Central nervous system complications of cardiac surgery†

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While the number of patients undergoing surgery for valvular and other types of heart disease has remained fairly constant, the number undergoing coronary revascularization procedures is increasing (Fig. 1). Because of many technological advances over the past four decades, there has been a steady decrease in the mortality and morbidity associated with these procedures. Nevertheless, neurological injury remains an important cause of postoperative morbidity and is responsible for an increasing proportion of perioperative deaths. Since the introduction of cardiopulmonary bypass (CPB) in the early 1950s, the neurological sequelae of cardiac surgery have been a major concern. Identification of risk factors for adverse neurological and neuropsychological outcomes has led to the development of physical and pharmacological neuroprotective strategies targeted at the ‘at risk’ population.

Neurological injury after cardiac surgery

Advances in medical care and the introduction of broader indications for surgery has meant that patients previously deemed inoperable are now considered suitable candidates for surgery. Over the past 20 yr, there has been a steady increase in the average age of patients undergoing cardiac surgery. This increase has been accompanied by a rise in both the severity of cardiac disease at the time of surgery and the reoperation rate for recurrent disease. Nevertheless, the likelihood of dying or sustaining a major complication after cardiac surgery in the late 1990s is significantly lower than that in the 1950s. Not unreasonably, most patients expect to survive cardiac surgery intact, make a good functional recovery and live longer. A significant number of patients however suffer a perioperative complication involving the central nervous system (CNS).

Adverse neurological outcome from cardiac surgery is the result of damage to the brain, spinal cord and/or peripheral nerves. CNS injury ranges in severity from subtle changes in personality, behaviour and cognitive function to fatal brain injury—the ‘cerebral catastrophe’ (Table 1). A major neurological complication after otherwise successful surgery represents a devastating outcome for patient and their family. The social and economic impact is enormous.

Measures of neurological outcome after cardiac surgery

A wide variety of techniques have been used to assess adverse neurological events after cardiac surgery (Table 2) with the incidence of stroke and cognitive dysfunction being the most frequently used outcome measures. Early retrospective studies in this area could only detect what they set out to look for—neurological (e.g. coma, hemiparesis, seizures, blindness) and psychological (e.g. depression, disorientation and confusion)—problems that were sufficiently obvious to be noticed and documented.

The introduction of psychometric testing, typically measures of memory, attention, visuospatial ability and motor speed, broadened the scope and power of investigations. Prospective studies not only demonstrated the value of a multimodal (i.e. neurological and neuropsychological) approach, but highlighted the need for investigators to have the appropriate training and background.

Several difficulties associated with perioperative neurocognitive testing continue to challenge the research community. There is as yet no ‘gold standard’ against which to compare new tests. In addition, there is neither agreement

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CNS complications of cardiac surgery

Table 1

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence</th>
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</thead>
<tbody>
<tr>
<td>Fatal brain injury</td>
<td>0.3%</td>
</tr>
<tr>
<td>Non-fatal diffuse encephalopathy</td>
<td>3%</td>
</tr>
<tr>
<td>Depressed conscious level</td>
<td>1%</td>
</tr>
<tr>
<td>Behavioural changes</td>
<td>30–79%</td>
</tr>
<tr>
<td>Intellectual/cognitive dysfunction</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>0.3%</td>
</tr>
<tr>
<td>Ophthalmological</td>
<td></td>
</tr>
<tr>
<td>Visual field defects</td>
<td>25%</td>
</tr>
<tr>
<td>Reduced visual acuity</td>
<td>4.5%</td>
</tr>
<tr>
<td>Focal brain injury (stroke)</td>
<td>2–5%</td>
</tr>
<tr>
<td>Primitive reflexes</td>
<td>39%</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>0–0.1%</td>
</tr>
<tr>
<td>Peripheral nerve injury</td>
<td></td>
</tr>
<tr>
<td>Brachial plexopathy</td>
<td>7%</td>
</tr>
<tr>
<td>Other peripheral neuropathy</td>
<td>6%</td>
</tr>
</tbody>
</table>

Fig 1 The UK Society of Cardiothoracic Surgeons (SCTS) register 1977–1998. Summary of procedures carried out for ischaemic, valvular and miscellaneous acquired heart disease, and overall operative mortality. Adapted from data obtained from the SCTS web site (http://www.scts.org/doc/2104) and reproduced with permission.

Table 1 Types and initial incidence of neurological complications after cardiac surgery (reproduced and modified with permission from Shaw and colleagues)

on which tests or groups of tests should be used, nor what is (are) the optimal time(s) for administration. There is broad agreement that using a large number of tests is preferable to using only a few. The incidence of cognitive decline is reported to be higher in studies in which a larger number of tests were used than in those where only a few tests were used. Using a larger number of tests however, increases both administration time and the likelihood that some patients will not be able to complete all tests. The number of tests used and their timing in relation to surgery affects measured outcome.

There is no universally accepted method of analysing neurocognitive test results and therefore no standard for defining the incidence and severity of cognitive decline based on changes in test performance. By focusing solely on a decline in cognitive function, most investigators have ignored the fact that, with repeated testing, normal volunteers tend to show improvement in performance, a phenomenon known as the practice effect. Cognitive impairment should perhaps more correctly be defined as decline and failure to improve. Furthermore, if an age-matched control group is not used in late follow-up studies, it may be impossible to distinguish persistent perioperative neurological problems from the effects of normal ageing processes, depression or dementia.

Many confounding factors make it difficult to attempt direct comparisons between studies that have used different methodologies. In an effort to address these problems, a consensus on the use of these tests is beginning to emerge.

Markers of neuronal injury

In addition to neurocognitive testing, proteins released by the injured brain have been used to measure brain injury. After cerebral hypoxia–ischaemia, numerous substances have been shown to be released from neurones, glia, endothelium, platelets and leucocytes (Table 3). Quantification of these substances offers the potential for rapid diagnosis, making possible early interventions aimed at reducing cerebral injury. Furthermore, if the degree of elaboration of a biochemical marker can be shown to correlate with clinical (neurological and cognitive) outcome, large interventional studies could be designed that do not rely on costly and time consuming neurological and neuropsychological testing.

Although a marker of neuronal injury may provide an indication of the severity of a cerebral injury, it cannot provide information on the anatomical distribution and clinical impact of that injury. A small infarct in the internal capsule may be associated with modest release of a marker substance yet produce a disabling hemiplegia, whereas a considerably larger infarct in a frontal lobe, accompanied by massive release of marker, may produce few symptoms or physical signs.

Brain-specific creatine phosphokinase (CPK-BB) was one of the first markers to be evaluated. Marked increases in cerebrospinal fluid (CSF) concentrations were detected in dogs subjected to 60 min of CPB. Incorporation of a 40-µm arterial line filter resulted in significantly lower CSF CPK-BB concentrations compared with those in unfiltered animals. In a clinical study conducted at the Cleveland Clinic, 413 of 421 (98%) patients undergoing coronary artery bypass surgery (CABS) had increased blood concentrations of CPK-BB after surgery. There was, however, no correlation between CPK-BB concentration and the occurrence of encephalopathy or stroke.

The use of CSF adenylate kinase (CSF-AK) as a marker of cerebral injury after cardiac surgery was reported by Åberg and colleagues. A subsequent publication reported a significant correlation between CSF-AK and performance in psychometric tests. Further work characterizing CSF markers has been limited because of the methodological problems of lumbar puncture in patients who have been heparinized for CPB.

The marker that has received the most interest recently is astroglial protein $\text{S100}_\beta$. The numerous functions of
S100β include promotion of axonal growth, glial proliferation, neuronal differentiation and calcium homeostasis. Increased concentrations of S100β in both blood and CSF have been found after acute stroke, transient ischaemic attacks, head injury, intracranial haemorrhage and post-cardiac arrest coma, in addition to Alzheimer’s disease and Down’s syndrome. In acute stroke, the degree of S100β elevation correlates well with infarct volume and neurological outcome.

Several studies have demonstrated an increase in S100β after cardiac surgery. Westaby and colleagues reported a relationship between S100β concentrations and age, aortic cross-clamp time and CPB duration. Patients with carotid artery stenosis had higher concentrations of S100β than those who did not and patients who had CABS without CPB showed no increase in S100β. Peak postoperative concentrations of S100β have been shown to correlate with intraoperative cerebral microemboli quantified with transcranial Doppler sonography. The Oxford group has shown that, compared with controls, the use of an arterial line filter decreased the number of patients who had abnormal increases in S100β after surgery. The same group has also shown that intracardiac surgery (e.g. mitral or aortic valve procedures) is associated with a greater postoperative increase in S100β than CABS.

**Risk factors for adverse neurological outcome**

Soon after the introduction of CPB into clinical practice, reports of neurological injury after cardiac surgery began to appear in the literature. Early reports were small and retrospective, focusing on clinical manifestations in survivors and neuropsychological findings in non-survivors. The late 1960s and early 1970s heralded the publication of several large, retrospective studies and the recognition of the importance of patient age, cerebral hypoperfusion and cerebral embolism. During the next decade, the focus of prospective investigation moved away from stroke and coma (which were becoming increasingly uncommon) to more subtle psychological, cognitive and behavioural outcomes. More recently, investigators have examined the causes and mechanisms of neurological injury, developed indices of risk by defining predictive periooperative risk factors, and tested the beneficial effects of physical and pharmacological interventions.

Arguably one of the most significant contributions in recent years is the prospective, observational study conducted by the Multicenter Study of Perioperative Ischemia (McSPI) group at 24 US medical institutions between 1992 and 1994. The study sought to determine the incidence of neurological injury after CABS, identify independent predictors of these adverse outcomes and assess their impact on resource utilization. Two categories of adverse neurological outcome were defined: type I—non-fatal stroke, transient ischaemic attack (TIA), stupor or coma at the time of discharge, or death caused by stroke or hypoxic encephalopathy; and type II—new deterioration in intellectual function, confusion, agitation, disorientation, memory

### Table 2 Investigational methods used in the study of adverse neurological outcome after cardiac surgery

<table>
<thead>
<tr>
<th>Pathological</th>
<th>Gross and microscopic postmortem examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Retrospective chart review for mortality and gross neurological, psychiatric, cognitive complications</td>
</tr>
<tr>
<td></td>
<td>Prospective neurological and psychiatric examination</td>
</tr>
<tr>
<td></td>
<td>Neuropsychological/cognitive function testing, anxiety and depression inventories</td>
</tr>
<tr>
<td></td>
<td>Subjective (patient/spouse) reports of cognitive function</td>
</tr>
<tr>
<td>Financial</td>
<td>Duration of intensive care</td>
</tr>
<tr>
<td></td>
<td>Length of hospital stay</td>
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<tr>
<td></td>
<td>Patient charges</td>
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<tr>
<td>Social</td>
<td>Activities of daily living</td>
</tr>
<tr>
<td></td>
<td>Return to work</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Resumption of sexual activity</td>
</tr>
<tr>
<td>Brain imaging</td>
<td>Transoesophageal echocardiography</td>
</tr>
<tr>
<td></td>
<td>Carotid and transcranial Doppler quantification of microemboli</td>
</tr>
<tr>
<td>Electrophysiological</td>
<td>Brain computed tomography (CT)</td>
</tr>
<tr>
<td></td>
<td>Magnetic resonance imaging and spectroscopy (MRS)</td>
</tr>
<tr>
<td></td>
<td>Positron emission tomography (PET)</td>
</tr>
<tr>
<td>Electrophysiological</td>
<td>Electroencephalography (EEG)</td>
</tr>
<tr>
<td>Biochemical</td>
<td>Blood and cerebrospinal fluid markers of cerebral injury</td>
</tr>
<tr>
<td></td>
<td>Blood glucose, arterial pH and blood gases</td>
</tr>
<tr>
<td>Others</td>
<td>Cerebral near infra-red spectroscopy (NIRS)</td>
</tr>
<tr>
<td></td>
<td>Jugular bulb oxygen saturation</td>
</tr>
<tr>
<td></td>
<td>Retinal fluorescein angiography</td>
</tr>
<tr>
<td></td>
<td>Regional cerebral blood flow (CBF)</td>
</tr>
</tbody>
</table>

### Table 3 Potential biochemical markers of brain injury

<table>
<thead>
<tr>
<th>Source</th>
<th>Marker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glia</td>
<td>S100b, myelin basic protein (MBP)</td>
</tr>
<tr>
<td></td>
<td>Gial fibrillary acidic protein (GFAP)</td>
</tr>
<tr>
<td>Neurones</td>
<td>Neurone specific enolase (NSE), adenylate kinase (AK)</td>
</tr>
<tr>
<td></td>
<td>Creatine phosphokinase brain isoform (CPK-BB)</td>
</tr>
<tr>
<td></td>
<td>Guanine nucleotide binding protein G0, calbindin-D</td>
</tr>
<tr>
<td></td>
<td>Lactate dehydrogenase (LDH), glutamate</td>
</tr>
<tr>
<td>Inflammatory cells</td>
<td>Interleukin-6, transforming growth factor-β</td>
</tr>
<tr>
<td></td>
<td>Adhesion molecules (ICAM-1, E-selectin, neural cell adhesion molecule-NCAM)</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Lactate, Cu-Zn superoxide dismutase (CuZn-SOD)</td>
</tr>
</tbody>
</table>

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Table 4  Adjusted odds ratios [95% confidence intervals] for type I and type II cerebral outcomes associated with selected risk factors from the McSPI and IREF study. IABP = intra-aortic balloon pump; AP = arterial pressure; CABS = coronary artery bypass surgery (reproduced with permission from Roach and colleagues)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Type I outcomes</th>
<th>Type II outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal aortic atherosclerosis</td>
<td>4.52 [2.52–8.09]</td>
<td></td>
</tr>
<tr>
<td>History of neurological disease</td>
<td>3.19 [1.65–6.15]</td>
<td></td>
</tr>
<tr>
<td>Use of IABP</td>
<td>2.60 [1.21–5.58]</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.59 [1.46–4.60]</td>
<td></td>
</tr>
<tr>
<td>History of hypertension</td>
<td>2.31 [1.20–4.47]</td>
<td></td>
</tr>
<tr>
<td>History of pulmonary disease</td>
<td>2.09 [1.14–3.85]</td>
<td>2.37 [1.34–4.18]</td>
</tr>
<tr>
<td>History of unstable angina</td>
<td>1.83 [1.03–3.27]</td>
<td></td>
</tr>
<tr>
<td>Age (per additional decade)</td>
<td>1.75 [1.27–2.43]</td>
<td>2.20 [1.60–3.02]</td>
</tr>
<tr>
<td>Admission systolic AP &gt;180 mm Hg</td>
<td>3.47 [1.41–8.55]</td>
<td></td>
</tr>
<tr>
<td>History of excessive alcohol intake</td>
<td>2.64 [1.27–5.47]</td>
<td></td>
</tr>
<tr>
<td>History of CABS</td>
<td>2.18 [1.14–4.17]</td>
<td></td>
</tr>
<tr>
<td>Arrhythmia on day of surgery</td>
<td>1.97 [1.12–3.46]</td>
<td></td>
</tr>
<tr>
<td>Antihypertensive therapy</td>
<td>1.78 [1.02–3.10]</td>
<td></td>
</tr>
</tbody>
</table>

Stepwise logistic regression analysis identified eight significant, independent predictors of type I outcomes and seven significant, independent predictors of type II outcomes (Table 4). Although similar, the predictors for the two outcome types were not identical.

Factors found not to be significant predictors were: perioperative hypotension (systolic arterial pressure <40 mm Hg during CPB or <80 mm Hg at other times for more than 10 min), intraoperative use of an apical vent to decompress the left ventricle, congestive cardiac failure on the day of surgery and a history of peripheral vascular disease. Adverse neurological outcome was associated with higher in hospital mortality, increased duration of intensive care and postoperative hospital stay, increased patient charges and increased likelihood of being discharged to an intermediate or long-term care facility.

Using data obtained from the McSPI study, the Duke group went on to develop a model to predict the development of stroke after CABS. Using preoperative patient factors, the so-called stroke index allows rapid assessment of risk (Fig. 2). More recently, the McSPI group have reported adverse neurological outcomes in 43 of 273 (16%) patients undergoing combined intracardiac and coronary artery procedures. The authors concluded that this surgical population was at extraordinary risk of adverse cerebral outcome.

Patient age

Of all the factors thought to be predictive of neurological and neuropsychological injury in cardiac surgery, age is probably the most robust. The elderly appear to retain cerebral autoregulation, they are at increased risk of stroke, particularly in the presence of severe aortic atherosclerosis and occult cerebrovascular disease. The elderly are more likely to have reduced baseline cognitive function so that a relatively small perioperative decline may have a significant impact on independent living.

CNS complications of cardiac surgery
Sex

Few studies have specifically examined the influence of sex on neurological outcome after cardiac surgery.33 The main reason for this is that men greatly outnumber women in the adult cardiac surgical population. Data from the US Society of Thoracic Surgeons (http://www.sts.org/outcomes) for the years 1995 to 1996 suggest that operative mortality was significantly greater in females after both repeat and/or emergency CABS (4.30% vs 2.63%; P<0.0001) and primary elective CABS (2.9% vs 1.5%; P<0.0001). A recent report from the Bypass Angioplasty Revascularization Investigation (BARI) group however, suggests that the higher mortality observed in women is a product of higher risk profiles rather than increased gender susceptibility.65 When risk factors are controlled for, female sex was an independent predictor of improved 5-yr survival.

Laboratory evidence suggests that oestrogens have a vital role in neuronal growth, differentiation and survival.141 Furthermore, oestrogens also appear to play an important and specific role in cognitive function in women.136 The finding that oestrogen administration reverses memory deficits in women rendered hypo-oestrogenic with leuprolide acetate (a gonadotrophin releasing hormone agonist) suggests that a study of oestrogen replacement in postmenopausal women undergoing cardiac surgery is warranted.137

Severity of cardiac disease and cardiac function

An early study by Blachly and Kloster suggested that low postoperative cardiac output was related to the occurrence and severity of a postoperative brain syndrome or hallucinosis.12 Lee and colleagues reported that patients who had symptoms of cardiac disease for more than 6 months were more likely to develop neurological damage after coronary artery surgery.74 Poor preoperative left ventricular function and/or episodes of left ventricular failure have been reported to be associated with worse neurological outcome.131 134 Interestingly, the McSPI study found that neither congestive cardiac failure nor arrhythmia on the day of surgery were associated with adverse neurological outcome.123 It is possible that improvements in critical care, anti-arrhythmic therapy and support of the failing heart have reduced the impact of poor cardiac function on neurological outcome.

Cerebrovascular disease

Patients with a history of stroke or TIA are more likely to sustain a perioperative stroke.80 148 159 Patients with significant but asymptomatic atheromatus disease in the extracranial cerebral arteries may be at increased risk on the grounds that they will be more vulnerable to regional ischaemia during periods of hypoperfusion. Although preoperative detection of a carotid bruit is associated with a two-fold increase in absolute perioperative stroke risk after CABS, it is a poor measure of the severity of stenosis and has been shown not to correlate well with angiographic findings.37 In the presence of carotid disease detected by Doppler sonography, the risk of stroke is increased three-fold.20 As expected, the risk of stroke increases with the severity of carotid disease. In a follow-up study of 4047 patients examined before CABS, Brener and colleagues demonstrated that in the presence of >50% carotid stenosis, the risk of stroke increased from 1.9% to 6.3%.19 In 32 patients with complete carotid occlusion, the stroke rate was 15.6%.

In a study of 47 patients undergoing CABS at the Middlesex Hospital, studied with i.v. digital subtraction carotid angiography, 51% had evidence of atheroma and 17% had stenosis of at least one carotid artery in the neck.57 The incidence of cognitive deficit at 8 days and 8 weeks after surgery was not significantly greater in those patients with angiographically visible carotid artery disease.

A retrospective study at the Cleveland Clinic revealed that the incidence of new stroke after open-heart surgery was 13.4% in 126 patients with previous stroke.128 The likelihood of a new perioperative stroke was not related to the time interval between the previous stroke and surgery. Furthermore, the presence of extracranial occlusive disease appeared to be non-contributory. Patients who had had a stroke in the 3 months before surgery were more likely to have worsening of a prior deficit whereas those with a more remote history of stroke were more likely to have a stroke in a different brain region. Intraoperative hypotension was found to be more frequent in those patients with recent
preoperative stroke, suggesting persistent haemodynamic vulnerability. Current evidence suggests that asymptomatic extracranial cerebrovascular disease represents a modest increase in the risk of perioperative stroke, but other factors, such as embolism or hypoperfusion, are probably more important.

**Diabetes mellitus and hyperglycaemia**

For many years, the use of glucose-containing priming solutions in the extracorporeal circuit was commonplace. Although there is evidence that outcome from stroke in humans is worse in diabetics, there are no data unequivocally implicating hyperglycaemia as the cause. The higher incidence of hypertension, renal impairment and vascular disease may partly explain a worse outcome in diabetic patients. In a study of 70 patients conducted at the Middlesex Hospital, allocated randomly to either electrolyte or dextrose prime, neuropsychological outcome was found to be worse in the latter group. In a recent study using \( ^{133}\text{Xe} \) clearance, the Duke group demonstrated that insulin-dependent diabetic patients had impaired cerebral blood flow autoregulation, characterized by increased oxygen extraction, during CPB. Several reports have suggested that diabetes mellitus is a risk factor for poor neurological outcome after CPB.

In recent years, there has been a re-evaluation of the use of glucose-containing priming solutions in cardiac surgery. On the grounds that hyperglycaemia appears to worsen neurological outcome in both focal and global cerebral ischaemia, some investigators claim that hyperglycaemia during cardiac surgery is detrimental and should be avoided. Others, however, suggest that glucose administration may be beneficial.

In our experience, most centres avoid deliberate hyperglycaemia and treat intraoperative hyperglycaemia with insulin. The critical glucose concentration at which treatment should be instituted is unknown.

**Genetic susceptibility**

It is known that patients with similar physical characteristics, identical medical histories and cardiac disease of equivalent severity have markedly differing neurological and neuropsychological outcomes from uneventful cardiac surgery. This observation led investigators at Duke University to speculate that genetic factors may account for this variability. Concurrent laboratory studies, focusing on apolipoprotein E, prompted a clinical investigation.

Apolipoprotein E (APOE), a 34 kD glycosylated lipoprotein, is expressed as three common isoforms (\( \varepsilon2 \), \( \varepsilon3 \) or \( \varepsilon4 \)) in humans. Possession of the APOE\( \varepsilon4 \) allele is now known to be a risk factor for the development of late-onset and sporadic forms of Alzheimer’s disease. It may also be associated with a worse outcome after subarachnoid haemorrhage and increased severity of chronic neurological deficits in boxers exposed to chronic head trauma. Interestingly, accelerated aortic atheromatous disease and early re-stenosis after coronary angioplasty, independent of serum cholesterol, may also be associated with APOE\( \varepsilon4 \).

APOE was evaluated as a predictor of postoperative cognitive dysfunction in 65 patients undergoing CABS. A significant association was found between the APOE\( \varepsilon4 \) allele and decline in four of nine measures of cognitive function at discharge from hospital and 6 weeks after surgery.

The notion that APOE isoforms may have a role in dictating the expression of early immediate genes after neuronal injury, and thus the balance between neuronal repair and neuronal death, is attractive but requires further investigation.

**Education level, socioeconomic status and mood**

An interesting observation is that a higher number of years of formal education appears to protect patients from cognitive decline. Level of educational achievement however, correlates poorly with baseline (preoperative) cognitive function test scores.

Depression is commonly reported after cardiac surgery. The use of non-standard measures of depression, however, may have overestimated its frequency. A presumed association between postoperative depression and poor performance on psychometric tests has meant that mood assessment has become an integral component of many studies. In a recent study, the Center for Epidemiological Study of Depression (CES-D) depression questionnaire and a battery of neuropsychological tests were used to assess outcome in 124 CABS patients 1 month and 1 yr after surgery. Depression was defined as a CES-D score >16. Only 12 (13%) patients not depressed before surgery were depressed 1 month afterwards, whereas 18 (53%) of those who were depressed before surgery were depressed at 1 month (\( P=0.001 \)). One year after surgery, values were eight (9%) and 16 (47%), respectively (\( P=0.001 \)). There was little or no correlation between depression and changes in cognitive function. The inference is that cardiac surgery neither causes nor cures depression.

**Cerebral microembolization**

Emboli, which may be gaseous or particulate, can be conveniently divided into ‘macro’ and ‘micro’ according to size. Macroemboli occlude flow in arteries 200 µm or greater in diameter, whereas microemboli occlude flow in small arteries, arterioles and capillaries.

Air may reach the systemic circulation from the bypass circuit via the venous cannula, or as an inevitable consequence of left-heart surgery. Not surprisingly, systemic embolization is more common during valve surgery than CABS. The ultimate fate of bubbles depends on their initial size, the partial pressure of gases in solution and temperature, which dictates the solubility of gases in liquids. Because of high surface tension forces, small bubbles are unstable and tend to collapse. Bubbles are more likely to
grow in size during rewarming when gas solubility decreases. Although bubbles are known to traverse the cerebral vasculature, they may cause endothelial injury. 

Particulate matter can also be categorized according to composition and origin. Biological particles arise from components of the circulation (aggregates of erythrocytes, leucocytes, platelets, denatured protein, fibrin) and the operative site (thrombus, fat, calcium, cellular aggregates, atheroma, valve debris, muscle fragments, hair). Non-biological particles arise from the extracorporeal circuit and cardiotomy reservoir (polyvinyl chloride, silicone rubber, antifoam, priming solutions, cardioplegia solutions) and from foreign material introduced into the operative field (fibres from swabs, glove talc, dust).

Considerable histological, angiographic and ultrasonographic evidence suggests that cerebral embolization occurs in all patients subjected to CPB. Although it is not clear which types of microemboli cause most damage to the brain, a correlation between intraoperative cerebral microembolic load and postoperative neuropsychological dysfunction has been demonstrated. The finding, in a recent animal study, that the use of cardiotomy suction was associated with histological evidence of increased cerebral microembolization suggests that blood aspirated from the surgical field can be a major source of microemboli.

Aortic atheromatous disease

Although the possibility of atheromatous cerebral embolism during aortic surgery was recognized many years ago, it is only in recent years that this problem has been revisited. The severity of aortic atheromatous disease increases sharply with age. Postmortem studies indicate a prevalence of 20% in the fifth decade increasing to 80% in the eighth decade. The prevalence of ulcerated aortic arch atheroma at autopsy has been shown to be higher (26% vs 5%) in patients with cerebrovascular disease but appears not to be correlated with the presence of extracranial internal carotid artery stenosis. Surgical manipulations of the proximal aorta, cannulation through an atheromatous plaque or ‘sandblasting’ of the aortic wall during perfusion may cause atheroembolism. The advent of transoesophageal echocardiography (TOE) and intraoperative epicardial ultrasound has allowed a more detailed view of the aorta during surgery and quantification of atheromatous plaques according to thickness and the presence of mobile components.

The importance of aortic atheroembolism has been highlighted by Katz and colleagues who found that the incidence of stroke was 25% in patients with a mobile plaque of the aortic arch compared with 2% in those with sessile plaque. A strong association between severe aortic atheroma and postoperative stroke or death has been confirmed by others.

The successful use of intraoperative epicardial ultrasound in surgery for congenital heart lesions stimulated use of the technique in adults. Recent comparisons between intraoperative TOE and epicardial ultrasound showed conclusively that TOE underestimated the presence and severity of aortic atherosclerosis.

Several centres are currently investigating the efficacy of alterations in surgical technique based on ultrasonic evaluation of the aorta. Such alterations include aortic cannulation at a different site, avoidance of aortic cannulation altogether, avoidance of aortic cross clamping and replacement of the ascending aorta and/or aortic arch.

**Duration of cardiopulmonary bypass**

The suggestion that CPB is associated with progressive, embolic cerebral microvascular obstruction suggests a relationship between duration of bypass and adverse neurological outcome. Many investigators have either observed or suggested that neurological outcome is related to the duration of bypass but others have suggested otherwise. The finding that progressive cerebral vasoconstriction leads to a gradual decrease in cerebral blood flow during prolonged non-pulsatile hypothermic bypass may be an additional factor, but has not been substantiated.

It is important to note that bypass time may be prolonged by several factors which may themselves contribute to cerebral injury. A slow (meticulous) or ‘delayed’ surgeon may occasionally increase bypass time. It is more usual, however, that complicated surgical procedures (e.g. combined valve and CABS), complications or technical problems (e.g. haemorrhage, aortic dissection) and difficulty weaning from bypass are the main causes of prolonged bypass. It is clear that all of these factors may reflect a greater severity of cardiac disease in a population of surgical patients that have a higher incidence of adverse neurological outcomes.

**Perfusion: pressure, flow and pulsation**

Few would doubt that prolonged periods of profound arterial hypotension and cerebral hypoperfusion are bad for the brain and that certain areas, at the boundaries of cerebral artery territories (so-called ‘watersheds’), are particularly vulnerable. The influence of systemic (arterial or ‘pump’) blood flow, flow character and cerebral perfusion pressure (CPP) on CBF during CPB and neurological outcome has been the subject of considerable debate.

In addition to pressure and flow, actual CBF during CPB is determined by other factors including: acid–base management strategy, temperature, depth of anaesthesia, packed cell volume and oxygen saturation. During moderate hypothermia, cerebral autoregulation remains intact at a mean arterial pressure (MAP) as low as 30 mm Hg such that, in α-stat managed patients, CBF remains virtually constant within the range 30–100 mm Hg. Children appear to tolerate a MAP as low as 15 mm Hg. Recent evidence suggests that MAP in the range 51–75 mm Hg has a small effect on CBF during both hypothermic (+0.086 ml
100 g\(^{-1}\) min\(^{-1}\) mm Hg\(^{-1}\)) and normothermic (\(+0.178\) ml 100 g\(^{-1}\) min\(^{-1}\) mm Hg\(^{-1}\)) CPB.\(^{106, 107}\) These findings are supported by the observation that at constant pump flow, jugular venous oxygen saturation (\(S_O_2\)) correlates with CPP during hypothermic, pulsatile CPB.\(^{55}\)

Although maintenance of a perfusion pressure \(\geq 50\) mm Hg during hypothermic CPB appears to be tolerated by the majority of patients, the safety of this practice has been questioned.\(^{24}\) The obvious question is, could higher perfusion pressures (i.e. \(\geq 70\) mm Hg) improve outcome?\(^{58}\) In an attempt to answer the question, Gold and colleagues prospectively compared cardiac and neurological outcome variables in 248 patients undergoing elective CABS, allocated randomly to either lower (50–60 mm Hg) or higher (80–100 mm Hg) perfusion pressures.\(^{46}\) Six months after surgery, the overall incidence of combined cardiac and neurological complications was significantly lower in the higher pressure group (4.8% vs 12.9%; \(P=0.026\) as was the stroke rate (2.4% vs 7.2%). There were no differences in cognitive and functional outcomes. The small study population, unusually high baseline stroke rate (7.2%) and method of data analysis makes it hard to reach any definite conclusion.\(^{70, 121}\)

The observed differences in outcome could have occurred by chance but may be accounted for by the greater number of patients with aortic atherosclerosis in the lower pressure group.

During CPB, systemic flow rate is usually based on body surface area and the degree of hypothermia (typically 1.6–2.4 litre min\(^{-1}\) m\(^{-2}\)) and adjusted according to indices of the adequacy of organ perfusion (e.g. arterial blood gases). Although it is well established that low pump flow with concomitant arterial hypotension results in decreased CBF, the independent effects of low flow and low pressure are less well characterized. In a baboon model of non-pulsatile hypothermic (28°C) CPB, Schwartz and colleagues showed that, regardless of pump flow, CBF was governed by mean arterial pressure (20–60 mm Hg). Furthermore, when mean arterial pressure was maintained constant, changes in pump flow (0.75–2.25 litre min\(^{-1}\) m\(^{-2}\)) did not alter CBF.\(^{133}\) These findings are at odds with the results of several other studies of CBF during CPB.\(^{47, 125–127, 147}\)

Gouver and colleagues showed no correlation between CBF and either mean arterial pressure (30–110 mm Hg) or pump flow rate (1.0–2.2 litre min\(^{-1}\) m\(^{-2}\)) in 67 patients undergoing CABS.\(^{47}\) In contrast, Soma and colleagues reported that CBF was directly dependent on pump flow rate (40–70 ml kg\(^{-1}\) min\(^{-1}\)).\(^{147}\) The Bowman Gray group have reported the effects on CBF of alterations in arterial pressure with administration of sodium nitroprusside\(^{126}\) and phenylephrine\(^{127}\) (measured by \(^{133}\)Xe clearance) at constant pump flow. In \(\alpha\)-stat managed patients, changes in arterial pressure had no effect on CBF whereas in pH-stat managed patients, CBF was correlated positively with pressure. A subsequent study showed that modest changes in pump flow rate (1.75–2.25 litre min\(^{-1}\) m\(^{-2}\)) had no influence on arterial pressure or CBF.\(^{125}\)

Non-pulsatile perfusion is associated with diminished endothelial shear stress and a reduction in endothelial nitric oxide production leading to increased vascular resistance and end-organ dysfunction.\(^{77}\) Furthermore, it is suggested that non-pulsatile flow may cause stasis of cerebral interstitial fluid\(^{167}\) and also the cerebral swelling demonstrated after hypothermic\(^{34}\) and normothermic\(^{55}\) bypass. In a canine model of extracorporeal perfusion after 15 min of cardiac arrest, non-pulsatile perfusion was associated with worse cerebral hyperaemia and lower oxygen consumption compared with pulsatile perfusion.\(^{5}\) In a prospective study of 316 patients undergoing CABS, however, Murkin and colleagues were unable to demonstrate any influence of mode of perfusion on neurobehavioural outcome.\(^{96}\)

Despite considerable research, the characteristics of ‘optimal’ CPB perfusion remain to be defined. Within the bounds of usual CPB conduct, pressure, flow and flow character appear to have little influence on CBF.\(^{132}\) In the absence of unequivocal evidence suggesting otherwise, there seems little reason to alter perfusion practices that are tolerated by the vast majority of patients.

**Temperature**

Since the early days of cardiac surgery, systemic and regional hypothermia has been the mainstay of organ protection during CPB. Hypothermia is unique among neuroprotective modalities in that it reduces energy consumption (about 7% per °C) associated with both electrophysiological function and maintenance of cellular integrity. At modest hypothermia, autoregulation of CBF is such that CBF is tightly coupled to cerebral metabolic rate (CMRO\(_2\)). With decreasing temperature, the CBF:CMRO\(_2\) ratio increases resulting in ‘luxury’ brain blood flow. At temperatures of 15–20°C (deep hypothermia), pressure-flow autoregulation is lost. In animal models of cerebral ischaemia, mild hypothermia reduces neuronal adenosine triphosphate (ATP) depletion,\(^{169}\) and both delays the onset and reduces the rate of excitatory amino acid release.\(^{102}\)

Hypothermia does, however, have several distinct disadvantages, not least of which is the requirement for rewarming the patient at the end of the procedure. Placement of the arterial cannula in the ascending aorta results in cerebral perfusion with blood at a temperature close to that of blood leaving the heat-exchanger. For this reason it is easy to produce inadvertent cerebral hyperthermia during rewarming. The observation that warming from moderate hypothermic CPB is associated with jugular venous desaturation (\(S_O_2 <50\%\)) suggests that cerebral oxygen extraction during this period exceeds supply.\(^{29, 34}\) In a series of 255 patients studied at Duke University, the cerebral arteriovenous oxygen difference (\(C_A-O_2-C_V-O_2\)) on rewarming was significantly associated with overall cognitive decline (\(P=0.0013\)).\(^{35}\)

Rapid rates of warming, using temperatures >41°C, have long been considered a potential cause of neurological injury during CPB.\(^{22}\) Hyperthermia increases CMRO\(_2\) and
may cause protein denaturation and air embolism, in addition to tissue ischaemia.\textsuperscript{30} In a recent study, nasopharyngeal temperature ($T_{NP}$) monitoring was compared with continuous jugular venous temperature monitoring.\textsuperscript{51} Although there was a high degree of precision between the two monitoring sites, there was a marked difference in bias. This was most pronounced during rewarming when jugular venous temperature was 3.4°C higher than $T_{NP}$. The authors concluded that $T_{NP}$ monitoring underestimated brain temperature during rewarming and speculated that as a result, the brain may be at increased risk of neurological injury. However, in an unrandomized and unblinded study of 28 CABS patients, von Knobelsdorff and colleagues suggested that the use of a ‘slow’ rewarming regimen did not attenuate reductions in $S_{\text{O}_2}$.\textsuperscript{163} An accompanying editorial raised several methodological issues and advised caution in interpreting these findings.\textsuperscript{110}

The finding that even mild hyperthermia (38–39°C) increases excitotoxnic neurotransmitter release during cerebral hypoxia and delays recovery of energy metabolism is cause for concern.\textsuperscript{93} The use of mild hypothermia (34°C) after CPB and in the early postoperative period has been shown not to be associated with increased bleeding, cardiac morbidity or time to tracheal extubation.\textsuperscript{103} Any neuroprotective effect of this strategy remains to be established in prospective, randomized studies.

In recent years, studies have suggested that normothermic cardioplegia may improve myocardial protection during heart operations.\textsuperscript{93} As interest in these so-called ‘warm-hearted’ techniques has increased, their use has become widespread. The immediate concern was that abandonment of hypothermic perfusion during CPB would compromise cerebral protection and lead to a higher incidence of neurological morbidity.

To date, studies that have examined the effect of normothermic cardioplegia and CPB on myocardial and neurological outcome have yielded conflicting results. Singh and colleagues,\textsuperscript{142} 143 the Warm Heart Investigators\textsuperscript{165} and McLean and colleagues\textsuperscript{86} reported no increase in neurological complications. Martin and colleagues\textsuperscript{79} however, demonstrated a marked increase in neurological injury in patients maintained at normothermia during CPB. Directly comparing these studies is difficult because actual brain temperature was not measured and small variations in the conduct of CPB and operative technique may have had a crucial influence on temperature. This is further confounded by relatively low mean patient ages and the deliberate exclusion of patients with increased risk of perioperative stroke.

In an attempt to resolve the issue, Mora and colleagues\textsuperscript{93} compared neurological and neuropsychological outcomes in 138 patients allocated randomly to receive either intermittent cold oxygenated crystalloid cardioplegia during hypothermic ($\leq 28^\circ$C) bypass or continuous retrograde normothermic blood cardioplegia during normothermic ($\geq 35^\circ$C) bypass. All seven patients found to have new focal neurological deficits came from the normothermic group. One patient died as a result of cerebral infarction. In contrast, there were no significant differences in neurocognitive test performances, although the study was not sufficiently powered to detect a difference.

Hypothermic neuroprotection is consistent with the findings of Regragui and colleagues\textsuperscript{120} who prospectively investigated the effect of perfusion temperature (28°C, 32°C or 37°C) on postoperative cognitive function in 96 adults undergoing elective CABS with CPB. Compared with patients perfused at 32°C, the incidence of cognitive deficits was significantly higher in patients perfused at 37°C ($P = 0.021$). Cooling to 28°C appeared to offer no additional benefit.

Despite suggestions that normothermic bypass does not increase risk,\textsuperscript{85} it is interesting to note that at a meeting of researchers in the field, held in Oxford at the end of 1996, the majority of participants indicated that they would rather undergo hypothermic (32°C), rather than normothermic, bypass if they required cardiac surgery (personal communication)!

\textbf{Acid–base management}

The importance of maintaining normocapnia before the onset of CPB was highlighted by Nevin and colleagues in 1987. Three days after surgery, patients who had been inadvertently hyperventilated ($P_{\text{aCO}_2} \leq 4.7$ kPa) had a higher incidence of neurological (46% vs 27%) and psychometric (71% vs 40%) deficits than patients who were normocapnic ($P_{\text{aCO}_2} 4.7–6.0$ kPa).\textsuperscript{104}

The solubility of gases in a liquid, including blood, increases as temperature decreases. When arterial blood gases are analysed with a temperature correction during hypothermia, patients appear to have a respiratory alkalosis (decreased $P_{\text{aCO}_2}$ and increased pH). Addition of carbon dioxide to ‘normalize’ $P_{\text{aCO}_2}$ and maintain a pH of 7.40 is known as ‘pH-stat’ acid–base management. The use of arterial blood gases without temperature correction is known as ‘$\alpha$-stat’ management.

During moderate hypothermic CPB, pressure–flow autoregulation of CBF is maintained when $\alpha$-stat blood-gas management is used but lost when pH-stat management is used. The inability to autoregulate CBF at low perfusion pressures, the possibility of ‘steal’ in patients with intracranial cerebrovascular disease and the presence of ‘acidosis’ during rewarming associated with the pH-stat strategy increase the potential for brain injury. Furthermore, the excessive CBF associated with pH-stat may substantially increase the delivery of emboli to the brain.\textsuperscript{94}

The influence of pH management has been assessed by several groups. In a study of 86 patients undergoing CABS, Bashein and colleagues reported that the pH management strategy had no influence on either cardiac or neurocognitive outcome.\textsuperscript{11} Stephan and colleagues, in a prospective, randomized study of 65 patients undergoing CABS with hypothermic (26°C) CPB, reported that use of...
the pH-stat strategy was associated with cerebral hyperaemia (+191% vs -18%) and a higher incidence of neurological dysfunction 7 days after surgery (P=0.036). In a study of 316 patients undergoing CABS, cognitive dysfunction at 2 months was less prevalent after 90 min of CPB in patients managed with α-stat than with the pH-stat strategy (27% vs 44%; P=0.047). Similar findings have been reported in a study of 70 patients undergoing CABS at St Thomas’ Hospital (20% vs 48.6%; P<0.05).

In patients and animals undergoing deep hypothermic cardiac arrest (DHCA) however, pH-stat management before the onset of circulation arrest appears to improve neurological outcome. Using magnetic resonance spectroscopy in an immature piglet model of DHCA, Aoki and colleagues have shown that recovery of cerebral ATP and intracellular pH in the initial 30 min of reperfusion is faster in pH-stat managed animals. In α-stat managed animals, cerebral intracellular pH decreased during early reperfusion, whereas it showed continuous recovery in pH-stat managed animals. Postoperative brain water content (oedema) was also significantly lower in pH-stat managed animals. Possible reasons for these observations include improved brain cooling by increased blood flow to subcortical areas, improved oxygen delivery and reduction of reperfusion injury, in addition to an alkaline shift in intracellular pH with hypothermia in spite of a stable blood pH.

**Neuroprotective interventions**

It is clear that risk factors for adverse neurological outcome fall into two categories: those that cannot be modified (i.e. age, sex, genotype and medical history) and those that may (i.e. cerebral embolism, aortic atheroma, CPB duration and cerebral perfusion). Interventions designed to reduce or prevent neurological injury during cardiac surgery can be divided into two categories: (1) physical and (2) pharmacological. Table 5 summarizes some of the physical interventions that have been used or advocated.

**Pharmacological interventions**

A greater understanding of the pathophysiology of neurological injury offers the hope of pharmacological neuroprotection. At present, however, there is no agreement on the need for prophylactic neuroprotectants in cardiac surgery, much less the choice of drug.

With the exception of some anaesthetic drugs, many of the prototype neuroprotective agents studied in cardiac surgery were developed originally for the treatment of stroke. In many ways, cardiac surgery is a convenient model with which to test these agents—a large number of patients sustaining a cerebral injury at a predictable time. Unfortunately, disagreement over the precise nature of heart surgery related brain injury (focal vs diffuse ‘micro-focal’ vs diffuse), the confounding influences of other ‘standard’ neuroprotective strategies (hypothermia, blood-gas management, arterial line filtration, etc.) and the lack of a gold standard for assessment of neurological and cognitive outcomes, reduces its use as an experimental model.

The observation that certain barbiturates could reduce CMRO₂ led to extensive research into their neuroprotective potential. In 1986, Nussmeier, Arlund and Slogoff were first to report barbiturate neuroprotection in humans. One hundred and eighty-two patients undergoing open-ventricle procedures were randomized to either thiopental (an initial bolus followed by a continuous infusion—mean total dose 39.5 mg kg⁻¹), sufficient to maintain electroencephalographic silence throughout the period from before aortic cannulation to termination of bypass (n=89) or fentanyl (n=93). On the first postoperative day, clinical neuropsychiatric abnormalities were found to be more common in the control group (5.6% vs 8.6%). By day 10 after operation, all neuropsychiatric dysfunction had resolved in the thiopental group but persisted in seven (7.5%) control patients (P<0.025). The incidence of complications was related significantly to calcification of replaced valves, aortic valve replacement, advanced age and prolonged bypass, but not to hypotension during perfusion. It is curious to note that in a later publication by the same group, the background incidence of new neurological deficit was much lower.

In a similar study of patients undergoing CABS, however, no protective effect could be demonstrated. Mortality in the thiopental; group was, however, lower than in controls (0.7% vs 2.6%; P=0.018). More recently, a retrospective evaluation of 227 open-heart surgery patients revealed that thiopental (mean dose 38.1 mg kg⁻¹) had no beneficial effect on neurological outcome although mortality was significantly lower in the thiopental group (1.2% vs 9.6%; P=0.034).

Propofol has similar effects to thiopental on CMRO₂ and CBF. Although in vitro evidence suggests a direct neuroprotective action, perhaps via GABA_A receptors, it is suggested that a propofol-induced reduction in CBF reduces the delivery of microemboli to the cerebral circulation.

Calcium channel antagonists have stimulated considerable research. Of these, nimodipine, an L-type calcium channel blocker, has shown considerable promise in the management of subarachnoid haemorrhage but not acute head injury. A prospective, double-blind, randomized study of nimodipine in 400 patients undergoing valve surgery was terminated because of lack of efficacy and significant adverse events. The incidence of new neurological deficits was no different to placebo (72% vs 77%; P=0.55). In the 6-month follow-up period, mortality was significantly higher in the nimodipine group (10.7% vs 1.3%; P=0.02). Major haemorrhage was also significantly more common in the nimodipine group (13.3% vs 4.1%; P=0.04).

Prostacyclin has been used in addition to, or as a replacement for, heparin during CPB. It is known to reduce platelet aggregation during extracorporeal circulation and may therefore be neuroprotective. In 1987, Fish and
Table 5 Potentially neuroprotective physical interventions in cardiac surgery

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<tr>
<th>General considerations</th>
<th>Expeditious surgery</th>
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<tr>
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<td>Attention to myocardial preservation and haemostasis</td>
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<td>Maintaining cerebral perfusion</td>
<td>Avoid prolonged/profound arterial hypotension</td>
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<td>Avoid prolonged systemic hypoperfusion</td>
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<td>Avoid prolonged superior vena caval obstruction</td>
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<td>Consider retrograde cerebral perfusion during DHCA</td>
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<td>Reducing cerebral embolization</td>
<td>Adequate anticoagulation</td>
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<td>Minimize aortic manipulation/instrumentation</td>
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<td>Careful (de)canulation of the aorta</td>
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<td>Avoid venous air entrainment</td>
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<td>Use of arterial line filter</td>
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<td>Avoid CPB altogether (i.e. ‘beating heart’ procedures)</td>
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<td>Use of exhaustive deairing/debridement procedures</td>
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<td>Avoid or reduce use of cardiotomy suction</td>
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<td>Consider heparin-bonded circuits</td>
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<td>Temperature management</td>
<td>Moderate hypothermia (i.e. 32°C)</td>
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<td>Avoid rapid/excessive rewarming</td>
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<td>Acid–base management</td>
<td>Alpha-stat regimen (pH-stat during cooling before DHCA and in patients with significant aorto-pulmonary anastomoses)</td>
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<td>Avoid hypercapnia and hypocapnia</td>
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<td>Other</td>
<td>Avoid/treat hyperglycaemia</td>
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<td>Advanced neurological monitoring</td>
<td>Jugular venous oxygen saturation</td>
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<td>Near infrared spectroscopy (NIRS)</td>
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<td>Electroencephalography (EEG)</td>
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<td>Transcranial Doppler sonography</td>
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colleagues reported the results of a randomized, double-blind study designed to evaluate the effect of prostacyclin on the incidence and severity of postoperative neuropsychological dysfunction in 100 patients undergoing CABS. Of 96 patients who completed the psychological and neurological evaluations 1 week after surgery, 74 were evaluated psychologically 2 months after surgery. There were no differences in neurological outcome or psychological test performance.

Grieco and colleagues have recently reported the results of a double-blind, placebo-controlled pilot study of GM1 ganglioside in patients undergoing cardiac surgery. Although there was a trend towards improved neurological and neuropsychological outcome in the ganglioside treated group, the differences did not reach statistical significance. The systemic inflammatory response associated with CPB, characterized by the release of cytokines in response to activation of the coagulation, fibrinolytic and complement cascades, has been the subject of recent discussion. The bovine serine protease inhibitor, aprotinin, has been shown to significantly reduce intraoperative bleeding and transfusion requirements in a variety of settings, including cardiac surgery with CPB. Despite an early report suggesting an increased incidence in perioperative myocardial infarction there is now a suggestion, from a meta-analysis of several studies, that high-dose aprotinin may actually reduce the incidence of perioperative stroke. Whether or not this action is a result of the non-specific anti-inflammatory properties of antiproteases remains unclear. Nafamostat mesilate (FUT-175), a synthetic serine protease inhibitor, is currently under investigation in cardiac surgery. Although it is known that glucocorticoids can suppress some of the inflammatory cytokines liberated during CPB, recent laboratory evidence suggests that they may worsen neurological outcome.

Indications that free radical production increases during CPB and in cerebral ischaemia suggests a possible neuroprotective role for free radical scavengers. Desferrioxamine, which may reduce iron-catalysed free radical production, has been evaluated in 24 adult patients (12 controls, 12 treated) undergoing CPB for various cardiac operations. Desferrioxamine was given both i.v. and with the cardioplegic solution. Polymorphonuclear neutrophils (PMN) harvested from desferrioxamine-treated patients produced significantly fewer superoxide radicals than those of control patients. It was concluded that desferrioxamine-exposed PMN had decreased oxidative responsiveness. These results were thought to be consistent with the hypothesis that desferrioxamine reduces free radical-mediated amplification of the inflammatory response to CPB. Although this could be effective in reducing the harmful effects of extracorporeal circulation, no evaluation of any neuroprotective effect has been reported.

In light of experimental evidence indicating a role for excitatory amino acid neurotransmission in the pathogenesis of brain injury occurring during cardiac surgery with CPB, several compounds have reached phase II clinical trials. Of these, the competitive glutamate antagonist, remacemide hydrochloride, has been shown to improve neuropsychological outcome in a prospective, randomized, double-blind study in patients undergoing CABS. Compared with the placebo group, patients treated with remacemide showed significantly superior performance on three of 10 neuropsychological tests. Furthermore, the remacemide group had significantly greater improvement in performance on a composite measure (total z score) of neuropsychological performance ($P = 0.028$).
Numerous drugs are currently being evaluated in stroke, epilepsy, head injury, subarachnoid haemorrhage and cardiac arrest. Putative neuroprotective drugs currently under investigation in cardiac surgery include chlorpromazine, lidocaine, nicorandil and magnesium sulphate.

Summary

The neurological complications of cardiac surgery are associated with significantly increased mortality, morbidity and resource utilization. The use of new surgical techniques, introduction of wider indications for surgery and increased public expectation has led to an increase in the average age of cardiac surgical patients and an increased incidence of repeat procedures. With these changes there has come an increased risk of neurological complications.

The likelihood of perioperative stroke varies between 1% and 5% in most published series and is dependent on a multitude of risk factors. Of these, patient age, aortic atheroma, symptomatic cerebrovascular disease, diabetes mellitus and the type of surgery appear to be most important. Cognitive deterioration after cardiac surgery is far more common, affecting as many as 80% of patients a few days after surgery and persisting in one-third. Despite an increase in the age of the cardiac surgical population, the reported incidence of cognitive dysfunction after cardiac surgery seems to have fallen in recent years. Whether this is a real phenomenon or the result of changes in the use of psychometric testing and the definition of cognitive decline remains unclear.

Recognition that certain equipment, surgical practices and patient factors contribute to neurological morbidity has prompted ‘neuroprotective’ interventions. Some of these (e.g. arterial line filtration and α-stat management) have been shown to improve outcome. Despite these measures, a small number of patients will inevitably sustain cerebral injury during otherwise successful cardiac surgery. Although pharmacological neuroprotection may, in the future, offer some of these patients an improved outcome, it is unlikely that any single agent will prevent neurological injury. In the meantime, the CNS complications of cardiac surgery remain a fertile area of research.

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