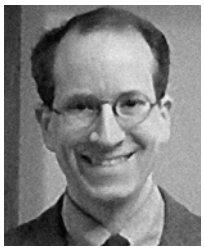
The Heart Surgery Forum #2004-1103
7 (6), 2004 [Epub November 2004]
doi:10.1532/HSF98.20041103

Online address: www.hsforum.com/vol7/issue6/2004-1103.html

REVIEW

Neurologic Injury Associated with CABG Surgery: Outcomes, Mechanisms, and Opportunities for Improvement



Dr. Likosky

Donald S. Likosky, PhD,[1] Robert M. Roth, PhD,[2] Andrew J. Saykin, PsyD,[2] Clifford J. Eskey, MD, PhD,[2] Cathy S. Ross, MS,[3] Gerald T. O'Connor, DSc, PhD[3]

Departments of [1]Surgery, [2]Psychiatry and Radiology, and [3]Medicine and Community and Family Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, USA

ABSTRACT

Neurologic injuries, whether subtle or overt, are a major source of morbidity secondary to coronary artery bypass graft (CABG) surgery. A comprehensive review of research in the area of neurologic injury is provided. We conclude this article by providing insight regarding areas requiring further investigation in order to reduce sustainably the risk of these iatrogenic events among patient undergoing CABG surgery.

INTRODUCTION

Neurologic injury is a major source of morbidity and mortality following coronary artery bypass graft (CABG) surgery. Patients may have deficits ranging from subclinical cognitive changes to death and from transient events to longstanding disability. The aim of this paper is to provide the reader with a comprehensive review of issues associated with the following areas: epidemiology of neurologic injury, neuropsychological and neurobehavioral outcomes, strokes, neuroimaging modalities, use of biomarkers to measure tissue-level injury, identification of intraoperative care and management opportunities to reduce the risk of injury, and the use off-pump CABG.

EPIDEMIOLOGY OF NEUROLOGIC INJURY ASSOCIATED WITH CABG SURGERY

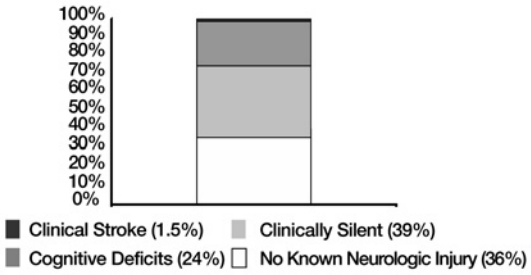
CABG surgery is an operation used to revascularize atherosclerotic coronary arteries in patients suffering from ischemic heart disease. Renee Favaloro, who along with others pioneered the technique using saphenous vein grafts, first reported CABG surgery as a viable treatment option in 1968 [Favaloro 1968, Favaloro 1978]. Since then, the use of this operation has increased, with approximately 739,000 operations performed in the United States during 1997 [Braunwald 1997]. This surgery, undeniably effective in reducing anginal symptoms and, for certain patients, increasing life expectancy, is a relatively safe procedure, with adjusted mortality rates for CABG surgery approaching 2%. Although improvements in CABG surgery, such as a nearly 50% reduction in in-hospital mortality, have been realized in the northern New England region via focused interventions aimed at reducing fatal low cardiac output, rates of neurologic injuries have not been impacted in kind [O'Connor 1996, Charlesworth 2003].

It has long been observed that the benefits of CABG surgery come at the risk of adverse neurologic outcomes [Kennedy 1980, Frye 1992] (Figure). Neurologic complications including global encephalopathy and focal neurologic syndromes have long been reported following cardiac surgery. These deficits vary widely in severity and in permanence and may be the consequence of several factors including hypoxia, embolism, and hemodynamic or metabolic derangements. The most commonly cited etiologies are hypotension and embolization [Selnes 2001, Likosky 2003b]. Clinically apparent stroke, although relatively rare (1.3% to 4.3% depending on patient age and other risk factors), is a potentially devastating complication of CABG surgery. This complication is associated with increased morbidity, cost, length of stay, and mortality [Roach 1996]. Furthermore, despite sensitive detection with sophisticated neuroimaging studies or neuropsychological testing, this figure is likely an underestimate of the frequency of neurologic injury associated with CABG surgery.

In the course of clinical care, only symptomatic clinical outcomes are routinely detected. One study using magnetic resonance imaging (MRI) to detect new brain lesions after CABG surgery found that upwards of 39% of patients have clinically silent infarcts [Goto 2001]. Studies by Newman et al suggest that patients undergoing CABG surgery are at high risk for both short-term (50% at discharge, 24% at 6 months) and long-term (42% at 5 years) cognitive deficits, which are often called subclinical because they have a subtle clinical presentation and thus are not customarily detected through clinical care [Newman 2001]. Although compelling, prior studies fall short of

Received June 22, 2004; accepted August 12, 2004.

Address correspondence and reprint requests to: Donald S. Likosky, PhD, Instructor, Department of Surgery, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756, USA; 1-603-653-3546; fax: 1-603-653-3554 (e-mail: donald.s.likosky@dartmouth.edu).



Risk of neurologic sequelae from coronary artery bypass graft surgery.

identifying intraoperative events associated with the creation of these deficits. The consequence is that little progress has been made in understanding the mechanisms of these prevalent but subclinical adverse neurologic outcomes and more importantly in improving surgical care to minimize the risk of creating them.

NEUROPSYCHOLOGICAL AND NEUROBEHAVIORAL OUTCOMES

Since the study by Gilman and colleagues in 1965, numerous investigations have reported significant cognitive decline after CABG, with memory, complex attention, and psychomotor skills being most commonly affected (Table 1) [Benedict 1994, Borowicz 1996, Selnes 1999a, Selnes 1999b, Symes 2000, Newman 2001, Browndyke 2002, Dogan 2002, Keith 2002]. However, discrepancies exist in the literature with respect to the incidence of cognitive decline, the temporal course of cognitive changes, and the risk factors for postsurgical cognitive decline. The incidence of cognitive decline within the first postoperative week has ranged approximately from 30% to 80%. Approximately a third of patients may continue to experience cognitive problems, such as the inability to balance a checkbook, up to approximately a year after surgery [Benedict 1994, Newman 2001]. The rate of continued cognitive problems beyond the acute postoperative period has varied widely. The cause of this variation is likely multifactorial and includes differences in retest intervals, patient population characteristics, and concomitant procedures as well as the actual nature of the cardiac surgery performed. Nonetheless, persisting cognitive problems have been noted in at least a subset of patients for up to 5 years [Newman 2001, Mullges 2002, Selnes 2002].

Several potential risk factors for cognitive decline following CABG have been identified, although firm conclusions remain elusive [Hammon 1997, Arrowsmith 2000, Kilo 2001, Newman 2001, Grocott 2002b, Van Dijk 2002, Mathew 2003]. Patient characteristics that may predispose to postoperative cognitive decline include apolipoprotein E-4 allele positivity, concomitant illnesses such as diabetes, reduced preoperative endotoxin immunity, preoperative cognitive deficits, lower level of education, and older age. Surgical variables that appear to increase the risk of cognitive decline include the use of cardiopulmonary bypass, microembolic load during surgery, and cerebral hypoperfusion [Pugsley 1994, Newman 1995, Borowicz 1996]. Intra- and postoperative hyperthermia may also pose a risk for cognitive decline. Of note, patients undergoing CABG surgery may be prone to postoperative cognitive decline, even without the exposure of CABG surgery, due to the prevalence of vascular disease in this patient population.

Furthermore, in a recent small MRI study new brain infarcts were observed to occur 3 to 12 months after surgery [Kohn 2002]. This finding suggests that brain damage outside the perioperative period, possibly secondary to the inflammatory process, may contribute to the persistence or exacerbation of cognitive deficits in some patients. Importantly, recent evidence suggests that different variables may be predictive of level of cognitive functioning for different postoperative time frames, again highlighting the need for standardized retest intervals across studies [Murkin 1995, Selnes 1999a]. It is thus likely that the etiology of cognitive outcomes following CABG is multifactorial and includes preoperative, operative, and postoperative variables.

In addition to cognitive changes, a number of studies have reported high rates of depressed and anxious mood following CABG [Vingerhoets 1996, Fraguas Junior 2000]. Other studies have reported decreased anxiety and depression [Vanninen 1998]. Evidence suggests that postoperative mood problems are more likely to be observed in patients who were already experiencing these problems prior to surgery [Papadantonaki 1994, McKhann 1997a, Timberlake 1997]. Furthermore, mood symptoms have not been clearly associated with greater cognitive impairment following CABG [Vingerhoets 1995, McKhann 1997a].

Numerous methodological issues may underlie the myriad discrepancies in the neuropsychological literature on CABG. Different criteria have been used to define significant cognitive decline, such as a 20% change from baseline or decline of more than 1 SD from the baseline distribution of scores on a given test [Kneebone 1998, Collie 2002, Keith 2002]. The specific neuropsychological tests employed and the comprehensiveness of test batteries has varied considerably [Murkin 1995]. The psychometric properties of tests, such as test-retest reliability, have been taken into account in only a limited number of investigations. When during the postoperative period patients are evaluated may also contribute to discrepant findings.

Neuropsychological changes are a frequent outcome secondary to CABG surgery. Potential etiologies for this outcome include micro- and macroembolization, hypoxia, and hypotension. Although consensus documents have encouraged homogeneity in methodology and evaluation of results, significant heterogeneity exists across published studies. Furthermore, most studies have not examined pathophysiology. Consequently, inferences with respect to the specific mechanisms underlying cognitive and emotional effects of CABG at this time should be required as hypotheses warranting evaluation.

Table 1. Summary of Neuropsychological Studies in Coronary Artery Bypass Grafting (CABG)*

Reference	Sample Size	Follow-up Interval	Definition of Decline	Post-CABG Findings
[Savageau 1982a]	227	9 d	≥1SD decline on at least 1 index	11%-17% with decline
[Savageau 1982b]	245	6 mo	≥1 SD decline on at least 1 index	24% with decline
[Shaw 1986]	298	7 d	≥1 SD decline on at least 1 test	79% with decline
[Sotaniemi 1986]	49	2 mo, 1 and 5 y	Neuropsychological index score	Decline only 5 y after CABG
[Fish 1987]	96	7 d, 2 mo	Group comparison	Decline on 4/10 tests at 7 d, all patients back to baseline at 2 mo
[Shaw 1987a]	298	7 d	≥1 SD decline on at least 1 test	79% with decline
[Shaw 1987b]	259	6 mo	≥1 SD decline on at least 1 test	57% with decline
[Folks 1988]	391	21 mo	Cutoff of 20 on MMSE	5.6% with decline
[Smith 1988]	67	8 d, 2 mo	≥1 SD decline on at least 2 tests	73% with decline at 8 d, 37% with decline at 2 mo
[Harrison 1989]	47	8 d, 2 mo	Reduced score on at least 2/10 of tests	77% with decline at 8 d, 36% with decline at 2 mo
[Klonoff 1989]	135	3 mo, 1 and 2 y	Any change	No evidence of decline
[Stump 1993b]	54	5-7 d	20% on at least 3 tests	76% with decline
[Newman 1994]	215	7-10 d	ANOVA	Significant decline on 5/6 tests
[Pugsley 1994]	100	8 d, 8 weeks	≥1 SD decline on at least 2 tests	34% with decline at 8 d, 16% with decline at 8 weeks
[Bruggemans 1995]	63 CABG, 63 control	1 wk, 1 mo, 6 mo	ANOVA	Visual memory decline at 1 week, learning and recent memory decline at 1 mo, attention and psychomotor speed decline at all postoperative assessments, verbal fluency decline at 1 wk and 1 mo
[Clark 1995]	41	5-10 d	Group comparison	73% with memory decline, 49% with comprehension decline, 46% with attention decline, 44% with construction decline
[Hlatky 1997]	61	5 y	Group comparison	No significant decline
[Mckhann 1997c]	127	1 mo, 1 year	≥0.5 SD decline on at least 1 test	26% with decline at 1 mo, improved by 1 y, 11% with decline at 1 month and 1 year, 24% with decline at 12 mo but not 1 mo
[Jacobs 1998]	18	3 mo	Correlation	No significant decline
[Vanninen 1998]	38	3 mo	≥1 SD decline on at least 3 tests	No overall decline
[Wimmer-Greinecker 1998]	76	5 d, 2 mo	ANOVA	No decline at 5 d, improved visuoconstruction and attention
[Diegeler 2000]	20 CABG, 20 OPCAB	7 d	Group comparison	90% of CABG with decline, 0% of OPCAB with decline
[Robson 2000]	102	3 mo	≥1 SD decline on at least 1 test	7% with decline
[Ebert 2001]	42 CABG, 42 VRS	2 and 7 d	≥1 SD decline on at least 2 domains	57% of CABG with decline at 2 to 3 d, 19% of CABG with decline at 7 d
[Kilo 2001]	308	7 d, 4 mo	Paired *t* tests	No significant decline
[Millar 2001]	81	6 d, 6 mo	Not specified	16% with preoperative impairment, 85% of these impaired at 6 d, 39% still impaired at 6 mo; 84% without preoperative impairment, 14% of these impaired at 6 d, 2% still impaired at 6 mo
[Newman 2001]	261	7 d, 6 weeks, 6 mo, 5 y	≥1 SD decline on at least 1 test	53% with decline at 7 d, 36% with decline at 6 weeks, 24% with decline at 6 mo, 42% with decline at 5 y
[Browndyke 2002]	20 CABG, 11 VRS, 25 controls	7-10 d, 1 month	Multiple ANOVA	Both patient groups had mild attention and learning decline at 7-10 d, returned to baseline by 1 month
[Dogan 2002]	40	5 d, 2 mo	Nonparametric tests	No significant decline
[Grocott 2002a]	227	6 weeks	≥1 SD decline on at least 1 domain	39% with decline
[Keith 2002]	39 CABG, 49 control	3-4 weeks	Group comparison	Decline on 2 attention tests
[Mullges 2002]	52	32-65 mo	≥1 SD decline on at least 2 tests	8% with decline relative to discharge
[Swaminathan 2002]	282	6 weeks	≥1SD decline on at least one domain	40% with decline

Continued

Table 1. *Continued*

Reference	Sample Size	Follow-up Interval	Definition of Decline	Post-CABG Findings
[Rasmussen 2002]	15	Discharge, 3 mo	2 Test z-scores or composite z-score above 1.96	46.7% with decline at discharge, 6.7% with decline at 3 mo
[Reents 2002]	47	6 d	≥1 SD decline on at least 2 tests	34% with decline
[Restrepo 2002a]	39	7 d	≥0.5 SD decline on at least 1 test	77% with decline
[Reynolds 2002]	33	5-6 d	≥1 SD decline on at least 1 domain	% Not reported
[Stroobant 2002]	49	6-7 d, 6 mo	20% decline on 2 or more tests	61% with decline at 6-7 d, 11% with decline at 6 mo
[Van Dijk 2002]	128 OPCAB, 120 CABG	3 mo, 1 year	20% decline on 20% of tests	29.2% CABG with decline at 3 mo, 21.1% OPCAB with decline at 3 mo, 33.6% CABG with decline at 3 mo, 30.8% OPCAB with decline at 3 mo
[Ahlgren 2003]	23 CABG, 19 PCI	4-6 weeks	≥1 SD decline on at least two test variables	48% of CABG with decline, 10% of PCI with decline
[Lee 2003]	30 CABG, 30 OPCAB	2 weeks, 1 year	20% decline on 20% of tests, ANOVA	15.4% of CABG with decline at 2 weeks, 16.1% of OPCAB with decline at 2 weeks, 14.8% of CABG with decline at 1 year, 18.5% of OPCAB with decline at 1 year
[Lund 2003]	23 CABG, 29 OPCAB	3 mo	Parametric and nonparametric tests	35% of CABG with decline, 29% of OPCAB with decline
[Mathew 2003]	460 CABG	6 weeks	≥1 SD decline on at least 1 of 4 cognitive factors	36% with decline
[Selnes 2003]	140 CABG, 92 controls	3 mo, 1 year	ANOVA	Both groups improved by 3 mo, with greater improvement in verbal memory for CABG, no group differences at 1 year
[Knipp 2004a]	35	1-7 d, 3 mo	ANOVA	Decline in attention, memory and spatial skills at 1-7 d, Decline in memory and reasoning at 3 mo

*MMSE indicates Mini–Mental State Examination; ANOVA, analysis of variance; OPCAB, off-pump coronary artery bypass; VRS, valve replacement surgery; PCI, pericutaneous coronary intervention;

STROKES

Patients undergoing CABG surgery are at risk for a wide range of neurologic injuries, such as a transient ischemic attack, encephalopathy, and delirium. Strokes have been the most widely studied in the cardiac literature, and perhaps may be the most devastating and long lasting. A stroke is "a syndrome characterized by the acute onset of a neurologic deficit that persists for at least 24 hours, reflects focal involvement of the central nervous system, and is the result of a disturbance of the cerebral circulation,"[Simon 1999]. In the setting of CABG surgery, reported stroke rates vary from 1.3% to 4.3% [Gonzalez-Scarano 1981, Gardner 1985, Jones 1991, Blossom 1992, Frye 1992, Lynn 1992, Ricotta 1995]. Strokes may have either mild to moderate (eg, problems generalizing information) or severe (eg, hemiplegia or aphasia) impact on a patient's quality of life.

Table 2 summarizes the work reported by our group and others focused on identifying risk factors associated with strokes [Newman 1996, Hogue 1999, Stamou 2001, McKhann 2002, Charlesworth 2003, Likosky 2003a]. Preoperative risk factors common to many of these models include: age, diabetes, vascular disease, acuity, and low ejection fraction [Newman 1996, Roach 1996, Hogue 1999, Stamou 2001, Charlesworth 2003]. Intra- and postoperative factors associated with stroke include: duration of cardiopulmonary bypass, atrial fibrillation, and low cardiac output syndrome [Likosky 2003a].

Embolism and cerebral hypoperfusion have been identified as the principal mechanisms associated with strokes. In a recent study by our group, we identified the principal mechanisms of 388 strokes occurring secondary to isolated CABG surgery. Using detailed information abstracted from each patient's medical record, regional endpoint committees classified the strokes into one of the following etiologies: embolism, hypoperfusion, lacunar, thrombosis, hemorrhage, multiple, or unclassified [Likosky 2003b]. We found that embolism accounted for 62% of strokes, hypoperfusion 9%, and multiple mechanisms an additional 10%. The mechanism of a minority (14%) of these strokes remained unclassified. Our findings are in agreement with work done by other research groups [Shaw 1989, Blossom 1992, Boyd 1999].

The lack in improvement surrounding stroke outcomes may be attributed in part to two factors. First, whereas large prospective databases, such as the Society of Thoracic Surgeons and the Northern New England Cardiovascular Disease Study Group, have relatively consistent definitions for stroke, it is unclear if the same is true for smaller local or regional databases [STS 1999]. Of 64 articles in Medline from 1965 to 1999 meeting the inclusion criterion (article's principal topic was neurologic morbidity subsequent to cardiac surgery), only 19 (29.7%) offered an explicit definition of stroke. Such a lack

Table 2. Summary of Studies Identifying Predictors of Neurologic Deficits after Coronary Artery Bypass Grafting (CABG)

Author Reference	Sample Size	Risk Factors Identified	Definition of Neurologic Deficit	Reported Model Performance
[Newman 1996]	2107 patients undergoing elective CABG	Age, history of previous neurological disease, diabetes, history of vascular disease, previous coronary artery surgery, unstable angina, and history of pulmonary disease	Neurologic deficit: cerebrovascular accident or stroke, transient ischemic attack, coma at discharge, or central nervous system death. No further definitions were provided.	ROC area: 0.78
[Mckhann 1997b]	456 patients undergoing CABG and validation sample of 1298 patients	Preoperative: previous stroke, presence of carotid bruit, history of hypertension, increasing age, and history of diabetes mellitus; intraoperative: cardiopulmonary bypass time	Stroke: any persistent focal neurologic deficit lasting 24 hours or more	NA
[Hogue 1999]	2972 patients undergoing CABG and/or valve surgery	Early stroke: prior neurological event, aortic atherosclerosis, and duration of cardio pulmonary bypass; delayed stroke: prior neurological event, diabetes, aortic atherosclerosis, and combined end points of low cardiac output and atrial fibrillation	Stroke: any new permanent global or focal neurological deficit that could not be attributed to other neurological (eg, dementia) and/or medical (ie, metabolic abnormalities, hypoxia, or drugs) processes.	NA
[Stamou 2001]	16,528 consecutive patients who underwent CABG	Preoperative: chronic renal insufficiency, and moderate/severe left ventricular dysfunction; intra- and postoperative: low cardiac output syndrome, and atrial fibrillation	Stroke: any new major (type II) neurological deficit presenting in the hospital and persisting >72 hours	NA
[Likosky 2003b]	11,825 consecutive patients undergoing isolated CABG	Intra- and postoperative: cardiopulmonary bypass duration >90 minutes, prolonged inotrope use, and atrial fibrillation	Stroke: a new neurologic deficit which appears and is still at least partially evident more than 24 hours after its onset, occurring during or following the CABG procedure and established before discharge	ROC area: 0.73
[Charlesworth 2003]	33,062 consecutive patients undergoing isolated CABG	Preoperative: age, gender, presence of diabetes, presence of vascular disease, renal failure or creatinine greater than or equal to 2 mg/dL, ejection fraction less than 40%, and urgent or emergency	Stroke: a new neurologic deficit which appears and is still at least partially evident more than 24 hours after its onset, occurring during or following the CABG procedure and established before discharge	ROC area: 0.70

of explicit outcome variable definitions makes comparison and/or verification of findings difficult and therefore hinders progress in improving stroke outcomes. Second, most studies investigating strokes after CABG surgery are insufficiently powered due to the rarity of this event. Conclusions drawn from these studies often lead to misleading results and unstable estimates of associations between risk factors and stroke.

Stroke, although rare, is often a devastating complication of CABG surgery. Although much work has focused on identifying preoperative risk factors, greatest benefit will likely result from efforts aimed at reducing modifiable factors during the intra- and postoperative care and course.

CEREBROVASCULAR NEUROIMAGING

It is clear that reliance on clinical signs and symptoms will lead to detection of only a minority of adverse neurologic outcomes. In our experience within northern New England, the overall rate of new fixed neurologic deficits (1992-2001) was 1.7%, with a case-fatality rate of 22.9%. Nearly 80% of patients having strokes had brain imaging performed in response to their clinical presentation. In patients undergoing brain imaging, more than 90% of the examinations were performed using computed tomograpy (CT). CT was chosen because it can be rapidly performed, requires no screening for contraindicated implants (eg, cardiac pacemakers) or conditions (eg, claustrophobia), and reliably shows acute intracerebral hemorrhage. Our regional experience is similar to that reported by other large clinical series [Selnes 1999b]. Unfortunately CT will detect only large areas of recent cerebral ischemia, is particularly insensitive in the posterior fossa, and often does not distinguish acute versus chronic injury.

MRI for acute stroke has improved markedly in the last 5 years. Conventional MRI, generally consisting of T1- and T2-weighted images, is more sensitive and specific than CT for small acute infarcts. The infarct becomes visible as an area of abnormal signal, hyperintense on T2-weighted images and hypointense on T1-weighted images within 12 to 24 hours. For the cortical infarcts common in the setting of embolism, the infarct will extend to the brain surface, involving both the cortex and the subcortical white matter. FLAIR (fluid-attenuated inversion recovery) imaging improves the conspicuity of

these acute infarcts. However, in older people there are often many foci of signal abnormality that may mimic an acute infarct, and none of these conventional MRI sequences may make this differentiation for small infarcts. The real breakthrough in early infarct detection has come with diffusion-weighted MRI (DWI). This technique has a sensitivity and specificity of 97% and 100%, respectively, at 6 hours post ictus [Mullins 2002].

New brain imaging approaches offer earlier detection of new lesions and quantification of later atrophic changes. DWI appears to characterize and measure much more accurately the extent of recent cerebral ischemia [Kelly 2001, Kohn 2002]. The apparent diffusion coefficient (ADC) measured from DWI becomes abnormal within minutes to hours after injury and remains so for up to 7 days. In the appropriate clinical setting, the specificity of ADC maps for acute ischemia is high. When using DWI to assess intraoperative events, preoperative imaging is important to exclude infarcts not related to the surgery, because many CABG patients have diabetes and peripheral vascular disease and are predisposed to ischemic events. Only few small-scale studies have used this pre- and postoperative MRI protocol [Schmidt 1993, Kohn 2002, Restrepo 2002, Knipp 2004].

Although previous studies have provided information surrounding the quantification of acute lesions after cardiac surgery, new imaging methodology and protocols are warranted. Advances in computational approaches for analyzing more conventional MRI sequences (eg, T1-weighted volumetric scans) make it possible to automatically segment the brain into gray and white matter and cerebrospinal fluid and to measure these tissue compartments to document atrophic and other changes [Van Leemput 1999, Agartz 2001, Bokde 2002, Fischl 2002]. Voxel-based morphometry (VBM), which involves analysis of tissue characteristics on a voxel-by-voxel basis using brain-mapping statistics similar to those used for functional brain imaging [Ashburner 2000], has begun to be widely applied to analysis of structural MRI scans in other clinical settings [Keller 2002, Salgado-Pineda 2003]. Cerebrovascular risk factors have been associated with global and local brain atrophy [Meyer 2000, DeCarli 2001], but there has been little systematic or quantitative long-term follow-up investigation of atrophic changes after CABG. These changes might explain the cognitive deficits observed in many long-term follow-up studies.

Great technical strides have been made in neuroimaging modalities. These devices have allowed clinicians and researchers to identify the presence/absence of acute lesions more reliably in the postoperative setting. In addition, functional MRI technology offers opportunities for researchers to map regional brain activity during cognitive function, which could permit quantification of the extent of functional injury secondary to CABG surgery, but such studies remain to be done.

BIOMARKERS OF CEREBRAL DAMAGE

Current methods (neurologic exam, CT or MRI, neuropsychological evaluation) for detecting and diagnosing subtle neurologic injuries are not suitable in the immediate postoperative period after coronary revascularization procedures. During this time, patients are often unconscious, sedated, or uncooperative. As such, a serum-based test (eg, S-100) may provide the opportunity to detect these neurologic deficits at a more opportune time [Ali 2000, Matata 2000].

S-100 is an acidic calcium-binding protein that is found in high concentrations in glial and Schwann cells and is metabolized in the kidney and excreted in urine [Buttner 1997]. S-100 has several subunits, but its β subunit is highly brain specific and has a half-life of approximately 2 hours. S-100 has been considered to play a contributory role in Alzheimer's disease [Griffin 1989]. Levels of S-100 have been reported in patients with acute stroke and in patients undergoing coronary revascularization procedures [Johnsson 1995, Westaby 1996, Blomquist 1997, Buttner 1997, Missler 1997, Grocott 1998a, Jonsson 1998, Georgiadis 2000]. In these studies, S-100 levels have been correlated with infarct volume (using volumetric CT) [Missler 1997]. In addition, S-100 levels have reportedly increased shortly after bypass and have been correlated with microembolic load, age, history of stroke or transient ischemic attack, degree of carotid stenoses, and duration of cardiopulmonary bypass, all of which have previously been identified as risk factors for stroke [Johnsson 1995, Westaby 1996, Blomquist 1997, Grocott 1998a]. Westaby, in a study of 34 patients free from neurologic deficits who underwent CABG surgery, did not find detectable levels of S-100 in patients undergoing off-pump CABG [Westaby 1996]. Jonsson and colleagues have shown that blood from both the surgical field and the mediastinum may inflate early sampling of S-100 values shortly after surgery [Jonsson 1999] and therefore suggest the use of cell-saving devices and sampling periods greater than 24 hours after surgery. Grocott and colleagues identified associations between number of detected cerebral embolic signals (using transcranial Doppler ultrasonography) with processes of clinical care and biological markers of cerebral injury [Grocott 1998b]. In this series of 156 patients, the authors divided the surgical procedure into 4 intervals: (1) incision to aortic cannulation, (2) aortic cannulation to aortic cross clamp, (3) aortic cross-clamp onset to aortic cross-clamp release, (4) aortic cross-clamp release to decannulation, and (5) decannulation to chest closure. The authors found the highest correlation between embolic signals and S100β levels during period 2. Although this study is important in its linkage between process of care, embolization, and S100β levels, a few limitations are noteworthy: (1) the authors did not conduct bilateral Doppler monitoring, (2) the authors did not identify variations in the conduct of each of the processes of care, (3) the authors did not link S100β levels with other mechanisms of neurologic injury, such as cerebral hypoperfusion.

Apolipoprotein E4 (ApoE-4) has been implicated as a risk factor for development of Alzheimer's disease [Edwardson 1998]. Controversy currently exists regarding its influence on neuropsychological decline after CABG surgery. Tardiff studied the risk of cognitive deficit among 65 patients who carried the ApoE-4 allele and underwent cardiac operations [Tardiff 1997]. A significant association existed between the presence

of the ApoE-4 allele and risk of cognitive decline at 6 weeks following surgery, once results were adjusted for year of education. Tardiff noted that educational level modulated the extent of association between ApoE-4 allele and risk of cognitive decline. The effect seen in this cohort with regard to memory and cognitive decline was similar to that seen in the early stages of Alzheimer's disease. Steed repeated the analysis performed by Tardiff on a larger sample of patients undergoing CABG surgery [Steed 2001]. Steed reported no significant association between the ApoE-4 allele and cognitive change, measured either by individual genotype or categorized by the presence or absence of the ApoE-4 allele. Other genetic risk factors in surgical candidates remain to be examined.

The full benefit of measuring biomarkers of neurologic injury has yet to be realized, likely as a consequence of a lack of sensitivity/specificity of the current assays. Future work should be focused on more brain-sensitive markers, as well as further linkage between these assays and the mechanisms causing the neurologic injuries. It is likely that polygenic models of vulnerability to brain insult will need to be developed.

OFF-PUMP VERSUS TRADITIONAL CABG

There has been a great deal of interest in the off-pump coronary artery bypass (OPCAB) procedure and its use to avoid the associated deleterious effects of the cardiopulmonary bypass machine, such neurologic injury. Exposure to the bypass machine may be associated with an increase in embolic burden to the brain and other end organs, platelet dysfunction, and initiation of the inflammatory process [Inada 1990, Murkin 1997, Brown 2000, Rose 2003]. As such, the use of the OPCAB procedure has been heralded as a safe alternative for myocardial revascularization. There have been numerous reports in the literature concerning the relationship between OPCAB and neurologic injury [Hernandez 2000, Svennevig 2000, Grunkemeier 2002, Karamanoukian 2002, Van Dijk 2002, Lazar 2003, Lee 2003, Nathoe 2003, Schmitz 2003]. We shall highlight the current state of this debate.

Several studies have suggested associations between the use of the cardiopulmonary bypass circuit and the occurrence of adverse neurologic outcomes. Selnes, in a 1999 review article, described a variety of neurologic deficits experienced secondary to cardiopulmonary bypass [Selnes 1999a]. These included strokes, postoperative delirium, short- or long-term cognitive changes, and depression [Selnes 1999a]. Studies by Mills and colleagues determined that these changes may not be related to depression or anxiety but may likely be a consequence of cardiopulmonary bypass [Mills 1993]. Van Dijk and colleagues randomized 248 patients to undergo on- versus off-pump CABG surgery. Cognitive outcome was measured in accordance with published standards and was assessed at baseline and at 3, and 12 months [Murkin 1995]. There was an initial benefit in cognitive function at 3 months, although differences between groups were diminished at 12 months. However, studies assessing clinical stroke have found only slightly lower stroke rates among patients having beating heart surgery than those having cardiopulmonary bypass. Among 7867 consecutive patients (1741 OPCAB, 6126 CABG) having surgery between 1998 and 2000, Hernandez and colleagues showed that there was a 35% reduction in stroke risk for patients undergoing OPCAB versus traditional CABG surgery (1.34% versus 1.81%) [Hernandez 2001]. More recently, Nathoe and colleagues, in a study of 281 patients randomized to OPCAB (142 patients) versus CABG (139 patients) found that patients in both groups had equivalent graft patency, death, stroke, and Q-wave and non–Q-wave myocardial infarction [Nathoe 2003]. These results persisted both during and 1 year after the index admission. One limitation to this study was that fewer enrolled patients had 3-vessel disease than patients in other published studies.

It is plausible that cardiopulmonary bypass plays a role in producing adverse neurologic outcomes following CABG surgery, but the etiology is as yet unclear. The most commonly reported mechanisms associating cardiopulmonary bypass with neurologic injury appear to be the initiation of the systemic inflammatory response and microembolization via the manipulation of atherosclerotic aortas. In a study by Matata and colleagues, OPCAB was associated with lower levels of oxidative stress and less systematic inflammatory response [Matata 2000]. OPCAB might influence neurologic injury in ways other than embolization and initiation of the systemic inflammatory response. Do and colleagues reported results on 55 patients undergoing OPCAB between 1998 and 1999 [Do 2002]. Comparisons were made between hemodynamics (systemic arterial pressure, pulmonary artery pressure, cardiac output, and mixed venous oxygen saturation) at the end of an anastomosis and at baseline. The investigators found changes in hemodynamics more pronounced during the manipulation of the anterior arteries, especially in regard to pulmonary artery pressure and cardiac output. These findings were further elucidated in a review article by Couture and colleagues, who outlined the differences in the hypotension profiles of various stabilizing devices [Couture 2002]. Couture concluded that compression-type stabilizing devices resulted in compression of the left ventricular outflow tract, whereas suction-type devices likely result in compression of the right ventricle. Murkin further elucidated the relationship between hemodynamic instability and neurologic injury via cardiac manipulation and subsequent right ventricular compression [Murkin 2002]. Murkin concluded that the surgical team should use cerebral monitoring and avoid aortic manipulation for patients considered at risk for neurologic injury.

Numerous comparisons have been made between on- and off-pump surgery. Neurologic outcomes, whether defined as focal or global, seem to be equivalent across the 2 groups. Off-pump surgery seems to afford a protective effect for cerebral embolization, although possibly with the consequence of greater hypoxia.

INTRAOPERATIVE CARE AND MANAGEMENT OPPORTUNITIES

Evidence regarding the source, extent, and effects of embolic load during and after surgery comes from several sources. Baker, using transcranial Doppler to measure emboli, found the highest embolic load associated with the

application of the aortic cross clamp, and the highest rate of emboli at the onset of cardiopulmonary bypass [Baker 1995]. In a subsequent study, Barbut reported that the number of emboli is often unevenly distributed among the different stages of surgery [Barbut 1997]. Although the application and subsequent removal of the aortic cross clamp has accounted for more than 60% of the total number of emboli in some studies, flurries have also been detected during aortic cannulation and inception and termination of bypass. Increased numbers of emboli are likely to be associated with increased risk of neurologic injury. Pugsley found an increased risk of neuropsychological deficits among patients having increased numbers of detected emboli [Pugsley 1994]. If surgical techniques are associated with the creation of emboli and subsequent identification of neurologic injuries, as the work by Barbut, Baker, and Pugsley suggests, modifications of these techniques are likely to reduce the occurrence of neurologic injury.

Detailed analyses have revealed that emboli may be attributed to processes controlled by both surgeons and perfusionists. Stump and colleagues, monitoring the left common carotid artery, identified specific surgical events/techniques associated with emboli. These researchers found that the greatest percentage of emboli came from the removal of the partial occlusion clamp. However, the authors could not identify any surgical events/techniques associated with nearly one third of all detected emboli [Stump 1993a]. Taylor and colleagues suggested that a portion of these latter emboli may be attributed to interventions controlled by the perfusionist, such as the injection of medication [Taylor 1999].

Regional cerebral hypoperfusion may result from patients suffering from chronic hypertension, diabetes, or senile atherosclerotic disease. Chronic hypertension may result in a narrowing of penetrating arteries (leading to susceptibility to a lacunar stroke in the setting of cerebral hypoperfusion), decreased collateral flow, or reduction in ischemic tolerance through alterations in the autoregulatory curve [Cook 2000]. Controversy surrounds the appropriate level of mean arterial blood pressure (MAP) during and following surgery. Gold, in a prospective randomized study of 248 elective CABG patients, found that patients maintained at higher levels of MAP (80-100 mm Hg) during cardiopulmonary bypass had lower levels of neurologic deficits [Gold 1995]. Stockard, in a prospective study of 25 consecutive CABG patients, did not find an association between neurologic deficits and the extent or duration of hypotension [Stockard 1973]. Barbut, in a series of 100 patients continuously monitored by transcranial Doppler, found a relationship between neurologic outcome and duration of cerebral hypoperfusion, defined as cerebral flow velocity. They found a 17% reduction from baseline perfusion rates in patients without neurologic deficits, and a 43% reduction in patients suffering strokes. Those free from deficits were perfused <50% from baseline, one third less, on average, than those suffering strokes. Notably, the number of emboli was lower in those without neurologic deficits [Barbut 1997].

Several small studies have used levels of measured mixed venous cerebral oxygenation during CABG surgery as a proxy for identifying intervals of intraoperative cerebral ischemia. Edmonds, using near infrared spectroscopy to measure mixed venous cerebral oxygenation, found that 18% of patients undergoing revascularization procedures had oxygen saturations 25% below preoperative baseline [Edmonds 2000]. Cerebral oxygen desaturation was not found to be associated with either systemic arterial or mixed venous oxygen saturation, suggesting that measurements of systemic oxygenation, often used to infer levels of cerebral oxygenation, are unsuitable [Edmonds 1997]. Oxygen saturation levels below 25% of baseline have been found to be associated with disorientation and subtle frontal lobe injury [Edmonds 1998a, 1998b].

Measurements of hemodynamics have been studied among patients undergoing both off- and on-pump procedures. In one cohort study of 55 patients undergoing CABG surgery without extracorporeal circulation, significant drops occurred in mean systemic arterial pressure and cardiac output after the completion of anastomoses, and significant increases occurred in mean pulmonary arterial pressure [Do 2002]. Reich quantified the association between intraoperative hemodynamic information and a patient's risk of death, stroke, or perioperative myocardial infarction [Reich 1999]. Reich found that both hypertension (pulmonary and postbypass pulmonary diastolic) and hypotension during cardiopulmonary bypass were associated with each of these 3 outcome measures. Most associations found between hemodynamics and adverse outcomes stem from predefined aberrations (mean arterial blood pressure <70 mm Hg) from normality [Cartwright 1998, Hartman 1998]. These relatively arbitrary cutoffs prohibit identification of the natural forms of the distribution of, for instance, mean arterial pressure. Additionally, hemodynamic information is often sampled every 5 minutes, making it impossible to investigate at a higher resolution the relationship between hemodynamic changes and potential outcome variables such as neurologic injuries. Criticisms regarding the use of these cutoff points and of hand-written anesthesia records have surfaced and focused on arbitrary standards of normality and inaccuracies, respectively [Hollenberg 1997].

Sustained reductions in neurologic injury will likely result from the redesign of clinical care to reduce modifiable clinical techniques associated with embolization, hypoxia, and sustained hypotension. This redesign will require the combined efforts of all clinical stakeholders: surgeons, anesthesiologists, perfusionists, and nursing staff.

WHAT THE FUTURE HOLDS

Although interesting and important, much of the literature surrounding neurologic injury has lacked critical information in part because (1) many preoperative variables are nonmodifiable (such as age, sex, and medical comorbidities) and (2) some of the modifiable factors associated with the onset of neurologic injury may be a consequence of currently unidentified and unstudied surgical and perfusion techniques. The 3 dominant mechanisms of neurologic injury are embolization, hypoxia, and hypotension. Sustainable reductions in neurologic injury will likely occur through the identification of associations between potentially modifiable surgical and perfusion techniques with the causes of neurologic

injury (embolism, cerebral hypoperfusion, and hemodynamic instability, respectively). To date, no single study has currently combined information concerning all 3 of these, nor identified the surgical techniques that are associated with their creation. Our group has begun such a study among patients undergoing coronary and/or valvular procedures [Likosky 2004].

CONCLUSION

Reduction in the extent of neurologic injury after CABG will require 3 factors. First, studies must be appropriately powered to detect the most plausible effect, whether a rare outcome such as stroke or the more prevalent cognitive deficit. Second, editors must require authors to provide information (operational definitions for outcome variables, similar statistical analyses, and measurement tools) sufficient for comparisons across studies, as suggested by Murkin and colleagues [1995]. Third, information concerning the association between clinical events/techniques and the causes of neurologic injury (embolism, cerebral oxygen desaturation, and hemodynamics) should be used to redesign cardiac surgery to minimize their occurrence.

REFERENCES

Agartz I, Okuguwa G, Nordstrom M, et al. 2001. Reliability and reproducibility of brain tissue volumetry from segmented MR scans. Eur Arch Psychiatry Clin Neurosci. 251(6):255-61.

Ahlgren E, Lundqvist A, Nordlund A, Aren C, Rutberg H. 2003. Neurocognitive impairment and driving performance after coronary artery bypass surgery. European J Cardiothorac Surg 23(3):334-40.

Ali MS, Harmer M, Vaughan R. 2000. Serum S100 protein as a marker of cerebral damage during cardiac surgery. Br J Anaesth 85(2):287-98.

Arrowsmith JE, Grocott HP, Reves JG, Newman MF. 2000. Central nervous system complications of cardiac surgery. Br J Anaesth 84(3):378-93.

Ashburner J, Andersson JLR, Friston KJ. 2000. Image registration using a symmetric prior—in three dimensions. Hum Brain Mapp 9(4):212-25.

Baker AJ, Naser B, Benaroia M, Mazer CD. 1995. Cerebral microemboli during coronary artery bypass using different cardioplegia techniques. Ann Thorac Surg 59(5):1187-91.

Barbut D, Caplan LR. 1997. Brain complications of cardiac surgery. Curr Probl Cardiol 22(9):449-80.

Benedict RH. 1994. Cognitive function after open-heart surgery: are postoperative neuropsychological deficits caused by cardiopulmonary bypass? Neuropsychol Rev 4(3):223-55.

Blomquist S, Johnsson P, Luhrs C, et al. 1997. The appearance of S-100 protein in serum during and immediately after cardiopulmonary bypass surgery: a possible marker for cerebral injury. J Cardiothorac Vasc Anesth 11(6):699-703.

Blossom GB, Fietsam R, Jr., Bassett JS, Glover JL, Bendick PJ. 1992. Characteristics of cerebrovascular accidents after coronary artery bypass grafting. Am Surg 58(9):584-9, discussion 9.

Bokde AL, Teipel SJ, Zebuhr Y, et al. 2002. A new rapid landmark-based regional MRI segmentation method of the brain. J Neurol Sci 194(1):35-40.

Borowicz LM, Goldsborough MA, Selnes OA, McKhann GM. 1996. Neuropsychologic change after cardiac surgery: a critical review. J Cardiothorac Vasc Anesth 10(1):105-11; quiz 11-2.

Boyd W, Hartman G. 1999. Neurologic dysfunction in cardiac surgery. New Horizons 7(6):h1-10.

Braunwald E. 1997. Heart disease: a textbook of cardiovascular medicine. Philadelphia: WB Saunders Company.

Brown WR, Moody DM, Challa VR, Stump DA, Hammon JW. 2000. Longer duration of cardiopulmonary bypass is associated with greater numbers of cerebral microemboli. Stroke 31(3):707-13.

Browndyke JN, Moser DJ, Cohen RA, et al. 2002. Acute neuropsychological functioning following cardiosurgical interventions associated with the production of intraoperative cerebral microemboli. Clin Neuropsychol 16(4):463-71.

Bruggemans EF, Van Dijk JG, Huysmans HA. 1995. Residual cognitive dysfunctioning at 6 months following coronary artery bypass graft surgery. European J Cardiothorac Surg 9(11):636-43.

Buttner T, Weyers S, Postert T, Sprengelmeyer R, Kuhn W. 1997. S-100 protein: serum marker of focal brain damage after ischemic territorial MCA infarction. Stroke 28(10):1961-5.

Cartwright CR, Mangano CM. 1998. Con: during cardiopulmonary bypass for elective coronary artery bypass grafting, perfusion pressure should not routinely be greater than 70 mmHg. J Cardiothorac Vasc Anesth 12(3):361-4.

Charlesworth DC, Likosky DS, Marrin CA, et al. 2003. Development and validation of a prediction model for strokes after coronary artery bypass grafting. Ann Thorac Surg 76(2):436-43.

Clark RE, Brillman J, Davis DA, Lovell MR, Price TR, Magovern GJ. 1995. Microemboli during coronary artery bypass grafting. Genesis and effect on outcome [see comments]. J Thorac Cardiovasc Surg 109(2):249-57, discussion 257-248.

Collie A, Darby DG, Falleti MG, Silbert BS, Maruff P. 2002. Determining the extent of cognitive change after coronary surgery: a review of statistical procedures. Ann Thorac Surg 73(6):2005-11.

Cook D. 2000. Neurological effects. In: Gravlee G, ed. Cardiopulmonary bypass: principles and practice. 2nd ed. Baltimore, Md: Lippincott Williams & Wilkins. p 768.

Couture P, Denault A, Limoges P, et al. 2002. Mechanisms of hemodynamic changes during off-pump coronary artery bypass surgery. Can J Anaesth 49(8):835-49.

DeCarli C, Miller BL, Swan GE, et al. 2001. Cerebrovascular and brain morphologic correlates of mild cognitive impairment in the National Heart, Lung, and Blood Institute Twin Study. Arch Neurol 58(4):643-7.

Diegeler A, Hirsch R, Schneider F, et al. 2000. Neuromonitoring and neurocognitive outcome in off-pump versus conventional coronary bypass operation. Ann Thorac Surg 69(4):1162-6.

Do QB, Goyer C, Chavanon O, et al. 2002. Hemodynamic changes during off-pump CABG surgery. Eur J Cardiothorac Surg 21(3):385-90.

Dogan S, Graubitz K, Aybek T, et al. 2002. How safe is the port access technique in minimally invasive coronary artery bypass grafting? Ann Thorac Surg 74(5):1537-43, discussion 43.

Ebert AD, Walzer TA, Huth C, Herrmann M. 2001. Early neurobehavioral disorders after cardiac surgery: a comparative analysis of coronary artery bypass graft surgery and valve replacement. J Cardiothorac Vasc Anesth 15(1):15-9.

Edmonds HL. 2000. Detection and treatment of cerebral hypoxia key to avoiding intraoperative brain injuries. J Clin Monit Comput 16(1): 69-74.

Edmonds HL, Sehic A, Pollock SB, Ganzel BL. 1998. Low cerebrovenous oxygen saturation predicts disorientation. Anesthesiology 89(3A):U825-U.

Edmonds HL, Thomas MH, Sehic A, Pollock SB, Ganzel BL. 1998. Cerebral oxygen desaturation during myocardial revascularization is associated with frontal lobe injury. Anesth Analg 86(4):SCA13.

Edmonds HL, Toney KA, Thomas MH, Pollock SB, Strickland TJ. 1997. Neuromonitoring cost-benefit for adult cardiac surgery. Anesthesiology 87(3):A426-A.

Edwardson J, Morris C. 1998. The genetics of Alzheimer's disease. The number of genetic risk factors associated with this disorder is increasing steadily. BMJ 317(7155):361-2.

Favaloro RG. 1978. The first decade of bypass graft surgery for coronary artery disease. Summary of conference. Cleve Clin Q 45(1):189-96.

Favaloro RG. 1968. Saphenous vein autograft replacement of severe segmental coronary artery occlusion: operative technique. Ann Thorac Surg 5(4):334-9.

Fischl B, Salat DH, Busa E, et al. 2002. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 33(3):341-55.

Fish KJ, Helms KN, Sarnquist FH, et al. 1987. A prospective, randomized study of the effects of prostacyclin on neuropsychologic dysfunction after coronary artery operation. J Thorac Cardiovasc Surg 93(4):609-15.

Folks DG, Freeman AM 3rd, Sokol RS, Govier AV, Reves JG, Baker DM. 1988. Cognitive dysfunction after coronary artery bypass surgery: a case-controlled study. South Med J 81(2):202-6.

Fraguas Junior R, Ramadan ZB, Pereira AN, Wajngarten M. 2000. Depression with irritability in patients undergoing coronary artery bypass graft surgery: the cardiologist's role. Gen Hosp Psychiatry 22(5):365-74.

Frye RL, Kronmal R, Schaff HV, Myers WO, Gersh BJ. 1992. Stroke in coronary artery bypass graft surgery: an analysis of the CASS experience. The participants in the Coronary Artery Surgery Study. Int J Card 36(2):213-21.

Gardner TJ, Horneffer PJ, Manolio TA, et al. 1985. Stroke following coronary artery bypass grafting: a ten-year study. Ann Thorac Surg 40(6):574-81.

Georgiadis D, Berger A, Kowatschev E, et al. 2000. Predictive value of S-100beta and neuron-specific enolase serum levels for adverse neurologic outcome after cardiac surgery. J Thorac Cardiovasc Surg 119(1):138-47.

Gold JP, Charlson ME, Williams-Russo P, et al. 1995. Improvement of outcomes after coronary artery bypass. A randomized trial comparing intraoperative high versus low mean arterial pressure [see comments]. J Thorac Cardiovasc Surg 110(5):1302-11, discussion 11-4.

Gonzalez-Scarano F, Hurtig HI. 1981. Neurologic complications of coronary artery bypass grafting: case-control study. Neurology 31(8):1032-5.

Goto T, Baba T, Honma K, et al. 2001. Magnetic resonance imaging findings and postoperative neurologic dysfunction in elderly patients undergoing coronary artery bypass grafting. Ann Thorac Surg 72(1):137-42.

Griffin WS, Stanley LC, Ling C, et al. 1989. Brain interleukin 1 and S-100 immunoreactivity are elevated in Down syndrome and Alzheimer disease. Proc Natl Acad Sci U S A 86(19):7611-5.

Grocott HP, Amory DW, Lowry E, Croughwell ND, Newman MF. 1998. Transcranial Doppler blood flow velocity versus 133Xe clearance cerebral blood flow during mild hypothermic cardiopulmonary bypass. J Clin Monit Comput 14(1):35-9.

Grocott HP, Croughwell ND, Amory DW, et al. 1998. Cerebral emboli and serum S100beta during cardiac operations. Ann Thorac Surg 65(6):1645-9, discussion 9-50.

Grocott HP, Mackensen GB, Grigore AM, et al. 2002. Postoperative hyperthermia is associated with cognitive dysfunction after coronary artery bypass graft surgery. Stroke 33(2):537-541.

Grunkemeier GL, Payne N, Jin R, Handy JR, Jr. 2002. Propensity score analysis of stroke after off-pump coronary artery bypass grafting. Ann Thorac Surg 74(2):301-5.

Hammon JW Jr, Stump DA, Kon ND, et al. 1997. Risk factors and solutions for the development of neurobehavioral changes after coronary artery bypass grafting. Ann Thorac Surg 63(6):1613-8.

Harrison MJ, Schneidau A, Ho R, Smith PL, Newman S, Treasure T. 1989. Cerebrovascular disease and functional outcome after coronary artery bypass surgery. Stroke 20(2):235-7.

Hartman G. 1998. Pro: during cardiopulmonary bypass for elective coronary artery bypass grafting, perfusion pressure should routinely be greater than 70 mmHg. J Cardiothorac Vasc Anesth 12(3):358-60.

Hernandez F, Clough RA, Klemperer JD, Blum JM. 2000. Off-pump coronary artery bypass grafting: initial experience at one community hospital. Ann Thorac Surg 70(3):1070-2.

Hernandez F, Cohn WE, Baribeau YR, et al. 2001. In-hospital outcomes of off-pump versus on-pump coronary artery bypass procedures: a multicenter experience. Ann Thorac Surg 72(5):1528-33; discussion 33-4.

Hlatky MA, Bacon C, Boothroyd D, et al. 1997. Cognitive function 5 years after randomization to coronary angioplasty or coronary artery bypass graft surgery. Circulation 96(9 suppl):11-4.

Hogue CW, Jr, Murphy SF, Schechtman KB, Da-Ra VG . 1999. Risk factors for early or delayed stroke after cardiac surgery. Circulation 100(6):642-7.

Hollenberg JP, Pirraglia PA, Williams-Russo P, et al. 1997. Computerized data collection in the operating room during coronary artery bypass surgery: a comparison to the hand-written anesthesia record. J Cardiothorac Vasc Anesth 11(5):545-51.

Inada E. 1990. Blood coagulation and autologous blood transfusion in cardiac surgery. J Clin Anesth 2(6):393-406.

Jacobs A, Neveling M, Horst M, et al. 1998. Alterations of neuropsychological function and cerebral glucose metabolism after cardiac surgery are not related only to intraoperative microembolic events. Stroke 29(3):660-7.

Johnsson P, Lundqvist C, Lindgren A, et al. 1995. Cerebral complications after cardiac surgery assessed by S-100 and NSE levels in blood. J Cardiothorac Vasc Anesth 9(6):694-9.

Jones EL, Weintraub WS, Craver JM, Guyton RA, Cohen CL. 1991. Coronary bypass surgery: is the operation different today? J Thorac Cardiovasc Surg 101(1):108-15.

Jonsson H, Johnsson P, Alling C, et al. 1999. S100beta after coronary artery surgery: release pattern, source of contamination, and relation to neuropsychological outcome. Ann Thorac Surg 68(6):2202-8.

Jonsson H, Johnsson P, Alling C, Westaby S, Blomquist S. 1998. Significance of serum S100 release after coronary artery bypass grafting. Ann Thorac Surg 65(6):1639-44.

Karamanoukian HL, Donias HW, Bergsland J. 2002. Decreased incidence of postoperative stroke following off-pump coronary artery bypass. J Am Coll Cardiol 39(5):917-8.

Johnsson P, Lundqvist C, Lindgren A, Ferencz I, Alling C, Stahl E. 1995. Cerebral complications after cardiac surgery assessed by S-100 and NSE levels in blood. J Cardiothorac Vasc Anesth 9(6):694-9.

Keith JR, Puente AE, Malcolmson KL, et al. 2002. Assessing postoperative cognitive change after cardiopulmonary bypass surgery. Neuropsychology 16(3):411-21.

Keller SS, Wieshmann UC, Mackay CE, Denby CE, Webb J, Roberts N. 2002. Voxel based morphometry of grey matter abnormalities in patients with medically intractable temporal lobe epilepsy: effects of side of seizure onset and epilepsy duration. J Neurol Neurosurg Psychiatry 73(6):648-55.

Kelly PJ, Hedley-Whyte ET, Primavera J, He J, Gonzalez RG. 2001. Diffusion MRI in ischemic stroke compared to pathologically verified infarction. Neurology 56(7):914-20.

Kennedy JW, Kaiser GC, Fisher LD, et al. 1980. Multivariate discriminant analysis of the clinical and angiographic predictors of operative mortality from the Collaborative Study in Coronary Artery Surgery (CASS). J Thorac Cardiovasc Surg 80(6):876-87.

Kilo J, Czerny M, Gorlitzer M, et al. 2001. Cardiopulmonary bypass affects cognitive brain function after coronary artery bypass grafting. Ann Thorac Surg 72(6):1926-32.

Klonoff H, Clark C, Kavanagh-Gray D, Mizgala H, Munro I. 1989. Two-year follow-up study of coronary bypass surgery. Psychologic status, employment status, and quality of life. J Thorac Cardiovasc Surg 97(1):78-85.

Kneebone AC, Andrew MJ, Baker RA, Knight JL. 1998. Neuropsychologic changes after coronary artery bypass grafting: use of reliable change indices. Ann Thorac Surg 65(5):1320-5.

Knipp SC, Matatko N, Wilhelm H, et al. 2004. Evaluation of brain injury after coronary artery bypass grafting. A prospective study using neuropsychological assessment and diffusion-weighted magnetic resonance imaging. Eur J Cardiothorac Surg 25(5):791-800.

Kohn A. 2002. Magnetic resonance imaging registration and quantitation of the brain before and after coronary artery bypass graft surgery. Ann Thorac Surg 73(1):S363-5.

Lazar RM, Oz MC, Festa J, et al. 2003. Diffusion-weighted imaging of the brain following on- vs. off-pump CABG. Stroke 34:P362.

Lee JD, Lee SJ, Tsushima WT, et al. 2003. Benefits of off-pump bypass on neurologic and clinical morbidity: a prospective randomized trial. Ann Thorac Surg 76(1):18-25, discussion 6.

Likosky D, Caplan L, Landis E, et al. 2002. Functional impairment and mortality of stroke subtypes following CABG. In: 4th Scientific Forum on Quality of Care and Outcomes Research in CVD and Stroke. Washington, DC.

Likosky DS, Groom RC, Clark C, et al. 2004. A Method for Identifying Mechanisms of Neurologic Injury From Cardiac Surgery. The Heart Surgery Forum 7(6):E348-52.

Likosky DS, Leavitt BJ, Marrin CA, et al. 2003. Intra- and postoperative predictors of stroke after coronary artery bypass grafting. Ann Thorac Surg 76(2):428-34.

Likosky DS, Marrin CAS, Caplan LR, et al. 2003. Determination of etiologic mechanisms of strokes secondary to CABG surgery. Stroke 34(12):2830-4.

Lund C, Hol PK, Lundblad R, et al. 2003. Comparison of cerebral embolization during off-pump and on-pump coronary artery bypass surgery. Ann Thorac Surg 76(3):765-70.

Lynn GM, Stefanko K, Reed JF 3rd, Gee W, Nicholas G. 1992. Risk factors for stroke after coronary artery bypass. J Thorac Cardiovasc Surg 104(6):1518-23.

Matata BM, Sosnowski AW, Galinanes M. 2000. Off-pump bypass graft operation significantly reduces oxidative stress and inflammation. Ann Thorac Surg 69(3):785-91.

Mathew JP, Grocott HP, Phillips-Bute B, et al. 2003. Lower endotoxin immunity predicts increased cognitive dysfunction in elderly patients after cardiac surgery. Stroke 34(2):508-13.

McKhann GM, Borowicz LM, Goldsborough MA, Enger C, Selnes OA. 1997. Depression and cognitive decline after coronary artery bypass grafting. Lancet 349(9061):1282-4.

Mckhann GM, Goldsborough MA, Borowicz LM Jr, et al. 1997. Predictors of stroke risk in coronary artery bypass patients [see comments]. Ann Thorac Surg 63(2):516-21.

Mckhann GM, Goldsborough MA, Borowicz LM Jr, et al. 1997. Cognitive outcome after coronary artery bypass: a one-year prospective study [see comments]. Ann Thorac Surg 63(2):510-5.

McKhann GM, Grega MA, Borowicz LM Jr, et al. 2002. Encephalopathy and stroke after coronary artery bypass grafting: incidence, consequences, and prediction. Arch Neurol 59(9):1422-8.

Meyer JS, Rauch G, Rauch RA, Haque A. 2000. Risk factors for cerebral hypoperfusion, mild cognitive impairment, and dementia. Neurobiol Aging 21(2):161-9.

Millar K, Asbury AJ, Murray GD. 2001. Pre-existing cognitive impairment as a factor influencing outcome after cardiac surgery. Br J Anaesth 86(1):63-7.

Mills SA. 1993. Cerebral injury and cardiac operations. Ann Thorac Surg 56(5 suppl):S86-91.

Missler U, Wiesmann M, Friedrich C, Kaps M. 1997. S-100 protein and neuron-specific enolase concentrations in blood as indicators of infarction volume and prognosis in acute ischemic stroke. Stroke 28(10):1956-60.

Mullges W, Babin-Ebell J, Reents W, Toyka KV. 2002. Cognitive performance after coronary artery bypass grafting: a follow-up study. Neurology 59(5):741-3.

Mullins ME, Schaefer PW, Sorensen AG, et al. 2002. CT and conventional and diffusion-weighted MR imaging in acute stroke: study in 691 patients at presentation to the emergency department. Radiology 224(2):353-60.

Murkin JM. 1997. Cardiopulmonary bypass and the inflammatory response: a role for serine protease inhibitors? J Cardiothorac Vasc Anesth 11(2 Suppl 1):19-23, discussion 4-5.

Murkin JM. 2002. Hemodynamic changes during cardiac manipulation in off-CPB surgery: relevance in brain perfusion. Heart Surg Forum 5(3):221-4.

Murkin JM, Newman SP, Stump DA, Blumenthal JA. 1995. Statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery. Ann Thorac Surg 59(5):1289-95.

Nathoe HM, van Dijk D, Jansen EW, et al. 2003. A comparison of on-pump and off-pump coronary bypass surgery in low-risk patients. N Engl J Med 348(5):394-402.

Newman MF, Croughwell ND, Blumenthal JA, et al. 1994. Effect of aging on cerebral autoregulation during cardiopulmonary bypass. Association with postoperative cognitive dysfunction. Circulation 90(5 pt 2):II243-9.

Newman MF, Croughwell ND, Blumenthal JA, et al. 1995. Predictors of cognitive decline after cardiac operation. Ann Thorac Surg 59(5):1326-30.

Newman MF, Kirchner JL, Phillips-Bute B, et al. 2001. Longitudinal assessment of neurocognitive function after coronary- artery bypass surgery. N Engl J Med 344(6):395-402.

Newman MF, Wolman R, Kanchuger M, et al. 1996. Multicenter preoperative stroke risk index for patients undergoing coronary artery bypass graft surgery. Multicenter Study of Perioperative Ischemia (McSPI) Research Group. Circulation 94(9 suppl):II74-80.

O'Connor GT, Plume SK, Olmstead EM, et al. 1996. A regional intervention to improve the hospital mortality associated with coronary artery bypass graft surgery. The Northern New England Cardiovasc Disease Study Group [see comments]. JAMA 275(11):841-6.

Papadantonaki A, Stotts NA, Paul SM. 1994. Comparison of quality of life before and after coronary artery bypass surgery and percutaneous transluminal angioplasty. Heart Lung 23(1):45-52.

Pugsley W, Klinger L, Paschalis C, et al. 1994. The impact of microemboli during cardiopulmonary bypass on neuropsychological functioning. Stroke 25(7):1393-9.

Rasmussen LS, Sperling B, Abildtrom HH, Moller JT. 2002. Neuron loss after coronary bypass detected by SPECT estimation of benzodiazepine receptors. Ann Thorac Surg 74:1576-80.

Reents W, Muellges W, Franke D, Babin-Ebell J, Elert O. 2002. Cerebral oxygen saturation assessed by near-infrared spectroscopy during coronary artery bypass grafting and early postoperative cognitive function. Ann Thorac Surg 74(1):109-14.

Reich DL, Bodian CA, Krol M, et al. 1999. Intraoperative hemodynamic predictors of mortality, stroke, and myocardial infarction after coronary artery bypass surgery [see comments]. Anesth Analg 89(4):814-22.

Restrepo L, Wityk RJ. 2002. Stroke after coronary artery bypass surgery. Stroke Clinical Updates 12(2).

Restrepo L, Wityk RJ, Grega MA, et al. 2002. Diffusion- and perfusion-weighted magnetic resonance imaging of the brain before and after coronary artery bypass grafting surgery. Stroke 33(12):2909-15.

Reynolds JD, Amory DW, Grocott HP, White WD, Newman MF. 2002. Change in plasma glutamate concentration during cardiac surgery is a poor predictor of cognitive outcome. J Cardiothorac Vasc Anesth 16(4):431-6.

Ricotta JJ, Faggioli GL, Castilone A, Hassett JM. 1995. Risk factors for stroke after cardiac surgery: Buffalo Cardiac-Cerebral Study Group. J Vasc Surg 21(2):359-63, discussion 64.

Roach GW, Kanchuger M, Mangano CM, et al. 1996. Adverse cerebral outcomes after coronary bypass surgery. Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation Investigators [see comments]. New Engl J Med 335(25):1857-63.

Robson MJ, Alston RP, Deary IJ, Andrews PJ, Souter MJ, Yates S. 2000. Cognition after coronary artery surgery is not related to postoperative jugular bulb oxyhemoglobin desaturation. Anesth Analg 91(6):1317-26.

Rose EA. 2003. Off-pump coronary-artery bypass surgery. N Engl J Med 348(5):379-80.

Salgado-Pineda P, Baeza I, Perez-Gomez M, et al. 2003. Sustained attention impairment correlates to gray matter decreases in first episode neuroleptic-naive schizophrenic patients. Neuroimage 19(2 pt 1):365-75.

Savageau JA, Stanton BA, Jenkins CD, Frater RW. 1982. Neuropsychological dysfunction following elective cardiac operation, I: Early assessment. J Thorac Cardiovasc Surg 84(4):585-94.

Savageau JA, Stanton BA, Jenkins CD, Frater RW. 1982. Neuropsychological dysfunction following elective cardiac operation, II: a six-month reassessment. J Thorac Cardiovasc Surg 84(4):595-600.

Schmidt R, Fazekas F, Offenbacher H, et al. 1993. Brain magnetic resonance imaging in coronary artery bypass grafts: a pre- and postoperative assessment. Neurology 43(4):775-8.

Schmitz C, Weinreich S, Schneider R, et al. 2003. Off-pump versus on-pump coronary artery bypass: can OPCAB reduce neurologic injury? Heart Surg Forum 6(3):127-30.

Selnes OA, Goldsborough MA, Borowicz LM Jr, et al. 1999. Determinants of cognitive change after coronary artery bypass surgery: a multifactorial problem. Ann Thorac Surg 67(6):1669-76.

Selnes OA, Goldsborough MA, Borowicz LM, McKhann GM. 1999. Neurobehavioural sequelae of cardiopulmonary bypass. Lancet 353(9164):1601-6.

Selnes OA, Grega MA, Borowicz LM, Jr., Royall RM, Mckhann GM, Baumgartner WA. 2003. Cognitive changes with coronary artery disease: a prospective study of coronary artery bypass graft patients and nonsurgical controls. Ann Thorac Surg 75(5):1377-84, discussion 1384-1376.

Selnes OA, McKhann G. 2002. Late cognitive decline after CABG: inevitable or preventable? Neurology 59(5):660-1.

Selnes OA, Mckhann GM. 2001. Coronary-artery bypass surgery and the brain. N Engl J Med 344(6):451-2.

Shaw PJ, Bates D, Cartlidge NE, et al. 1986. Early intellectual dysfunction following coronary bypass surgery. Q J Med 58(225):59-68.

Shaw PJ, Bates D, Cartlidge NE, et al. 1987. Long-term intellectual dysfunction following coronary artery bypass graft surgery: a six month follow-up study. Q J Med 62(239):259-68.

Shaw PJ, Bates D, Cartlidge NE, et al. 1989. An analysis of factors predisposing to neurological injury in patients undergoing coronary bypass operations. Q J Med 72(267): 633-46.

Simon R, Aminoff M, Greenberg D. 1999. Clinical neurology. 4th ed. Stamford, Ct: Appleton & Lange.

Smith PL. 1988. The cerebral complications of coronary artery bypass surgery. Ann R Coll Surg Engl 70(4):212-6.

Society of Thoracic Surgeons (STS). 1999. Data analyses of the STS National Cardiac Surgery Database. Vol. 2000. Available at: http://www.ctsnet.org/doc/2986. Accessed October 11, 2004.

Sotaniemi KA, Mononen H, Hokkanen TE. 1986. Long-term cerebral outcome after open-heart surgery. A five-year neuropsychological follow-up study. Stroke 17(3):410-6.

Stamou SC, Hill PC, Dangas G, et al. 2001. Stroke after coronary artery bypass: incidence, predictors, and clinical outcome. Stroke 32(7):1508-13.

Steed L, Kong R, Stygall J, et al. 2001. The role of apolipoprotein E in cognitive decline after cardiac operation. Ann Thorac Surg 71(3):823-6.

Stockard JJ, Bickford RG, Schauble JF. 1973. Pressure-dependent cerebral ischemia during cardiopulmonary bypass. Neurology 23(5):521-9.

Stroobant N, Van Nooten G, Belleghem Y, Vingerhoets G. 2002. Short-term and long-term neurocognitive outcome in on-pump versus off-pump CABG. Eur J Cardiothorac Surg 22(4):559-64.

Stump D, Rogers A, Kahn N, Wallenhaupt S, Hammon J. 1993. When emboli occur during coronary artery bypass graft surgery. Anesthesiology 79(suppl 3A)A49.

Stump D, Tegeler C, Rogers A, et al. 1993. Neuropsychological deficits are associated with the number of emboli detected during cardiac surgery. Stroke 24(3):509.

Svennevig JL. 2000. Off-pump vs on-pump surgery. A review. Scand Cardiovasc J 34(1):7-11.

Swaminathan M, Mccreath BJ, Phillips-Bute BG, et al. 2002. Serum creatinine patterns in coronary bypass surgery patients with and without postoperative cognitive dysfunction. Anesth Analg 95(1):1-8.

Symes E, Maruff P, Ajani A, Currie J. 2000. Issues associated with the identification of cognitive change following coronary artery bypass grafting. Aust N Z J Psychiatry 34(5):770-84.

Tardiff BE, Newman MF, Saunders AM, et al. 1997. Preliminary report of a genetic basis for cognitive decline after cardiac operations. The Neurologic Outcome Research Group of the Duke Heart Center. Ann Thorac Surg 64(3):715-20.

Taylor RL, Borger MA, Weisel RD, Fedorko L, Feindel CM. 1999. Cerebral microemboli during cardiopulmonary bypass: increased emboli during perfusionist interventions. Ann Thorac Surg 68(1):89-93.

Timberlake N, Klinger L, Smith P, et al. 1997. Incidence and patterns of depression following coronary artery bypass graft surgery. J Psychosom Res 43(2):197-207.

Van Dijk D, Jansen EW, Hijman R, et al. 2002. Cognitive outcome after off-pump and on-pump coronary artery bypass graft surgery: a randomized trial. JAMA 287(11):1405-12.

Van Leemput K, Maes F, Vandermeulen D, Suetens P. 1999. Automated model-based tissue classification of MR images of the brain. IEEE Trans Med Imaging 18(10):897-908.

Vanninen R, Aikia M, Kononen M, et al. 1998. Subclinical cerebral complications after coronary artery bypass grafting: prospective analysis with magnetic resonance imaging, quantitative electroencephalography, and neuropsychological assessment. Arch Neurol 55(5):618-27.

Vingerhoets G, De Soete G, Jannes C. 1995. Relationship between emotional variables and cognitive test performance before and after open-heart surgery. Clin Neuropsychologist 9:198-202.

Vingerhoets G, Jannes C, De Soete G, Van Nooten G. 1996. Prospective evaluation of verbal memory performance after cardiopulmonary bypass surgery. J Clin Exp Neuropsychol 18(2):187-96.

Westaby S, Johnsson P, Parry AJ, et al. 1996. Serum S100 protein: a potential marker for cerebral events during cardiopulmonary bypass. Ann Thorac Surg 61(1):88-92.

Wimmer-Greinecker G, Matheis G, Brieden M. 1998. Neuropsychological changes after cardiopulmonary bypass for coronary artery bypass grafting. Thorac Cardiovasc Surg 46(4):207-12.