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Open heart surgery and cognitive decline

Mild cognitive decline occurs normally as people age, and specific at-risk populations, such as those with cerebral vascular disease or coronary disease, decline faster. Patients who undergo coronary artery bypass graft surgery (CABG) are known to have an increased risk of stroke, other serious adverse cerebral events, and cognitive decline.

This paper reviews the incidence and the short-term and long-term sequelae of neurologic injury following cardiac surgery. Possible causes of neurologic injury are discussed, as well as strategies for prevention. The potential contributions of genomics in identifying patients at high risk for neurologic injury from surgery are also discussed.

SHORT-TERM NEUROLOGIC SEQUELAE FROM CARDIAC SURGERY

Researchers from 24 US institutions evaluated 2,108 patients who had cerebral injury following cardiac surgery.[1] Outcomes were categorized into type I (stroke, coma, or death due to cerebral injury) and type II (confusion, agitation, deterioration in intellectual function, memory deficit, or seizures).

In patients who underwent CABG, the incidence of type I and type II injuries was about 3% each. Patient age was one of the strongest predictors of cerebral injury and was more important than surgical technique. The short-term consequences of neurologic injury were severe. Only 32% of patients with type I injury and 60% of patients with type II injury were discharged home vs 90% of those who did not sustain neurologic injury. In addition, 21% of patients with type I injury and 10% of patients with type II injury died during hospitalization vs 2% of those without neurologic injury. Hospital and intensive care department stays were also longer in patients with neurologic injury.

LONG-TERM NEUROLOGIC EFFECTS

The short-term effects of neurologic injury are likely the tip of the iceberg of neurologic sequelae. Our next step was to assess cognitive function and the long-term neurologic effects of cardiac surgery.

We performed neurologic and cognitive testing on 261 patients before they underwent CABG, as well as at discharge and at 6 weeks, 6 months, and 5 years.[2] Patients who had a deficit at baseline were excluded.

Four domains of cognitive function were identified that accounted for almost 80% of the variability found:

- Verbal memory and language comprehension (short-term and delayed)
- Abstraction and visuospatial orientation
- Attention, psychomotor processing speed, and concentration
- Visual memory.

Neurocognitive outcomes were defined in two ways:

- Cognitive deficit—a decline in performance in any one of the domains by 1 standard deviation or more (a reduction of 1 standard deviation represented an approximately 20% decline in function)
- Composite cognitive deficit—the reduction in the sum of scores of the four domains.

Initial deficit predicts long-term outcome

The pattern of cognitive deficits is outlined in **Figures 1 and 2**. At discharge, about half of the patients had declined in one or more domains; at 6 weeks, the percentage dropped to 36%; at 6 months, 24%; but at 5 years, 42% of the patients again had a deficit. Therefore, the pattern is one of early improvement followed by later decline.

A cognitive deficit from baseline that was evident at discharge predicted long-term outcome, even if short-term gains occurred in the meantime. At 6 weeks, patients who initially had a deficit improved to a level similar to those who never deviated from baseline levels. But after 5 years, patients who had deficits at discharge had significantly worse outcomes than those without initial deficits **(Figure 2)**.

In addition to cognitive deficit at discharge, predic-

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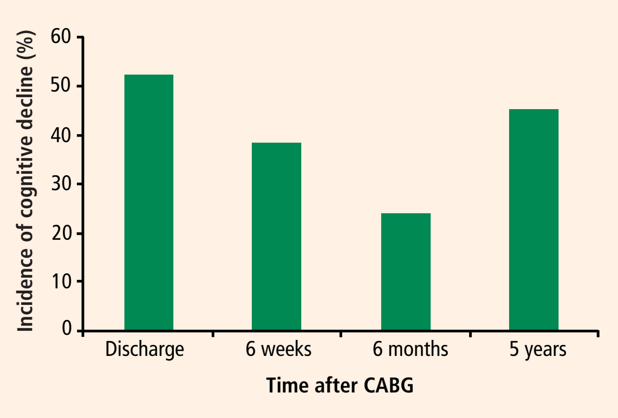

FIGURE 1. Analysis of a subset of 261 patients (from a prospective study of 2,108 patients) who underwent coronary artery bypass graft surgery (CABG) and were followed for 5 years using neurocognitive tests. Results demonstrate cognitive decline following CABG, with short-term improvement followed by a decline in cognitive function.

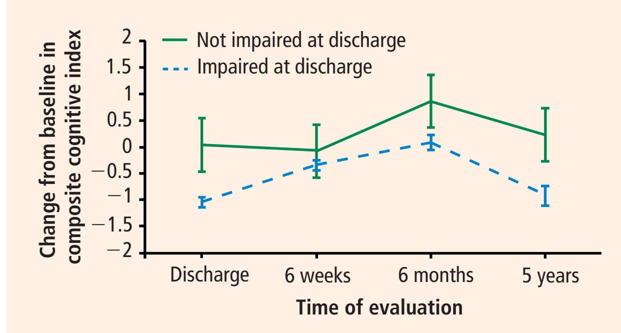

FIGURE 2. Evidence of cognitive decline at discharge, as ascertained by a composite index of four cognitive domains, was a major predictor of cognitive decline over 5 years in a longitudinal study of 261 patients who underwent elective coronary artery bypass graft surgery. Reprinted, with permission, from reference 2, copyright © 2001 Massachusetts Medical Society.

tors of cognitive dysfunction at 5 years included baseline cognitive level, age, and years of education. Ejection fraction, history of hypertension, diabetes, and surgical variables were found to be insignificant factors.

We also assessed quality-of-life factors 5 years following cardiac surgery.[3] Patients with higher levels of cognitive functioning were more likely to describe their health as excellent or very good rather than as only good, fair, or poor. Patients with higher cognitive function were also likelier to be working, either full-time or part-time, and less likely to be unemployed or disabled.

Lyketsos et al[4] took another approach to measuring neurologic effects of cardiac surgery by comparing patients who underwent CABG to those who did not. Using the Modified Mini Mental State examination, they evaluated 5,092 patients age 65 years or older, and repeated the evaluation after 3 years, then after another 4 years. Those who at baseline reported having undergone CABG or who underwent this surgery between follow-up evaluations had a significantly greater decline from baseline in mental status than those who had never undergone CABG. The decline was not evident immediately following surgery but only 5 years later. The authors noted that the cognitive decline in the CABG recipients was small, and its clinical significance not known.

POSSIBLE CAUSES OF NEUROLOGIC INJURY DURING SURGERY

Understanding the mechanisms that lead to cognitive decline following CABG may yield possible targets for prevention.

Embolic events

Neurologic sequelae could result from unstable plaques in the aortic or transverse arch breaking off and lodging in the brain during surgery. Transcranial Doppler flow studies indicate that up to several thousand air or particulate emboli commonly occur in patients undergoing bypass procedures. New devices are under investigation that can catch particulate matter or redirect it away from the brain.

More evidence that embolization occurs during cardiac surgery is revealed through alkaline phosphatase staining of the brain at autopsy. Small capillary arterial dilatations, most likely from fat or other lipids, commonly develop immediately after cardiopulmonary bypass or catheterization. These tend to disappear a month or so following the procedure.

Hyperthermia

While hypothermia has been found to be neuroprotective in several animal and human models due to reduction in glutamate release and slowing of the ischemic cascade, hyperthermia is associated with a worsening of neurologic outcomes in those same models.[5] From this work and from our work described below,[6] there has been concern that the rate at which the patients are rewarmed and the peak temperature on rewarming may alter the severity of postoperative cognitive dysfunction. At our institution, Grigore et al[6] compared patients who were rewarmed slowly (maintaining no more than 2°C difference between nasopharyngeal and cardiopulmonary bypass perfusate temperature) with patients warmed in a conventional manner (4°C to 6°C difference) following hypothermic cardiopulmonary bypass. Slower rewarming was associated with better neurocognitive function 6 weeks following surgery.

It is clear that close monitoring of nasopharyngeal temperature and control of rewarming rate and inflow temperature may have an overall effect on both the incidence and severity of neurologic injury.

STRATEGIES TO REDUCE RISK

To help determine the risk of patients who are about to undergo cardiac surgery at Duke Heart Center, we use transesophageal echocardiography, epiaortic scanning, and a stroke risk index that we developed several years ago. The stroke risk index allows rapid assessment of stroke risk by awarding points for perioperative risk factors (age, unstable angina, diabetes mellitus, neurologic disease, prior CABG, vascular disease, and pulmonary disease). These preoperative measures help us decide how we will manage temperature and mean arterial pressure during surgery.

Unfortunately, many strategies used for reducing risk are not supported by evidence from randomized controlled clinical trials showing efficacy. Once a certain technique or intervention is believed to offer a better outcome, physicians tend to adopt it, and doing otherwise seems unethical.

Hemodynamic management during cardiopulmonary bypass

Through the use of epiaortic scanning, a relationship between atherosclerotic load in the aorta and perioperative stroke risk has been firmly established.[7] Use of epiaortic scanning may represent a simple means to reduce aortic instrumentation during CABG to reduce perioperative stroke risk. In a clinical trial of 15 patients undergoing elective CABG in which intraoperative palpation alone was compared with epiaortic scanning in addition to palpation, epiaortic scanning was more sensitive than palpation alone in identifying cerebral emboli.[8] Eight of the 15 patients had an abnormal epiaortic scan with detection of plaque, whereas 4 of 15 had an abnormal aorta by palpation.

Gold et al[9] randomized 248 patients undergoing primary, nonemergency CABG to either low (50 to 60 mm Hg) or high (80 to 100 mm Hg) mean arterial pressure. The rates of both neurologic and cardiac complications were lower in patients maintained at higher arterial pressures.

Identifying risk by transesophageal echocardiography

Increasing mean arterial pressure is especially important for high-risk patients to increase collateral flow. We use transesophageal echocardiography and/or epiaortic scans to preoperatively assess risk for all CABG patients at Duke Heart Center.

Hartman et al[10] further analyzed the study by Gold et al[9] and found that patients who were at highest risk of stroke or death following CABG were those with advanced atheromatous disease of the thoracic aorta identified by transesophageal echocardiography.

Temperature management

At Duke Heart Center, in accordance with the data described previously,[5,6] we recommend avoiding hyperthermia in all patients: inflow temperature is kept at or below 37°C.

PERIOPERATIVE GENOMICS

We are starting to recognize the importance of genetic variability in the response to surgery (J.P. Mathew, MD, unpublished data, 2006). Patients enter surgery with a unique genome, which in part determines their baseline health status and disease state, as well as their response to surgical injury, cardiopulmonary bypass, anesthesia, and medications. Most patients respond well, but others respond poorly to similar circumstances; the new field of genomics may help better identify patients at high risk.

The Perioperative Genetics and Safety Outcomes Study (PEGASUS) is an ongoing prospective, longitudinal study at Duke University Medical Center involving more than 5,000 patients that is evaluating the association of clinical and genetic factors with perioperative outcomes.

Some of our preliminary findings have been published by Grocott et al.[11] Of 1,635 patients who underwent cardiac surgery, 28 (1.7%) experienced ischemic strokes. Patients having both one of the interleukin-6 minor alleles as well as one of the C-reactive protein (CRP) minor alleles had more than three times the risk of stroke as those who did not.

We also evaluated genetic factors and neurocognitive function and found that two minor alleles—one for CRP and another involved in platelet activation (P1A2)—appeared to be protective: they were associated with less than half the incidence of neurocognitive decline.[5] Genetic differences for platelet activation levels were also found in response to cross-clamp release time.[5]

Future applications

Although the types of intervention that genetic information may lead to are still uncertain, it could provide us with important future targets. We can already deduce by history and clinical factors many patients who are at high risk as well as those at the lowest risk. Patients in a "medium-risk" group, however, could be further stratified with the use of genetic information, and treated differently if additional risk factors are found.

Many controversies still surround cardiac surgery, including the use of off-pump CABG and the proper use of pharmacologic interventions such as aprotinin. Further defining patient risk could help clarify when the use of these and other interventions is appropriate.

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