

Protecting the anaesthetised brain

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Abstract

The anaesthetized brain is vulnerable to ischaemic insults, which could result in neurological deficits ranging from neuropsychological disturbances to stroke and even death. The risk of perioperative brain injury is relatively high in cardiac, neurosurgical and major vascular surgery, although it has also rarely been reported in noncardiac nonneurosurgical operations. Besides underlying risk factors such as cerebrovascular disease, advanced age, and cardiovascular disease, anaesthesia and surgery per se could also be a contributory factor. The anaesthesiologist plays a pivotal role in protecting the anaesthetized brain, both by taking preventive measures and instituting brain protection strategies. Despite advances and breakthroughs in pharmacological neuroprotection in the laboratory, currently there is no drug, anaesthetic or non-anaesthetic, which is available for clinical use. The anaesthesiologist has to rely on non-pharmacological modalities and neuromonitoring to prevent intraoperative brain injury

Key words: Cerebral ischaemia, intraoperative, neuroprotection

INTRODUCTION

The normal homeostasis, which protects the brain of the intact individual from both physiological and traumatic insult by various mechanisms, could be disturbed by anaesthesia and surgery and this could lead to cerebral ischaemia and peri-operative brain injury. In fact, the risk of stroke in the surgical population is six times higher than in the general population because of various risk factors inherent in anaesthesia and surgery. The risk of cerebral ischaemic insults varies depending on the surgery being performed and it is high in neurosurgery, cardiac surgery and vascular surgery and relatively lower in the general surgical population. Wong *et al.*, in a population-based case controlled study, found that after adjusting for risk factors, patients who had a surgery in the previous 30 days were more likely than controls to have a cerebrovascular accident (odds ratio 3.9).^[1] After excluding high risk surgery, such as cardiac, vascular and neurological procedures, the risk was still

high (odds ratio 2.9). Thus anaesthesia and surgery could be an independent predictor for developing ischaemic stroke in the peri-operative period. The effects of peri-operative brain damage can be devastating as it not only increases mortality, but it also decreases the quality of life, increases length of hospital stay, along with increased costs.

The anaesthesiologist plays a very major role in protecting the anaesthetised brain from ischaemic insults. In order to do this effectively, the anaesthesiologist must have a proper understanding of the risk factors that predispose a patient to intra-operative cerebral ischaemia and the various preventive and therapeutic measures that must be instituted to prevent intra-operative brain damage in these patients.

WHAT ARE THE RISK FACTORS THAT MAKE THE ANAESTHETISED PATIENT VULNERABLE TO BRAIN ISCHAEMIA?

The risk factors that can make the brain susceptible to ischaemia can be broadly classified as patient factors, surgical factors and intra-operative adverse events. Patient factors include the presence of co-existing disease such as history of cerebrovascular disease, underlying carotid artery disease, atrial fibrillation, advanced age, patent foramen ovale, infective endocarditis, diabetes mellitus, male gender, cigarette smoking,

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etc., Surgical factors that could predispose to cerebral ischaemia include patients undergoing neurosurgical operations, cardiac surgery and major vascular surgery. Intra-operative adverse events could also result in cerebral ischaemia and this includes cardiac arrest, severe hypotension, life-threatening arrhythmia, embolic phenomena, etc., The latter may be due to air, dislodgement of clot/plaques or other particulate matter. Besides this, surgery *per se*, as a result of the increased stress response, confers a state of 'hypercoagulability' due to increased concentration of coagulation factors, decreased concentration of coagulation inhibition factors and alterations in fibrinolysis.

The spectrum of cerebral ischaemia in the anaesthetised patient varies from global ischaemia, which may be complete or incomplete, to focal ischaemia. The classical situation where global ischaemia occurs is following intra-operative cardiac arrest. Incomplete global ischaemia occurs when there is severe hypotension (mean arterial pressure [MAP] less than 50 mmHg), or during cardiac surgery under cardiopulmonary bypass. Focal ischaemia can occur when blood flow to a specific vascular territory is interrupted and it manifests as an ischaemic stroke.

CEREBRAL ISCHAEMIA DURING SPECIFIC TYPES OF SURGERY

Cerebral Ischaemia in Neurosurgery

Patients undergoing neurosurgery are particularly vulnerable to global as well as focal ischaemia.

Global cerebral ischaemia can occur as a result of air embolism or due to severe hypotension secondary to excessive blood loss or as a result of haemodynamic changes induced by surgical manipulation of the brain or neural structures. In addition, patients may have intracranial hypertension secondary to either a space occupying lesion or intracranial bleed (traumatic or spontaneous) and this makes them vulnerable to cerebral ischaemia due to a fall in cerebral perfusion pressure (CPP). A number of neurosurgical operations are also performed in varying degrees of head up positions and care must be taken to maintain cerebral perfusion. Lastly, deliberate hypotension may be instituted during excision of highly vascular tumours or arterio-venous malformations and the neuroanaesthesiologist should maintain a CPP not less than 50 mmHg during the phase of induced hypotension. Focal cerebral ischaemia during neurosurgery could be due to direct surgical manipulation of the brain or temporary vascular occlusion (TVO) as during aneurysm clipping surgery. Direct manipulation of brain tissue can occur due to cortical incisions, retraction of brain tissue or application of ultrasonic energy or electrocautery.

Cerebral Ischaemia in Cardiac Surgery

Although there has been a progressive decline in post-operative morbidity and mortality following cardiac surgery, post-operative neurological complications still occur probably because there is a rise in the ageing population with underlying cerebrovascular disease undergoing cardiac surgery. The majority of strokes usually occur intra-operatively during cardiopulmonary bypass, although 20% can occur in the post-operative period. While the incidence of stroke following cardiac surgery is between 1% and 3%, the incidence of post-operative neurocognitive decline is seen in more than 50% of patients at hospital discharge and persisting in 30% after 6 months.^[2,3] The main causes of neurological dysfunction after cardiac surgery are due to air and particulate embolism, cerebral hypoperfusion, ischaemia-reperfusion injury, genetic predisposition and an exaggerated inflammatory response.^[4,5] More than two-thirds of strokes after cardiac surgery, as detected by diffusion weighted magnetic resonance imaging (MRI), has been found to be due to hypoperfusion and causes watershed type strokes.^[6] Even a decrease of >10 mmHg MAP during cardiopulmonary bypass (CPB), can lead to this type of hypoperfusion brain injury especially in the ageing population. Brain imaging studies have also shown that occurrence of overt strokes after cardiac surgery can be due to macroemboli resulting from atherosclerosis of the ascending aorta.^[7] Post-operative encephalopathy or neurocognitive dysfunction, in contrast, is more likely to arise from particulate matter inadvertently introduced into the surgical field, fat globules from epicardial fat or air entrained from cardiopulmonary circuit.^[8]

Studies identifying a relationship between genotype and risk for neurological complications after cardiac surgery have suggested that there could be an individual susceptibility to brain injury. Individuals with the apolipoprotein E $\epsilon 4$ allele were at higher risk for post-operative neurocognitive dysfunction than non-carriers.^[9]

Cerebral Ischaemia in Vascular Surgery

Carotid endarterectomy (CEA) is performed in patients with significant carotid artery stenosis to decrease the risk of fatal or disabling stroke. But the benefits of surgery would only be realised if peri-operative morbidity and mortality, especially the occurrence of neurological complications, is low. The risk of peri-operative stroke in patients undergoing CEA is 3.4% in asymptomatic patients and 5.2% in symptomatic patients.^[10-13] Patients undergoing CEA at risk for peri-operative stroke include those with history of recent stroke, intracranial luminal narrowing, significant contralateral narrowing or vertebral narrowing, and contralateral carotid narrowing with a history of stroke. Peri-operative stroke can be due to either intra-operative or post-operative cerebral hypoperfusion or due to embolic events. Embolism

occurring during or after the operation contributes to 60% of procedure-related stroke. Significant particulate embolism has been found to correlate with deterioration in post-operative cognitive function and evidence of new lesions on brain MRI.^[14] Cerebral hypoperfusion, in contrast, can occur either immediately after clamping or can occur 20-30 min after clamping due to relative hypotension, which reduces collateral blood flow in the contralateral carotid and vertebral arteries.^[15]

Cerebral Ischaemia in Non-cardiac, Non-neurological Surgery

A lot of attention has been focused on peri-operative neurological sequelae following cardiac surgery, neurosurgery and major vascular surgery, but there is not much data on stroke or other neurological sequelae following non-cardiac, non-neurosurgical operations such as orthopaedic, gynaecologic, thoracic, general or urologic surgery. One of the reasons is that the incidence of peri-operative neurological sequelae in this group of patients is very low (0.08-0.7%).^[16] The pathophysiology of peri-operative strokes in these patients is less well-defined as compared with other high risk surgeries and there are only few studies that have reported strokes in non-cardiac and non-neurosurgical operations.^[16-20] Based on these studies, the significant risk factors that predisposed patients to develop stroke included advanced age, history of prior stroke, renal impairment and cardiovascular disorders such as atrial fibrillation, valvular heart disease and congestive heart failure. Patients aged over 80 years have a 6-fold increase in the risk of peri-operative stroke.^[21] In contrast to patients undergoing cardiac surgery, most of the strokes in this population were due to cerebral thrombosis (68%), followed by embolism (16%) and intra-cerebral haemorrhage (5%). There are also reports of stroke and ischaemic spinal cord injury following shoulder surgery in the beach chair position (nearly 90° upright) due to possible cerebral hypoperfusion and extreme rotation of the head. Despite studies using surrogate endpoints, the risk of stroke after shoulder surgery in beach-chair position remains undefined.^[22,23]

The detection of stroke following non-cardiac, non-neurosurgical patients is quite often delayed, as it usually occurs after the patient has been shifted from the post-anaesthesia care unit, where the caregiver may not be able to detect minor strokes, covert strokes or transient ischaemic attacks. This is in contrast to peri-operative stroke in patients undergoing neurosurgery, cardiac surgery and vascular surgery where stroke is detected early as the patients are in intensive care units under close monitoring and vigilance. The mortality rate after peri-operative stroke is as high as 26%, which is twice as high as strokes occurring outside hospital. It is even higher (87%) in patients who have had previous strokes.^[24]

The neurological sequelae of intra-operative cerebral ischaemia, whatever the cause, could range from coma, seizures, stroke, delirium and neurocognitive impairment. Post-operative cognitive decline (POCD) as a result of intra-operative cerebral ischaemia is not uncommon in the post-operative period and its incidence ranges from 28% to 100% after cardiac surgery to 7-26% after non-cardiac surgical procedures.^[25,26] The anaesthesiologist could play a pivotal role in conferring cerebral protection to prevent or attenuate some of the intra-operative cerebral insults and decrease the incidence of adverse neurological sequelae. Protecting the anaesthetised brain is a paramount concern of all anaesthesiologists.

STRATEGIES FOR CEREBRAL PROTECTION

The primary prevention of peri-operative stroke is identifying patients with risk factors and optimising them before surgery to decrease their impact on neurological outcome. During anaesthesia and surgery, cerebral protection strategies need to be instituted, especially in patients at high risk for ischaemic events. These can be broadly classified as non-pharmacological or pharmacological. Despite decades of research, no major breakthrough has been achieved in the field of pharmacological neuroprotection, and the anaesthesiologist is to a large extent dependent on non-pharmacological methods for cerebral protection.

NON-PHARMACOLOGICAL METHODS – AN OVERVIEW

The advantages of non-pharmacological strategies are, they are simple, have a high risk-benefit ratio and are relatively inexpensive. They include the following:

- Hypothermia
- Maintenance of CPP
- Blood glucose concentration
- Haemoglobin concentration
- Arterial CO₂ tension
- Brain tissue oxygen tension
- Osmotherapy
- Reducing embolic load.

Hypothermia

Moderate hypothermia has been found, *in vitro* as well as *in vivo*, to have cerebral protective effects, which is briefly summed up below:

- Reduces metabolic demand of neurons
- Cerebral vasoconstriction and, thereby, decrease in cerebral blood volume, brain oedema and intracranial pressure
- Delayed anoxic/ischaemic depolarisation

- Decreases excitatory neurotransmission
- Prevention or amelioration of damaging biochemical derangements secondary to ischaemia
- Depresses programmed cell death apoptotic cascade
- Inhibits the inflammatory pathway, which leads to delayed cell death.

Hypothermia is routinely being used in cardiac surgery during cardiopulmonary bypass for brain protection. Clinicians were hopeful that mild-to-moderate hypothermia would offer cerebral protection during brain surgery as well, especially for aneurysm and arterio-venous malformation surgeries. The results of the IHAST trial in patients with aneurysmal subarachnoid haemorrhage for clipping of aneurysm categorically showed that the use of mild hypothermia intra-operatively, failed to improve neurological outcome in this patient population.^[27] In a recent meta-analysis performed to evaluate the effectiveness and safety of induced mild hypothermia versus normothermia for cerebral protection in neurosurgical operations, mild hypothermia was found to be ineffective for cerebral protection.^[28] Four randomised controlled studies were included in the meta-analysis, which included the IHAST study as well as hemicraniectomy surgery for malignant ischaemic stroke and craniotomy for traumatic brain injury.^[29-31] However, there is a role for deep hypothermia and circulatory arrest in complex and giant intracranial aneurysm surgery as it can reduce the occurrence of post-operative neurological deficits.^[32]

While the neuroprotective role of hypothermia is being questioned in neurosurgery, it is imperative that hyperthermia be avoided because of its adverse effects on the ischaemic and vulnerable brain.^[33]

Arterial Blood Pressure

During neurosurgical operations, the brain is vulnerable to both global as well as focal ischaemic insults and it is absolutely imperative that adequate CPP be maintained. In healthy adults with intact cerebral autoregulation, cerebral blood flow is maintained in a MAP range of 50-150 mmHg, but this can be impaired in patients with underlying neurological disease as well as during certain neurosurgical operations. Moreover it has been reported that CPP <60 mmHg was not uncommon in patients for neurosurgical operations as well as in patients with traumatic brain injury for non-neurosurgical operations.^[34] In both patient groups, the intracranial pressure was found to be elevated whenever the CPP was less than 60 mmHg. Therefore, moderate and severe hypotension is treated vigorously and MAP be kept above 80 mmHG and CPP be kept above 70 mmHg. This can be done with adequate fluids, vasopressors and decreasing the depth of anaesthesia.

Since the majority of neurosurgical operations are performed with varying degrees of head up tilt, and some even being done in the sitting position, it is important to zero the arterial transducer at the level of the tragus of the ear so that the correct CPP is measured. Otherwise, the CPP could be dangerously low making the patient prone to cerebral ischaemia.

Induced arterial hypertension

Induced hypertension, done by raising the MAP 20-40% above the pre-operative levels, could increase CBF through the leptomeningeal circulation and prevent cerebral ischaemia, as the circle of Willis may be incomplete in 21% of patients.

Indications of induced arterial hypertension in neurosurgery:

- Endovascular procedures for aneurysm, carotid angioplasty and intra-arterial thrombolysis
- TVO during aneurysm surgery and CEA
- Traumatic brain injury with intracranial hypertension for surgical procedures
- Extracranial to intracranial bypass surgery.

Dankbaar and Treggiari *et al.*, reported that the haemodynamic component of the triple H therapy is more important than haemodilution and hypervolaemia. Induced hypertension increases cerebral blood flow and cerebral perfusion and results in reversal of neurological deficits in two-thirds of patients with subarachnoid haemorrhage.^[35,36] Stoneham has also reported reversal of neurological deficits due to cerebral ischaemia with elevation of blood pressure during CEA performed on awake patients under regional anaesthesia and an internal carotid artery shunt was not needed in these patients.^[37] Arterial hypertension can be induced with an alpha agonist like phenylephrine as it increases the CBF. Alternately, dopamine, dobutamine and vasopressin can also be used.

Normoglycaemia

There is a general consensus that hyperglycaemia in patients at risk of cerebral ischaemia, either general or focal, increases the likelihood of brain injury and is associated with a worse neurological outcome. Pasternak *et al.*, using a *post hoc* analysis of the IHAST study, found that patients who, at the time of clipping of aneurysms, had blood sugar levels >152 mg/dl had worse neurological outcome.^[38] He also reported that patients with a blood sugar level of >128 mg/dl had worse neuropsychological function. A review of patients with a variety of neurosurgical disorders undergoing interventional neuroradiology also found that high blood glucose levels were associated with unfavourable neurological outcomes.^[39] Hyperglycaemia appears to increase recruitment of ischaemic penumbral neurons

into the infarcted area, but it had little impact on irreversibly ischaemic neurons.^[40]

At the same time, the human brain depends on systemic glucose supply for its metabolism and hypoglycaemia is not well tolerated. Indeed, glucose deficit can have deleterious effects on the brain, as there are differences in cerebral versus systemic glucose metabolism and intensive insulin therapy to obtain tight glucose control may cause a substantial increase in the number of hypoglycaemic episodes and a high mortality rate.^[41,42] Thus, while hyperglycaemia may have numerous untoward consequences, iatrogenic hypoglycaemia may initiate a metabolic crisis in the brain that is even worse. A microdialysis study in patients with severe brain injury found that systemic glucose levels in the range of 80-120 mg/dl resulted in low cerebral microdialysis levels of glucose, high lactate/pyruvate ratio and increased rate of brain energy crisis as compared when the systemic glucose was maintained between 121 and 180 mg/dl.^[43] This could be associated with increased mortality and they concluded that intensive insulin therapy in patients with brain injury could impair cerebral glucose metabolism.

So what are the target blood sugar levels in neurosurgical patients?

At present, there is no consensus or data on the optimal intra-operative blood glucose level that would not compromise neurological integrity. The aim of the anaesthesiologist would be to prevent extremes of blood sugar fluctuations and maintain blood glucose level between 140 and 180 mg/dl.^[39,42]

Haemoglobin/Haematocrit

The potential mechanisms for anaemia-induced brain injury can be attributed to tissue hypoxia, inflammation, reactive oxygen species generation, excitotoxicity and activation of deleterious hypoxic cell signalling pathways.^[44] Hare *et al.*, identified the up-regulation of neuronal molecules that could be neuroprotective in response to severe acute anaemia.^[45] These include neuronal nitric oxide synthase (nNOS), hypoxia-inducible factor-1 α and vascular endothelial growth factor. A rise in nNOS causes the hypoxia-inducible factor to stimulate responses to anaemia like angiogenesis, erythropoiesis and increase in cellular glucose. He also reported a finding that methaemoglobin (MetHb) may be a potential biomarker of hypoxic-anaemic stress during haemodilution while on CPB. If increasing MetHb is associated with bad outcomes, then this could be a trigger for peri-operative blood transfusion.

Risks associated with allogenic transfusion, and based upon randomised, controlled trials, the current practice guidelines for blood transfusion recommend

a transfusion trigger of 7 g/dl in adults as well as in children.^[46] *But would this haemoglobin be appropriate for patients with neurological problems undergoing neurosurgical operations or patients undergoing cardiac surgery, where the risk of peri-operative brain injury and stroke is high?* There is a growing body of evidence, which suggest that anaemia is an independent risk factor for peri-operative neurological injury especially in cardiac surgical patients.^[47] But there is a dearth of clinical data regarding the association between pre-operative anaemia, low intra-operative haemoglobin and neurological outcomes in neurosurgical patients although there is evidence that low haemoglobin can be deleterious in patients with underlying neurological problems like non-traumatic intra-cerebral haemorrhage and subarachnoid haemorrhage.^[48-50]

The precise haemoglobin threshold for brain tissue injury during neurologic procedures leading to poor outcomes is not known. Recommendations on blood transfusion policy in order to avoid peri-operative neurological injury is difficult to make due to lack of prospective, randomised clinical trials to assess neurological outcomes at different haemoglobin levels. However, on the basis of the available evidence, it is recommended that in neurosurgical patients, pre-operative and intra-operative haemoglobin levels should be maintained at least 12 and 9 g/dl, respectively.^[51]

Meanwhile, in future, characterisation of cerebral protective mechanisms induced by anaemia may improve clinical outcomes and enable clinicians to develop treatment strategies that will prevent cerebral injury as a result of anaemia. These include NOS/NO dependent optimisation of cerebral oxygen delivery and cytoprotective mechanism including HIF-1 α , erythropoietin, and vascular endothelial growth factor. Lastly, ischaemic pre-conditioning by transient pre-operative exposure to mild anaemia can confer cerebral protection. This could be performed pre-operatively by using autologous blood donation as part of blood conservation techniques. Simultaneously, treatment with erythropoietin could restore baseline haemoglobin levels, which could not only avoid the risk of pre-operative anaemia but would also be cytoprotective, because it also can cause ischaemic pre-conditioning.^[44]

The other non-pharmacological measures to prevent cerebral ischaemia, particularly in neurosurgical patients, would be to maintain adequate cerebral blood flow by avoiding hypocarbia and provide brain relaxation by administering osmotic diuretics especially in the presence of intracranial hypertension. Occasionally, malignant brain oedema can occur during surgery, which could result in brain injury due to mechanical as well as ischaemic causes. This has to be treated aggressively in order to avoid post-operative neurological deficits.

NON-PHARMACOLOGICAL BRAIN PROTECTION IN CARDIAC SURGERY

Neuroprotection during cardiac surgery involves reducing the source of injury due to either hypoperfusion or embolic phenomena and increasing brain tolerance to ischaemic insults and involves both non-pharmacological and pharmacological neuroprotection.

Non-pharmacological neuroprotection includes the following:

- Epiaortic ultrasound
- Pericardial suction aspirate
- Mediastinal CO₂ insufflation
- Cardiopulmonary bypass flow
- Blood pressure management
- Avoidance of cardiopulmonary bypass
- Haemoglobin/haematocrit target
- Temperature management
- Glycaemic control.

Epiaortic Ultrasound

Embolisation of atheromatous plaques on the ascending aorta is an important cause for stroke and neurocognitive dysfunction after cardiac surgery.^[52] This usually occurs during surgical manipulation of the ascending aorta at the time of aortic cannulation or while applying the aortic cross clamp. Epiaortic ultrasound is one of the most sensitive devices to detect atheromas on the ascending aorta.^[53] Epiaortic-guided surgery leads to reduced cerebral embolic signals as detected by trans-cranial Doppler along with better neurological outcomes.^[54] But despite careful handling of the ascending aorta, peri-operative neurological events have occurred and this is best exemplified in 'off' pump cardiac surgery, where the aorta is not surgically manipulated.

Pericardial Suction Aspirate

Small arteriolar capillary dilatations (SCADs) in the brain can occur due to embolisation of fat returned unfiltered to the CPB circuit from the cardiotomy reservoir resulting in lipid laden cerebral embolisation.

Can processing the cardiotomy aspirate with a cell saver prevent SCADs?

Experimentally, it has been shown that arterial line filters are not efficient in preventing SCADs when compared with pericardial suction aspirate that has been processed through a cell saver.^[55] But human studies have not validated this finding. Kaza *et al.*, found that dual arterial filtration of shed cardiotomy blood was more efficient in preventing cerebral fat emboli when compared with cell saver.^[56] More recently, Rubens *et al.*, found that processing of cardiotomy reservoir blood before re-infusion was not superior to re-infusion of

unprocessed blood in terms of neurocognitive function at hospital discharge and at 3 months after surgery.^[57] In fact, these authors found that the group of patients who were re-infused blood processed in a cell saver had greater transfusion requirements. In contrast to this study, Djaiani *et al.*, found that using a cell saver in elderly patients lead to a lower incidence of cognitive dysfunction when compared with patients who received pericardial aspirate without processing and it may be useful to prevent neuropsychological dysfunction in this high risk group of patients undergoing coronary artery bypass grafting (CABG) surgery.^[58]

CO₂ Insufflation into Mediastinum

Since CO₂ is 50 times heavier and 25 times more soluble in blood than in air, it has been postulated that insufflation of CO₂ into the surgical field, would displace air and decrease the nitrogen content of gaseous emboli. Carbon dioxide containing emboli has a shorter lifespan in the microcirculation than nitrogen filled emboli and, therefore, can limit cerebral injury. Despite this, CO₂ insufflation during CPB has not shown to decrease cognitive dysfunction following cardiac surgery.^[59]

Cardiopulmonary By pass Flow

Pulsatile flow for CPB perfusion is superior to non-pulsatile flow as, besides its many other advantages, it has beneficial effects on the brain. In canine experimental models, pulsatile CPB was found to increase CBF and brain oxygenation as compared with non-pulsatile flow.^[60] The higher energy imparted by pulsatility could lead to better brain microcirculation and possibly improve flow to ischaemic areas of the brain. However, these findings could not be confirmed in animals that do not have the extensive external-to-internal carotid artery collateralisation seen in canines.^[61]

The neuroprotective effects of pulsatile CPB could be attributed to the following effects:

- Attenuation of inflammatory response to CPB
- Increased capillary patency and less venous sludging
- Enhanced NO and attenuated endothelin-I release reducing cerebral vascular resistance
- Increased regional CBF after hypothermic circulatory arrest
- Increased CBF when CBF auto-regulation is impaired
- Lesser number of S_{jv}O₂ de-saturations
- Less neuronal cell loss in CA1 region of the hippocampus after global cerebral ischaemia.

Clinical studies that have examined the impact of pulsatile CPB flow on neurologic outcomes have contradictory conclusions.^[62] This can be attributed to the varying methods to generate pulsatility, use of limited psychometric testing, non-randomised and retrospective study design, and inadequate study power in these reports.

Avoidance of Cardiopulmonary Bypass during Cardiac Surgery

Avoidance of CPB during CABG surgery could theoretically reduce post-operative neurological deficits by decreasing embolic phenomena and systemic inflammation. Although early reports showed that 'off' pump surgery was associated with a lower incidence of neurological events, later randomised studies performed at 1 and 5 years post-operatively, revealed no difference in neurocognitive function whether CABG was done under 'off' or 'on' CPB.^[63-65] But most of the studies were performed in young and otherwise low risk patients. Whether 'off' pump surgery would be beneficial in older and higher risk patients needs to be evaluated, although case series has shown that 'off' pump CABG surgery is indeed beneficial in preventing post-operative stroke in this high risk population.^[66,67]

Blood Pressure Management

Mean blood pressure during CPB is often kept at a minimum of 50 mmHg based on the view that with an intact cerebral auto-regulation this is sufficient to maintain cerebral oxygen delivery. A higher MAP could be associated with a higher embolic load to the brain, which could lead to adverse neurological events.

But with an increasing number of elderly patients, with possible cerebral atherosclerosis presenting for cardiac surgery, would this blood pressure be suitable to prevent post-operative neurocognitive dysfunction?

Gold *et al.*, in a prospectively randomised study, which compared a MAP of 'low' (50-60 mmHg) and 'high' (80-100 mmHg) during CPB in patients undergoing CABG surgery, found that the combined endpoints of stroke and/or myocardial infarction were lower in the 'high' MAP group, although the incidence of neurocognitive dysfunction was not different in the two groups.^[68] Thus, a higher MAP during CPB could prevent brain injury and it is advisable to keep the MAP >70 mmHg in high risk patients undergoing cardiac surgery such as those with aortic atherosclerosis. A good clinical dictum would be to keep the MAP target value in the same numerical value as the decade of the age of the patient (e.g. 70 mmHg for 70 year olds, 80 mmHg for 80 year olds etc).

Haemoglobin/Haematocrit Targets

Haemodilution is commonly used during CPB to decrease the viscosity of blood as well as to decrease the need for allogenic transfusion. Although the normal brain can compensate for this by increasing tissue oxygen extraction and increasing cerebral blood flow, patients with cerebrovascular disease may not be able to cope with the decreased oxygen delivery. Moreover, there is a theoretical risk of increased embolic load when

cerebral blood flow increases during haemodilution. Habib *et al.*, found that peri-operative outcomes, including stroke, was significantly and systematically increased when the lowest haematocrit during CPB fell below 22%.^[69] Karkouti *et al.*, also found that the nadir haemoglobin during CPB was an independent predictor of peri-operative stroke and that for each percent decrease in haemoglobin, there was a risk of 10% increase in the odds for suffering a peri-operative stroke.^[70] Mathew *et al.*, in a prospective study, found that profound haemodilution (haematocrit of 15-17%) was associated with greater cognitive decline 6 weeks after CABG surgery, especially in the elderly.^[71] In infants, too, low haematocrits (21% or 28%) were associated with lower psychometric development one year after surgery.^[72]

The optimal haemoglobin during cardiac surgery is not known and varies depending on the temperature, age of the patient and other risk factors for ischaemic brain injury. The guidelines released by the Society of Thoracic Surgeons and the Society of Cardiovascular Anaesthesiologists recommend that it is 'reasonable' to transfuse blood when the haemoglobin is 6 g/dl during CPB, and in patients at risk for stroke this target should be 7 g/dl.^[73]

Temperature Management

Hypothermia affords neuronal protection by several mechanisms and has traditionally been used during CPB for cardiac surgery. However, a meta-analysis of randomised trials by Rees *et al.*, in patients undergoing CABG under CPB, showed that there was no difference in the occurrence of stroke when either normothermia or hypothermia was used.^[74] The first documentation of cerebral hyperthermia was by Cook *et al.*, in 1996, when he demonstrated that brain temperatures could reach up to 40°C during re-warming, a period when cerebral embolic episodes are also most likely to occur, possibly because of the close proximity of the cerebral vessels to the aortic cannula.^[75] Moreover, the nasopharyngeal temperature that is usually measured during cardiac surgery may underestimate the brain temperature. Nathan *et al.*, compared patients who were partially re-warmed to 34°C and 37°C and showed that there was no difference in neurocognitive dysfunction at 1 and 3 weeks after hypothermic (32°C) CPB for CABG between the complete and partial re-warming groups.^[76] From these observations, there has been a change in clinical practice with the brain and perfusate temperatures being closely monitored so as to avoid inadvertent cerebral hyperthermia.

Glycaemic Control

Hyperglycaemia, even when mild (140 mg/dl), can lead to worsening of neurological outcomes after stroke.

However, there are only few clinical data regarding hyperglycaemia and post-operative neurological deficits in cardiac surgery. De Ferranti *et al.*, found that there was no relationship between blood sugar levels >150 mg/dl and neurodevelopment outcomes after complex congenital cardiac surgery.^[77] In contrast, hypoglycaemia (blood sugar levels <50 mg/dl) was associated with slower electroencephalographic (EEG) recovery and seizures after surgery. In a prospective, randomised study in non-diabetic patients undergoing CABG under CPB, it was found that there was no difference in neurological outcome at 6 weeks and 6 months after surgery when insulin infusion was given for blood sugar levels >100 mg/dl compared with placebo.^[78] Thus, whether maintaining lower blood sugar levels in diabetic and non-diabetic patients would have neuroprotective effects and improve neurological outcome is not clear.

Acid-Base Management: Alpha-stat versus pH stat

Prior to the 1980s, pH-stat management was used during hypothermic CPB, wherein the temperature corrected blood pH and PaCO₂ was kept at 7.4 and 40 mmHg, respectively. This is in contrast to the alpha-stat strategy, whereby, hypothermia-induced alkalaemia and hypocarbia are not corrected, and the pH and PaCO₂ are maintained at 7.4 and 40 mmHg at 37°C. But CBF during hypothermic CPB is linearly related to total CO₂ content and CBF is higher with pH-stat management as compared with alpha-stat management.^[79] In addition to maintaining CBF, the higher CO₂ content confers other neuroprotective effects including rightward shift of the oxy-haemoglobin dissociation curve and modulates the NMDA receptor that limits the neurotoxic effects of excitatory amino acids. Clinical work has shown less morbidity and earlier return of first EEG activity after deep hypothermic CPB using pH-stat rather than alpha-stat management during repair of complex congenital heart abnormalities.^[80] But there is a concern that increased CBF associated with pH-stat management could increase the risk of cerebral embolic phenomena and cause cerebral arterial steal, thereby causing adverse neurological sequelae.^[81]

Thus, there is controversy as to which strategy for acid-base management should be followed during hypothermic CPB. Randomised trials, which compared alpha-stat with pH-stat management, have produced conflicting data. While some reports have concluded that the type of acid-base management had no effect on neurological outcome,^[82-84] others have reported that alpha-stat management was associated with lesser neurological deficits as compared with pH-stat management.^[85]

So is there any recent evidence to suggest that CPB management could affect overall neurological outcome especially in the high risk cardiac surgical patient?

Hogue *et al.*, in an evidence-based appraisal of current practices of CPB management and their effect on neurologic outcomes, found that other than the use of 20-40 micron arterial line filters and membrane oxygenators, newer modifications of the basic CPB apparatus or the use of specialised equipment or procedures (including hypothermia and 'tight' glucose control) have unproven benefit on neurologic outcomes.^[86] Many of the current approaches regarding, flow, blood pressure and pH management techniques during CPB are supported by clinical data, but very few studies have been done in elderly, high risk patient with cerebrovascular disease. These authors were of the opinion that based upon the current evidence, there is a deficiency in knowledge base for physicians to prevent neurological complications in cardiac surgery.

PHARMACOLOGICAL NEUROPROTECTION – AN OVERVIEW

Pharmacological neuroprotection includes both anaesthetic and non-anaesthetic drugs both of which have been extensively studied in the laboratory. Based on sound experimental evidence, many neuroprotective drugs have been developed, but clinical trials of most drugs in man have been disappointing. Till date, there are no drugs, either anaesthetic or non-anaesthetic, with proven neuroprotective efficacy that can decrease brain injury in the peri-operative period.

ANAESTHETIC NEUROPROTECTION

Intra-operative cerebral ischaemia can be catastrophic, and volatile anaesthetic agents have been known for their potential neuroprotective properties since the 1960s. Anaesthetic-induced pharmacological neuroprotection was based on the fact that anaesthetics reduced the metabolism of the brain and thus may be able to confer protection in the event of decrease in substrate delivery. The other mechanisms for their neuroprotective effect include activation of ATP-dependent potassium channels, up-regulation of NOS, reduction of excitotoxic stressors, augmentation of peri-ischaemic cerebral blood flow and up-regulation of anti-apoptotic factors including MAP kinases.^[87]

But the major drawbacks of anaesthetics in their role as neuroprotective agents are that although they were found to be effective in experimental models of ischaemic as well as in traumatic brain injury, human studies have not yielded beneficial results. Secondly, these agents need to be present at the time of ischaemic insult, and

administering them post-ischaemia would not be useful. Lastly, although some agents like isoflurane were found to have short-term neuroprotective properties, they were not effective 2 weeks after the insult.^[88] This was presumably because of the apoptotic and inflammatory cascade that was activated as a result of the ischaemic insult.^[89]

ROLE OF VOLATILE AGENTS

Milde *et al.*, in a primate study, showed that isoflurane provides similar neuroprotection as compared with thiopental in temporary, focal cerebral ischaemia when blood pressure was maintained equal in the two groups.^[90] But in possible contradiction to this study, Nehls *et al.*, found that isoflurane failed to provide neuroprotection in comparison to thiopentone in primates subjected to focal cerebral ischaemia.^[91] In contrast to this finding, in a more recent study comparing the effects of thiopental and desflurane titrated to burst suppression during carotid occlusion, Hoffman *et al.*, found that brain tissue oxygenation, as detected by brain tissue oxygen (PtiO₂) monitoring was better preserved with desflurane as compared with thiopental in the area supplied by the occluded arteries.^[92] Michenfelder while monitoring EEG and CBF in a large retrospective study in patients undergoing CEA found that the critical CBF was lower with isoflurane as compared with halothane anaesthesia and suggested that isoflurane had neuroprotective effects in man.^[93] In a recent experimental study, Li and co-workers also showed that isoflurane prevented the neurocognitive dysfunction induced by CPB, which might involve the cerebral cholinergic system.^[94] Although volatile anaesthetics have been shown to have cerebral protection properties in experimental models of ischaemic brain injury, there is a paucity of clinical data pertaining to neuroprotection in man.

In a recent review of 25 randomised trials of peri-operative pharmacological neuroprotection, predominantly done in cardiac surgical patients, Bilotta *et al.*, concluded that based on single studies, pharmacological neuroprotection might reduce new post-operative neurological deficits or POCD, but it had no effect on overall mortality.^[95] But since the incidence of post-operative neurological deficits is higher in cardiac surgery as compared with other high risk surgery, whether these conclusions are applicable for non-cardiac surgery is not clear. In that review, it was found that the use of atorvastatin and magnesium sulphate was associated with a lower incidence of new post-operative neurological deficit.^[96,97] The effect of lidocaine^[98-101] and ketamine^[102] on POCD was associated with controversial results. The incidence of POCD did not differ between treated patients and control group for other tested drugs (thiopental, propofol, nimodipine, GM1 ganglioside, lexipafant, glutamate/aspartate, xenon, erythropoietin, remacemide, piracetam,

rivastigmine, pegorgotein and 17 β -estradiol). None of the tested drugs was associated with a reduction in mortality rate.^[95] One agent that has shown promising results where cerebral protection is concerned is dexmedetomidine, an alpha₂-adrenoceptor agonist, which needs to be further evaluated.^[103,104]

Since there has been little headway with pharmacological neuroprotection despite intensive research, the concept of ischaemic preconditioning, either pre- or post-ischaemic, would seem to offer some hope for patients at risk of cerebral ischaemia.

Ischaemic pre-conditioning involves applying brief episodes of sub-lethal ischaemia to induce a robust protection against the deleterious effects of subsequent, prolonged, lethal ischaemia. Great strides have been made to identify the mechanisms of pre-conditioning-induced neuroprotection in animal models of brain injury. Volatile anaesthetics, such as isoflurane and sevoflurane, have also been found to induce pre-conditioning effect in the brain.^[105,106] However, this is useful only in the scenario when occurrence of ischaemia is predictable, such as in the anaesthetised patient, undergoing high risk surgery, where cerebral ischaemia is likely to occur. But the clinical utility of this modality is questionable with respect to the narrow therapeutic windows, safety and the need to give it prior to the injury.

To overcome the drawback of ischaemic pre-conditioning, the concept of *ischaemic post-conditioning* was later introduced, where application of ischaemia after the cerebral insult would induce cerebral protection. Lee *et al.*, showed that isoflurane, in clinically relevant concentrations, can induce ischaemic post-conditioning and lead to improved neurological outcome in rats. The mechanism for this protection may involve the activation/opening of mitochondrial KATP channels.^[107]

PHARMACOLOGICAL NEUROPROTECTION IN CARDIAC SURGERY

Anaesthetic drugs, both intravenous agents as well as inhalational agents, have been extensively studied for their potential role in neuroprotection, based on the fact that they decrease the CMRO₂ and thus produce increased tolerance to ischaemia. Nussmeier *et al.*, in the first human randomised controlled study, demonstrated that barbiturate-induced EEG burst suppression during CPB prevented neuropsychiatric complications following open heart valvular surgery assessed on the 10th post-operative day.^[108] But in a later study, Zaiden *et al.*, showed that thiopental, titrated to burst suppression, does not reduce the incidence of stroke in patients undergoing CABG surgery.^[109] Propofol also has cerebral depressant effects similar to thiopentone. Moreover, its antioxidant effects

has been found to decrease infarct size in animals even when given 1 hour after ischaemia.^[110] However, Roach *et al.*, showed that propofol-induced EEG suppression was not effective in reducing the incidence or severity of neurologic or neuropsychological complications in patients undergoing heart valve surgery.^[111] As far as clinical applications are concerned, anaesthesia-induced reduction in cerebral metabolism may not be effective for brain protection in cardiac surgery.^[112]

In a first randomised clinical study that showed drug-based neuroprotection, the neuropsychological performance was studied in patients undergoing cardiac surgery who received remacemide, an NMDA receptor antagonist, versus a placebo. In addition to providing improvement in cerebral outcome, it also showed that drugs that act to prevent post-ischaemic excitotoxic events might be useful in providing cerebral protection.^[113]

Based on experimental work that lidocaine improves neurological outcome, Wang *et al.*, and Mitchell *et al.*, showed that an infusion of a standard anti-arrhythmic dose of lidocaine improves neurocognitive function in patients following valvular heart surgery under CPB.^[98,99] However, in a follow up study, Mitchell *et al.*, found that lidocaine was not neuroprotective in cardiac surgery.^[100] A more recent prospective, randomised controlled study using lidocaine in CABG surgery under CPB, also showed no difference between the lidocaine and placebo groups.^[101] In contrast, it was found to be detrimental in diabetic patients and also when it was given at higher doses. Further studies are ongoing to evaluate the neuroprotective effect of lidocaine in cardiac surgery.

Aprotonin, a drug used to decrease bleeding and transfusion in cardiac surgery patients, may have some benefit in prevention of stroke. A meta-analysis of randomised controlled trials involving 3879 patients showed that compared with placebo, patients receiving aprotonin had a lower incidence of stroke following cardiac surgery.^[114] However, retrospective, observational data comparing various anti-fibrinolytic agents, showed that there was a higher incidence of stroke with aprotonin as compared with amino-caproic acid, tranexemic acid or no anti-fibrinolytic agent.^[115] It is postulated that cerebral protective effects of aprotonin may be due to its anti-inflammatory effects. Or, because of the decrease in blood loss, it might have limited the volume of pericardial aspirate that is indirectly implicated in cerebral microembolism.^[116] Further studies are needed to prove the neuroprotective effects of aprotonin in cardiac surgery. Moreover, the primary indication of administering aprotonin is to decrease bleeding. Therefore, whether it could be given for a different purpose, like neuroprotection, is a moot point.

PHARMACOLOGICAL NEUROPROTECTION IN ANEURYSM SURGERY

TVO is often required during clipping of intracranial aneurysms as it facilitates dissection and prevents rupture of the aneurysm. The potential adverse effect of TVO is the occurrence of focal cerebral ischaemia and associated neurological injury and this is related to the duration of TVO.^[117] The safe limit for TVO is not known, but a general guideline for occlusion time is 10 min. If TVO needs to be extended beyond that, as in complex or multiple aneurysms, intermittent reperfusion is recommended to avoid post-operative neurological damage.^[118,119]

Suzuki *et al.*, advocated a combination of mannitol (500 ml of 20% solution), Vitamin E (500 mg) and dexamethasone (50 mg), referred to as the Sendai cocktail for TVO, particularly if it needs to be prolonged.^[120] Lavine *et al.*, found that patients undergoing TVO during aneurysm surgery have a significant advantage when they are administered pentobarbital as the primary neuroprotective agent or when they receive propofol or etomidate titrated to burst suppression, particularly if more than 10 min of occlusion time is required.^[118] Most studies done in the 1990s had reported good outcome with administration of thiopentone, etomidate, propofol and mannitol for cerebral protection during TVO.^[118,121,122] However, an analysis of the IHAST study patients showed that neither systemic hypothermia nor supplemental neuroprotective drug administration had any clinically detectable effect on short-term or long-term outcome following aneurysm surgery.^[123]

NEUROPROTECTIVE STRATEGIES IN CAROTID ENDARTERECTOMY

One of the goals of the anaesthesiologist in surgery for CEA is to protect the brain from ischaemic injury, secondary to either hypoperfusion or embolic episodes. Therefore, the key concerns to prevent neurological complications during CEA are:

- Detection of any embolic phenomena, known as microembolic signals (MES)
- Evaluate neurologic tolerance to carotid clamping.

Adverse neurological events during CEA can be prevented by appropriate intra-operative neuromonitoring, placing an intra-luminal shunt during cross clamping and instituting cerebral protection measures. Placement of a shunt is not a benign intervention and it could result in air or plaque embolisation, intimal tears and carotid dissection leading to neurological insults. Therefore, it is important to identify patients who are at risk for cerebral ischaemia during carotid clamping who can benefit from shunting.

REGIONAL VERSUS GENERAL ANAESTHESIA: WHICH IS BETTER?

Awake patient monitoring under local or regional anaesthesia is the most reliable method of preventing intra-operative brain injury as it predicts the need for a shunt during carotid clamping and is the accepted standard for intra-operative neuromonitoring.^[124] It offers the additional advantage of excellent haemodynamic stability, which is also very important to maintain adequate CPP and prevent intra-operative cerebral ischaemia. The incidence of shunt placement is also decreased to 5% of cases when the surgery is performed under regional anaesthesia. Despite the relative merits of CEA under regional anaesthesia, there is little evidence, from the results of large randomised trials to suggest that neurologic outcome following CEA is significantly affected by the choice of anaesthetic.^[125-128] Thus, based on the available data, it can be inferred that other factors such as patient selection, adequate optimisation of associated co-morbid conditions and an experienced surgical and anaesthetic team may be more important in preventing neurological morbidity rather than the choice of anaesthetic technique during surgery for CEA.^[129]

The first and foremost intervention that needs to be done, when cerebral ischaemia is detected either by clinical assessment, as in an awake patient or based on neuromonitoring, is to insert a shunt.

However, the anaesthesiologist can also play a major role by tailoring the anaesthetic technique, either by non-pharmacological or pharmacological interventions so as to prevent the occurrence of intra-operative cerebral ischaemia and ensure adequate cerebral perfusion.

NON-PHARMACOLOGICAL STRATEGIES IN CAROTID ENDARTERECTOMY

Non-pharmacological methods of neuroprotection include blood pressure management, oxygenation, ventilation and glucose control.

Blood Pressure Management

Blood pressure fluctuations are not uncommon during CEA and it is recommended that blood pressure be maintained between normal and 20% above pre-operative values to maintain adequate perfusion through the circle of Willis. This is based on the apprehension that 'watershed' stroke can occur during the period of carotid cross-clamping and also from evidence in patients undergoing awake CEA under regional anaesthesia, where neurological deficits were reversed by elevation of blood pressure.^[37,130] Kobayashi *et al.*, showed in a non-randomised controlled study that intentional hypertension during dissection of carotid arteries in CEA

prevents post-operative development of new cerebral lesions caused by intra-operative microemboli.^[131] They used a novel surrogate endpoint, diffusion-weighted MRI for this purpose. In a retrospective review of 102 patients undergoing CEA without shunting under EEG monitoring, where EEG changes during cross clamping were treated with induced arterial hypertension with or without etomidate-induced burst suppression, the authors reported good results with a stroke rate of just 0.98%.^[132] Thus, induced arterial hypertension has a major role to play in cerebral protection during CEA. However, in patients undergoing CEA with co-existing cardiac dysfunction, hypertension has to be instituted with caution with appropriate haemodynamic monitoring.

Control of Carbon dioxide, Oxygenation and Glucose Levels

Although both hypocarbia and hypercarbia were advocated to increase ipsilateral cerebral blood flow during CEA, both are associated with deleterious effects on cerebral blood flow. Hypocarbia can cause ipsilateral cerebral vasoconstriction and increase the area of cerebral ischaemia and hypercarbia can cause contralateral cerebral vasodilatation resulting in cerebral steal phenomenon. It is, therefore, recommended that normocarbia be maintained to optimise cerebral blood flow. Stoneham has reported that oxygen supplementation during CEA performed under regional anaesthesia can in some patients reverse cerebral ischaemia.^[133] Hyperglycaemia during CEA has been found to be associated with increased risk of stroke, myocardial infarction and death and this was independent of previous cardiac disease, diabetes or other co-morbidities.^[134] Therefore, normoglycaemia should be maintained during surgery to prevent adverse neurological outcomes.

PHARMACOLOGICAL NEUROPROTECTION IN CAROTID ENDARTERECTOMY

Cheng *et al.*, in a survey conducted in 1997, reported that despite the advantages of regional anaesthesia, the majority of centres (84.7%) used general anaesthesia.^[135] Only 22.2% of respondents administered pharmacological neuroprotection and the drug of choice was thiopentone (50.0%). The technique of intra-operative hypertension for neuroprotection was practiced in most centres (61.1%) with the target blood pressure being 20% of baseline values. Messick *et al.*, in a prospective study, determined the critical CBF in patients undergoing CEA under isoflurane anaesthesia as 8-10 ml/100 g/min, which is significantly less than the critical CBF under halothane anaesthesia, which was 18-20 ml/100 g/min.^[136] Michenfelder *et al.*, in a

retrospective analysis of over 2000 patients undergoing CEA found that isoflurane anaesthesia was associated with significantly less EEG changes during carotid artery cross clamping as compared with halothane or enflurane anaesthesia.^[93] They concluded that isoflurane offers some degree of cerebral protection in transient, incomplete, regional cerebral ischaemia that occurs during CEA. However, studies by Nehls and Drummond *et al.*, have shown that neither etomidate nor isoflurane are able to provide significant protection against focal ischaemia. In fact, they can even worsen the outcome of the patients.^[91,137]

Thus, the anaesthesiologist has to rely primarily on neuromonitoring and non-pharmacological strategies for intra-operative neuroprotection during CEA so as to prevent cerebral insults.

ROLE OF NEUROMONITORING IN INTRA-OPERATIVE CEREBRAL PROTECTION

Neuromonitoring has a major role to play in the detection of intra-operative brain insults so that peri-operative brain injury is prevented. The aim of neuromonitoring is to provide early warning of secondary brain injury due to hypoxia/ischaemia and consequent cellular energy crisis so that prompt and remedial measures are instituted. This is particularly relevant in anaesthetised patients under going surgical procedures that stand a high risk for cerebral ischaemia such as neurosurgery, cardiac surgery and major vascular surgery.

Neuromonitoring during Cardiac Surgery

Neurophysiological studies have shown that hypoperfusion and desaturation could be the cause for brain injury after cardiac surgery and continuous real-time monitoring can provide information regarding the adequacy of cerebral perfusion. This can be detected by appropriate neuromonitoring, and various devices such as EEG, transcranial Doppler (TCD), cerebral oximetry, jugular venous oxygen saturation (SjvO₂) and PtiO₂ monitoring have been used for neuroprotection. Yao *et al.*, found a higher incidence of neurophysiological dysfunction in patients who had intra-operative de-saturation episodes (nadir rSO₂ <35%) during cardiac surgery.^[138] In a retrospective study, Goldman *et al.*, showed that in patients in whom interventions were done to optimise cerebral oxygen delivery based on cerebral oximetry, there was a lower incidence of permanent stroke.^[139] Murkin *et al.*, also showed that patients who underwent cerebral oximetry monitoring during CABG surgery had significantly less profound oxygen

de-saturation than control patients and they also had significantly less major organ dysfunction and mortality in the post-operative period.^[140] Cerebral oximetry monitoring is also useful for early detection of potentially catastrophic brain injury as well as vulnerable periods of regional oxygen de-saturation during CPB requiring immediate intervention.^[141-143]

However, the disadvantage with cerebral oximetry is that it can monitor only regional cerebral oxygenation. Lozano and Mossad have advocated multi-modality neurophysiologic monitoring to identify and manage the vulnerable periods during CPB and deep hypothermic circulatory arrest.^[144]

Edmonds *et al.*, retrospectively studied the effect of multi-modality neuromonitoring using EEG, cerebral oximetry and TCD for brain protection during cardiac surgery.^[145] They found that disturbances detected by these modalities could be corrected by adjustments in perfusion, oxygenation or anaesthetic administration and found that multi-modality neuromonitoring in cardiac surgery is safe, beneficial and cost-effective. Whether this would lead to improved neurologic outcome needs to be evaluated more rigorously. A survey conducted to evaluate the current practice of neuromonitoring and neuroprotection strategies in a German population, revealed that although EEG, evoked potential monitoring, near infrared spectroscopy (NIRS) and TCD were used in a proportion of patients undergoing major vascular surgery, patients undergoing CABG and valvular heart surgery did not undergo any method of neuromonitoring.^[146] These authors reported that neuroprotective strategies during cardiac surgery were not standardised. At present, there are no widely accepted monitors to assess the adequacy of global or regional CBF during CPB and there are no clear recommendations for neuromonitoring in cardiac surgery.

Neuromonitoring during Carotid Endarterectomy

Neuromonitoring for CEA is undertaken to detect signs of cerebral ischaemia either during cross clamping of the carotid artery or to detect embolic episodes during surgery. It comprises either cerebral function monitoring or monitoring of cerebral blood flow. Cerebral function monitoring includes neurological assessment as in an awake patient, EEG and evoked potential monitoring. Cerebral blood flow monitoring modalities that are commonly used includes TCD, SjvO₂, stump pressure monitoring, cerebral oximetry and PtiO₂ monitoring.

However, no single monitoring method provides 100% sensitivity and 100% specificity as compared with awake monitoring.

Electroencephalography

This is the most commonly used monitoring modality in CEA and decades of its use have shown a strong correlation between EEG changes and cerebral ischaemia.^[147] It reflects the balance between cerebral oxygen supply and oxygen demand during carotid surgery.^[136] It must be noted that the EEG becomes isoelectric before irreversible damage to the brain occurs and, thus, it provides a warning to the anaesthesiologist to take appropriate measures to protect the ischaemic brain. It should also be noted that increasing duration of severe EEG changes, increases the likelihood of stroke after CEA. However, there is evidence that although the specificity of EEG to detect cerebral ischaemia is significantly less than perfect, it is associated with excellent sensitivity for detection of ischaemic changes under general anaesthesia and it provides an excellent guide for selective shunting.^[148,149] Schneider *et al.*, reported that with EEG monitoring and selective shunting, the incidence of intra-operative stroke was completely eliminated and post-operative stroke occurred only in 1% of patients.^[150] Ballotta also reported good results with EEG monitoring and selective shunting in a series of 369 patients undergoing carotid artery revascularisation.^[151] Cheng *et al.*, in a survey conducted to evaluate the anaesthetic practice for CEA, found that neuromonitoring was being done by 90% of respondents, the favourite modality being EEG (67.5%).^[135] Thus EEG monitoring during CEA to detect intra-operative neurological insults is still a popular modality, almost a gold standard, although its routine use requires technical support and real-time interpretation.

Somatosensory evoked potential

Somatosensory evoked potential (SSEP) monitoring has been in use for CEA, but its reliability is questionable. The drawbacks of SSEP monitoring to detect adverse neurological events is that it is less accurate than EEG and is less robust during general anaesthesia.

Transcranial doppler sonography

This modality is not only useful to measure flow velocity, and thus CBF, but it is also a sensitive method to detect cerebral emboli that accompanies manipulation, cross clamping of the carotid artery and during placement of the intra-luminal shunt. A reduction in middle cerebral artery flow velocity (MCAv) on cross clamping has been taken as an indication for inserting a shunt. The International Transcranial Doppler Collaborators have stated that a persistent reduction in mean MCAv on cross clamping to between 0% and 15% of the baseline value is strongly associated with post-operative stroke, and, such patients, would need shunting. Despite these recommendations, TCD is not a reliable method for detection of cerebral ischaemia and the identification of patients requiring shunting.^[152,153] Although its efficacy in detecting cerebral ischaemia secondary to

cross clamping is doubtful, it is a sensitive method for detecting cerebral emboli that occurs during CEA. MES have been detected particularly during declamping and insertion of shunt.^[154] These authors reported an increase in peri-operative neurological morbidity if more than 10 particulate embolic event were detected during surgery.

Wolf *et al.*, used TCD to detect MES during different stages of surgery and correlated it with cerebral ischaemia as detected by diffusion-weighted imaging (DWI) and cerebral infarction as detected by contrast-enhanced MRI.^[155] A significant correlation between MES during dissection and DWI and also between MES during dissection and shunting and cerebral infarction were noted. They concluded that MES, leading to peri-operative neurological sequelae, occurred mainly during dissection and shunting during CEA. However, this monitor, as a tool for detection of cerebral ischaemia, has not been validated against established monitors used in CEA such as EEG.

Carotid stump pressure

Monitoring of carotid stump pressure (CSP) has been postulated to reflect the adequacy of the collateral circulation via the circle of Willis or the external carotid circulation. But CSP monitoring is not undertaken as a sole monitoring modality for the adequacy of cerebral perfusion and there is controversy as to the level of CSP that reflects inadequate collateral circulation. It is, therefore, used primarily as an adjunct to another neuromonitoring modality for detection of intra-operative cerebral ischaemia.

Near infrared spectroscopy

The disadvantages of some of the monitoring techniques routinely done during CEA relate to cost, setup, equipment and the need for a neurophysiologist. In an effort to simplify neuromonitoring for CEA under general anaesthesia, regional cerebral oxygen saturation (rSO₂) monitoring using cerebral oximetry was proposed as a simple, inexpensive, real-time way to determine the need for shunting during CEA.

A drop in rSO₂ values with carotid cross clamping, and reversion to baseline with subsequent shunt insertion, have been reported in various studies.^[156,157] Samra *et al.*, showed that a 20% fall in rSO₂ had a high negative predictive value (97.4%) and a low positive predictive value (33.3%) for occurrence of peri-operative stroke in patients undergoing CEA under regional anaesthesia.^[158] Although it is relatively easy to use as compared with EEG and SSEP monitoring, there is no available data, which suggests that changes in rSO₂ correlate with changes in CBF, unlike EEG and SSEP. Roberts *et al.*, also showed that a fall in rSO₂ >27% required shunting in patients undergoing CEA under

regional anesthesia.^[159] One of the major drawback of NIRS to detect intra-operative cerebral ischaemia during CEA is that the sensors are placed over the frontal lobes, which is not the ideal position to detect reduction in middle cerebral artery blood flow. But, so far, there is no recommendation for an absolute threshold value or change in rSO₂ from baseline, which could be taken as alarm criteria for shunting.

A comparative evaluation of the accuracy of TCD, NIRS and evoked potential monitoring done to detect cerebral ischaemia during cross clamping in carotid surgery revealed that the percentage change in flow velocity and rSO₂ to be more useful than the absolute values.^[160] These authors also found that TCD%, NIRS% and SSEP monitoring provided equal sensitivity and specificity although SSEP monitoring was the least accurate. Friedell *et al.*, compared rSO₂ with EEG/SSEP monitoring during CEA and found that the sensitivity of rSO₂ was 68% with a specificity of 94%, giving a positive predictive value of 47% and a negative predictive value of 98%.^[161] They concluded that relying on rSO₂ alone is potentially dangerous and it can lead to peri-operative stroke and it could also lead to unnecessary insertion of a shunt. These authors were of the opinion that rSO₂ adds nothing to the information provided by EEG/SEP in determining the need for a shunt.

So far, there is no single monitoring modality that is completely reliable for accurately detecting intra-operative neurological insults during CEA surgery. A combination of monitoring modalities is recommended so that, in the event of ischaemic changes occurring on cross clamping, selective shunting can be done.

Neuromonitoring during aneurysm surgery

TVO during intracranial aneurysm surgery is a key element in facilitating aneurysm dissection and clipping. It is advocated that neuromonitoring be done during TVO to detect evidence of cerebral ischaemia so that prompt remedial measures are taken.

The monitoring modalities in current use during aneurysm clipping surgery are the following:

- EEG
- Evoked potential monitoring
- PtiO₂ monitoring.

Neurophysiological monitoring (electroencephalography and evoked potentials)

Neurophysiological monitoring such as EEG and evoked potentials allows the detection of intra-operative cerebral ischaemia during clipping of intracranial aneurysms. It is helpful in recognising the upper limit of occlusion duration and any deterioration in parameters is an indication for intermittent reperfusion to be established so that cerebral ischaemia is prevented. EEG is also

useful to determine whether electrical silence has been achieved when pharmacological metabolic suppression is being used, as beyond that no further metabolic benefits can be achieved. Thus it enables drugs such as thiopentone, propofol and etomidate to be used effectively without undue side effects. However, Warner and Schmid-Elsaesser *et al.*, have observed in experimental ischaemia that maximal protection with barbiturates could occur at less than burst suppression doses, although this is not yet proved clinically.^[162,163]

SSEP and motor evoked potential (MEP) monitoring are useful modalities for detecting cerebral ischaemia during TVO and is increasingly being used in combination with EEG for aneurysm surgery. The ischaemic tolerance ratio (ITR) in SEP recordings was found to be valuable in predicting post-operative neurological deficits caused by TVO.^[164] These authors recommended that maintaining ITR below 50% intra-operatively can effectively avoid post-operative neurological deficits and an ITR above 80% reliably forecasts post-operative neurological deficits. They also found that MEP recordings are particularly valuable in monitoring ischaemic effects caused by accidentally clamping perforating branches. Thus a combination of SEP and MEP makes it possible to promptly adjust surgery procedures and minimise post-operative neurological deficits. A major advantage of SEP monitoring is that it is the only electrophysiological monitoring available to detect ischaemia when EEG is totally suppressed with high dose barbiturates. But one of the drawbacks of SEP is its lack of specificity. While SEP is used for both anterior and posterior circulation aneurysm surgery, brain stem auditory evoked potential (BAEP) monitoring is used for posterior circulation aneurysms.^[165]

MEP monitoring is a simple, safe and reliable tool to detect and predict development of motor deficits during aneurysm surgery. A decrement >50% from baseline is taken as a warning sign and is promptly indicated to the surgeon. Prompt corrective measures during TVO as indicated by change in MEP can reduce ischaemic complications resulting in neurological deficits.^[166] Addition of MEP monitoring to the existing neurophysiological monitoring armamentarium has improved the sensitivity and specificity to detect intra-operative cerebral ischaemia during aneurysm surgery. However, a major disadvantage is that during pharmacological burst suppression, the quality of MEP signals may be lost.

Spontaneous respiration was used in the past for early detection of brain stem dysfunction especially during surgical manipulation of the brain stem or surgery for posterior fossa aneurysms. These authors were of the opinion that along with BAEP monitoring, it could enable early detection of brain stem ischaemia.^[167]

Brain tissue oxygen monitoring

Jodicke *et al.*, evaluated the feasibility of monitoring PtiO₂ for detection of procedure-related ischaemia during TVO.^[168] They concluded that using 15 mmHg as a dichotomising threshold, intra-operative PtiO₂ monitoring helps identify patients at risk for procedure-related ischaemia and even surpassed SEP monitoring and that this modality needs to be further evaluated. It not only helps detect cerebral ischaemia during TVO, but also helps confirm the correct placement of the definitive clip. The occurrence of an abrupt decrease in PtiO₂ values, which is persistent and an incomplete recovery or a persistent fall after definitive clipping could indicate compromise of the cerebral circulation and cerebral ischaemia.^[169] In a study on the use of combined cerebral oxygen and microdialysis monitoring during aneurysm surgery, it was found that PtiO₂ decreases with hypotension, and, when it is below 8 mmHg for longer than 30 min during temporary clipping, it is associated with increasing extracellular glutamate levels and cerebral infarction.^[170]

SUMMARY

The anaesthetised brain is vulnerable to ischaemia and intra-operative cerebral insults can occur not only in neurosurgical, cardiac and major vascular surgery but also in the general surgical operations. This could lead to disastrous consequences culminating in sometimes, irreversible neurological deficits, which could range from stroke to neuropsychological dysfunction. The anaesthesiologist should have a clear understanding about the various risk factors that could predispose the anaesthetised patient to intra-operative cerebral ischaemia, both patient factors as well as surgical factors, so that appropriate preventive pre-emptive measures are undertaken. There are no clear recommendations with regard to pharmacological neuroprotection strategies and the current practice for intra-operative neuroprotection is mainly based on non-pharmacological strategies.

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