Cognitive and Neurologic Outcomes after Coronary-Artery Bypass Surgery

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Patients referred for coronary revascularization procedures are older and are likely to have more extensive extracardiac vascular disease than those referred for such procedures in the past. Despite these trends, mortality rates for coronary-artery bypass grafting (CABG), without concurrent procedures, have continued to decline.[1] Nevertheless, adverse neurologic outcomes, including stroke and cognitive decline, remain a major concern for these older patients.

The development of strategies to reduce the incidence of postoperative neurologic events has been hampered by the lack of a clear understanding of the pathophysiology of such outcomes. Owing partly to the assumption that adverse neurologic events were specifically related to the use of extracorporeal cardiopulmonary bypass, techniques were developed for performing CABG without the use of cardiopulmonary bypass (i.e., off-pump surgery). However, recent large, prospective, randomized studies comparing the rate of adverse neurologic outcomes after conventional on-pump surgery with the rate after off-pump surgery have not shown a significant risk reduction associated with the use of off-pump surgery.[2-4] Consequently, efforts to reduce the incidence of postoperative neurologic injury have begun to focus on patient-related risk factors, such as the degree of atherosclerosis of the aorta, the carotid arteries, and the brain, rather than procedure-related variables.[5] Although more surgical centers now use preoperative and perioperative screening to identify patients who have an increased risk for stroke, and to modify surgical techniques according to the results of such screening, this approach is not yet the standard of care.[6] Not surprisingly, the rates of adverse neurologic outcomes vary considerably among institutions. In this review, we discuss the pathophysiology of the outcomes of stroke and cognitive decline after CABG as currently practiced, as well as emerging strategies for reducing the rate of such events.

STROKE

INCIDENCE AND DIAGNOSIS

Despite the increasing prevalence of atherosclerotic disease in patients undergoing CABG, the incidence of stroke after CABG has declined over the past decade, with a recent study reporting an overall rate of stroke of 1.6% after isolated CABG.[7] Stroke rates vary, depending on the underlying risks of the patient population as well as on the definition of stroke. Estimated frequencies are increased by a factor of 10 when radiographic infarct is included in the definition of stroke, and the use of magnetic resonance imaging (MRI) rather than computed tomography results in higher rates of radiographic infarct. These radiographic infarcts are not always accompanied by clinical deficits. In addition, more subtle deficits from stroke are frequently not diag-

nosed in the perioperative period, since patients are often experiencing pain or are receiving medications or sedatives, which can mask subtle neurologic signs. In other cases, because perioperative strokes are not necessarily confined to a single vascular territory, deficits may not follow the presentations typically associated with stroke in a nonsurgical setting.

PATHOPHYSIOLOGY

The traditionally invoked mechanism of brain infarction occurring during cardiac surgery is that of macroembolization or microembolization. More recent data suggest, however, that hypoperfusion and the systemic inflammatory response may also be presumed sources of neurologic injury.[8] To date, most adaptations in surgical technique have focused on reducing the embolic burden, with the assumption that this is the primary mechanism by which neurologic injury occurs. It is likely, however, that other mechanisms of injury are involved, possibly in conjunction with embolization. Persons with chronic hypertension may be exposed to relative intraoperative hypotension to the brain if their blood pressure is maintained at a normal or slightly low level during surgery, thus placing them at risk for a watershed stroke.[9,10] In many cases, however, neurologic injury is due to a combination of these factors. Caplan and Hennerici have proposed that the combination of hypoperfusion and microembolization increases the risk of neurologic injury owing to decreased washout of emboli.[11] Because of the likely multifactorial mechanisms underlying stroke after CABG, preventive strategies may need to be designed not only to avoid excessive release of emboli (e.g., from clamping of a particularly diseased part of the aorta) but also to avoid relative hypotension or a systemic inflammatory response.

PATIENT-RELATED FACTORS ASSOCIATED WITH NEUROLOGIC MORBIDITY

Older age, history of stroke, and history of hypertension and diabetes are each predictors of postoperative neurologic complications, including stroke,[12,13] along with several other risk factors that have been identified (Table 1). The mechanisms of these associations are probably related to the health of the blood vessels, both those surrounding the heart and those in the neck and brain. Persons with chronic hyperlipidemia and diabetes may have plaque in the aorta, for instance, increasing the risk of a perioperative embolism to the brain if that

portion of the diseased aorta were clamped. Anemia is also strongly associated with the risk of adverse perioperative and postoperative outcomes, including stroke.[23] These factors may not only affect stroke that occurs during the intraoperative period but may also affect or lead to stroke with an onset in the postoperative period (which accounts for up to two thirds of all perioperative strokes).[7] Postoperative atrial fibrillation is a major macroembolic cause of stroke, which tends to present later during the hospitalization, after an interval with normal postoperative neurologic status.[14]

With the increasing availability of MRI, more emphasis has been placed on preoperative subclinical vascular disease of the brain as a potential predictor of postoperative neurologic complications. In a study involving patients who underwent brain MRI before CABG, those with small (often subclinical) infarctions had increased rates of clinical stroke (5.6%, vs. 1.4% among patients with normal preoperative MRI scans), with the rate increasing to more than 8% among patients with multiple brain infarcts before surgery.[16] Not only are chronic white-matter ischemic disease and old infarcts common in candidates for CABG, but new deficits on diffusion-weighted imaging have been identified preoperatively in 4.5% of patients, most likely owing to recent cardiac catheterization.[24]

Although off-pump CABG was developed in part with the goal of reducing neurologic complications, multiple randomized trials have not shown decreased rates of postoperative stroke with this procedure (Table 2). In other, nonrandomized studies, off-pump CABG was associated with lower rates of early strokes but with similar rates of delayed stroke.[15] The mechanisms of stroke after on- and off-pump surgery may thus be slightly different. The finding that stroke rates are similar, however, supports the concept that patient-related factors, including arteriosclerotic burden, are more important predictors of the risk of stroke than is the type of surgery.

STROKE PREVENTION

One major change in strategies to prevent adverse neurologic events after cardiac surgery has been to individualize surgical-management strategies for high-risk patients. Another change during the past 10 years is the now practically ubiquitous use of statin medications among patients undergoing CABG. The role of statins in the risk of postoperative stroke and adverse cognitive outcomes remains

Table 1. Risk Factors for Perioperative Stroke during On-Pump CABG.

Risk Factor	Odds Ratio (Study)*
Preoperative	
Atherosclerosis of the ascending aorta	2.0 (Hogue et al.[14])
History of cerebrovascular disease (transient ischemic attack or stroke)	2.1 (Tarakji et al.[7]) 2.09 (Nishiyama et al.[15])
History of subcortical small-vessel ischemic disease	4.1 (Goto et al.[16])†
Carotid stenosis	5.3 (Li et al.[17])†
History of peripheral vascular disease	2.0 (Tarakji et al.[7])
History of diabetes	1.2 (Shahian et al.[18]) 2.8 (Hogue et al.[14])
History of hypertension	1.8 (Tarakji et al.[7]) 1.3 (Shahian et al.[18])
History of elevated pulse pressure	1.12 per 10 mm Hg increase (Fontes et al.[19])
Previous cardiac surgery	1.4 (Tarakji et al.[7])
History of smoking	1.6 (Tarakji et al.[7])
Intraoperative	
Severe hypotension	8.4 (Gardner et al.[20])
Manipulation of atherosclerotic ascending aorta	1.8 (Kapetanakis et al.[21])
Cardiopulmonary-bypass time >2 hr	1.4 (Bucerius et al.[13])
Postoperative	
Atrial fibrillation	0.6 (Tarakji et al.[7]) 2.6 (Hedberg et al.[22])

* Adjusted odds ratios are shown, except where otherwise noted.
† Univariate odds ratio is shown, calculated on the basis of numbers provided in the study report.

the location and severity of aortic plaque, but this approach is not yet used universally. Results of epiaortic ultrasonography can be used to modify intraoperative decisions about aortic cross-clamp placement and the ascending aortic cannula site.[33] Data from randomized trials are not yet available, but observational studies have shown reduced stroke rates when the surgical decision making was guided by the results of epiaortic scanning.[7,33]

Routine Carotid-Artery Screening
Duplex ultrasonography of the carotid artery is now routinely performed in patients before they undergo CABG. Considerable stenosis (>60%) is found in 7 to 12% of patients, depending on the age group.[34] What remains unclear is how the results of preoperative carotid-artery screening can be used to modify surgical management. A recent nonrandomized study has shown an increased risk of stroke among patients undergoing combined carotid endarterectomy and CABG, as compared with patients with a similar degree of carotid stenosis undergoing CABG alone.[17] There are currently no randomized trials comparing outcomes for patients who undergo carotid endarterectomy before CABG with those for patients who undergo combined carotid endarterectomy and CABG. For now, the strategy for treating patients who have both carotid artery and coronary artery disease depends on the characteristics of the individual patient and the degree of urgency of CABG.

Intraoperative Monitoring of the Central Nervous System
Monitoring with near-infrared spectroscopy has a potential role in assessing cerebral-tissue oxygenation and the adequacy of perfusion, although persuasive data from randomized clinical trials are still lacking. Measurement of the combination of venous and arterial blood with the use of near-infrared spectroscopy may provide information about autoregulation of cerebral blood flow.[35] Desaturation of cerebral oxygenation can occur during either on- or off-pump surgery and, in observational studies, has been associated with an increased frequency of neurologic complications,[36] including a greater risk of early cognitive decline.[37]

Transcranial Doppler studies may also have a role in intraoperative monitoring of patients undergoing CABG, because microemboli from the aorta, in the form of atheroemboli, fat, or even air, can be detected by means of this imaging tech-

controversial, and evidence regarding the effect of statin use is limited to observational studies. A recent study suggests that the combination of a preoperative statin and beta-blockers may reduce the risk of postoperative stroke.[30]

Aspirin is also frequently used by patients undergoing CABG. It is safe when given during the first 48 hours after CABG, and it is associated with a reduced risk of postoperative stroke.[31] The use of aspirin before surgery has been more controversial. Although preoperative aspirin use does not appear to reduce the risk of postoperative cerebrovascular events, it has been associated with lower in-hospital mortality.[32]

Evaluation of the Heart and Aorta
More medical centers now use intraoperative epiaortic ultrasonography in an attempt to determine

Table 2. Summary of Data from Randomized, Controlled Trials Comparing the Rate of Stroke after On-Pump and Off-Pump CABG.

Study	Type of Study or Patient Population	Sample Size	Stroke Rate		Duration of Follow-up	P Value*
			On Pump	Off Pump		
		no. of patients	*percent*			
Angelini et al.[25]	Phase 1 trial†	200	3	2	1–3 yr	NS
Angelini et al.[25]	Phase 2 trial†	201	3	1	1–3 yr	NS
Nathoe et al.[26]	Low-risk patients	281	1.4	0.7	1 yr	0.55
Muneretto et al.[27]	Low-risk patients	176	2.2	0	1 yr	NS
Légaré et al.[28]	Single institution	300	0	1.3	In hospital	0.50
Puskas et al.[29]	Single surgeon	197	2.0	1.0	12 mo	NS
Shroyer et al.[2]	Male patients	2203	0.7	1.3	30 days	0.28
Møller et al.[3]	High-risk patients	341	3.7	4.0	30 days	1.00
Hueb et al.[4]	Single institution	308	2.6	1.3	In hospital	0.45

* NS denotes not significant.
† The phase 1 trial excluded patients with recent myocardial infarction and those requiring a distal circumflex graft; the phase 2 trial did not exclude these patients.

nique. However, its clinical usefulness remains limited, since emboli detected by transcranial Doppler monitoring do not appear to have clear neurologic consequences.[38]

MANAGEMENT IMPLICATIONS

Stroke continues to be a major complication of otherwise successful cardiac surgical procedures. Prediction models for stroke have been available for some time,[13] but individualized surgical-management strategies based on preoperative or perioperative screening have only recently become widely used in an effort to reduce this serious neurologic outcome.[7,39] From the preoperative to the postoperative period, the care of patients undergoing CABG is still far from standardized. Although the use of screening procedures such as epiaortic scanning may be standard at a given institution, there is still wide variation among institutions in the use of such procedures.

COGNITIVE DECLINE

The most commonly used method of assessing patients for cognitive decline after cardiac surgery is neuropsychological testing. This typically involves administering a battery of tests, before and after surgery, that examine several cognitive domains, including memory, attention, language, executive

functions, and motor speed. Although such testing allows for detection of even subtle changes in cognitive performance, it is now increasingly apparent that the incidence of both short- and long-term cognitive decline after CABG has been greatly overestimated, owing to the lack of a uniform definition of what constitutes cognitive decline, the use of inappropriate statistical methods, and a lack of control groups.

The majority of studies investigating the incidence of short-term cognitive decline after CABG assumed that any postoperative decline was specifically related to the use of cardiopulmonary bypass and therefore did not include control groups. Instead, the incidence of cognitive decline was estimated on the basis of arbitrary criteria such as "20% decline on 20% of the tests." It is now clear that the inclusion of comparison groups with risk profiles for cerebrovascular disease that are similar to those of patients who have undergone CABG is critical for determining whether postoperative cognitive decline is due to surgical events, as opposed to coexisting conditions. Thus, contemporary studies have included control groups, such as patients with or without risk factors for cerebrovascular disease who have not undergone cardiac surgery,[40] patients who have undergone percutaneous coronary intervention,[41] those who have undergone off-pump surgery,[42] and those

who have undergone noncardiac surgery.[43] Rather than using arbitrary cutoff points for decline, these studies have compared the degree of change from preoperative to postoperative cognitive performance, as a continuous variable, between the CABG group and the control group.

PREOPERATIVE COGNITIVE STATUS

An important finding for understanding the dynamics of cognitive change in the context of bypass surgery is the evidence that a considerable proportion of candidates for CABG have impaired cognitive performance even before surgery.[44] The frequency of preoperative cognitive impairment has been reported to range from 20 to 46%, with age, presence or absence of hypertension, and educational level being predictors of baseline cognitive performance.[45] Preoperative MRI studies have also documented a high prevalence of small-vessel ischemic disease, lacunar infarctions, and other brain abnormalities,[16,24,46] and patients with such preexisting imaging abnormalities or cognitive impairment have been shown to have worse postoperative cognitive outcomes than patients with normal preoperative findings.[16,47] Preoperative cognitive impairment may thus be a surrogate marker for the degree of underlying cerebrovascular disease. Because preexisting, undiagnosed silent infarctions and small-vessel disease are risk factors for adverse neurologic outcomes, it has been proposed that preoperative cognitive testing may be a cost-efficient means of identifying high-risk patients.[48]

SHORT-TERM POSTOPERATIVE COGNITIVE DECLINE

Short-term cognitive decline after CABG typically refers to changes in cognitive performance observed up to several weeks after surgery. Results from studies that have included comparison groups with coronary artery disease indicate that although mild cognitive decline does occur in some patients, there are no substantive differences in the degree of short-term cognitive change after CABG as compared with that after cardiac interventions that do not involve cardiopulmonary bypass.[41,42] Mild postoperative cognitive decline also has been reported after noncardiac surgery performed while the patient was under general anesthesia,[49] suggesting that when short-term postoperative decline does occur after CABG, it is not specific to the use of cardiopulmonary bypass.

Risk factors for cognitive decline after both cardiac and noncardiac surgery include older age and risk factors for cerebrovascular disease.[50] The pathophysiology of transient cognitive decline after cardiac and noncardiac surgery remains poorly understood. Microemboli released during the surgery have been widely assumed to be the principal cause, but few studies have shown a robust correlation between the number of emboli and cognitive outcomes.[38] There is some evidence that the systemic inflammatory response associated with the use of cardiopulmonary bypass may also play a role, but the lack of an association between levels of inflammatory markers and cognitive outcomes suggests that there may be other explanations for postoperative cognitive changes.[51] It has been hypothesized that nonspecific effects of major surgery, including postoperative pain, medications, and sleep disturbances, may also be contributing factors.[52]

Most patients in whom new cognitive symptoms develop during the immediate postoperative period can be reassured that these symptoms generally resolve within 1 to 3 months. Some patients have a subjective sense of postoperative cognitive impairment that cannot be detected by standardized neuropsychological testing. Such self-reported cognitive symptoms most commonly involve memory, as opposed to other aspects of cognition. Attempts to explain the cause of subjective memory problems have focused on psychological factors, including anxiety, depression, and coping styles, but other explanations have also been proposed.[53]

LONG-TERM POSTOPERATIVE COGNITIVE DECLINE

A study by Newman and colleagues, published in 2001, showed that 5 years after CABG, 41% of their patients had a cognitive performance that was lower than their baseline performance.[54] This finding focused attention on the possibility that cognitive decline might occur several years after surgery. The study did not include any control subjects, and its conclusions reinforced misconceptions generated by previous uncontrolled studies suggesting that cognitive decline after CABG is not only very common but is also specifically related to the use of cardiopulmonary bypass. Subsequent long-term follow-up studies comparing outcomes after CABG with those of nonsurgical controls have not confirmed this hypothesis but instead have shown that even nonsurgical patients with diagnosed coronary artery disease have a degree of late cognitive decline that is similar to the decline in patients who have
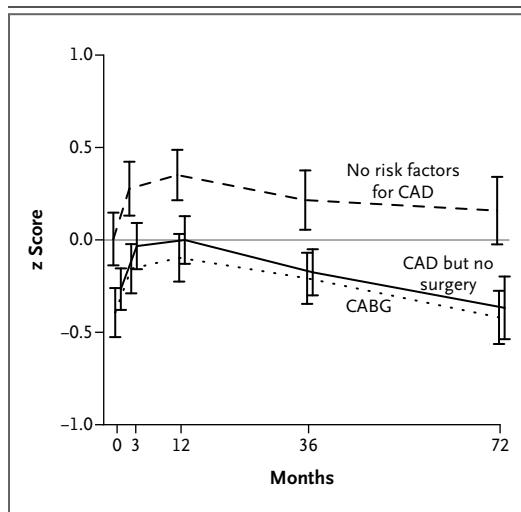
undergone CABG (Fig. 1).[40] Studies comparing cognitive outcomes after CABG with those after off-pump surgery have shown late cognitive decline in both groups, suggesting that although some degree of late decline does occur, it appears to be related to mechanisms other than cardiopulmonary bypass.[55]

Specifically, the risk of cognitive decline after coronary revascularization procedures appears to be more closely linked to the degree of preoperative cerebrovascular disease than to the surgical procedure itself. Given that many candidates for CABG have MRI evidence of cerebral infarction even before surgery,[16] it is likely that the late cognitive decline previously reported in the literature is related to the progression of underlying cerebrovascular disease. If this is the case, more consistent postoperative control of modifiable risk factors for cardiovascular and cerebrovascular disease, as well as use of lipid-lowering agents and beta-blockers, might reduce the risk of long-term cognitive changes.[56] Although the finding of mild late cognitive decline after CABG fueled speculation that the use of on-pump surgery might increase the risk of Alzheimer's disease, there are no compelling data to support this hypothesis.[57] By contrast, a recent observational study has suggested that some coronary revascularization procedures may actually confer protection from future dementia, as compared with medical management alone, although this study is limited by lack of randomization and lack of baseline cognitive assessment.[58]

Figure 1. Longitudinal Trends in Overall Cognitive Performance in Patients Who Underwent Coronary-Artery Bypass Grafting (CABG) and Two Comparison Groups.

Shown are composite z scores for overall cognitive performance in patients who underwent CABG (on-pump or off-pump), patients with coronary artery disease (CAD) who did not undergo CABG, and healthy subjects with no risk factors for CAD. The overall cognitive performance at baseline was lower in both groups with CAD than in the group of healthy subjects, and it remained lower at all follow-up times. Both groups with CAD had some cognitive decline between 12 and 72 months (referred to as late decline), but the degree of decline did not differ significantly between the nonsurgical and surgical groups. I bars indicate the 95% confidence interval for the mean of each measure. For more details, see Selnes et al.[40]

CONCLUSIONS

Although the pathogenesis of adverse neurologic events after CABG is probably multifactorial, there is growing evidence that patient-related risk factors, such as the extent of preexisting cerebrovascular and systemic vascular disease, have a greater effect on both short- and long-term neurologic sequelae than do procedural variables, such as on-pump versus off-pump surgery. Therefore, the risk of postoperative stroke or cognitive decline should not be a factor in the choice of surgical therapy for coronary artery disease.

Strategies to minimize the incidence of postoperative stroke and cognitive decline should focus on careful preoperative assessment of known risk factors, such as a history of preoperative anemia or preexisting cerebrovascular disease or infarctions. More widespread use of preoperative and

intraoperative assessment of specific risk factors, such as ascending aortic atherosclerosis, has now made it possible to individualize the surgical approach in high-risk patients and thus potentially reduce the occurrence of perioperative and postoperative strokes.

Another risk factor is the presence of preoperative mild cognitive impairment. Undiagnosed mild cognitive deficits are common in candidates for CABG even before surgery and may be a surrogate marker for underlying cerebrovascular disease. Preoperative cognitive screening may be a cost-effective way of identifying such patients. Although some degree of short-term cognitive decline may occur days to weeks after CABG, these changes are generally minor and temporary. Mild cognitive decline has also been observed years after CABG, but a similar degree of late decline has been re-

ported in patients with coronary artery disease who have not undergone bypass surgery. Late cognitive decline is thus most likely related to progression of underlying cardiovascular and cerebrovascular disease rather than to the use of cardiopulmonary bypass. One strategy for minimizing the risk of late cognitive decline after CABG may thus be strict postoperative control of modifiable risk factors for cerebrovascular disease, including diet, exercise, blood pressure, and cholesterol.

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