hallucinations, no perfusion abnormalities were seen on SPECT imaging. In the two patients with agitation, confusion and disorientation, one could not be imaged during the symptomatic period because of immobilization; six weeks postoperatively, there was no abnormality on SPECT imaging. Brain perfusion SPECT imaging on the other symptomatic patient on the ninth postoperative day after CABG disclosed marked frontal and temporoparietal hypoperfusion. Six weeks after surgery, SPECT imaging disclosed that frontal and parietal cortical perfusion had improved, as had the patient's symptoms. Of all variables studied, longer aortic cross-clamp time was seen in the symptomatic patients than in asymptomatic patients. Gokgoz et al (102) reported regional brain perfusion changes on SPECT imaging in nine of 50 patients undergoing CABG, six of whom were diagnosed to have delirium on psychiatric examination. They found that right and left anterior parietotemporal, right frontal, left occipital and right and left temporoparietal cortices demonstrated significant postoperative hypoperfusion on the 4th postoperative day. Risk factors for postoperative delirium in this study were found to be age, long aortic cross-clamp time, high-dose inotropic support and excessive transfusion of blood or blood products.

Hypothermic circulatory arrest may be required during CABG surgery when patients need extensive surgical intervention, such as congenital cardiac disease that needs simultaneous repair, or when the patient needs concomitant aortic surgery. In such situations the "safe" duration of hypothermic circulatory arrest has been reported to be between 29 and 45 minutes, depending upon the degree of cooling (41, 114).

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Some postoperative neurobehavioral abnormalities have been referred to as a Type II neurologic outcome (114). These include seizures, deterioration in intellectual function, and memory loss. Significant risk factors for a type II neurological outcome are a history of heavy alcohol abuse, older age, and hypertension (114). Of course, as with any postoperative patient, the patient with postoperative seizures may be symptomatic because of a past history of seizures and abrupt discontinuation of anticonvulsants, cerebral embolism, or withdrawal of medication that the patient was taking preoperatively. Electrolyte or other metabolic derangement must be excluded.

Depression—in the absence of cerebral injury—occurring after bypass is now felt to be most common in those patients who had pre-operative depression, or in those patients with a difficult postoperative course (97). Depression after myocardial infarction is now increasingly recognized. There is less support for the hypothesis that depression alone is caused by ischemic brain injury (97). The patient with depression may demonstrate deficits on cognitive tests which require attention, concentration and effort. The "pseudodementia" of depression can usually be differentiated from the postoperative cognitive decline secondary to ischemic brain injury when assessed by those familiar with these syndromes, such as psychiatrists and neurologists. Certainly depression is seen to accompany ischemic brain injury, and is particularly associated in some types of strokes—most often left frontal infarcts (135). Kim et al reported that, in their study of 148 patients with stroke, twenty-seven (18%) had post-stroke depression, and 50% had pseudobulbar symptoms of emotional incontinence (34%). Eighteen of these 50 patients had both post-stroke depression and emotional incontinence. The prevalence of post-stroke depression was 75% in frontal lobe ACA territory strokes; 30% in frontal MCA territory strokes; 50% in temporal lobe strokes; 25% in subcortical MCA strokes; 13% in occipital lobe strokes; 19% in lenticulocapsular strokes; 11% in thalamic strokes; 16% in pontine strokes; and 36% in medullary strokes (135). An association was seen between post-stroke depression and the presence of motor dysfunction with lesion location (i.e. frontal as opposed to posterior) most important. In this study, an association was not seen between post-stroke depression and laterality or size of the lesion (135).

Postoperative Neuropsychological Deficit: Clinical Assessment

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Affected patients present with syndromes along a spectrum demonstrating mild to profound impairment of memory, confusion, sleep disturbance, and/or attention/concentration difficulties. Severe features include hallucinations, depressed level of consciousness, and delirium states which interfere with weaning from the ventilator because of the need to control agitation with sedative medications.

Clinical assessment of patients with neuropsychological deficits primarily focuses on discovering a focal neurological abnormality on exam or on imaging studies. This might indicate that the patient has actually suffered a stroke, which would change the focus of evaluation and management. It is also important to discover other factors which could be causing or contributing to the patient's altered mental status. The differential diagnosis for postoperative altered mental status is necessarily extensive, including infection or sepsis, metabolic or endocrine abnormalities, drug or alcohol withdrawal, polypharmacy, drug toxicity, nonconvulsive status epilepticus, ischemic or hemorrhagic stroke, electrolyte imbalance, hypotension, hypoxia, CO₂ retention, and Wernicke's encephalopathy. The diagnosis of an ischemic etiology of the patient's postoperative altered mental status is often a diagnosis of exclusion. Even in cases where there is a high index of suspicion that the etiology is ischemic, other causes need to be excluded to ensure that the cause is not multifactorial. Routine radiographic imaging, for example computed tomography, may not disclose abnormalities even if ischemic injury has occurred.

Postoperative Neuropsychological Deficit: Clinical Management

The majority of neuropsychological deficits in patient's undergoing CABG resolve by the time of hospital discharge. In patients with clinically recognizable encephalopathy continuing to the third or fourth postoperative day, approximately 80% recover to the point that they perform well on a simple bedside mental status examination by the time of discharge (114). Some patients examined one year after CABG show subtle defects in verbal or visuospatial memory testing or may have visual-motor difficulties (praxis) (97).

Treatment of the patient with severe agitation and delirium postoperatively often poses a major management challenge to physicians, and often requires an interdisciplinary approach. This frequently includes the cardio thoracic surgeon, pulmonary/critical care, infectious disease, cardiology, neurology and psychiatry

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consultants. Patients with severe agitation and/or delirium require sedating medications, which often mandate prolonged intubation or re-intubation, and are thus more at risk for nosocomial infection and other complications. Patients with severe agitation and psychosis associated with delirium usually require treatment with antipsychotic medications. Haloperidol, despite the associated risk of neuroleptic malignant syndrome and extrapyramidal symptoms, is usually the medication most often utilized in the critical care setting because of its efficacy and multiple routes of administration (IV, IM, PO). Overmedication of these patients frequently cannot be avoided because of the damage that these patients can inflict upon themselves because of their agitation. Complications of uncontrolled agitation may include an increased risk of serious arrhythmias, poor sternal wound healing and infection, and self-extubation. Vigilance and continual reassessment to identify other complicating conditions that contribute to the patient's agitation or mental status changes is crucial.

Identification of systemic illness or infection, potential sources of pain that could agitate the patient further, and prior medication or alcohol abuse is essential. It is not infrequent that important information about a patient's prior medications or alcohol abuse may not come to light until the patient is in the throes of alcohol or drug withdrawal, or Wernicke's encephalopathy. Seizures in the postoperative setting can be convulsive or nonconvulsive, and are most commonly associated with cerebral embolism, alcohol or other medication withdrawal, or in patients with an antecedent history of seizures either on or off anticonvulsant medication. Nonconvulsive seizures are an important treatable condition to be ruled out by electroencephalogram. Treatment options in the ICU setting usually include those medications, which can be administered intravenously, such as Dilantin (phenytoin) or Cerebyx (fosphenytoin), Depacon, phenobarbital, and benzodiazepines. Hypotension due to anticonvulsant therapy with Dilantin, phenobarbital and benzodiazepines can be a significant issue in the treatment of seizures in the postoperative setting. Anti-convulsant toxicity may occur unexpectedly, mandating that anticonvulsant levels (particularly free levels of Dilantin) be monitored frequently. Since some anticonvulsant medications, particularly valproic acid, have been effective in the treatment of agitation, a trial of one medication such as Depacon for both seizures and agitation may be an attractive option, as it can be used intravenously and does not cause hypotension.

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Treatment of depression should be promptly initiated. The effect of depression on cardiovascular disease is receiving increasing attention as there is some evidence that depression is associated with increased mortality and poorer cardiac outcomes after CABG (97). Depression is associated with poorer outcomes after myocardial infarction, with as high as a four-fold increase in mortality in these patients (97). However, whether better recognition of depression and more effective treatment would improve outcome is currently uncertain. The cognitive recovery of patients whose depression is treated can be very striking. Antidepressants most often used in the postoperative setting in patients who are depressed and have undergone CABG include those medications with the best safety profile. The potential for few cardiac side effects, medication interactions, and a shorter half-life so that adverse reactions will abate more rapidly are key properties. Serotonin reuptake inhibitor antidepressants are most commonly cited in the literature as being relatively safe, efficacious, and well tolerated by patients, particularly paroxetine (Paxil) (149, 150, 151, 152).

OTHER NEUROLOGIC COMPLICATIONS

Other rare complications of CABG include ischemic optic neuropathy (129), intracranial hemorrhage, pituitary apoplexy, and hearing loss. Brachial plexopathy due to such local factors as position and attempted cannulation of arteries proximal to the brachial plexus during surgery, is an uncommon problem because of precautions taken by contemporary surgical teams. Saphenous neuropathy associated with saphenous vein harvesting, occurred with a frequency of 3% in one reported series of 421 patients (154).

Another rare complication is femoral neuropathy in patients who have required perioperative intra-aortic balloon pressure support. In one series of 100 patients who required intra-aortic balloon pump support, the incidence of femoral neuropathy was 1% (133). Spinal cord ischemia with paraplegia is also a rare IABP-related neurological complication. In one series of 100,000 IABP insertions, eight patients were reported to develop paraplegia; however in only one of these was a pathologic diagnosis confirmed (144). In another study of 178 patients, IABP-related spinal cord paralysis developed in 1.7% (3 patients) (145).

If the patient has undergone the combined procedures of CEA and CABG, then one must be aware of the peripheral cranial nerve palsies, which may result as a complication of carotid

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endarterectomy. In the NASCET trial, the incidence of peripheral cranial nerve palsies in aggregate was 7.6% (122), and in other series of patients undergoing carotid endarterectomy the aggregate incidence of peripheral cranial nerve injury is as high as 13.5% (138, 139, 140). Cranial nerves VII, IX, X, XII injuries are most commonly reported. Vagus nerve injury and facial nerve injury are the most frequent cranial nerves injured, despite not being immediately adjacent to the internal carotid artery. Hypoglossal nerve injury also occurs, but less frequently, despite its proximity to the internal carotid artery (139). The lower (cervical) branch of the facial nerve is most often injured. On exam, the patient will have a downward droop of the ipsilateral lower lip, but preserved facial movement otherwise. No weakness of ipsilateral eye closure or palpebral fissure asymmetry is evident. Sensory nerves to the submandibular skin and ear lobe are often damaged. The most common mechanism of injury is felt to be edema and stretch injury from retraction. Interruption of carotid sinus innervation by the ninth cranial nerve is common post CEA. This denervation results in less neuronal discharge received by the brainstem with a resulting hypertensive response. Active antihypertensive treatment may be required temporarily until the opposite side takes over control, which ordinarily takes several hours. Rarely a previous contralateral CEA may result in a prolonged hypertensive episode lasting days. The prognosis is good in most cases of peripheral cranial nerve injury.

More ominous in the patient in whom carotid endarterectomy has just been performed is the development of the triad of severe headache, focal seizures, and development of hemiparesis contralateral to the side of the endarterectomy; such a triad of complications is indicative of an intracranial hemorrhage until proven otherwise. This entity is most often attributed to reperfusion of a vascular territory which may have lost some or all of its autoregulatory function due to chronic underperfusion from the stenotic carotid artery. Postoperative hypertension increases the likelihood of intracranial hemorrhage.

Implications of Current Research Regarding Prevention of Stroke and Neuropsychologic Deficits After Coronary Bypass Surgery

Coronary artery bypass surgery represents an ideal setting in which novel preventative strategies to prevent cerebral injury can be tested, as such interventions can be implemented before, during or immediately after surgery, and the effects measured in comparison to a control group. Current research efforts are

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attempting to define more precisely the indications for combined carotid endarterectomy (or perhaps, in the future, carotid angioplasty and stenting) and coronary artery bypass surgery. Other issues raised concern whether pulsatile flow during cardiopulmonary bypass is better than nonpulsatile flow, whether beating heart surgery is better, and whether there are substances, which can be infused before or during cardiopulmonary bypass (as in the current interest in aprotinin), which might prove neuroprotective. Some stroke experts, including Dr. Louis Caplan, advocate greater utilization of preoperative screening studies, such as transesophageal echocardiography of the heart and aortic arch to determine potential sources of embolization during CABG, and intraoperative epiaortic ultrasound, which might alter the surgical procedure with the aim of reducing perioperative neurological complications (127). There is also some evidence to suggest that early post-operative use of perfusion-weighted magnetic resonance imaging in patients who are unstable neurologically may better guide medical therapy to optimize cerebral perfusion (128).