Deep hypothermic circulatory arrest

Most cardiac surgical procedures can be accomplished using cardioplegia-induced cardiac arrest and cardiopulmonary bypass (CPB) to maintain perfusion of other organs. In some situations, however, the underlying pathology or the nature of the surgery proposed necessitates complete cessation of the circulation. The use of profound systemic hypothermia to preserve organ function during cessation of the circulation is termed deep hypothermic circulatory arrest (DHCA). The technique provides excellent operating conditions while reducing the consequences of organ ischaemia. As the brain is the organ most susceptible to ischaemia during circulatory arrest, it follows that other organs will also be protected by this strategy.

Historical roots

In pioneering experiments conducted in the 1940s and 1950s, Bigelow demonstrated that at 30°C, the ‘safe’ period of cerebral ischaemia could be increased from 3 to 10 min—time enough for expeditious surgery. Surface cooling with cold rubber blankets or an iced water bath and caval (‘inflow’) occlusion permitted procedures such as atrial septal defect repair, valvectomy, and valvotomy to be undertaken. Despite considerable success, the incidence of death and serious complications were high by today’s standards. Subsequent reports of the use of more profound degrees of hypothermia highlighted the risks of cold-induced ventricular fibrillation and coagulopathic haemorrhage. The modern era of cardiac surgery, heralded by the introduction of CPB into clinical practice in 1953, provided surgeons with the means to both cool and warm patients while maintaining organ perfusion. Although reports of the use of CPB-induced hypothermia and DHCA to facilitate aortic arch surgery appeared in the 1960s, it was Griep, in 1975, who demonstrated that the technique offered a practical and safe approach for aortic arch surgery. Since then DHCA has remained the mainstay of cerebral protection during complex cardiac, vascular, neurological, and urological procedures (Table 1).

Despite its benefits, DHCA necessitates prolonged CPB with the associated problems of coagulopathy and cerebral microembolism. Profound hypothermia is associated with dysrhythmias (due to loss of potassium), increased plasma viscosity and erythrocyte rigidity, metabolic acidosis, hyperglycaemia, and altered drug distribution and elimination (Table 2).

Safe period for DHCA

At normothermia, brain injury occurs after around 4 min of circulatory arrest. Cerebral metabolism decreases by 6–7% for every 1°C decrease in temperature from 37°C; therefore, brain cooling results in a reduction in oxygen requirements. Circulatory arrest is typically undertaken at 18–20°C and a range of safe periods for DHCA have been reported at this temperature. Most patients tolerate 30 min of DHCA without significant neurological dysfunction, but when this is extended to longer than 40 min, there is a marked increase in the incidence of brain injury. Above 60 min, the majority of patients will suffer irreversible brain injury, although there are still a small number of patients who can tolerate this. Longer periods of DHCA are tolerated in neonates and infants compared with adults. It should be borne in mind that neurological injury may occur as a result of prolonged CPB and rewarming (Fig. 1).

Anaesthesia for DHCA

Premedication

All patients should undergo thorough preoperative assessment and be prepared for the extent of invasive monitoring and the potential for prolonged postoperative intensive care. When a

Sarah Conolly FRCA
Fellow in Cardiothoracic Anaesthesia and Intensive Care
Papworth Hospital
Papworth Everard
Cambridge CB23 3RE
UK

Joseph E Arrowsmith MD FRCP FRCA
Consultant in Cardiothoracic Anaesthesia and Intensive Care
Papworth Hospital
Papworth Everard
Cambridge CB23 3RE
UK

Andrew A Klein FRCA
Consultant in Cardiothoracic Anaesthesia and Intensive Care
Papworth Hospital
Papworth Everard
Cambridge CB23 3RE
UK
Tel: +44 1480 364406
Fax: +44 1480 364936
E-mail: andrew.klein@papworth.nhs.uk
(for correspondence)
patient requires emergency surgery, however, detailed assessment and prolonged discussion may be neither practical nor possible. Sedative premedication may be appropriate for patients undergoing an elective procedure involving DHCA, although care should be taken in patients in whom respiratory depression and hypoxia may induce haemodynamic disturbance—for example, patients with severe pulmonary hypertension. The use of corticosteroids should be considered, as there is some evidence—albeit inconclusive—that they are neuroprotective. This is thought to occur by decreasing the release of inflammatory cytokines and preventing lysosomal breakdown during hypothermia. To be effective, corticosteroids (e.g. prednisolone 1 mg kg\(^{-1}\)) should be administered at least 6–8 h before surgery, any resultant hyperglycaemia is probably best treated using insulin.

**Induction and monitoring**

In addition to routine non-invasive monitoring, all patients undergoing surgery with DHCA require invasive arterial and central venous pressure monitoring. In some instances, femoral or bilateral radial arterial monitoring may be appropriate. In addition to allowing measurement of central arterial pressure, placement of a femoral arterial cannula may aid the surgeon should an intra-aortic balloon pump be required. Measurement of right heart pressures using a pulmonary artery catheter or the use of transoesophageal echocardiography (TOE) may be indicated in some patients. Temperature monitoring at two sites, typically the nasopharynx and bladder, is used to estimate brain and body temperatures, respectively. Studies have shown that bladder and tympanic temperatures correlate most closely with brain temperature. There is poor correlation between pulmonary artery catheter and rectal temperature measurements, and brain temperature.\(^1\)

Despite limited evidence of outcome benefit, neurological monitoring is routinely used in many centres. Broadly speaking, these fall into one of two categories: monitors of cerebral substrate delivery [jugular bulb oximetry, transcranial Doppler sonography, and near infrared spectroscopy (NIRS)] and monitors of cerebral function [quantitative electroencephalography (qEEG) and evoked potential monitoring]. Measurement of jugular venous oxygen saturation (\(S_{jO_2}\)) provides an indication of the balance between cerebral oxygen supply and demand. Its use is limited as \(S_{jO_2}\) reflects global cerebral blood flow and may be unaffected by regional cerebral ischaemia. Low \(S_{jO_2}\) before the start of DHCA has been shown to

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**Table 1** Indications for DHCA

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Neurological</th>
<th>Other</th>
</tr>
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<tbody>
<tr>
<td>Aortic surgery</td>
<td>Cerebral aneurysms</td>
<td>Renal cell carcinoma with caval invasion</td>
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<tr>
<td>Pulmonary thromboendarterectomy</td>
<td>Arterio-venous malformations</td>
<td>Other - Renal cell carcinoma with caval invasion</td>
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<tr>
<td>Complex congenital surgery</td>
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</table>

**Table 2** Adverse consequences of hypothermia

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Coagulation</th>
<th>Renal and metabolic</th>
<th>Cerebral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmias secondary to potassium loss</td>
<td>Impaired coagulation</td>
<td>Reduced glomerular filtration rate</td>
<td>Vasoconstriction during cooling</td>
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<tr>
<td>Increased plasma viscosity</td>
<td></td>
<td>Metabolic acidosis</td>
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<tr>
<td>Vasoconstriction impairing microcirculation</td>
<td></td>
<td>Hyperglycaemia secondary to impaired glucose metabolism</td>
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<td></td>
<td></td>
<td>Effects on pharmacodynamics and pharmacokinetics</td>
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**Fig 1** Effect of brain temperature on reported safe duration of DHCA. Reproduced from Arrowsmith and Hogue\(^1\) with permission.
be associated with adverse neurological outcome. Transcranial Doppler is used to measure cerebral blood flow velocity (a surrogate for cerebral blood flow) in the basilar cerebral arteries and to detect microemboli. Using paired optical sensors placed on the scalp, NIRS measures the oxygen saturation of blood in all vessels to a depth of 20–40 mm. Ease of use and limited potential for harm have prompted the increasing use of NIRS monitoring.

qEEG is a sensitive monitor of cerebral ischaemia but may be affected by electromagnetic interference, hypothermia, and anaesthetic agents. In some centres, the EEG is used to assess the adequacy of cooling before DHCA. However, the temperature at which the EEG becomes isoelectric varies widely between patients—as low as 12.5°C in some studies—and appears to be higher during cooling than rewarming.

The choice of anaesthetic drugs is largely a matter of personal and institutional preference. Theoretically, avoiding volatile agents, which uncouple cerebral blood flow from cerebral metabolism (autoregulation), may confer some benefit. The influence of hypothermia on drug metabolism and elimination should be considered and doses altered accordingly.

Anticoagulation

Unfractionated heparin (3–5 mg kg⁻¹) is typically used to maintain an activated clotting time (ACT) >400 s. Inadequate anticoagulation during CPB increases the consumption of clotting factors and may paradoxically worsen postoperative coagulopathies. Lysine analogues (e.g. tranexamic acid, ε-aminocaproic acid) are frequently used to reduce fibrinolytic haemorrhage. It should be borne in mind that tranexamic acid may cause postoperative seizures.

General considerations

The duration of surgery conducted with DHCA mandates careful attention to the prevention of pressure sores and damage to the eyes, nerve plexuses, and peripheral nerves. Particular attention should be paid to cannulation sites, monitoring lines, airway connectors, and TOE probe which may cause pressure necrosis of the skin.

Measures should be taken to assist rewarming and prevent hypothermia after separation from CPB. An i.v. fluid warmer, heated mattress, and forced-air blanket should be considered in all cases.

Cerebral protection

Cooling and rewarming

Systemic cooling is achieved during CPB by pumping water from a heater/cooler reservoir through a heat exchanger in the CPB oxygenator. The temperature gradient between water and blood is typically maintained at <10°C. Additional cerebral cooling can be achieved using a head-cooling jacket through which iced water is circulated or ice packed around the head. Although topical cooling of the head has been shown to be of some benefit in animal models, there is as yet no evidence of outcome benefit in humans.

When CPB is resumed after a period of DHCA, hypothermic perfusion should be maintained for 10–20 min before rewarming commences. This is thought to reduce the risk of raised intracranial pressure which can occur during this period. Once rewarming commences, the gradient between core and peripheral temperatures should be <5°C. Excessively rapid rewarming with perfusion temperatures >37°C may induce cerebral ischaemia secondary to an imbalance between oxygen supply and demand. Similarly, cerebral hyperthermia should be avoided as this may exacerbate neurological injury and increase the risk of adverse neurological outcomes.

Acid–base management

The solubility of gases in blood increases as temperature decreases. When corrected for body temperature, arterial blood gas (ABG) analysis during hypothermia reveals reduced $p_{a\mathrm{CO}_2}$, $p_{a\mathrm{CO}_2}$, and an alkalosis. Acid–base balance can be managed in two ways during hypothermia. Using the ‘alpha-stat’ strategy uncorrected (i.e. 37°C), ABG analysis is used to guide the maintenance of a normal $p_{a\mathrm{CO}_2}$. In contrast, the ‘pH-stat’ strategy uses temperature-corrected ABG analysis to maintain a normal pH regardless of the measured increase in $p_{a\mathrm{CO}_2}$. This is commonly done by adding CO$_2$ to the CPB sweep gas. At mild-to-moderate hypothermia, alpha-stat management maintains cerebral blood flow–metabolism coupling whereas pH-stat management progressively obtunds cerebral auto-regulation and cerebral blood becomes pressure passive. The pH-stat strategy leads to increased cerebral oxygen delivery and is thought to give more even cooling of the brain at the expense of increasing the number of microemboli delivered to the brain. More recently, quantitative acid–base analysis (Stewart’s method) has been applied to hypotermic CPB. In this model, water is considered to be the main source of H⁺ ions and pH is determined solely by alterations in the concentrations of strong ions (Na⁺, K⁺, Mg²⁺, Ca²⁺, Cl⁻), weak acids (e.g. albumin and inorganic phosphate), and CO$_2$.

There is no evidence of the superiority of one technique over the other in adults. In piglet models of DHCA and in neonatal humans, however, the use of pH-stat during cooling appears to be associated with improved histological and clinical neurological outcomes. In light of this evidence and the benefit of improved global cerebral cooling, it is recommended that pH-stat be used during cooling before DHCA. During rewarming, the use of alpha-stat is thought to be beneficial as it prevents increased cerebral blood flow and the risk of cerebral oedema. If DHCA is not used, however, the routine use of pH-stat is not advocated.

Haemodilution

During hypothermia, the combination of increased plasma viscosity, erythrocyte rigidity, and progressive vasoconstriction leads
to impairment of the microcirculation. Haemodilution, typically to a haematocrit of 20%, is thought to improve flow in the microcirculation. Excessive haemodilution (e.g. haematocrit <10%) significantly reduces oxygen carrying capacity and causes tissue ischaemia. Normovolaemic haemodilution is often achieved by removing heparinized blood via the arterial cannula immediately before commencement of CPB. Any blood removed is labelled and stored for retransfusion during rewarming.

Pharmacological neuroprotection

In a recent survey of members of the Association of Cardiothoracic Anaesthetists, 83% reported using some form of pharmacological cerebral protection during DHCA in adult thoracic aortic surgery.5 Drugs used for this purpose included thiopental (59%), propofol (29%), and others (48%), most commonly corticosteroids.4 Thiopental and propofol have both been investigated at doses sufficient to cause burst suppression. Propofol does not appear to be associated with cardiac depression or delayed emergence from anaesthesia.5 Although the use of thiopental is associated with dose-dependent myocardial depression and delayed emergence, it does not adversely impact on the ability to separate from CPB. There is no evidence that either drug improves neurological outcome in adults.

A variety of other drugs have been investigated for their putative neuroprotective effects, including calcium channel blockers, protease inhibitors (aprotinin, nafamostat), free radical scavengers (mannitol, deferoxamine), amino acid receptor antagonists (magnesium), glutamate release inhibitors (lidocaine, fosphenytoin), and thromboxane A2 receptor blockers. Although many have shown considerable promise in preclinical and early clinical studies, none has been shown to unequivocally improve neurological outcome in adults.

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Glycaemic control

There is evidence that hyperglycaemia during periods of hypothermia worsens the impact of ischaemia through increased glycolysis and intracellular acidosis. Virtually, all patients undergoing DHCA develop impairment of glucose metabolism and will require control of glucose with insulin. Concurrent corticosteroid administration is likely to increase the risk of perioperative hyperglycaemia.

Cardiopulmonary bypass

In many instances, the use of DHCA necessitates modifications to the standard extracorporeal circuit (Table 3). The use of a magnetically coupled centrifugal pump—in preference to an occlusive roller pump—reduces haemolysis, maintains the leucocyte count, and preserves platelet function. Further discussion of CPB in the setting of DHCA is beyond the scope of this article.

Surgical techniques

In many centres, the duration of safe DHCA is extended by the use of retrograde cerebral perfusion (RCP) or selective antegrade cerebral perfusion (SACP). Although both techniques increase the complexity of surgery, they do permit a lesser degree of systemic hypothermia to be used (22–25°C) without compromising safety.7 The known advantages and disadvantages of RCP and SACP are shown in Table 4.

When using RCP, cold oxygenated blood is directed into the snared superior vena cava (SVC) via an arterio-venous CPB shunt. The technique is predicated on the assumption that the cerebral veins have no valves. A significant degree of shunting between the superficial and deep cerebral veins occurs, leading to limited delivery of oxygenated blood to the cerebral arteries. Advocates of the technique recommend that flow rates of 200–500 ml min⁻¹ at a pressure of no greater than 25 mm Hg are used, although emerging evidence suggests that perfusion pressures of up to 40 mm Hg are both safe and more effective.

When using SACP, the right or both carotid arteries are perfused using one of several techniques. Balloon-tipped arterial cannulae placed directly in the proximal common carotid arteries, the left subclavian artery is clamped, and perfusion commenced at

| Table 3 Modifications to standard extracorporeal circuit required for DHCA |
|--------------------------------|--------------------------|
| Inline infusion bags for collection and storage of blood during haemodilution |
| A centrifugal pump—in preference to a roller pump—to reduce haemolysis |
| Incorporation of a haemofilter to enable haemofiltration |
| Incorporation of a leucocyte-depleting filter |
| A cardiotomy reservoir of sufficient capacity to accommodate the circulating volume during exsanguination before DHCA |
| Arterio-venous bypass and accessory lines to permit retrograde or SACP |
| An efficient heat exchanger |
| Consideration of use of heparin-bonded tubing |

| Table 4 Advantages and disadvantages of RCP and SACP during DHCA |
|--------------------------------|--------------------------|
| **Advantages** | **Disadvantages** |
| SACP | Prolongs safe length of DHCA more than RCP | Risk of embolization |
| Less hypothermia required | Increases the complexity of surgery |
| Helps maintain cerebral cooling | Risk of cannula displacing or kinking |
| More reliable global oxygenation than RCP | Decreasing oxygen supply |
| RCP | Helps maintain cerebral cooling | Need intact circle of Willis if unilateral perfusion used |
| Helps prolong safe length of DHCA to 60 min | Variable amount of oxygen delivery due to shunt |
| | Cerebral oedema |
| | Raised ICP |
10–20 ml kg⁻¹ min⁻¹ in order to maintain a right radial artery pressure of 50–70 mm Hg. Alternative approaches include perfusion via the brachiocephalic artery or via the side branch of an arch graft. Reduced cerebral blood flow secondary to kinking or malposition of cannulae can be detected by cerebral NIRS as unilateral cerebral desaturation will be observed.

**Postoperative care**

After surgery with DHCA, patients should be transferred to the intensive care unit (ICU). Although patients are fully rewarmed before discontinuation of CPB, their temperature will decrease by the time of arrival in the ICU, despite active warming methods. Care should be taken to avoid hyperthermia which may potentially worsen any brain injury. Attention should also be paid to avoiding other factors, such as hypotension and hypoxaemia, that exacerbate brain injury.

The pattern of brain injury after DHCA varies between adults and neonates. Adults tend to have specific intellectual or motor deficits secondary to infarction in the cerebellum, striatum, and neocortex. Neonates tend to have seizures or choreoathetoid movements due to injury in the hippocampus and grey matter of the cerebral cortex.

Mortality rates of between 8% and 15% have been reported following DHCA with stroke rates of 7–11%. Predictors of stroke after DHCA are increased age, longer length of DHCA, and atheroma or thrombus in the aorta. Subtle, long-term cognitive dysfunction is common, particularly problems with short- and long-term memory and information processing.

Coagulopathic haemorrhage remains a significant cause of morbidity and early death after DHCA. In most centres, thromboelastography during surgery and laboratory tests of coagulation are used to guide early, aggressive correction of thrombocytopenia and clotting factor deficiency. The use of human prothrombin complex concentrate may be considered in patients receiving warfarin before surgery.

**Conflict of interest**

None declared.