Perioperative stroke Part II: Cardiac surgery and cardiogenic embolic stroke

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The major mechanism of stroke in cardiac surgery is embolization. The risk is higher in intracardiac than in extracardiac surgery. The incidence of stoke associated with CABG is about 5%. The cerebral protective properties of isoflurane and thiopentone, acid–base management, and monitoring of cerebral perfusion during cardiopulmonary bypass are discussed. Prophylactic carotid endarterectomy for patients with asymptomatic carotid disease before cardiac surgery is not necessary. Symptomatic carotid disease increases the risk of stroke, and the management of patients who have both symptomatic coronary and carotid artery diseases is discussed. Cardiogenic embolism is probably responsible for many perioperative strokes. Patients with atrial fibrillation, valvular disease, and prosthetic heart valves are at high risk of cardiogenic embolism. Strokes associated with cardioversion, pacemaker insertion, coronary arteriography and angioplasty are explored.

La plus importante cause d'apoplexie lors de la chirurgie cardiaque demeure l'embolisation. Le risque est plus grand lorsque la chirurgie est intracardiaque plutôt qu'extracardiaque. L'incidence d'apoplexie associée au pontage aorto-coronarien est à peu près 5%. Les propriétés protectrices du cerveau, de l'isoflurane et du thiopentone, la conduite de l'équilibre acido-basique et la surveillance de la perfusion cérébrale durant la circulation extracorporelle sont discutées. L'andartérectomie carotidienne prophylactique pour les patients atteints de maladie carotidienne asymptomatique avant la chirurgie cardiaque n'est pas nécessaire. Les maladies carotidiennes symptomatiques augmentent le risque d'apoplexie, et la conduite à faire chez les patients qui ont une symptomatologie coronarienne et carotidienne est discutée. L'embolisation cardiogénique est probablement responsable de plusieurs épisodes d'apoplexie périopératoire. Les patients atteints de fibrillation auriculaire, de maladies valvulaires, et ayant des valves cardiaques prosthétiques sont à risque élevé d'embolisation cardiogénique. Les apoplexies associées à la cardioversion, l'insertion de pace maker, l'artériographie coronarienne et l'angioplastie sont explorées.

Key words
BRAIN: infarction;
COMPLICATION: stroke, perioperative;
EMBOLISM: cerebral.

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Cardiac surgery

Stroke associated with cardiopulmonary bypass

The incidence of neurological injury in patients undergoing cardiac surgery varies with the methods of evaluation. These may be based on clinical examination, neuropsychological testing, biochemical variables or EEG. The incidence of abnormalities tends to be underestimated in retrospective chart reviews,[1] and in studies performed by non-neurologists.[2]

Because of an increased risk of embolization, neurological complications are more frequent following intracardiac surgery such as valve replacement than following extracardiac procedures such as coronary artery bypass. Earlier studies reported persistent neurological deficits in more than 15% of patients following intracardiac surgery.[3-5] In a survey of 1689 consecutive patients who underwent isolated aortic valve replacement at the Cleveland Clinic Foundation from 1972 through 1989, stroke occurred in 29 patients (1.7%).[6] In 1980 Sotaniemi's prospective study of 100 patients undergoing valve replacement surgery showed a 37% incidence of postoperative deficit, but only 7% had a persistent severe deficit.[7]

Most retrospective studies of coronary artery bypass surgery show a low neurological complication rate. Lee *et al.* reported an occurrence of cerebral infarction in 0.7% of 943 patients.[8] In Gonzaalez-Scarano and Hurtig's series of 1427 patients, there were 19 (1.3%) who developed postoperative neurological complications.[9] Martin and Hashimoto reported postoperative stroke in eight patients among 253 (3.7%).[10] In a series of 3206 patients reported by Bojar *et al.*, there were 32 (1%) who developed major neurological deficits.[11] Coffey *et al.* reported 63 of 1669 patients (3.8%) developed postoperative neurological complications such as altered mental state, stroke or seizure.[12] On the other hand, prospective studies revealed a higher incidence of stroke. In the prospective study of Shaw *et al.* neurological complications occurred in 191 of their 312 patients (61%), and 15 patients (4.8%) suffered a stroke.[13] Similarly, Breuer *et al.*'s prospective study or 421 patients revealed 22 (5.2%) postoperative strokes.[14] Thus the current incidence of perioperative stroke associated with cardiac surgery is about 5% (Table I).

Following cardiac transplantation, 50 to 60% of patients developed neurological complications.[15,16] Cerebral infarcts were present in 20% of cases in autopsy series and in 13 to 15% in clinical series,[15,17] and were primarily due to embolism. Intracerebral haemorrhage occurred in 5% of early transplants, and were probably due to relative cerebral hyperperfusion from abrupt increases in blood pressure and cerebral blood flow in the presence of a disordered cerebral autoregulatory response.[18]

Mechanism of intraoperative neurological injury

Neurological damage may result from inadequate cerebral perfusion or embolization. The primary mechanism causing focal ischaemia and infarction associated with cardiac surgery is embolization.

SURGICAL FACTORS

Gaseous or particulate emboli may be introduced into the arterial circulation during surgery, especially when the heart or aorta are opened. Embolic phenomena are more common in intracardiac surgery than in closed cardiac procedures.[19] Gaseous microemboli can be detected in the majority of cases by using an ultrasonic microbubble detector[20] or oesophageal M-mode echocardiography.[21] Surgical manoeuvres such as detection and removal of intracardiac air, filling the heart with fluid before unclamping the aorta greatly reduces gaseous microembolism.[22-25] Lowering the head[26] and digital compression of the carotid arteries[27] may prevent emboli from entering the cerebral circulation when the heart begins to eject at the time of coming off cardiopulmonary bypass. Avoidance of nitrous oxide may help to minimize the potential exacerbation of neurological injury.[28]

Calcification and atheroma of the ascending aorta[29,30] and thrombi in the left ventricle[31] are important sources of emboli. It has been suggested that, in patients with severe calcific disease of the aorta, femoral artery cannulation is preferable to aortic cannulation to avoid aortic manipulation.[32]

CARDIOPULMONARY BYPASS

Cardiopulmonary bypass (CPB) may introduce a wide variety of material, including air, fat, antifoaming agents, plastic chips, leukocytes, platelets and fibrin aggregates,

TABLE I Perioperative stroke in CABG

Author	*No. patients*	*Perioperative stroke*
Retrospective studies		
Lee *et al.*[8]	943	0.7%
Gonzaalez-Scarano *et al.*[9]	1,427	1.3%
Martin *et al.*[10]	253	3.7%
Bojar *et al.*[11]	3,206	1.0%
Coffey *et al.*[12]	1,669	3.8%*
Prospective studies		
Shaw *et al.*[13]	312	4.8%
Breuer *et al.*[14]	421	5.2%

*Included altered mental state, stroke and seizure.

TABLE II Effects of isoflurane on cerebral perfusion and metabolism

Author	*Effect of isoflurane*
Newberg & Michenfelder (1983)[48]	Hypoxemic mice: ↑ survival time. Haemorrhagic hypotension in dogs: preserved energy stores better than N_2O.
Todd & Drummond (1984)[49]	Normocarbic cats: no significant changes in CBF, greater ↓ $CMRO_2$, and less impairment of autoregulation, compared to halothane.
Baughman *et al.* (1988)[50]	Incomplete cerebral ischaemia in rats: provided better neurological and histological outcomes, compared to N_2O.
Newberg *et al.* (1983)[51]	Dogs: dose-related ↓ $CMRO_2$ until isoelectric EEG at 3% end-tidal concentration, with preservation of brain energy state.
Nehls *et al.* (1987)[52]	Focal ischaemia in baboons: no protection, compared to thiopentone.
Young *et al.* (1989)[53]	Carotid endarterectomy: CBF less, but $CMRO_2$ was the same, compared to halothane.
Newberg *et al.* (1984)[54]	Isoflurane-induced hypotension in dogs: ↓ $CMRO_2$, ↓ CBF, normal aerobic metabolism.
Newman *et al.* (1986)[55]	Isoflurane-induced hypotension during cerebral aneurysm clipping: ↔ CBF, ↓ $CMRO_2$.
Artru (1986)[56]	Isoflurane-induced hypotension during hypocapnia in dogs: no adverse effect on cerebral metabolism and EEG.
Mutch *et al.* (1989)[57]	Phenylephrine treatment for haemorrhagic hypotension during isoflurane anaesthesia in rats: no cerebral vasoconstriction, total and rCBF maintained.
Ruta *et al.* (1989)[58]	Isoflurane-induced hypotension in rabbits: rCBF supratentorial < infratentorial. Treatment methods to support BP in presence of haemorrhage differed in effects on rCBF.
Messick *et al.* (1987)[59]	Carotid endarterectomy: critical rCBF < 10 $ml \cdot 100\,g^{-1} \cdot min^{-1}$, much lower than that previous reported for halothane.
Michenfelder *et al.* (1987)[60]	Carotid endarterectomy, retrospective:

	Critical CBF	*EEG ischaemic change*
Isoflurane	$10\,ml \cdot 100\,g^{-1} \cdot min^{-1}$	18%
Enflurane	$15\,ml \cdot 100\,g^{-1} \cdot min^{-1}$	26%
Halothane	$20\,ml \cdot 100\,g^{-1} \cdot min^{-1}$	25%

No difference in neurological outcome, as shunt was inserted based on EEG changes.

Woodcock *et al.* (1987)[61]	Cardiopulmonary bypass: EEG suppression by: Thiopental → ↓ $CMRO_2$ & ↓ CBF Isoflurane → ↓ $CMRO_2$ & ↔ CBF

into the systemic circulation.[33–35] Membrane oxygenators produce fewer microemboli than bubble oxyyenators.[36–38] Proper priming procedures can reduce foreign particles from entering the system.[34] Adequate anticoagulation, maintaining the activated clotting time greater than 400 sec, is essential in reducing fibrin and platelet aggregation.[39] Arterial filters[37,40–42] and filtration of the cardiotomy suction returns[43,44] are effective in removing both solid and gaseous microparticles and reducing the number of microemboli delivered to the arterial circulation. Some studies have shown that filters are effective in reducing the incidence or severity of neurological injury following CPB.[45–47]

Intraoperative management

PROTECTIVE EFFECT OF ANAESTHETIC AGENTS

Many animal and clinical studies have attempted to examine if isoflurane provides cerebral protection against ischaemia (Table II).

Newberg and Michenfelder reported that the survival time of severely hypoxaemic mice was increased when they were exposed to 1.0% and 1.4% isoflurane.[48] In normocarbic mechanically ventilated cats, isoflurane at 0.5, 1.0 and 1.5 MAC, caused no changes in CBF, greater decreases in $CMRO_2$, and less impairment of autoregulation than comparable MACs of halothane.[49] Baughman *et al.* found that, in rats with incomplete cerebral ischaemia produced by carotid artery occlusion, combined with haemorrhagic hypotension, isoflurane and halothane both provided better neurological and histological outcomes than N_2O controls.[50] In dogs, a dose-related decrease in cerebral oxygen consumption ($CMRO_2$) was evident until the onset of isoelectric EEG, which occurred at an isoflurane end-expired concentration of 3%. Further increases of the isoflurane concentration did not produce any more reduction of the $CMRO_2$. The normal concentrations of ATP and phosphocreatine in the brain biopsies suggested that this concentration of isoflurane had no direct toxic effect on the cerebral metabolic pathways.[51] Nehls *et al.*, however, in a focal ischaemia model using transorbital middle cerebral artery occlusion in baboons, could not demonstrate any protective value of isoflurane in concentrations sufficient to maintain burst suppression on the EEG, when compared with thiopental.[52] One possible explanation for the apparent negative effects was that isoflurane, in contrast to the cerebral vasoconstricting properties of thiopentone, was a mild cerebral vasodilator and could cause an unfavourable redistribution of blood flow during regional ischaemia. Furthermore, Young *et al.* showed that although the CBF was greater during halothane than during isoflurane or fentanyl anaesthesia in patients undergoing carotid endarterectomy, there was no demonstrable difference in the $CMRO_2$ between the three anaesthetic agents.[53]

The cerebral effects of isoflurane during hypotension have also been studied. The cerebral energy stores of ATP and phosphocreatine, and the cerebral energy charge in dogs, during a nine-minute haemorrhagic hypotension to 30 mmHg, were sustained at much higher levels when exposed to 3% isoflurane than N_2O controls.[48] Normal aerobic metabolism was preserved in association with decreases in both the CBF and the $CMRO_2$ during isoflurane-induced hypotension in dogs.[54] During isoflurane-induced hypotension to a mean arterial pressure of 50 mmHg in patients undergoing craniotomy for clipping of cerebral aneurysms, Newman *et al.* found that the $CMRO_2$ was reduced while the mean CBF remained relatively unchanged, indicating that the global oxygen supply-demand balance was favourably influenced by isoflurane.[55] Artru found no adverse effect on cerebral metabolism and the EEG during hypocapnia (to $PaCO_2$ of 20 mmHg) plus isoflurane-induced hypotension (cerebral perfusion pressure to as low as 40 mmHg for 30 minutes) in dogs.[56] Mutch *et al.* showed that during isoflurane anaesthesia (at inspired 1.5 MAC) in rats subjected to haemorrhagic hypotension, phenylephrine infusion did not cause cerebral vasoconstriction and effectively maintained both total and regional CBF.[57] Ruta and Mutch found that, in rabbits, isoflurane-induced hypotension to a mean arterial pressure (MAP) of 50 mmHg (the lower limit of the autoregulatory range) produced regional differences in cerebral perfusion, with decreased rCBF to the supratentorial structures, increased rCBF to the cerebellum and the brain stem, and unchanged total CBF (tCBF). The rCBF to all regions of the brain became pressure passive, as expected, when MAP was further decreased to 30 mmHg by haemorrhage. Raising the MAP back to 50 mmHg by a reduction of the inspired isoflurane concentration, restoration of blood volume, or infusion of phenylephrine was effective in improving the tCBF and the rCBF to the supratentorial structures. However, reduction of the inspired isoflurane concentration did not improve the rCBF to the posterior fossa structures. Nevertheless, the rCBF to these structures at this time was not different from that before hypotension was induced with isoflurane. The rCBF autoregulation curve was shifted downward and to the right in the infratentorial structures.[58]

Messick *et al.*, in a study on isoflurane anaesthesia for carotid endarterectomy, found that the level of rCBF below which EEG signs of ischaemia occurred (critical rCBF) was $< 10\ ml \cdot 100\ g^{-1} \cdot min^{-1}$, much lower than that previously reported for halothane ($18–20\ ml \cdot 100\ g^{-1} \cdot min^{-1}$).[59] This lower value of critical rCBF for isoflurane was also found by Michenfelder *et al.* in their retrospective review of 2010 carotid endarterectomies in which both EEG and CBF were measured.[60]

It appears that isoflurane is the preferred volatile anaesthetic for protection against cerebral ischaemia. The mechanism of cerebral protection is similar to that of the barbiturates, and is mainly by a reduction in $CMRO_2$ through a depression of synaptic transmission. The reduction in $CMRO_2$ is maximum when the EEG becomes isoelectric. A high inspiratory concentration of isoflurane (2.5 to 3.5%) is required to induce EEG burst suppression. Woodcock *et al.* compared the cerebral haemodynamic and metabolic effects of isoflurane and thiopentone EEG suppression during CPB. The thiopentone-induced EEG suppression was associated with a reduction of both the $CMRO_2$ and the CBF. However, although isoflurane-induced EEG suppression reduced the $CMRO_2$, it was not associated with a reduction of CBF.[61] The authors suggested that the thiopentone-induced reduction in CBF

would produce a proportionate reduction in the delivery of emboli to the cerebral circulation. In addition, the cerebral vasoconstrictive properties of thiopentone may induce a more favourable redistribution of CBF towards an ischaemic focus.

Isoflurane may produce myocardial ischaemia by inducing coronary steal. The studies by Slogoff *et al.* and Tuman *et al.*, however, did not show deleterious effects of isoflurane in CABG.[62,63] On the other hand, Inoue *et al.* showed that isoflurane produced significantly worse outcomes than enflurane when used in CABG, with higher postoperative myocardial infarction (4.0% vs 1.8%) and higher in-hospital deaths (2.1% vs 0.3%). Cardioplegic solutions were not used for myocardial protection, and the volatile agent was used as the primary anaesthetic during CPB in this series.[64]

Barbiturates in high doses suppress neuronal electrical activity and reduce cerebral metabolic demands. The reduction of cerebral metabolism is maximal when the EEG becomes isoelectric, at which level the membrane ion pumps remain intact.[65–67] Barbiturates, in sufficient dosage to cause electrical silence in nonischaemic brain, may divert flow to ischaemic areas.[68] However, to provide cerebral protection, they must be given either before or soon after an insult, and the protection is effective in temporary, rather than permanent, focal ischaemia.[69] Nussmeier *et al.*, in a prospective randomized study of open-ventricle operations requiring CPB, found that thiopentone, given in sufficient doses to maintain electroencephalographic silence for the duration of bypass, reduced the neuropsychiatric dysfunction of cerebral embolism associated with open heart operations. The neuropsychiatric dysfunction, which included hemiparesis, homonymous hemianopsia, dysarthria, disorientation, memory loss, excessive lethargy, hallucinations, delusions and hostility, occurred in 5.6% of 89 patients treated with thiopentone, and in 8.6% of 93 patients not treated. By the tenth postoperative day, all neuropsychiatric abnormalities disappeared in the thiopentone-treated patients, but persisted in 7.5% of patients in the untreated group.[70] The authors recommended this therapy for patients undergoing valve replacement, resection of ventricular aneurysms, and other operations requiring opening of the ventricle. However, barbiturates in such doses may create additional problems of cardiovascular instability and prolonged emergence from anaesthesia.

HYPOTHERMIA, HAEMODILUTION AND ACID-BASE MANAGEMENT

Mild hypothermia (28 to 30°C) and haemodilution (20 to 30%) are used routinely during CPB. Hypothermia reduces cerebral requirements for oxygen and glucose and, theoretically, may confer protection in cerebral ischaemia.[71,72] As hypothermia increases blood viscosity, haemodilution is used during bypass to minimize driving pressures required to maintain flow.[73]

While we generally agree that the normal arterial pH and PCO_2 values at 37° C are 7.4 and 40 mmHg respectively, the values at lower body temperatures that we consider to be ideal are not clear. The solubility of CO_2 in blood increases as temperature decreases, such that PCO_2 decreases and pH increases. Results from blood gas analysis corrected to the patient's temperature will indicate respiratory alkalosis. Whether we should use values temperature-corrected to actual body temperature or uncorrected at the measuring electrode's temperature is controversial.

Some believe that it is desirable to maintain a normal acid–base relationship, and adjust the pH to 7.4, and PCO_2 to 40 mmHg, irrespective of the temperature.[74] This is the "pH-stat" approach. It is often necessary to add CO_2 to the oxygenator to achieve these values during hypothermic CPB. These values would correspond to hypercapnia and acidosis at the electrode temperature. The temperature chosen for correction is inconsistent, and may be nasopharyngeal, oesophageal, tympanic, bladder or that of the perfusate. Over- or under-correction often results as temperature gradients exist between tissues during cooling and rewarming.

Cold-blooded animals behave quite differently from this in a cold environment. As their body temperature falls, their arterial PCO_2 decreases and pH increases, and the content of CO_2 remains constant. The pH of their arterial blood is maintained at 7.4 when measured with a 37° C electrode without temperature correction. The charge state of the imidazole radical of histidine (the alpha charge), upon which many enzymatic and transport activities are dependent, is influenced by the arterial PCO_2. Maintenance of a constant alpha charge allows the cold-blooded animal to survive at low temperatures in an active state.[75] The "alpha-stat" approach imitates the cold-blooded animals, maintaining uncorrected values at normal ranges. As the pH of neutrality (where $H^+ = OH^-$) increases when temperature decreases, this approach maintains electrochemical neutrality.

McConnell *et al.* showed that, in dogs undergoing hypothermic CPB at 28° C, an increase of the arterial pH from 7.40 to 7.70 produced an increase in coronary blood flow and myocardial lactate utilization with an improvement of the left ventricular performance.[76] Ohmura *et al.* found that, in dogs subjected to surface-induced hypothermia to 24° C, maintaining normocarbia by the addition of CO_2 caused a rapid decrease in the cardiac index and an increase in both pulmonary and systemic

vascular resistances.[77] The alpha-stat approach thus appears to be more beneficial to the cardiovascular system than the pH-stat approach.

However, the cerebral circulation is a concern here. Since both hypothermia and low PCO_2 decrease CBF, cerebral ischaemia is a potential problem with the alpha-stat approach. Differences in the anaesthetic techniques and the methods of CBF measurements resulted in conflicting data regarding the effect of CO_2 on CBF during hypothermic CPB. Henriksen *et al.* reported that, in patients anaesthetized with enflurane during the prebypass period, hypothermic CPB was associated with an increase in CBF and impairment of CO_2 responsiveness.[78] Govier *et al.*, on the other hand, using diazepam and fentanyl, found that CBF decreased during hypothermic CPB, and the responsiveness of the CBF to changes in $PaCO_2$ was maintained.[79] Prough *et al.* also found that CBF remained responsive to changes in $PaCO_2$ during hypothermic, nonpulsatile CPB in patients anaesthetized with high-dose fentanyl.[80] Hägerdal *et al.* found that, in rats, although the CBF decreased with decreasing $PaCO_2$ during hypothermia, there was no evidence of tissue hypoxia, as the $CMRO_2$ decreased with hypothermia.[81] Murkin *et al.* found that, during hypothermic CPB in patients anaesthetized with fentanyl and diazepam, the cerebral metabolic rate for oxygen ($CMRO_2$) was reduced. In patients managed with the pH-stat approach (temperature-corrected), the CBF was higher, and was independent of $CMRO_2$, but correlated with cerebral perfusion pressure (CPP). This led to hyperperfusion relative to the cerebral oxygen demand. On the other hand, in patients managed with the alpha-stat approach (non-temperature-corrected), the CBF was lower, and correlated well with $CMRO_2$, but not with CPP.[82] The fact that most centres use temperature-corrected CO_2 for acid–base management suggests that the particular method of acid–base management may not be crucial.[82] However, any unnecessary increase in CBF may increase the delivery of micro-emboli to the cerebral circulation. Furthermore, unnecessary elevations of $PaCO_2$ may lead to intracerebral steal phenomenon in patients with cerebrovascular disease. It remains to be seen if clinical data can substantiate these theoretical concerns.

CEREBRAL PERFUSION

Pulsatile perfusion techniques offer theoretical advantages such as better distribution of myocardial perfusion, capillary perfusion, urine output, and preservation of normal pituitary-adrenal stress-response.[83–91] However, they have the disadvantage of creating increased turbulence of blood flow and thus increased haemolysis. No study has yet shown that pulsatile perfusion can improve neurological outcome in cardiac surgery. The safety and simplicity of the nonocclusive roller nonpulsatile pump make it the most widely used system.

The limits of hypotension that can be tolerated during CPB without neurological injury have not been precisely defined. While early studies showed an increased incidence of neurological damage when the mean arterial pressure decreased below 50 mmHg,[5,92–95] the association has not been confirmed subsequently.[7,9,19,96] It appears that, when alpha-stat acid–base management is used, cerebral perfusion is well maintained at a decreased systemic flow and pressure during CPB.[79,80,82] Nevertheless, maintenance of adequate flow and pressure can minimize the autoregulatory cerebral vasodilatation associated with marginal cerebral perfusion pressures. Following an unavoidable hypotensive episode, an even higher cerebral perfusion pressure is required to overcome the no-reflow phenomenon.[94,97–100]

MONITORING OF CEREBRAL PERFUSION

Since perioperative stroke occurs in about 5% of patients undergoing CABG and CPB, monitoring techniques capable of early detection of potentially reversible problems would be most useful. The EEG has helped to identify inadequate cerebral perfusion during carotid surgery, and it is logical to extend its use in cardiac surgery.

Witoszka *et al.*, in a retrospective study, found no relationship between the intraoperative EEG abnormalities and the outcome of a selected group of patients (consisting of five intraoperative deaths, 45 postoperative deaths, and 50 survivors) who had cardiac surgery and CPB. They concluded that localizing neurological deficits were likely related to embolism, and were not detectable by the EEG.[101] Salerno *et al.*, in a prospective study of the value of EEG monitoring during CABG and valve replacement in 118 patients, found EEG abnormalities in 22 patients (18.6%). Most of these were transient, but five patients showed severe EEG suppression, which led to the correction of technical problems and subsequent return of normal EEG, and no neurological damage. However, two patients who had normal intraoperative EEG developed postoperative cerebral infarction. They had severe calcific aortic stenosis. The deficit was either missed by the EEG, or developed postoperatively.[102]

Computer-processed EEG monitors can make the interpretation much easier than with conventional EEG. Many models have been evaluated for use during cardiac surgery and CPB. In 1973, Schwartz *et al.* compared retrospectively the neurological outcome of 100 patients undergoing cardiac surgery, with the information obtained from the Cerebral Function Monitor (CFM, Devices Ltd.), which produced a filtered and compressed EEG signal as a single trace from a pair of parietal

electrodes. It was possible to predict correctly the neurological outcome in 83% of the patients by simple quantification of the CFM trace alone.[103] The Cerebral Function Analysing Monitor (CFAM), which analyzed both the amplitude and the frequency of the EEG as recorded from biparietal electrodes, was evaluated by Nevin *et al.* in a prospective study on 65 patients undergoing CABG. Unexplained acute changes in both amplitude and frequency distribution (such as sudden reduction in amplitude and frequency, or opening up of the amplitude envelope together with slowing) lasting more than three minutes were considered to be significant CFAM changes. These occurred at various times throughout the operation, although mostly at the beginning of bypass. All patients with two or more CFAM changes during the course of their operation were found to have significant postoperative neuropsychometric deficits. However, 21% false positive results were seen.[104] El-Fiki and Fish reported the detection of two ischaemic episodes in a patient undergoing myomectomy for idiopathic hypertrophic subaortic stenosis, using a two-channel Cerebro Trac 2500 EEG Monitor (SRD, Peekskill, NY) which displayed the power/frequency spectrum in DSA and spectral edge frequency set at 95%. An accidental pump disconnection led to an almost total loss of the EEG activity within ten seconds. The EEG recovered in four minutes after perfusion was restored. Air embolization occurred during manipulation of the heart to remove air from the left ventricle. This was associated with severe and prolonged EEG changes. Thiopental infusion was given for protection. The patient recovered with only minimal neurological deficits.[105] Jones and Scheller reported a case of unexpected interruption in CPB which resulted in profound EEG changes easily detected with a Lifescan processed EEG monitor (Neurometrics, San Diego, CA) in a patient undergoing mitral valve replacement and CABG. The change in the EEG spectral edge (95%) was easily seen, and returned to normal when perfusion was restored.[106]

The EEG is used to provide warning of decreases in the cerebral perfusion to marginal levels as evidenced by a decrease in the frequency and amplitude of electrical activity. However, EEG changes are commonly seen at the onset of CPB.[104,105] Slowing of the EEG may also be caused by hypothermia[107] or high-dose narcotic anaesthesia,[108,109] both of which are commonly used in cardiac surgery. In addition, roller-pumps often produce EEG artifacts.[110] The development of permanent neurological damage depends on both the severity and the duration of ischaemia, and therefore not all ischaemic EEG changes are associated with postoperative morbidity. Furthermore, strokes caused by small emboli may not be detected by EEG monitoring. For these reasons, routine use of EEG monitoring during cardiac surgery has not been shown to reduce neurological morbidity, except in the presence of unexpected events.[105,106] On the other hand, the EEG may be useful in detecting unexpected cerebral hypoperfusion in patients with cerebrovascular disease.[111] However, von Reutern *et al.*, using transcranial Doppler ultrasonography, could not demonstrate any significant reduction of blood flow in the middle cerebral artery on the side of a severe (>80%) carotid obstruction during CPB. The authors concluded that carotid obstruction could not be considered a significant risk factor for the development of intraoperative stroke.[112]

Cardiac surgical patients with carotid artery disease

The natural histories of carotid and coronary artery atherosclerosis are closely related. Indeed, transient ischaemic attacks should be looked upon as a warning for cardiac as well as cerebrovascular disease.[113] The risk of stroke associated with coronary artery revascularization is increased in patients with symptomatic carotid artery disease.[114] On the other hand, myocardial infarction is a major cause of morbidity and mortality associated with carotid endarterectomy.[115–118]

ASYMPTOMATIC BRUIT OR CAROTID STENOSIS

Central nervous system complications are more common and more severe after CABG surgery than after peripheral vascular surgery.[119] Does the presence of asymptomatic bruit or asymptomatic carotid stenosis increase the risk of perioperative stroke during cardiac surgery using CPB?

Reed and associates compared 54 patients who developed stroke or transient ischaemic attacks following coronary artery bypass surgery, with 54 randomly selected patients who also had the same operation but had no neurological complications. The number of patients with bruits was small. Nonetheless, their analysis showed that the presence of a preoperative carotid bruit increased the risk of stroke or TIAs by a factor of 3.9. Their study was not specifically directed to asymptomatic bruits, and the postoperative deficits observed were not necessarily related to the side of carotid bruit.[120]

Since cervical bruits are not exclusively due to carotid artery disease, noninvasive evaluation of the carotid system should be performed. Using OPG or Doppler techniques, haemodynamically important carotid stenosis can be found in about 20% of patients with asymptomatic bruits.[121–123] Barnes *et al.* found no significant difference in the perioperative stroke rate between patients with Doppler-documented significant carotid obstruction (2.5%) and those who had normal or minor lesions in the carotid arteries (1.8%).[122] Ivey *et al.*, in their study of 1433 patients undergoing CPB, found no case of stroke in the 82 patients who had asymptomatic bruits, 66 of which

TABLE III Perioperative stroke in the territory of significant asymptomatic carotid stenosis in CABG

authors	*Diagnosis based on*	*Perioperative stroke*
Barnes *et al.*[122]	Doppler	2.5% of 40 pt with obstruction 1.8% of 284 pt without obstruction
Ivey *et al.*[124]	Ultrasonic duplex scan	0% of 66 pts with >50% stenosis
Furlan *et al.*[125]	Angiography	1.1% of 90 pt with 50–90% stenosis 6.2% of 16 pt with >90% stenosis 2.0% of 49 pt with ICA occlusion

were associated with more than 50% stenosis as demonstrated by ultrasonic carotid duplex scan.[124]

Furlan and Craciun studied the risk of stroke associated with CABG surgery in 144 patients with internal carotid artery (ICA) disease documented by angiography (11 with bilateral lesions). Ipsilateral stroke occurred in one among 90 patients with 50 to 90% ICA obstruction (1.1%), in one among 16 patients with more than 90% ICA obstruction (6.2%), and in one among 49 patients with total ICA occlusion (2.0%). The authors concluded that asymptomatic unilateral ICA stenosis less than 90% or ICA occlusion did not increase the risk of stroke during coronary artery bypass surgery[125] (Table III).

It is logical to maintain a higher perfusion pressure and flow than normal during CPB, and to use EEG monitoring to evaluate cerebral perfusion in patients with carotid stenosis. Gibbs *et al.* have demonstrated that cerebral blood flow ipsilateral to ICA occlusion was inappropriately low.[126] However, recent studies on cerebral blood flow monitoring in patients with severe carotid stenosis or occlusion during nonpulsatile hypothermic bypass showed no evidence for decreased cerebral perfusion.[112,127]

There is no evidence to justify routine prophylactic carotid endarterectomy for patients with asymptomatic carotid disease before cardiac surgery.[128] Patients can undergo cardiac procedures without carotid surgery as safely as if the carotid artery were repaired.[129]

SYMPTOMATIC CAROTID ARTERY DISEASE

Patients with symptomatic carotid artery disease, on the other hand, have an increased risk of perioperative stroke if they are subjected to CBP.[114,130,131] These patients need revascularization of both the carotid and coronary arteries, and the choice is between staged and combined operations. A staged approach with carotid endarterectomy as the first procedure may result in some patients dying of cardiac complications before coronary surgery can be undertaken. Conversely, initial coronary revascularization may result in a high incidence of fatal stroke.[132] Under appropriate circumstances, both lesions can be treated simultaneously.[132–135]

The approach to the management of these patients varies among institutions. In general, each patient is assessed according to the severity of the disease, both clinically and anatomically, in each system. Staged procedures with carotid endarterectomy before coronary artery bypass is preferable for patients who have a low cardiac risk presenting with one- or two-vessel disease and stable angina. Combined procedures are appropriate for neurologically symptomatic patients who are at high cardiac risk presenting with left main coronary artery disease, severe multivessel lesions with inadequate collateral perfusion, or unstable angina.[136,137]

The combined carotid endarterectomy and coronary artery bypass procedure appears to be a logical approach for patients with high-risk cerebrovascular and coronary artery diseases, although it is not clear whether this approach increases or decreases the morbidity and mortality, compared with staged operations. A review of the combined procedures from 1972 to 1988 (a total of 1345 patients) revealed a mean operative mortality rate of 5.7%, permanent stroke rate of 3.0%, and myocardial infarction rate of 3.8%.[138] These figures are unacceptable for elective CABG in most institutions, and many institutions have discontinued the combined procedure approach. On the other hand, the recent experience from the Massachusetts General Hospital is encouraging. From 1983 to 1987, there was no significant difference in either operative mortality (2.0% vs 2.2%) or perioperative stroke (2.0% vs 0.6%) in patients undergoing combined procedures and isolated coronary bypass grafting, respectively.[138]

Few patients are suitable for the combined procedures: 9.5% of 679 carotid endarterectomies performed at the Johns Hopkins Hospital,[139] and 2.8% of 9714 coronary artery bypass procedures at the Cleveland Clinic.[140] Perler *et al.* found that mortality associated with the combined procedures was influenced by age, left main coronary artery disease, male sex, history of congestive heart failure, and presence of bilateral carotid disease.[139] Until further prospective studies are performed, the authors expressed caution in recommending the combined approach in elderly candidates or in those with three or more of the above risk factors.

Perioperative cardiogenic embolic stroke

Cardiogenic embolism accounts for 6 to 23% of all ischaemic strokes and is a frequent cause of fatal brain infarction.[141] Although data are lacking, cardiogenic embolism probably accounts for many perioperative strokes. Cardiogenic embolism is difficult to diagnose with certainty. Yasaka *et al.* found that intracardiac thrombi were frequently detected by repeated echocardiographic examination in patients with cerebral embolism. Dehydration seems to accelerate thrombus formation that is reflected by a decrease in antithrombin III.[142]

As cardiogenic strokes tend to be functionally devastating, and occur without warning, the primary emphasis must centre on their prevention. Perioperative cardiogenic stroke is more likely to occur in patients with some cardiac diseases, and may be associated with diagnostic and therapeutic procedures done to the heart.

Cardiac diseases

Patients who are at high risk of cardiogenic embolism include those with atrial fibrillation, valvular heart disease and prosthetic heart valves.[141, 143-145]

ATRIAL FIBRILLATION

Reed *et al.* found that atrial fibrillation increased the risk of perioperative stroke following CABG threefold.[120] Taylor *et al.* reported ten focal neurological deficits in a series of 453 patients undergoing CABG. Six of the deficits occurred in 86 patients who had postoperative atrial fibrillation (7%), and four occurred in 367 patients who had no postoperative atrial fibrillation (1%).[146]

Atrial fibrillation is found in 0.4% of the adult population; the prevalence increases with age, being 2–4% after 60 years of age. It is the most common underlying cardiac disorder predisposing to systemic embolism. In the Framingham Study, the risk of a cerebral infarct in patients with chronic atrial fibrillation was found to be 5.6 times greater than in patients with sinus rhythm. The risk of first stroke is 4.1% per year in patients with nonrheumatic atrial fibrillation, and 4.5% per year in patients with atrial fibrillation associated with rheumatic valve disease. Once cerebral embolism has occurred, the risk for recurrent stroke is considerably higher, with recurrence rates of approximately 20% for the first year and 37% for three years.[147]

Petersen and Hansen found that atrial fibrillation in the absence of rheumatic heart disease was associated with a more than five-fold increase in stroke incidence, whereas atrial fibrillation with rheumatic heart disease had a 17-fold increase when compared with patients without atrial fibrillation.[148] The risk of embolism is particularly high at the onset of atrial fibrillation.[149,150]

The first clinical presentation with an ischaemic stroke syndrome may not be the first episode of cardiogenic embolic brain infarction; cerebral emboli causing infarction may be asymptomatic. Silent cerebral infarctions are often demonstrated by computed tomogram in patients with chronic atrial fibrillation.[151,152]

Long-term warfarin therapy is indicated when atrial fibrillation is associated with documented systemic embolism or mitral valvular disease.[145,153,154]

VALVULAR HEART DISEASES

Rheumatic mitral valve disease is associated with a higher risk of systemic embolism than any other common form of heart disease. It is estimated that a patient with rheumatic mitral valve disease has at least a 20% chance of having a clinically detectable systemic embolus during the course of the disease.[155] When patients with mitral valve disease develop atrial fibrillation, the risk of systemic embolization increases dramatically. Therefore, all patients with rheumatic mitral valve disease associated with chronic or paroxysmal atrial fibrillation, or who have documented systemic embolism, should receive long-term warfarin therapy sufficient to prolong the prothrombin time to 1.5 times control.[143]

Mitral valve prolapse is the most common valve disease in adults, and is present in 2.5 to 17% of the general population[156-158] Although it is generally innocuous, mitral valve prolapse may be associated with an increased incidence of atrial fibrillation, mitral regurgitation, infective endocarditis and embolic phenomena. The exact role of mitral valve prolapse in cerebral ischaemia is not clear.[159] Sandok and Giuliani reported a four-fold increase in strokes in persons with mitral valve prolapse compared to the normal population.[160] However, in large prospective series of stroke patients, mitral valve prolapse is detected in only 0 to 5%.[161-166]

In young patients without other major risk factors for stroke, the presence of mitral valve prolapse may constitute a risk for cerebral ischaemia.[167] However, the overall incidence of stroke in young individuals with mitral valve prolapse is low, approximately one per 6,000 per year, or 0.2%.[168] Patients with asymptomatic mitral valve prolapse need not be on antithrombotic therapy. However, if unexplained TIAs occur, long-term aspirin is recommended.[143]

Aortic valve disease is associated with a low frequency of systemic thromboembolism, and long-term antithrombotic therapy is not indicated.[143]

PROSTHETIC HEART VALVES

The risk of thromboembolism depends on the type and site of the valve. Tissue valves are generally less thrombogenic than mechanical valves.[144,169] The velocity of blood flow across the mitral valve is less than across the

aortic valve. With a greater deposition of platelets and fibrin on the mitral valve, the risk of emboli arising from the mitral prosthetic valve is therefore greater than that from the aortic prosthetic valve.[170]

Patients with mechanical prosthetic valves are at a significant risk for thromboembolism and require long-term anticoagulation,[171] and also antiplatelet agents postoperatively.[172] Patients with tissue valves also require anticoagulation during the first 6 to 12 postoperative weeks. Anticoagulation is required for all patients with prosthetic valves if they have chronic atrial fibrillation or a previously documented embolic event.[171,173] The risk of embolism is reduced by therapy, but in about 2% of patients on long-term warfarin, the treatment is complicated by serious, frequent, intracranial haemorrhage.[174,175]

PERIOPERATIVE MANAGEMENT OF PATIENTS ON LONG-TERM ANTICOAGULANT THERAPY

The cardiac lesions for which long-term warfarin therapy is recommended by the American College of Chest Physicians and the National Heart, Lung and Blood Institute to prevent systemic embolism and stroke include: (1) atrial fibrillation with a history of systemic emboli, mitral valve disease, cardiomyopathy or thyrotoxicosis, (2) mitral valve disease with a history of systemic emboli, chronic or paroxysmal atrial fibrillation, (3) mitral valve prolapse with atrial fibrillation, (4) mechanical prosthetic heart valves, and (5) bioprosthetic heart valves with mitral placement, history of systemic emboli, atrial fibrillation or left atrial thrombus.[143–145]

In patients receiving long-term anticoagulation therapy and undergoing noncardiac operations, maintenance of anticoagulation can be associated with perioperative bleeding, and discontinuation can lead to thromboembolism.[176] For patients with isolated aortic prosthetic valves, warfarin should be discontinued two to three days before surgery to produce a normal prothrombin time on the day of operation, and resumed two days after the operation.[176–178] Tinker and Tarhan found that discontinuing anticoagulation to restore the prothrombin time to within 20% of control did not cause excessive perioperative bleeding, and was not associated with thromboembolic complications.[179] The risk of thromboembolism is greater in patients with mitral or combined prosthetic valves. In these patients, and in other patients at highest risk for thromboembolic complications, anticoagulation should be continued to within 24 hr of their surgery. The warfarin effect may be reversed with parenteral vitamin K or fresh-frozen plasma.[176,177] Intravenous heparin is started 12 hr after the procedure when adequate haemostasis has been secured. The partial thromboplastin time is maintained at 1.5 to 2.5 times the levels of normal controls. When adequate surgical haemostasis is assured, usually three days after operation, oral anticoagulation with warfarin is resumed and the heparin is stopped when the prothrombin time reaches a therapeutic level.[176,177]

Alternatively, anticoagulation can be switched from warfarin to heparin. Heparin is started two to three days preoperatively, stopped 8 to 12 hr before surgery, and restarted postoperatively as soon as haemostasis is assured. Warfarin is resumed two to three days later. Heparin is discontinued when the prothrombin time has returned to the desired range.[178] For the patient with a high risk of thromboembolism, who has a prosthetic heart valve, chronic atrial fibrillation or persistent congestive heart failure, it may be safe to perform minor operations such as dental extractions or other procedures in accessible areas, while maintaining anticoagulation.[178]

PERIOPERATIVE PROPHYLACTIC ANTIBIOTIC THERAPY

Infective endocarditis may lead to septic embolism, causing ischaemic stroke and intracranial haemorrhage.[180,181] Prophylactic antibiotic coverage during the perioperative period is important to prevent endocarditis in patients with valvular disease and prosthetic valves. Davenport and Hart retrospectively reviewed the outcomes of 61 patients with 62 episodes of prosthetic valve endocarditis. Eleven patients (18%) suffered an embolic stroke, usually within three days of diagnosis of endocarditis. No protective effect of anticoagulation therapy with warfarin was observed, and no specific risk of haemorrhagic stroke was evident with anticoagulant therapy.[182] It appears that antibiotic treatment is more important than anticoagulation for preventing neurological complications in patients with prosthetic valve endocarditis.

PATENT FORAMEN OVALE AND VENTRICULAR SEPTAL DEFECT

Patent foramen ovale may be present in up to 40% of routine autopsies.[183]Recent reports suggest paradoxical embolism is responsible for an increased incidence of stroke in patients with patent foramen ovale,[184–186] and perioperative stroke due to paradoxical embolism has been reported.[187,188] Black *et al.*, using preoperative precordial echocardiography along with the Valsalva manoeuvre, detected right-to-left shunting in only six of a series of 101 patients scheduled for neurosurgical procedures in the sitting position. As a result of these findings, five of the six patients had their surgery performed either in the horizontal or in the prone position. Transoesophageal echocardiography further detected right-to-left shunting in four of these patients during surgery.[189]

Normally, the pressures in the left chambers of the heart are higher than in the right, but coughing or the Valsalva manoeuvre may increase right-sided pressures so that a venous thrombus may pass into the systemic circulation and lead to cerebral embolism.

Paradoxical embolism and stroke may occur through

similar mechanisms in patients with other intracardiac shunts, such as ventricular septal defect.[190] Ventricular septal defect is found in 0.25 to 1% in autopsy studies, but its true incidence is difficult to assess, as many of the defects close spontaneously.[191]

The therapeutic implications in the perioperative period for patients with intracardiac shunts are obvious. Sources of venous emboli, such as deep venous thrombosis and those introduced through venous access lines, are to be prevented, and pressure increases on the right side of the heart, such as coughing and Valsalva manoeuvre, should be avoided.

Diagnostic and therapeutic procedures

DC CARDIOVERSION

Systemic embolism may complicate cardioversion of atrial fibrillation, especially in patients with mitral stenosis, prosthetic mitral valves, history of embolic phenomena, enlarged hearts, or congestive heart failure. Bjerkelund and Orning reported embolization complicating cardioversion in 5.3% of patients without anticoagulation, but in only 0.8% in those receiving anticoagulant therapy.[192] It is recommended that anticoagulation be started three weeks before elective cardioversion to maintain the prothrombin time in the therapeutic range of 1.2–1.5 times control. Anticoagulation should be continued for at least four weeks after cardioversion. This will reduce the formation of a new clot in a noncontractile atrium if mechanical resumption of atrial activity is delayed.[145]

PACEMAKER INSERTION

Disturbances of cardiac rhythm and manipulation of wires in the heart may generate thrombi. However, the risk of stroke associated with the insertion of intravenous endocardial pacemakers is not known. Patients with the sick sinus syndrome are at risk for cardioembolic stroke. Stroke after pacemaker insertion for sick sinus syndrome occurs often in the presence of paroxysmal or sustained atrial fibrillation. Pacing with a ventricular-demand pacemaker does not appear to be protective.[193]

CORONARY ARTERIOGRAPHY AND CORONARY ANGIOPLASTY

Stroke occasionally complicates coronary arteriography. Adams *et al.*, in a survey of complications in 46,904 cases of coronary arteriography in 1970 and 1971, found that the incidence of cerebral embolism was 0.23%. The risk was higher when the femoral route was used for catheter access.[194] Bourassa and Noble reported central nervous complications in ten of 5250 cases. Five patients had transient cerebral ischaemia, two had temporary disorientation, and three had transient blurred vision.[195] Transient visual disturbance occasionally complicates cardiac catheterization. Oliva and Scherokman reported computed-tomography-documented occipital lobe infarction in two patients with this complication.[196] Dawson and Fischer, in a survey of over 1000 cases, found ten cases of central nervous dysfunction. Nine of these were embolic in origin, mostly with focal disorder in the vertebrobasilar territory.[197] Sones found four cases of cerebral emboli resulting in long-term deficits among 52,953 cases.[198] In a study of 30,000 cardiac catheterizations, Lockwood *et al.* found 37 central nervous system complications, with two global ischaemia, 15 in the carotid, and 20 in the vertebrobasilar distribution. While the neurological deficit resolved in 19, and persisted in 16, two of the patients died. Embolization and hypotension were responsible in most of the cases. Cerebrovascular disease, ventricular hypokinesia, mural thrombus and valvular disease were found to be contributing factors.[199]

TABLE IV CNS complications associated with coronary arteriography

Authors	*Cases*	*CNS complications*
Adams *et al.*[194]	46,904	0.23% cerebral embolism
Bourassa *et al.*[195]	5,250	10 TIA, disorientation, recurrent blurred vision
Dawson *et al.*[197]	>1,000	10 CNS dysfunction, mostly embolic
Sones[198]	52,953	4 cerebral emboli with long term deficits
Lockwood *et al.*[199]	30,000	37 CNS complications

From these studies, the overall incidence of stroke associated with coronary arteriography is less than 1% (Table IV).

Stroke has been reported following percutaneous transluminal coronary angioplasty. Although stroke was not listed in an initial report of 631 cases from the registry of the National Heart, Lung, and Blood Institute,[200] five central nervous system events were seen in a subsequent report of 1500 patients (0.3%). There was one anoxic encephalopathy, one cerebrovascular accident, and three transient neurological deficits.[201] Galbreath *et al.* reported a similar experience, with four (0.2%) central nervous system complications among 1829 patients having 1968 percutaneous transluminal coronary angioplasties. One patient had a TIA, two had hemispheric infarcts, and one had a brainstem infarct.[202]

Conclusion

Stroke, defined as a focal neurological deficit, in the perioperative period is an uncommon but devastating complication. Although medical risk factors for stroke are well defined in the general population, no large scale data are available that identify the importance of the individual risk factors as a cause of perioperative stroke. In most clinical situations including general surgery, carotid

endarterectomy, and cardiac surgery involving CPB, thromboembolism appears to be the most important cause of perioperative stroke.

Cardiogenic embolism is a recognized complication of atrial fibrillation and valvular heart disease, and most perioperative strokes probably have a similar origin. With adequate monitoring and protection of the cerebral circulation, stroke associated with carotid surgery is most likely due to thromboembolism. Air and particle emboli are also the major causes of neurological deficits associated with CPB and open ventricle surgery. Patients with asymptomatic carotid disease do not appear to be at a higher risk of perioperative stroke than those with normal arteries. However, symptomatic carotid disease or critical carotid stenosis may increase this risk.

Because of prolonged changes of regional cerebral blood flow and enhanced thrombin activity following a stroke, elective surgery should be postponed for six to ten weeks. Anaesthetic agents such as isoflurane and thiopentone have cerebral protection properties, but they have to be given in sufficient doses to produce burst suppression in the EEG. Their use has been recommended in high-risk patients or procedures, but can be associated with cardiovascular instability and prolonged emergence from anaesthesia.

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