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ADVERSE CEREBRAL OUTCOMES AFTER CORONARY BYPASS SURGERY

GARY W. ROACH, M.D., MARC KANCHUGER, M.D., CHRISTINA MORA MANGANO, M.D., MARK NEWMAN, M.D., NANCY NUSSMEIER, M.D., RICHARD WOLMAN, M.D., ANIL AGGARWAL, M.D., KATHERINE MARSCHALL, M.D., STEVEN H. GRAHAM, M.D., PH.D., CATHERINE LEY, PH.D., GERARD OZANNE, M.D., AND DENNIS T. MANGANO, PH.D., M.D., FOR THE MULTICENTER STUDY OF PERIOPERATIVE ISCHEMIA RESEARCH GROUP AND THE ISCHEMIA RESEARCH AND EDUCATION FOUNDATION INVESTIGATORS*

ABSTRACT

Background Acute changes in cerebral function after elective coronary bypass surgery are a difficult clinical problem. We carried out a multicenter study to determine the incidence and predictors of — and the use of resources associated with — perioperative adverse neurologic events, including cerebral injury.

Methods In a prospective study, we evaluated 2108 patients from 24 U.S. institutions for two general categories of neurologic outcome: type I (focal injury, or stupor or coma at discharge) and type II (deterioration in intellectual function, memory deficit, or seizures).

Results Adverse cerebral outcomes occurred in 129 patients (6.1 percent). A total of 3.1 percent had type I neurologic outcomes (8 died of cerebral injury, 55 had nonfatal strokes, 2 had transient ischemic attacks, and 1 had stupor), and 3.0 percent had type II outcomes (55 had deterioration of intellectual function and 8 had seizures). Patients with adverse cerebral outcomes had higher in-hospital mortality (21 percent of patients with type I outcomes died, vs. 10 percent of those with type II and 2 percent of those with no adverse cerebral outcome; $P<0.001$ for all comparisons), longer hospitalization (25 days with type I outcomes, 21 days with type II, and 10 days with no adverse outcome; $P<0.001$), and a higher rate of discharge to facilities for intermediate- or long-term care (47 percent, 30 percent, and 8 percent; $P<0.001$). Predictors of type I outcomes were proximal aortic atherosclerosis, a history of neurologic disease, and older age; predictors of type II outcomes were older age, systolic hypertension on admission, pulmonary disease, and excessive consumption of alcohol.

Conclusions Adverse cerebral outcomes after coronary bypass surgery are relatively common and serious; they are associated with substantial increases in mortality, length of hospitalization, and use of intermediate- or long-term care facilities. New diagnostic and therapeutic strategies must be developed to lessen such injury. (N Engl J Med 1996;335:1857-63.)

STROKE, the third leading cause of death in the United States, will continue to be a challenging problem as the population ages. Patients who undergo myocardial revascularization procedures, now more than 800,000 a year throughout the world, are particularly prone to stroke, encephalopathy, and other neurologic dysfunction, because they are relatively old and have atherosclerotic disease. They are also subject to marked hemodynamic fluctuations; cerebral embolization of atherosclerotic plaque, air, fat, and platelet aggregates; cerebral hyperthermia after the discontinuation of cardiopulmonary bypass; and other inflammatory and neurohumoral derangements associated with surgery.[1-5]

Although cerebral complications are responsible for an increasing proportion of perioperative deaths,[6,7] their incidence and effects have not been rigorously investigated. The majority of studies have been performed only at one center, have enrolled a limited number of patients, or have been retrospective (all of which has resulted in substantial variability among findings). Among the studies, for example, there is a more than 10-fold variation in the reported incidence of perioperative stroke (from 0.4 to 5.4 percent) and

From Kaiser Permanente Medical Center, San Francisco (G.W.R.); New York University, N.Y. (M.K., K.M.); Stanford University, Stanford, Calif. (C.M.M.); Duke University, Durham, N.C. (M.N.); Mercy Medical Center, Redding, Calif. (N.N.); Medical College of Virginia, Richmond (R.W.); Veterans Affairs Medical Center, Milwaukee (A.A.); University of Pittsburgh, Pittsburgh (S.H.G.); the Ischemia Research and Education Foundation, San Francisco (C.L.); and the Veterans Affairs Medical Center, San Francisco (G.O., D.T.M.). Address reprint requests to Dr. Dennis Mangano at the Ischemia Research and Education Foundation, 250 Executive Park Blvd., Suite 3400, San Francisco, CA 94134.

Other authors were Ahvie Herskowitz, M.D., Vera Katseva, Ph.D., and Rita Sears, R.N., M.S.

*Participants in the study are listed in the Appendix.

a 3-fold variation (25 to 79 percent) in that of in-hospital neuropsychological dysfunction.[3,4,8,9] Studies of perioperative stroke have not attempted to identify potentially reversible risk factors, nor have they examined the long-term impact of perioperative cerebral outcomes on the use of resources.[3,7,10]

Our investigation was designed as a multi-institutional, prospective, observational study to determine the incidence of both stroke and encephalopathy after coronary-artery bypass graft (CABG) surgery, to identify the independent predictors of these cerebral outcomes, and to define their impact on the use of resources, as measured by the lengths of hospital stays and the need for intensive intermediate- or long-term care.

METHODS

The cardiac surgery study of the Multicenter Study of Perioperative Ischemia was a prospective observational study that enrolled 2417 patients who underwent elective CABG surgery in 24 U.S. medical institutions between September 1991 and September 1993. The goals of the study were to define the incidence of adverse perioperative outcomes, to measure the prevalence of selected characteristics of the patients, and to assess the use of resources. At each of the centers, between 100 and 108 patients were prospectively enrolled according to a systematic sampling scheme, and perioperative demographic, clinical, and laboratory data were collected on the patients from hospital entry to discharge. Data on all patients with new perioperative neurologic findings were independently reviewed by six investigators, who examined additional data (computed-tomography findings, autopsy reports, and hospital-discharge summaries) if necessary. Final classification of outcome was made by consensus of this panel in two categories: type I was defined as death due to stroke or hypoxic encephalopathy, nonfatal stroke, transient ischemic attack (TIA), or stupor or coma at the time of discharge; and type II was defined as a new deterioration in intellectual function, confusion, agitation, disorientation, memory deficit, or seizure without evidence of focal injury. Because the two types of neurologic outcome were assumed to have different causes and predictors, and because the predictors for type I outcome could potentially mask those for type II, patients with more than one type of neurologic outcome were classified, for analytic purposes, hierarchically, according to the severity of outcome. Type I outcomes were considered more severe than type II. Within type I, the diagnoses were ranked from most to least severe: fatal injury, stroke, stupor or coma, and TIA. The type II diagnoses were ranked in a similar fashion.

Patients excluded from the analysis (n = 309) could not be evaluated for neurologic outcome (6 patients), had undergone concomitant intracardiac or vascular procedures (299 patients), or had died during surgery (4 patients) (none died of cerebral causes). Variables considered potential predictors of neurologic outcome were categorized according to operative stage as preoperative (e.g., age, sex, a history of congestive heart failure or of CABG), intraoperative (e.g., the duration of cardiopulmonary bypass and aortic cross-clamping, surgical and anesthetic technique, hemodynamic changes, the use of transfusions), and postoperative (e.g., myocardial infarction, dysrhythmia, ventricular dysfunction). The use of resources was assessed on the basis of (1) the length of stay in the intensive care unit and the total postsurgical stay in the hospital, and (2) the site to which the patient was discharged (his or her home or an intermediate- or long-term care facility).

Statistical Analysis

The univariable associations between adverse neurologic outcome (type I or type II) and potential predictors were assessed with either Fisher's exact test or the Kruskal–Wallis test, as appropriate. Stepwise logistic regression was then performed separately for type I and type II outcomes, including predictors associated with P values no greater than 0.20 in univariable analyses and keeping predictors with P values no greater than 0.15 in the multivariable model. All models were sorted with Akaike's information criterion (AIC)[11]; goodness of fit for each model was determined with the Hosmer–Lemeshow test.[12] The model with the lowest AIC was considered to have the best fit.

The data in this study produced several models with similar low AIC values. Our final model was chosen on the basis of clinical relevance, and not all variables reached a P value of 0.05 or less. Results are reported as odds ratios with associated 95 percent confidence intervals.

RESULTS

Demographic and operative characteristics of the 2108 patients in this study are presented in Table 1. Patients were relatively old (32 percent were 70 years of age or more) and had a history of hypertension, unstable angina, heart failure, or diabetes; approximately 8 percent had a history of stroke or transient ischemic attack. A total of 6.1 percent of the patients (129) had perioperative adverse cerebral outcomes. Type I outcomes occurred in 3.1 percent (66), including 8 deaths due to cerebral injury, 55 nonfatal strokes, 2 TIAs, and 1 case of stupor at the time of discharge. Type II outcomes occurred in 3.0 percent (63), including 55 with deterioration in intellectual function and 8 with seizures. The outcome rates, according to institution, ranged from 1 percent to 13.8 percent (range for type I outcomes alone, 0 to 8.6 percent; for type II, 0 to 9.3 percent).

Predictors of Type I and Type II Outcomes

On the basis of our univariable analysis (Table 1), logistic regression identified eight independent predictors of type I cerebral outcomes (Table 2). Proximal aortic atherosclerosis, as identified by the cardiac surgeon, was the strongest independent predictor, associated with a more than fourfold increase in risk. It was followed by a history of neurologic disease, an age of 70 or more (Fig. 1), and a history of pulmonary disease. Both perioperative hypotension and the use of a ventricular venting procedure during surgery, although their point estimates were not statistically significant, were included in the final model since they did not detract from the statistical fit of the model and they have clinical relevance. Adjustment for the study site did not affect the results of the multivariable model. Ten independent predictors of type II cerebral outcome were identified, of which seven were statistically significant ($P \leq 0.05$) (Table 2). Predictors unique to type II were a history of excessive alcohol consumption, prior CABG surgery, dysrhythmia, a history of peripheral vascular disease, and congestive heart failure on the day of surgery (although the last two were not statistically significant). Predictors common to both type I and type II outcomes were older age, a history of pulmonary dis-

TABLE 1. SELECTED DEMOGRAPHIC, MEDICAL, AND OPERATIVE CHARACTERISTICS OF THE STUDY PATIENTS.

CHARACTERISTIC	PREVALENCE OF CHARACTERISTIC IN ALL PATIENTS	INCIDENCE OF TYPE I OUTCOME		INCIDENCE OF TYPE II OUTCOME	
		IN PATIENTS WITH CHARACTERISTIC	IN PATIENTS WITHOUT CHARACTERISTIC	IN PATIENTS WITH CHARACTERISTIC	IN PATIENTS WITHOUT CHARACTERISTIC
	percent				
Age ≥70 yr	31.9	6.1	1.9	5.8	1.8
Medical history*					
Neurologic disease	8.3	10.1	2.5	4.7	2.9
Carotid disease	14.7	7.8	2.5	4.5	2.8
Valve disease	19.9	6.14	1.3	4.6	2.1
Dysrhythmia	11.3	3.6	3.2	5.7	2.8
Unstable angina	47.7	4.4	2.2	3.7	2.4
CABG	12.9	6.2	2.8	5.5	2.7
Peripheral vascular disease	13.8	6.5	2.7	5.9	2.7
Congestive heart failure	26.4	4.9	2.6	4.9	2.4
Myocardial infarction	55.4	3.9	2.2	3.2	3.0
Diabetes mellitus	25.1	5.5	2.4	3.4	3.0
Pulmonary disease	17.5	6.1	2.7	6.3	2.4
Excessive alcohol consumption	9.8	5.6	3.0	5.6	2.8
Hypertension	57.2	4.5	1.6	3.3	2.4
Preoperative factors					
Systolic blood pressure >180 mm Hg	2.9	11.0	3.0	12.5	2.8
Antihypertensive therapy	20.7	4.6	2.9	5.7	2.4
Intraoperative factors					
Proximal aortic atherosclerosis	12.4	11.2	2.1	5.2	2.8
Intraoperative hypotension	10.6	6.2	2.9	6.2	2.7
Use of intraaortic balloon pump	7.6	9.0	2.8	4.1	3.0
Ventricular or atrial venting	76.3	3.6	1.9	3.4	2.1
Postoperative factors†					
Congestive heart failure	2.6	10.2	3.1	10.2	2.9
Dysrhythmia	18.0	3.6	3.1	5.7	2.5

*History of carotid disease includes carotid bruit, stenosis, and carotid endarterectomy. Excessive alcohol consumption indicates hospitalization because of alcohol consumption or alcohol withdrawal. CABG denotes coronary-artery bypass graft.

†These conditions were assessed in the intensive care unit immediately after surgery.

ease, a history of hypertension or existing hypertension, and perioperative hypotension.

Postoperative Course

Type I outcomes were associated with an approximately 10-fold increase in in-hospital mortality, and type II with an approximately 5-fold increase (Table 3). Similarly, the average length of the postsurgical hospital stay and the amount of time spent in intensive care were at least doubled in the patients with adverse cerebral outcomes. Of the patients with type I outcomes, 47 percent were discharged to skilled-nursing facilities or rehabilitation centers, as compared with 30 percent of patients with type II outcomes and 8 percent of patients without adverse cerebral outcomes.

DISCUSSION

This study was a large multicenter, prospective investigation of adverse cerebral outcomes after elective CABG surgery. Serious adverse cerebral outcomes occurred in 6.1 percent of patients, evenly divided between type I outcomes (fatal cerebral injury and nonfatal strokes) and type II (new deterioration in intellectual function or new onset of seizures). Adverse cerebral outcomes were associated with significantly increased mortality and use of medical resources. There was a 5-to-10-fold increase in mortality associated with type I and type II outcomes; furthermore, the 21 percent mortality rate found with perioperative stroke is similar to the rate reported from a single center more than a decade ago and suggests that stroke-related mortality has not decreased over the past decade.[6] The duration of intensive care and of the total hospital stay was prolonged by both type I and type II outcomes — a finding not previously reported with type II outcomes. High-risk characteristics were identified; they included, among others, advanced age, proximal aortic atherosclerosis, neurologic disease, pulmonary disease, and a history of or existing hypertension. These results emphasize the medical importance of adverse cerebral outcomes after CABG surgery; they have economic implications as well.[1,3,13]

TABLE 2. ADJUSTED ODDS RATIOS FOR TYPE I AND TYPE II CEREBRAL OUTCOMES ASSOCIATED WITH SELECTED RISK FACTORS.*

FACTOR	MODEL FOR TYPE I CEREBRAL OUTCOME	MODEL FOR TYPE II CEREBRAL OUTCOME
	odds ratio (95% confidence interval)	
Significant factors (P≤0.05)		
Proximal aortic atherosclerosis	4.52 (2.52–8.09)	
History of neurologic disease	3.19 (1.65–6.15)	
Use of intraaortic balloon pump	2.60 (1.21–5.58)	
Diabetes mellitus	2.59 (1.46–4.60)	
History of hypertension	2.31 (1.20–4.47)	
History of pulmonary disease	2.09 (1.14–3.85)	2.37 (1.34–4.18)
History of unstable angina	1.83 (1.03–3.27)	
Age (per additional decade)	1.75 (1.27–2.43)	2.20 (1.60–3.02)
Systolic blood pressure >180 mm Hg at admission		3.47 (1.41–8.55)
History of excessive alcohol consumption		2.64 (1.27–5.47)
History of CABG		2.18 (1.14–4.17)
Dysrhythmia on day of surgery		1.97 (1.12–3.46)
Antihypertensive therapy		1.78 (1.02–3.10)
Other factors (P not significant)†		
Perioperative hypotension	1.92 (0.93–3.97)	1.88 (0.97–3.65)
Ventricular venting	1.83 (0.86–3.90)	
Congestive heart failure on day of surgery		2.46 (0.85–7.09)
History of peripheral vascular disease		1.64 (0.89–3.04)

*Odds ratios are for the risk of a type I or II outcome in patients with the risk factor in question as compared with those without the risk factor. Odds ratios have been adjusted for all the factors listed for each model. Excessive alcohol consumption indicates hospitalization because of alcohol consumption or alcohol withdrawal. Perioperative hypotension indicates a systolic blood pressure <80 mm Hg (during surgery but before cardiopulmonary bypass, or after bypass) or <40 mm Hg (during bypass) for more than 10 minutes. CABG denotes coronary-artery bypass graft.

†In addition to factors from Table 1, the following characteristics, studied in univariable analysis, did not remain in the model: sex, aortic cross-clamping, duration of cardiopulmonary bypass and surgery, and institution.

We examined conservative measures of resource use — namely, the duration of intensive care, the total duration of the hospital stay after surgery, and the rate of discharge to intermediate- or long-term care facilities. All three measures were markedly prolonged for patients with either type I or type II adverse neurologic outcomes. As compared with patients without adverse cerebral outcomes, patients with stroke stayed an additional eight days in the intensive care unit and an additional seven days on the ward, suggesting that regardless of institutional practice, substantial resources are consumed by such patients. This confirms previous findings from single-center studies.[2,4,10,14] Again as compared with patients without adverse cerebral outcomes, patients with type II outcomes stayed an additional four days in the intensive care unit and seven days on the ward. On the basis of conservative estimates of boarding charges of $890 per day in an intensive care unit and $370 per day on a ward,[1,14] type I neurologic events are responsible for an additional $10,266 per patient in in-hospital boarding costs, and type II events for an additional $6,150 per patient.[1-3,10,14] If we apply these estimates to the 800,000 patients per year who undergo CABG surgery throughout the world, the additional in-hospital cost is approximately $400 million annually.[1] True in-hospital costs, including charges for personnel and in-hospital services, if added to the expense of an array of long-term out-of-hospital medical and rehabilitative services, probably result in an additional expenditure ranging from 5 to 10 times the narrowly defined in-hospital costs, or some $2 billion to $4 billion annually.[1] As an example of the increased cost, consider that 90 percent of patients without adverse cerebral outcomes were discharged to their homes, as compared with only 32 percent of patients with type I outcomes and 60 percent with type II outcomes. Whether the need for prolonged hospitalization and the changes in discharge patterns are caused directly by the neurologic complications or by other associated illness is uncertain, yet it is likely that adverse cerebral outcomes affect the use of health care resources profoundly.

Predictors Unique to Type I Outcomes

Moderate-to-severe proximal aortic atherosclerosis, as identified by intraoperative palpation of the

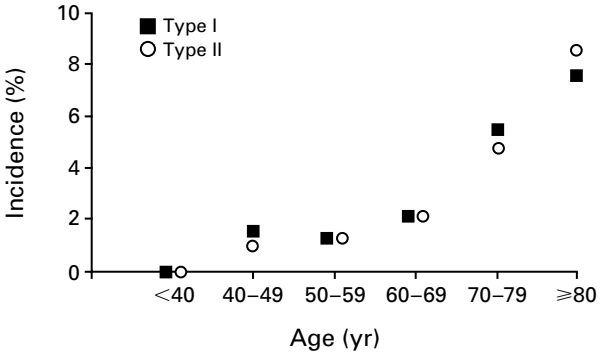

Figure 1. Incidence of Type I and Type II Cerebral Outcomes According to Age.

TABLE 3. MORTALITY AND POSTOPERATIVE RESOURCE USE, ACCORDING TO CEREBRAL OUTCOME.*

VARIABLE	TYPE I OUTCOME (N=66)	TYPE II OUTCOME (N=63)	NO ADVERSE CEREBRAL EVENT (N=1979)
Death during hospitalization — no. (%)	14 (21)	6 (10)	38 (2)
Duration of postoperative hospital stay — days			
Mean ±SD	25.3±22.2	20.5±25.2	9.5±12.4
Median	17.6	10.9	7.7
Duration of ICU stay — days			
Mean ±SD	11.1±15.4	6.6±7.9	2.6±3.5
Median	5.8	3.2	1.9
Discharged to home — no. (%)†	21 (32)	38 (60)	1773 (90)

*P<0.001 for all comparisons among the groups. ICU denotes intensive care unit.

†Patients not discharged to their homes either died or were discharged to intermediate- or long-term care facilities.

aorta, was associated with an incidence of type I adverse cerebral outcomes at least four times that among patients without the condition. This finding supports the theory that most strokes are caused by large atherosclerotic emboli liberated by surgical manipulation of the aorta.[3,15-22] In our study, proximal aortic atherosclerosis, detected by palpation, was found in approximately 12 percent of all patients and in 20 percent of patients ≥70 years of age. Moderate or severe atherosclerotic disease has been detected with ultrasonographic scanning in 14 to 20 percent of elderly patients.[3,23-27] Although palpation of the aorta is not as sensitive a measure as other techniques, such as echocardiography, the method is simple and can be used routinely to identify patients at risk and therefore to indicate alterations in surgical technique. Such alterations might include the adjustment of the site for aortic clamping and cannulation, to avoid atherosclerotic regions; the use of arterial conduits (e.g., internal thoracic or epigastric arteries) to avoid aortic anastomoses; the use of hypothermic fibrillatory arrest without clamping the aorta; or the use of hypothermic circulatory arrest, with replacement of the diseased aorta.[1,3,4,24,27-30]

A history of neurologic abnormality — for example, stroke or TIA — was also a significant risk factor for type I outcomes, a finding consistent with those of other studies.[7,31] A history of neurologic disease suggests existing pathologic cerebrovascular conditions, such as impaired cerebral blood flow and autoregulation or inadequate collateral vessels, which may predispose patients to a type I cerebral complication after CABG surgery. Patients with diabetes mellitus also had an increased risk of a type I outcome, perhaps reflecting these patients' impaired autoregulation during bypass[3,4,15,32] or more generalized atherosclerosis, involving the aorta or the carotid or cerebral arteries. Unstable angina has been associated with a prothrombotic state and systemic immunologic-cascade activation that may contribute to the development of neurologic injury.[33] The use of a left ventricular venting procedure was weakly associated with the occurrence of a type I adverse neurologic outcome, but the relatively small number of patients without vents limited statistical assessment. The placement of a vent may introduce air into the left side of the heart that subsequently embolizes and travels to the brain[3,4,19,34] — a danger that highlights the importance of fastidious surgical technique if a vent is used. A final factor, the use of an intraaortic balloon pump, may be associated with the dislodgment of aortic emboli or may be a marker of hypoperfusion.

Predictors Unique to Type II Outcomes

Proximal aortic atherosclerosis was not an independent predictor of type II cerebral outcomes, suggesting that large atherosclerotic emboli do not have a primary role in the pathophysiology of encephalopathy or seizures after bypass surgery. This is consistent with previous studies demonstrating an association between small emboli, or inadequate cerebral flow, and type II outcomes.[1,3,4,35,36] Risk factors unique to type II outcomes were a history of excessive alcohol consumption; postoperative dysrhythmia (mainly, atrial fibrillation), which may induce cerebral emboli or hypoperfusion[14]; and a history of CABG or peripheral vascular disease, which may reflect more advanced atherosclerosis.

Predictors of Both Type I and Type II Outcomes

Advanced age, particularly an age of 70 or more, was a leading factor associated with both type I and type II adverse cerebral outcomes. Aging is associated with atherosclerosis and an increased risk of embolic phenomena, as well as with alterations in cerebral vasculature[3,4,6,7,15,17,37-40] and the autoregulation of blood flow,[8,41-43] all of which may increase the in-

cidence of perioperative stroke, cognitive dysfunction, and delirium.[3,4,6,7,15,18,28,38-40,44,45] Pulmonary disease (emphysema, chronic bronchitis, restrictive lung disease, or asthma), a previously unreported risk factor for either type I or type II outcomes, was in our study a significant predictor of both; patients with pulmonary disease probably retained carbon dioxide (thus affecting cerebral vasoreactivity) or required prolonged mechanical ventilation (thus affecting the degree of cerebral perfusion and oxygenation).[1,3,16,28,46] Both a history of hypertension and existing hypertension were associated with adverse cerebral outcomes — a reflection of impaired cerebrovascular autoregulation and more generalized atherosclerotic disease in hypertensive patients.

Strengths and Limitations of the Study

The reported incidence of perioperative stroke in studies from only one center varies by a factor of more than 10, from 0.4 to 5.4 percent,[1-4,8,16,47] with similar variability in the rates of encephalopathy, delirium, and confusion. Most likely, this variability is due to differences in study design (for instance, whether the studies were retrospective or prospective), methods, sample size, and the effects of site-specific factors.[1-3,9,48,49] Our study addressed these limitations by enrolling patients at multiple diverse institutions, thereby minimizing distortion due to the effects of surgical, anesthetic, perfusion-related, and medical practices specific to a single center; randomizing enrollment and limiting it to a period of 24 months in order to decrease the impact of temporal changes in practice; collecting data prospectively; and excluding procedures, such as valve replacement or aneurysmectomy, that might increase a patient's risk of adverse neurologic events.[4,20,31]

Our study, however, has several limitations of its own. First, the neurologic findings were assessed by investigators at each site, not by a single neurologist performing all preoperative and postoperative examinations; there may be significant variations in clinical practice, and thus diagnosis, among the 24 centers (although no site-related effect was identified). Second, neuropsychological deficits were not formally assessed because of several constraints, including a lack of technical experience in neuropsychological testing and the time required for such testing. Our assessment of deterioration in intellectual function is thus open to criticism. Third, our categorization of outcomes as type I or type II presumed differences in the characteristic mechanisms of injury in the two types — focal and diffuse, respectively[35,36] (although this presumption is consistent with our finding that few of the predictors in the multivariable analysis of type I and type II outcomes were similar). Fourth, we detected aortic atherosclerosis by surgical palpation. Recent studies have shown that ultrasonography is superior to palpation in detecting aortic atheromas, but our study was designed and our data collected before the publication of those reports. Finally, several recent studies suggest an association between the presence of carotid-artery stenosis, as documented by carotid duplex scanning, and stroke after cardiac surgery.[1,3,4,24,31] We found a strong univariable correlation between the presence of carotid disease (including carotid bruit, stenosis, or endarterectomy) and type I cerebral outcomes ($P<0.001$), but carotid duplex scanning was not performed as part of the study. Perhaps because of the relatively poor specificity and selectivity of carotid bruit as a sign of hemodynamically important lesions, we were unable to document an association between carotid disease and adverse cerebral outcome in the multivariable analysis.

On the basis of data from 24 U.S. medical centers, we conclude that adverse perioperative cerebral outcomes are both relatively common (they occur in 6.1 percent of patients) and serious. As compared with patients with no adverse outcomes, the patients with such outcomes had 5 to 10 times the mortality, 2 to 4 times the time spent in intensive care and in the hospital, and 3 to 6 times the need for prolonged care. We were able to identify patients at high risk both for focal and for diffuse injury, thereby allowing improved stratification of risk. Further investigation is necessary, however, to develop diagnostic and therapeutic strategies[1,3,49] to reduce mortality and morbidity and to conserve resources.

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APPENDIX

The following coordinated the study and the analyses: **Study Director** — D. Mangano; **Coordinating Center, Ischemia Research and Education Foundation** — C. Dietzel, V. Katseva, E. Kwan, A. Herskowitz, C. Ley, and L. Ngo; **Outcome Validation Committee** — S. Graham, C. Mora Mangano, N. Nussmeier, G. Ozanne, G. Roach, and R. Wolman; **Editorial–Administrative Group** — D. Beatty, M. Riddle, I. Asturias, B. Xavier, and W. von Ehrenburg.

The following institutions and investigators participated in the study: **University of Alabama at Birmingham** — W. Lell; **Baylor College of Medicine** — S. Shenaq and R. Clark; **Cedars–Sinai Medical Center** — A. Friedman; **University of Chicago** — M. Trankina and W. Ruo; **Cleveland Clinic Foundation** — C. Koch and N. Starr; **Cornell University** — O. Patafio and R. Fine; **Duke University** — T. Stanley and M. Newman; **Emory University** — C. Mora Mangano and J. Ramsay; **Harvard University and Beth Israel Hospital** — M. Comunale; **Brigham and Women's Hospital** — S. Body and R. Maddi; **Massachusetts General Hospital** — M. D'Ambra; **University of Iowa** — A. Ross; **Kaiser Permanente Medical Center, San Francisco** — G. Roach and W. Bellows; **University of Michigan** — J. Wahr; **New York University** — M. Kanchuger and K. Marschall; **University of Pennsylvania** — J. Savino; **Rush–Presbyterian–St. Luke's Medical Center** — K. Tuman; **Stanford University** — E. Stover and L. Siegel; **Texas Heart Institute** —

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