Central nervous system injury associated with cardiac surgery

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Millions of individuals with coronary artery or valvular heart disease have been given a new chance at life by heart surgery, but the potential for neurological injury is an Achilles heel. Technological advancements and innovations in surgical and anaesthetic technique have allowed us to offer surgical treatment to patients at the extremes of age and infirmity—the group at greatest risk for neurological injury. Neurocognitive dysfunction is a complication of cardiac surgery that can restrict the improved quality of life that patients usually experience after heart surgery. With a broader understanding of the frequency and effects of neurological injury from cardiac surgery and its implications for patients in both the short term and the long term, we should be able to give personalised treatments and thus preserve both their quantity and quality of life. We describe these issues and the controversies that merit continued investigation.

The great reduction in overall cardiac morbidity and mortality associated with cardiac surgery has focused attention on central nervous system (CNS) complications, such as stroke, that can arise.[1–5] Studies suggest that elderly patients with comorbidities and advanced cardiovascular disease benefit more from cardiac surgery than from medical therapy alone,[6] yet these patients have greater morbidity and mortality, especially neurological dysfunction, after cardiac surgery.[4,7–12] CNS complications caused 7·2% of all deaths after cardiopulmonary bypass surgery in the 1970s, but rose to almost 20% by the mid-1980s, and it continues to increase.[5,13] Postoperative neurological dysfunction is also a concern because it affects quality of life and has implications for health economics.[2,14–16]

Neurological injury describes a range of disorders, from incapacitating or lethal stroke or coma to encephalopathy, delirium, and neurocognitive decline.[2,16–18] Although stroke after cardiac surgery is an important concern for both short term and long term disability, more subtle neurological effects, such as encephalopathy and neurocognitive dysfunction, are associated with increased medical costs and decreased cognitive function and quality of life.[2,16] Patients, their family members, and the medical teams find upsetting the situation of an operation being successful in its cardiac outcome, but resulting in substantial neurological or neurocognitive deficits that subsequently restrict the patient's ability to function independently.

To define the extent of perioperative neurological injury as a disease process, we reviewed studies that explored the type, incidence, and consequences of neurological injury. We excluded articles on surgery for congenital heart defects and clinical trials with a biochemical marker as the primary endpoint. We discuss the possible reasons for variability in the results of these assessments, examine the causes of neurological injury resulting from cardiac surgery, and debate the factors affecting the likelihood and the severity of injury. We conclude by examining controversial issues that need further investigation.

Search strategy and selection criteria

We searched PubMed of the National Library of Medicine for the years 1985–2005. The following search terms were used: "neurologic injury", "stroke", "cerebral injury", "cerebral complication", "cognitive disorders", "neurocognitive decline", and "neuropsychologic tests", combined with "heart surgery", "coronary artery bypass", "extracorporeal circulation", "cardiopulmonary bypass", or "CABG". This search was done to support a review of the subject area, and was not a formal meta-analysis. Although there was overlap in the articles on neurological and neurocognitive decline, we used separate criteria to assess the articles that were mainly included in our Review. We prioritised articles on "neurologic injury" on the basis of the assessment methodology used: prospective neurological evaluation, prospective data collection, or retrospective endpoint adjudication. Large-scale one-centre and multicentre databases were included, as well as frequently cited review articles or articles regarded as classic in their specialty. We limited our consideration of both neurological and neurocognitive decline to adult cardiac surgery not requiring circulatory arrest. Surgery for congenital heart defects and clinical trials with a biochemical marker as the primary outcome were also excluded. We prioritised articles on "neurocognitive decline" according to these criteria: primary assessment of cognition by well described neuropsychological tests, assessment both preoperatively and at least 1 month postoperatively, and studies published after 1980.

Incidence of perioperative central nervous system injury

To identify the incidence of neurological injury associated with cardiac surgery, we divided our discussion by the clinical outcomes that we previously mentioned, including stroke or coma, encephalopathy, and neurocognitive decline. The most frequently cited data on stroke and encephalopathy come from Roach and colleagues'[2] prospective observational study. Of 2108 patients undergoing elective coronary artery bypass grafting (CABG) in 24 institutions in the USA, there was a 6·1% incidence of adverse cerebral outcomes. Patients were assessed for two types of neurological outcome: type I outcome, which included fatal or non-fatal stroke, stupor, or coma at discharge, occurred in 3·1%; and 3% of patients had type II outcomes that included deterioration in intellectual function, memory deficit, or seizures.

In a retrospective review of 2972 consecutive cardiac surgery patients (including those with valvular surgery), Hogue and colleagues[19] showed a 1·6% incidence of stroke. 65% of these strokes happened in the postoperative period, whereby patients who had initially awakened from surgery without a deficit later had a stroke. In a report, published in 2001 based on data from the Society of Thoracic Surgery national cardiac surgery database (1996–1997), which contained information for 416 347 patients, the incidence of neurological events (stroke, transient ischaemic attack, or coma) was 3·3%.[20] Although the risk factors for perioperative stroke, which include age, presence of vascular disease, and diabetes, have increased substantially, the frequency of injury is falling in most prospective databases.[21]

Patients undergoing open-chamber procedures, such as mitral valve or aortic surgery, are believed to be at higher risk for adverse cerebral outcomes than patients whose hearts are not opened during surgery.[1,5] These patients generally have an increased risk of embolisation from vegetations, thrombi, and gaseous bubbles that are created by the intraoperative entrapment of air within the cardiac chambers. In prospective studies of patients undergoing combined intracardiac and coronary artery surgery there was a 16% incidence of adverse cerebral outcomes, divided equally between type I (8·4%; 5·9% non-fatal strokes and 1·8% death from cerebral injury) and type II (7·3%) outcomes.[5] Although retrospective evaluations show a lower rate of stroke than prospective studies, these retrospective analyses also show a two to three times higher rate of stroke in patients undergoing combined procedures than those undergoing one procedure.[19,20] Thus, patients undergoing combined intracardiac and revascularisation procedures should be judged at greatest risk for adverse cerebral outcomes.

CABG done on a beating heart (off-pump) has been said to have fewer neurological complications than other cardiac surgeries.[22] In a retrospective multivariable analysis of 16 184 adult patients undergoing cardiac surgery, Bucerius and colleagues[23] recorded a lower incidence of stroke in patients who underwent off-pump CABG than those who had other cardiac surgery. The overall frequency of stroke was 4·6% and varied between procedures: double valve or triple valve surgery, 9·7%; mitral-valve surgery, 8·8%; CABG and valve surgery, 7·4%; aortic valve surgery, 4·8%; CABG, 3·8%; off-pump CABG, 1·9%. Cleveland and others[1] reported data from the Society of Thoracic Surgeons database that showed a substantial reduction in stroke in patients who had off-pump CABG procedures. However, despite attempts to control for demographic and perioperative differences, the demographics for patients in the on-pump versus off-pump surgical groups make the results inconclusive. In the Octopus (Octopus Device, Medtronic, Minneapolis, MN, USA) study done in the Netherlands, the largest randomised trial to compare off-pump with on-pump CABG, there was no substantial difference between groups in neurological or neurocognitive injury.[24,25] Yet, despite its size (n=281), the trial was underpowered to identify neurological and neurocognitive outcome because of the inclusion of a lower-risk population. Overall, there has been insufficient randomised prospective controlled study of on-pump or off-pump CABG to assess whether either procedure is associated with improved cerebral outcome.

Perioperative neurocognitive decline

Although there is some variance in reported incidence of perioperative stroke and encephalopathy, that of perioperative neurocognitive decline shows striking variability according to the measurements included, the surgical procedure done, the inclusion and exclusion criteria for a specific study, and the criteria used to define neurocognitive decline or dysfunction.[26] A standard deviation or a percentage decline yields early dysfunction rates from 50% to 70% within the first postoperative week, which falls to 30–50% after 6 weeks, and 20–40% at 6 months and 1 year.

We examined the effect of different definitions of cognitive decline on the incidence of postoperative neurocognitive decline and noted large differences in event rates based on the definitions of deficit or decline.[26] Measurement of periprocedural change in neurological score is consistent with recommendations from consensus statements for assessment of neurocognitive decline, but other investigators have criticised the approach on the basis of statistical concerns about differences in baseline scores or absence of comparison with patients of normal neurological function.[27–29] Whichever statistical method is used, the rates of neurocognitive decline vary, dependent on the sensitivity of the test used and the degree of representation of the most sensitive and time-specific domains assessed. Neurocognitive dysfunction in the

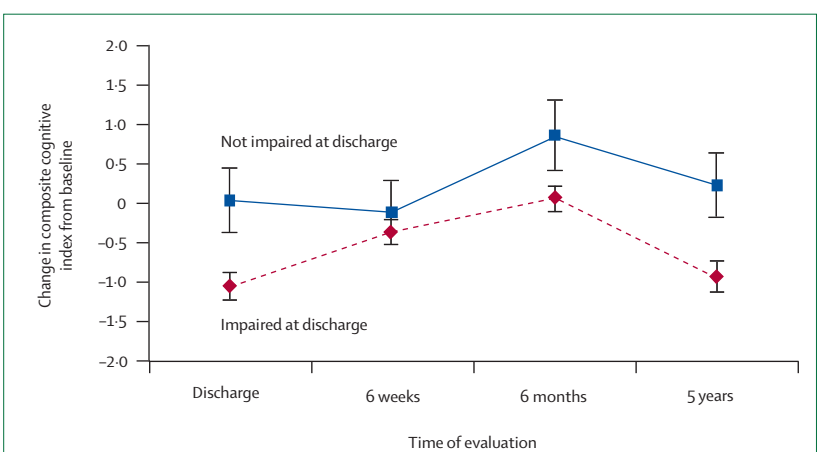


Figure 1: **Change in composite cognitive index from baseline**
The composite cognitive index is the sum of the scores for the four domains and includes cognitive decline, as well as increases in scores as a result of learning. Positive change represents an overall improvement (learning), whereas negative values indicate overall decline. Reproduced with permission of the authors[16] and the publisher.

immediate perioperative period could be related to the transient pharmacological effects of narcotics, benzodiazepines, or other anaesthetic drugs. Many investigators have therefore eliminated testing in the early postoperative period. However, later decline might be associated with factors other than perioperative neurological injuries, including recurrent injury, depression, or other neurological disorders that might not be directly related to cardiac surgery.

Precise measurement of incidence of neurocognitive decline related to cardiac surgery needs an appropriate control group. However, there has been no consensus as to whether an age-appropriate group, a group matched for coronary artery disease, or an additional surgical control is most appropriate for comparison. A substantial incidence of cognitive decline associated with non-cardiac surgery has been reported.[30,31] Therefore patients who need cardiac surgery might be appropriately compared with controls, matched by age and extent of coronary artery disease, to assess the degree of cognitive decline related to surgery compared with patient characteristics.

Several groups[16,18,32] have reported an association between early postoperative decline and long-term cognitive deterioration—both 1 and 5 years after cardiac surgery. Individuals who had cognitive decline after surgery were much more likely to have continued or increased deterioration over time, even if they showed improvement in the intervening period (figure 1).[16] There is debate as to the source of cognitive decline—ie, is the decline in function seen years after cardiac surgery directly related to the surgery or do some patients progress to cognitive deterioration, irrespective of whether they had had surgery and anaesthesia?[33] A longitudinal study is needed to ascertain the importance of both patient characteristics and surgical intervention in assessment of progression of cognitive deterioration.

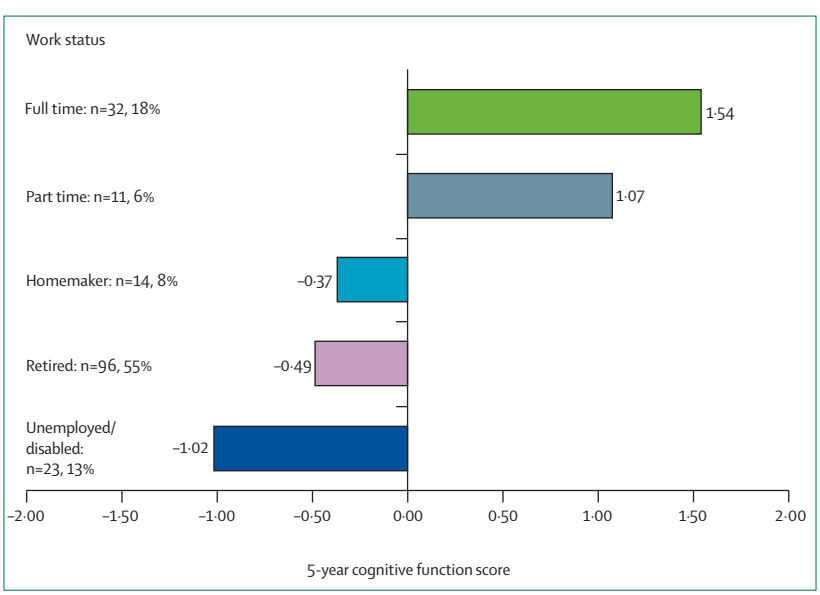


Figure 2: **Patient employment status and 5 year composite cognitive index**
The 5 year cognitive function score is the sum of the overall cognitive scores, including cognitive decline and learning effects. Reproduced with permission of the authors[14] and the publishers.

Cost of perioperative central nervous system injury

Stroke is the third leading cause of death in the USA and will continue to be a challenge as the population ages. The frequency of stroke after CABG makes this surgical procedure the leading cause of iatrogenic stroke in that country.[34] Perioperative stroke has a great cost to both the patient and to the health care system. In the early 1990s, Tuman and co-workers[35] clearly showed that perioperative CNS dysfunction increased intensive care unit stays from 3 (SD 3) days to 9 (11) days, and also resulted in a nine times greater perioperative mortality (36% *vs* 4%) than in patients without neurological injury. Similarly, Roach and colleagues[2] reported that patients with adverse cerebral outcomes had higher in-hospital mortality, longer hospital stay, and a higher rate of discharge to extended care facilities than did patients with no neurological deficit. Despite improvements in medical and surgical technology, data continue to show that postoperative stroke lengthens hospital length of stay (11 [SD 4] days *vs* 7 [3] days), days spent in the intensive care unit (2 [2] days *vs* 1 [1] days), and is associated with higher in-hospital mortality (14·4% *vs* 2·7%).[34] Treatment of perioperative stroke accounts for about 25% of the resources expended annually for stroke treatment in the USA.[36,37]

Although few people would question the importance of stroke in the perioperative period, the importance of cognitive decline after surgery has long been debated because such cognitive decline is transient in many patients. In a study using several standardised, validated assessments[14] in patients undergoing cardiac surgery, we recorded that lower cognitive function was associated with reduced quality of life measures at 5 years follow-up. Furthermore, multivariable logistic regression on a two-way classification of employment status—adjusted for age, sex, number of years in education, and diabetes showed the 5-year overall cognitive function score to be strongly correlated with productive employment (figure 2). Perception of general health also varied directly with cognitive functioning, whereby patients with lower cognitive function score at 5 years self-reported a lower quality of general health. A subsequent study in 732 patients that underwent assessment of cognitive function before and one year after coronary artery surgery noted that quality of life improved after cardiac surgery, but cognitive decline limited the improvement in activities of daily living and self-reported health.[38] Daily activities such as driving are also affected by postoperative cognitive decline. Cognitive impairment after cardiac surgery therefore can lead to various long-term consequences.[39,40]

Causes of neurological dysfunction

Understanding of risk factors patients have that are associated with perioperative CNS injury is an important

first step in beginning to understand the range of neurological dysfunctions that can occur. Several studies[18,41,42] have effectively defined stroke risk on the basis of patient characteristics and intraoperative echocardiography. The value of the use of preoperative characteristics to identify patients who are at greatest risk is the potential to alter care and give appropriate information to clinicians and patients in their treatment decisions. A stroke risk index (table 1, figure 3), on the basis of preoperative characteristics has been developed to predict a patient's risk of perioperative stroke. However, because of changes in clinical practice, the index might now overestimate true stroke risk. Nevertheless, the index does identify the key risk factors for stroke in this group of patients.

Risk factors	Score
Age (years)	(Age–25)×10/7
Unstable angina	14
Diabetes mellitus (history of either type I or type II diabetes or insulin use on admission or preoperatively)	17
History of neurological disease (previous stroke or transient ischaemic attack)	18
Previous coronary artery bypass surgery	15
History of vascular disease (peripheral vascular disease, known carotid vascular disease, claudication, or vascular surgery	18
History of pulmonary disease (emphysema, chronic bronchitis, asthma, restrictive lung disease)	15

Stroke risk is established by addition of the scores associated with the defined patient characteristic and then comparing that risk score with the predicted CNS injury risk in figure 3 (eg, risk score of 120 predicts a probability of CNS injury of 10%, about 3 times normal risk).[41]

Table 1: **Risk factors for neurological injury after cardiac surgery**

Aortic atherosclerosis and cerebral embolisation

Many investigators have identified proximal aortic atherosclerosis as a factor associated with a great increase in the risk of stroke.[43–45] Embolisation of aortic atheroma or other debris from the surgical area is an important causal factor in stroke and major neurological injury after cardiac surgery. In studies completed by Roach[2] and Waring[42] and their colleagues before the widespread use of transoesophageal echocardiography, overall risk of stroke in patients with surgeon-palpated aortic atherosclerosis was increased five-fold. Studies that used epiaortic ultrasonography confirmed the association of aortic atherosclerosis with perioperative stroke with rates increasing by five times if there was atherosclerosis in the ascending aorta.[45]

Further support for embolisation as a major factor in neurological injury has come from studies in which transcranial Doppler and carotid ultrasonography were used that have shown high rates of cerebral emboli, especially during aortic interventions, including cannulation, aortic cross-clamping or unclamping, use of partial occlusion clamps, and other non-aortic cardiac manipulations.[46–48] However, the correlation between neurological injury and the number of emboli is not as reliable as the correlation for aortic atherosclerosis measured by transoesophageal or epiaortic imaging.[49–52] This could be attributable to our inability to distinguish less harmful air emboli from the more dangerous particulate emboli.

Post-mortem examinations have revealed small capillary arteriolar dilatations[53–56] (figure 4) in the brains of patients who had recently undergone cardiac surgery with cardiopulmonary bypass.[57,58] These dilatations occur in large numbers and are the result of microembolisation of lipids or other substances that could cause perioperative neurological injury.[55]

Additional evidence showing that embolisation is an important factor in neurological injury includes studies that used MRI, which recorded that up to 45% of patients will have new diffusion-weighted magnetic resonance imaging lesions after CABG or aortic

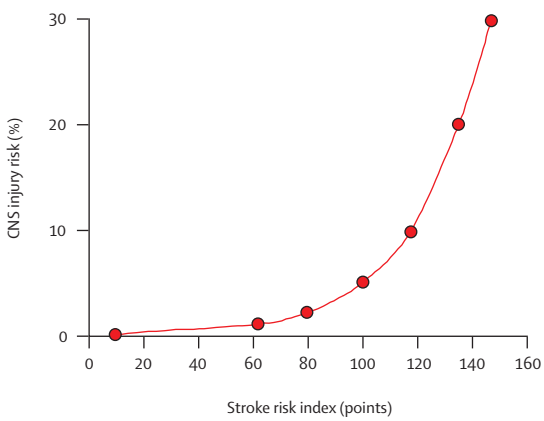


Figure 3: **The relation between stroke risk index and risk of adverse neurologic outcome**
For example, 100 total points predicts a risk of CNS injury of 5%. Reproduced with permission of the authors[96] and the publisher.

surgery.[50,51] This finding supports the arguement that persisting neurological injury happens with these procedures; however, such injury has yet to be directly linked to neurocognitive decline. Location of the neurological injury might help to predict its sequelae. For example, a small injury in the internal capsule could produce a profound stroke, whereas a large frontal or cerebellar infarct might not be detected without detailed functional investigation.

Hypoperfusion

Since the classic study by Gilman was published in 1965,[57] the presence of non-pulsatile perfusion and low blood pressure during cardiac surgery has been blamed for much of the neurological injury we have described. Features of watershed infarcts in elderly patients, especially those with carotid disease, have been important in identifying this association. Furthermore, Caplan and colleagues[58] recorded that low blood pressure can be associated with reduced washout of small emboli from

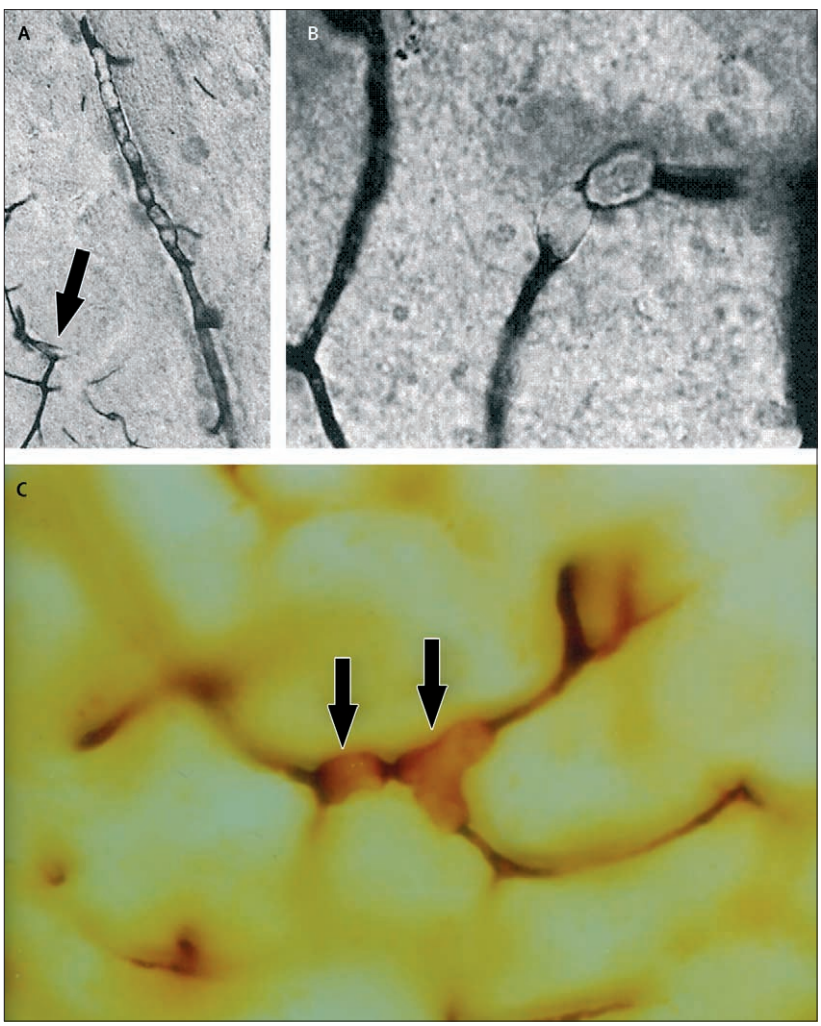


Figure 4: **Small capillary-arteriolar dilatations.**
Arrows show small capillary-arteriolar dilatations. Reproduced with permission of the authors[97] and the publisher.

the watershed areas, increasing the possibility that hypoperfusion contributes to watershed infarcts seen in cardiac surgery.

Gold and colleagues[59] did a randomised prospective trial of high (mean arterial pressure, 80–100 mm Hg) versus low perfusion pressure (50–70 mm Hg) during cardiopulmonary bypass for patients (n=240) undergoing CABG. The results of this trial did not show a significant difference in myocardial or neurological outcomes between the two groups. However, when the cardiovascular outcomes (myocardial and neurological) were combined, a greater benefit was shown for the high pressure group, suggesting that cardiovascular injury was associated, with low perfusion pressure. Hartman and colleagues[44] measured aortic atherosclerosis severity in a subset (n=189) and noted that high perfusion pressure was associated with a reduced frequency of neurological injury in individuals with severe aortic atherosclerosis. This finding suggests that in patients at high risk for embolisation, perfusion pressure could affect the severity or extent of measurable injury.

Arrythmia

Atrial fibrillation is common after cardiac surgery, with a prevalence of 20–40%.[2,60] The incidence of atrial fibrillation is increased in patients with advanced age,[2,60,61] of male sex,[61] with chronic obstructive pulmonary disease,[62,63] and with specific electrocardiographical disorders.[64] Atrial fibrillation increases intensive care unit and hospital lengths of stay, and increases the intensity of nursing care needed.[2,60,61,65,66] Atrial fibrillation is also associated with an increased incidence of postoperative neurological abnormalities (eg, stroke or transient ischaemic attack).[2,19,61,67] However, the association between atrial fibrillation and neurocognitive decline is less clear.

We investigated the association in a prospective trial of 308 patients who underwent CABG surgery and who completed cognitive testing both preoperatively and 6 weeks after surgery; 69 patients (22%) had postoperative atrial fibrillation.[68] Patients who developed atrial fibrillation showed more cognitive decline than those who did not (p=0·036). The mechanisms for this association have not been defined, but are postulated to relate to an increased risk of cerebral embolisation or hypoperfusion caused by a reduced cardiac output state. Prevention of atrial fibrillation could result in a reduced incidence of neurological injury.

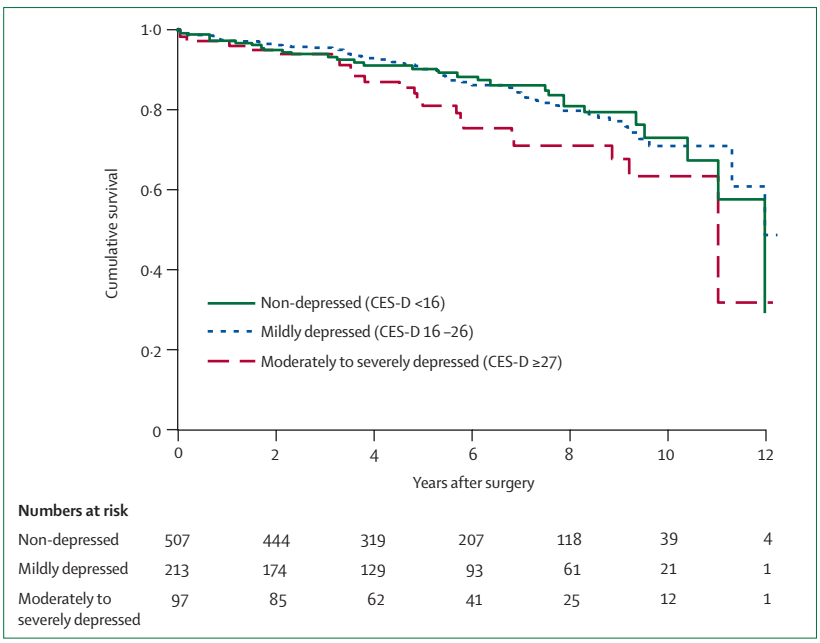
Systemic inflammatory response

Cardiac surgery is associated with a profound systemic inflammatory response, especially when cardiopulmonary bypass is used. Systemic inflammatory response might contribute to the overall severity of neurological injury,[69] but there are few data to lend support to inflammatory response alone as the causative factor. Westaby and co-workers[70] recorded no significant association between inflammatory markers and neurocognitive injury in a group of patients who underwent CABG. However, inflammation is probably a contributory factor, and not causal; thus, as we better understand the variables that affect severity of neurological injury and susceptibility factors, we can further ascertain the importance of these factors in neurological and neurocognitive injury.

Two trials that evaluated the use of a C5 complement inhibitor in cardiac surgery showed a small, but measurable beneficial effect on neurocognitive decline when complement inhibitor was given during surgery and for 24 h postoperatively.[71,72] Overall decline in neurological or neurocognitive function were not significantly changed; however, another study has shown an association between low baseline endotoxin immunity (increased susceptibility to endotoxin and subsequent inflammatory response) and cognitive decline after surgery, providing indirect evidence that individuals at heightened risk of inflammation have an increased risk of cognitive decline after cardiac surgery.[73]

Depression

Our group and other investigators have noted that depression is an independent predictor of long-term survival after surgery.[74,75] In Blumenthal's study of 817 patients, moderate-to-severe depression before CABG surgery that persisted afterwards, or postsurgical onset depression increased the risk of death to twice that of non-depressed patients[74] (figure 5). Although these findings have important implications for management of patients undergoing CABG, depression has not proved a major factor in neurocognitive decline caused by cardiac surgery.[18] Notwithstanding, depression affects patients' perceptions of their cognitive functioning, with depressed patients reporting more subjective complaints about their memory and other cognitive abilities than non-depressed patients.



Numbers at risk

Non-depressed	507	444	319	207	118	39	4
Mildly depressed	213	174	129	93	61	21	1
Moderately to severely depressed	97	85	62	41	25	12	1

Figure 5: **Kaplan-Meier survival curves for all cause mortality by baseline depression status**
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Genetic factors

An intriguing development in the specialty of neuroprotection is in the identification of genetic predisposition or susceptibility in cerebral injuries associated with cardiac surgery. In the PEGASUS study of 1635 patients who underwent cardiac surgery with cardiopulmonary bypass, DNA was isolated from preoperative blood and analysed for 26 different single-nucleotide polymorphisms. Multivariable logistic regression modeling was used to identify the association of clinical and genetic characteristics with stroke. Permutation analysis was used to adjust for multiple comparisons inherent in genetic association studies. Of 1635 patients, 28 (1·7%) had stroke and were included in the final genetic model. The combination of the two minor alleles of C-reactive protein (CRP; 3_UTR and 1846C/T) and interleukin 6 (IL-6; 174G/C) polymorphisms, occurring in 583 (35·7%) patients, was significantly associated with stroke (odds ratio 3·3; 95% CI 1·4–8·1; p=0·0023). In a multivariable logistic model adjusted for age, the CRP and IL-6 single-nucleotide polymorphism combination remained significantly associated with stroke (p=0·0020). Genetic factors associated with inflammation predicted a three-fold increase in stroke rate over and above other clinical risk factors, suggesting that genetic factors could possibly be used to identify patients for whom neuroprotective strategies would be effective.

That one's genetic makeup might alter neurocognitive outcome after cardiac surgery was first suggested in a 1997 study.[76] In that study, patients with the apolipoprotein ε4 allele had worse cognitive outcomes after cardiopulmonary bypass. Subsequent studies have not been able to replicate the results of this study, making the findings controversial.[77] Nevertheless, the 1997 study probably represents the start of our understanding of the complex role of individual genetic variations in perioperative brain injury.

Mathew and co-investigators[78] characterised Pl^{A2}, a polymorphism of the glycoprotein (GP) IIIa constituent of the platelet integrin receptor GP IIb/IIIa, and examined its effect on cognitive outcome after cardiac surgery. In their study, a multivariate analysis revealed that the Pl^{A2} genotype was significantly associated with greater decline on the mini-mental state examination (p=0·036) than other genotypes. The mechanism of this association with adverse cerebral outcome might be related to an increased prothrombotic activity, which has been shown in investigations of coronary artery thrombosis and myocardial infarction.[79,80] As technology has advanced, genetic association research has been moving from investigation of single candidate genes to multiple candidate genes to genome wide scans. Mathew and colleagues[81] have presented data related to identifying genes that better define the risk and mechanism of perioperative neurocognitive decline.

Anaesthesia

Cognitive impairment that happens up to 6 weeks after cardiac surgery has been likened to the cognitive decline after non-cardiac surgery reported by the International Study for Post-Operative Cognitive Dysfunction (ISPOCD) group.[30] The incidence of cognitive impairment with non-cardiac surgery originally seemed lower than that shown with cardiac surgery, and is comparable with the incidence in cardiac surgery patients younger than 60 years. However, there has been an increased recognition of the neurocognitive decline occurring in elderly patients after general anaesthesia for all surgeries.[31]

Although surgical stress and other factors affecting neurological outcome probably apply in cardiac and non-cardiac surgery, anaesthesia as a possible causal factor

has been incriminated by cell culture and whole animal studies.[82–84] General anaestheic agents, especially inhaled agents, could affect either short-term or long-term cognitive function, or both, by changing β amyloid deposition, protein-folding, or cholinergic receptors.[82–84] However, there are few clinical data to support the idea that repeated exposure to general anaesthesia greatly affects subsequent cognitive function.[85] Animal research and clinical trials are needed to establish whether any anaesthetic agents cause neurocognitive changes or if they affect ageing-related cognitive decline.

Pre-existing cerebrovascular disease

Studies using preoperative MRI or computer axial tomography scanning in asymptomatic elderly patients who were scheduled for cardiac surgery identified that the presence of silent infarcts could be associated with later decline in cognition or dementia.[86] The largest study, by Goto and colleagues,[86] consisted of 421 candidates scheduled for CABG; of those, 126 (30%) had small brain infarctions identified preoperatively and 83 (20%), had multiple infarctions. Half the patients had evidence of brain abnormalities before surgery; therefore, patient characteristics are probably important determinants of the probability for neurological injury seen after surgery. The findings suggest that severity of pre-existing atherosclerotic disease and amount of preoperative cognitive and neurological reserve affect postoperative cognitive function.

Controversies

In addition to the controversies discussed thus far, there are other issues surrounding the role of postoperative neurological injury in the risk of long term neurocognitive decline. These include the effect of surgical or cardiopulmonary bypass management, and the role of patient characteristics and risk factors.

Off-pump cardiac surgery

Many regard cardiopulmonary bypass as the culprit in organ dysfunction, especially neurological injury. However, the superiority of off-pump CABG in prevention of neurological or neurocognitive injury is controversial. Preliminary data suggest there is less cognitive decline and stroke associated with off-pump CABG than with on-pump CABG, but those studies were often flawed by non-random enrolment bias.[1,87] Skeptics note that many other factors are involved in triggering inflammatory processes including sternotomy, heparin administration, and wide haemodynamic swings during surgery. In addition, off-pump procedures still involve the manipulation of the ascending aorta, which is known to cause embolisation.

Van Djik and colleagues[25] showed that although there was less cognitive decline seen shortly after surgery in the off-pump group than in the on-pump group, at 1 year, no significant difference was found. There was a trend toward improvement in their low-risk trial. The failure to see a significant difference at 1 year could be because the study was underpowered.[88]

Concerns that off-pump CABG is associated with incomplete revascularisation or graft patency have added to the controversy.[89] Patients at high risk of neurological injury might accept a compromise, off-pump surgery to prevent debilitating stroke. A younger patient who has a lower risk of neurological complications, on the other hand, might instead choose to have conventional CABG to increase the chances of complete revascularisation and longer graft patency. This and other issues remain to be resolved.

Whereas there is clear radiological, pathological, and functional evidence of perioperative neurological injury after cardiac surgery,[16,50,51,53] and though we have shown an association between perioperative cognitive decline and long-term cognitive dysfunction, controversy surrounds the implications of the neurological injury and the rationale for the association. From results of 1 year and 3 year follow-up studies, Selnes[33] and McKhann[90] and their co-workers suggested that cognitive function changes in CABG patients are similar to those seen in a control group with risk factors for coronary artery disease who were followed over the same period. We investigated neurocognitive function 5 years after patients were randomised to CABG or angioplasty as part of the Bypass Angioplasty Revascularization Investigation (BARI) trial.[91] In that investigation, no difference was noted in cognitive function after 5 years; however, conclusions were limited by the lack of preoperative testing, substantial crossover between groups in the study, and patient drop-out.[91] Another small trial comparing CABG with angioplasty also failed to show a substantial difference in neurocognitive decline in patients with severe coronary artery disease undergoing revascularisation.[92,93] These trials underscore the possibility that patient characteristics might be more relevant than the type of intervention in prediction of neurological injury.[92]

Genetic and environmental factors are often impossible to characterise; thus, Potter and colleagues[94] used twins as controls and found no evidence that CABG was adversely related to cognitive function. By contrast, findings in younger patients (aged 63–70 years) revealed improvements in cognitive function after CABG. The most important issue for further longitudinal trials is whether cardiac surgery and anaesthesia interact with environmental and genetic factors to change the slope of ageing-related cognitive decline. Lyketsos and colleagues' longitudinal Cache County study[95] noted that CABG surgery increased the slope of age-related cognitive decline as measured by the mini-mental status examination. This association remained after controlling for vascular disease, but was only significant at 5 year follow-up, not at earlier milestones. Further investigation of this question will hopefully allow us to choose the most appropriate treatment for individual patients, preserving both the quantity and quality of life usually enjoyed with surgical repair of cardiac disease.

Conclusion

Almost 40 years have passed since cardiopulmonary bypass allowed the development of modern cardiac surgery. Questions immediately arose about the impact of cardiopulmonary bypass and cardiac surgery on neurological outcome. Clearly cardiac surgery has improved the quality of life of millions of patients, but despite substantial improvements in cardiopulmonary bypass technology, surgical and anaesthetic techniques, neurological injury remains a concern for the increasingly elderly patients undergoing cardiac surgery and the physicians that care for them. Large, prospective, longitudinal trials with appropriate controls remain necessary to identify how patient characteristics, disease progression, and surgical and anaesthetic technique contribute to ageing-related neurocognitive decline after anaesthesia and surgery. The brain is our most sensitive indicator of subtle organ injury. Strategies now under development to reduce perioperative neurological injury therefore not only hold the promise of protecting patients' neurocognitive function, but also of reducing the overall morbidity and mortality associated with these procedures.

Conflict of interest statement

We declare that we have no conflict of interest.

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