In this issue of Circulation, Djaiani and associates report that the processing of shed blood with a cell saver resulted in a significant reduction in postoperative neurocognitive dysfunction after coronary artery bypass surgery (CABG) in elderly patients. The authors further implied that this significant improvement in neurocognition was a result of less lipid embolization in those patients in whom a cell saver was used. The study was a randomized double-blinded trial that compared the use of a cell saver with cardiomyotomy suction (defined as control). Cardiomyotomy suction is a standard component of cardiopulmonary bypass (CPB), in which shed blood in the mediastinum is suctioned to a venous reservoir, where it is collected and then periodically reinfused through the arterial circuit to the patient. This technique was not used in patients in the cell saver group, but rather shed blood was suctioned via the cell saver system and processed, and red blood cells alone were infused to the patient through a similar arterial circuit. A standard 32-µm filter was used in the arterial pressure line in both groups.

Elderly patients who underwent CABG were chosen because it has been documented that these individuals are at increased risk to develop neurological dysfunction after cardiac surgery. The study was powered (n=209) to see a 50% reduction in cognitive dysfunction with additional patients added (for a total of 226 patients) to compensate for potential drop out, which turned out to be similar in both groups. The primary end point of neurocognitive evaluation was based on a battery of standardized and validated tests used to assess neuropsychological outcome. Evaluation was done at baseline and on follow-up at 6 weeks. In addition to neurocognitive decline, Figure 1 in Djaiani et al also demonstrates improvement in the battery of 12 tests documenting that not all patients have a decline in cognitive function, and in fact several show improvement. This analysis of improvement has often been overlooked in previously published papers.

The authors were careful to control for all the variables associated with neurological dysfunction in patients who undergo CABG. In addition to a systemic temperature of 33°C to 34°C (nasopharyngeal), the authors used alpha stat pH management, maintained hematocrit >20% and mean perfusion pressure between 60 and 80 mm Hg, and CPB flow rates between 2.0 to 2.4 L/min per m². To minimize aortic manipulation, a single cross-clamp was used in all procedures. Prior to separation from CPB, patients were rewarmed to 36°C to 37°C, with the maximum inflow temperature during rearming limited to 37°C. Cognitive dysfunction was noted in 6% of patients in the cell saver group compared with 15% of patients in the control group. The severity of aortic atheroma, cerebral atheroma, and cerebral embolic count were similar between the 2 groups.

Postoperative morbidity, as well as extubation times, was similar between the 2 groups. One stroke and 1 death occurred in the control group. Of note was a significant increase in the transfusion of fresh frozen plasma in the cell saver group, which directly correlated with the amount of cell saver blood transfusion. This would be expected because cell saver systems, because of the nature of the process, lead to loss of coagulation factors and platelets.

The authors also suggest that the cell saver processing system removes lipid particles that, with embolization, may contribute to the postoperative cognitive dysfunction in patients who undergo CPB. Although the authors have no conclusive evidence for this statement, data are accumulating in the literature that suggests a role of lipid microembolization in patients with neurological dysfunction. It has been demonstrated that blood suctioned via the standard cardiomomyotomy suction system contains high levels of cellular debris and lipid microparticles. It also has been demonstrated that these lipid particles do embolize to the brain and are found in cerebral blood vessels. The present study supports previous nonrandomized studies that suggest the important role of cell saver use in cardiac surgery to reduce neurological dysfunction after operation when CPB is used.

The recognition of neurological complications associated with cardiac surgery has been reported since the dawn of the specialty. Neurological dysfunction can be categorized as a cerebral vascular accident (1.0% to 5.2%), encephalopathy (∼10%), and neurocognitive dysfunction (8% to 36%). It was hypothesized that off-pump cardiac surgery would lead to fewer neurological complications. However, in randomized studies this has not been shown to be true. Recent studies suggest that, rather than the type of operation, the degree of aortic manipulation may be the predominant cause of neurological injury after cardiac surgery. The current authors' controlled for this variable by use of a single aortic cross-clamp for the construction of their proximal aortic anastomoses.

Our understanding of neurological injury has significantly evolved over the last 5 years. The initial study by Newman et al suggested that long-term neurological dysfunction was associated in a significant number of patients who had undergone cardiac surgery with CPB, implying that the...
dysfunction was related to the use of CPB. A similar study was reported by our own group, which also indicated a decline in neurocognitive function 5 years after cardiac surgery with CPB.

Recent studies, however, have recognized another very important factor when neurological dysfunction after cardiac surgery is considered, specifically the degree of cognitive impairment prior to operation. One of the initial reports of preoperative neurological impairment was by Goto and colleagues, who demonstrated a 50% preoperative magnetic resonance imaging presence of silent infarcts in patients scheduled for coronary artery bypass surgery. They then correlated the extent of neurological infarct with neurological dysfunction following operation. Rosengart and colleagues demonstrated with preoperative testing that patients planning to undergo CABG had poorer cognitive function than a normal control group. Similarly, Ernest and associates compared patients planning to undergo CABG with a group of control patients who had no cardiovascular risk factors. Preoperative cognitive testing revealed that the CABG patients had significantly lower cognitive function than the healthy control group.

The pathogenesis of late neurocognitive deficits is most likely different from factors associated with early (within 3 months of operation) postoperative changes. These early neurocognitive changes, which clearly occur in a proportion of patients, are most likely related to a combination of factors that include microemboli, relative hypotension, general anesthesia, and the overall inflammatory condition initiated by CPB.

It has been our hypothesis that late cognitive changes are more likely related to the presence of preoperative neurological conditions (both known and silent) and the number of cerebral vascular and cardiovascular comorbidities that influence long-term follow-up of this at-risk population. These causative factors are more likely associated with neurocognitive changes at long-term follow-up rather than upon exposure to CPB. Support of this hypothesis was first described by Selnes and associates in 2003 and further validated in 2005 with 3-year follow-up. This longitudinal controlled study compared patients who underwent standard CABG and the use of CPB with a nonsurgical cardiac control group that comprised patients with coronary artery disease (patients diagnosed by cardiac catheterization who subsequently underwent percutaneous intervention or medical management).

Both groups were matched for similar risk factors such as diabetes, hypertension, previous stroke, and atrial fibrillation. These studies demonstrated that neurocognitive outcomes in patients who underwent standard CABG did not differ from those in a comparable control group without surgery, both at 1 and 3 years. As reported, both groups showed mild but statistically nonspecific decline between 1 and 3 years. These findings suggest that previously reported late cognitive decline after cardiac surgery is not specific to the use of CPB but rather most likely caused by patient age and the degree of cardiovascular and cerebral vascular disease risk factors.

This suggestion has been further substantiated by Müllges and associates, who studied a group of patients who underwent CABG. These patients had rigid control of their atherosclerotic risk factors and were followed up for 5 years. The authors found that, although these patients exhibited a higher degree of cognitive dysfunction immediately after operation, no individual patient showed a global cognitive decline compared with baseline at 5 years, which suggests that long-term cognitive outcome can be modified with appropriate medical management. In the stent or surgery trial, patients were followed up for up to 12 months. The 2 groups consisted of patients who underwent standard CABG with CPB and those patients who underwent percutaneous coronary intervention. They were unable to demonstrate any significant difference in neurocognitive outcome between the 2 groups of patients. Similarly, a substudy of the randomized Best Bypass Surgery trial compared neurocognitive outcomes between off-pump patients and those patients who underwent conventional CABG with CPB. They concluded that “in elderly high-risk patients, no significant difference was found in the incidence of cognitive dysfunction 3 months after either OPCAB [off-pump coronary artery bypass] or CCAB [conventional coronary artery bypass].” Recent magnetic resonance imaging studies document the risk of strokes in patients. Leary and associates at University of California, Los Angeles, estimated that 3% to 5% of persons in their 70s will have a new infarct each year. Kohn and his associates in the United Kingdom followed up on patients who had undergone CABG with magnetic resonance imaging. They found new brain infarcts in 31% of patients between 3 months and 1 year after operation. These imaging studies add additional evidence to why patients with cerebral vascular disease could definitely have a decline in cognitive function in follow-up testing.

It has been suggested that patients who undergo cardiac surgery are at increased risk for the development of dementia or Alzheimer’s disease. Recent evidence does not support this assumption. Knopman and associates reported use of the infrastructure of the records-linkage system of the Rochester Epidemiology Project and the Mayo Clinic Alzheimer’s Disease Patient Registry to perform a case-control study of CABG and dementia. After adjustment for education, the perioperative courses of patients with the disease and controls were comparable. They concluded that CABG was not a major risk factor for dementia overall or for the development of Alzheimer’s disease. A neuropathological study by Emmrich and associates examined the brains of patients who had died after coronary artery surgery. Of the 262 patients who had open heart surgery, 125 patients had isolated CABG. They found both large infarcts and hemorrhages to be common. In addition, 30% of the patients had old infarcts. With regard to Alzheimer’s pathology, 12% had a mild form and 4% had moderate disease. The majority of the deaths were within 2 weeks of the operation, which suggests that preexisting Alzheimer’s pathology was present rather than that the operation as the causative factor.

In summary, much has been learned over the past few years about neurological dysfunction after cardiac surgery. It appears that patients who undergo CABG are high risk for postoperative neurocognitive impairment on the basis of their preoperative condition. Without question, neurocognitive
deficits occur when patients are tested early after their operation. However, by 3 months the majority of neurocognitive deficits have resolved and cardiac surgical groups are similar to control groups of patients. Some patients have persistent neurological decline, and others actually test better in the postoperative period.

Incorporation of changes in clinical practice, as the article by Djaiani et al suggests regarding the use of cell savers, will hopefully incrementally limit the degree of early neurological dysfunction seen in patients who undergo cardiac surgery. Long-term results indicate that mild decline does occur in both control patients as well as patients who underwent cardiac surgery, but this decline is more suggestive of the presence of cerebral vascular risk factors and aging rather than the cause being the operation itself.

Disclosures

None.

References


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