The Indian Anaesthetists' Forum – (http://www.theiaforum.org) Online ISSN 0973-0311
October 2011(1)

Deep Hypothermic Circulatory Arrest: Current Concepts

Ajmer Singh

Principal Consultant, Department of Anaesthesia, Escorts Heart Institute and Research Centre Ltd, Okhla Road, New Delhi-110025

Correspondence: ajmersingh@yahoo.com

About the Author: Dr Ajmer Singh did his MD (Anaesthesia) in 1993. He did senior residency in Cardiac Anaesthesia from AIIMS. He joined Escorts Heart Institute and Research Centre in 1996 and is working there as a Principal Consultant. His areas of interests are Anaesthesia for Paediatric and Congenital heart diseases.

Abstract: The use of hypothermia for therapeutic purposes dates back to ancient times, and has progressed from animal studies to an established technique in children with complex congenital cardiac lesions and in adults for aortic arch reconstruction. Deep hypothermia decreases brain metabolism and oxygen requirement, whereas circulatory arrest provide bloodless surgical field. To augment the safety of deep hypothermic circulatory arrest (DHCA) various pharmacological and non-pharmacological methods have become available, such as antegrade and retrograde cerebral perfusion, and low-flow perfusion. Multimodal neurophysiological monitoring is helpful for early detection and avoidance of factors leading to cognitive dysfunction. Optimal acid-base management during DHCA consists of using pH-stat method during cooling and alpha-stat during rewarming. A better understanding of the pathophysiology of ischaemic brain injury and advances in cerebral monitoring are essential to improve the outcome of patients undergoing surgery using DHCA.

Introduction: The use of hypothermia for therapeutic purposes dates back to ancient times, and is mentioned in Egyptian, Greek, and Roman mythology. In modern medical practice, the use of therapeutic hypothermia has progressed from observational case reports to animal studies, to clinical use in children and then in adults. Fay[1] in 1943 reported therapeutic use of hypothermia in patients with severe cerebral trauma. In 1950, Bigelow etal[2] reported an animal study that suggested a therapeutic role of hypothermia for cerebral protection during cardiac surgery. In 1959, Drew etal[3] reported the use of profound hypothermia with circulatory arrest in children undergoing repair of tetralogy of Fallot. In 1975, Griepp etal[4] described the use of deep hypothermic arrest (DHCA) for cerebral protection during the prosthetic replacement of the aortic arch.

Normal core temperature in humans ranges between 36.5^{0}C to 37.5^{0}C. Hypothermia is defined as core temperature below 35^{0}C. Depending on the temperature, hypothermia is further classified into mild (32-35^{0}C), moderate (26-31^{0}C), severe or deep (20-25^{0}C), and profound (less than 20^{0}C) categories. Circulatory arrest is defined as no flow in the blood vessels, and DHCA implies no blood flow during deep hypothermia. The deep hypothermic component of DHCA significantly

decreases brain metabolism and oxygen requirement and hence permits a longer period of interrupted perfusion to the brain. The cerebral metabolic rate is related exponentially to brain temperature, and decreases by about 50% for each 6^0C drop in brain temperature. The circulatory arrest component provides a bloodless surgical field without the need for cannulae, clamps, and suckers in the operative area, and thus offers improved exposure. DHCA obviates the need for cardiotomy suction, which is known to cause major damage to blood components during CPB. Potential disadvantages of DHCA include prolonged cardiopulmonary bypass (CPB) time, oedema formation, coagulopathy and alteration in function of organs like kidney, brain, liver, pancreas, vascular smooth muscles, intestine, and alveolar epithelium. Permanent neurological injury is the most dreaded complication of DHCA, and occurs in about 3-12% of patients after aortic arch surgery using DHCA. Renal dysfunction occurs in about 5-14% patients, while pulmonary insufficiency occurs in 5-39%, and left ventricular failure or low cardiac-output syndrome is seen in 7-34% patients after DHCA.[5]

Indications for the use of DHCA include surgery for vena cava, aortic aneurysm, rupture, dissection, and reconstruction of aortic arch. DHCA is also used for repair of complex congenital heart defects like hypoplastic left heart syndrome, transposition of great arteries, total anomalous pulmonary venous connection, and interrupted aortic arch. Pulmonary thromboendarterectomy and vascular reconstruction during heart transplantation are other indications for the use of DHCA. Non-cardiac indications include major vascular surgery (involving thoraco-abdominal aorta), repair of giant cerebral aneurysms, resection of cerebral arterio-venous malformations, and excision of extensive hepatic and renal cell carcinomas.

Pathophysiology of Circulatory Arrest: Circulatory arrest leads to tissue hypoxia, which affects all aerobic functions of the body, particularly the production of adenosine triphosphate (ATP) molecules. ATP depletion leads to the failure of Na^+K^+ ATPase pump, causing intracellular accumulation of Na^+ and Cl^-, which leads to cellular swelling and excessive neuronal depolarization. This depolarization causes an influx of Ca^{++} ions, which activates phospholipases, resulting in production of free fatty acids, particularly arachidonic acid, which leads to hydrolysis of mitochondrial and plasma membranes. All these reactions result in cellular death, which can be in the form of apoptosis (occurring in zones of borderline ischaemia) or necrosis (in zones of complete ischaemia).

Secondly, excessive neuronal depolarization leads to the excessive release of neuronal excitatory amino acids such as glutamate and aspartate. These amino acids are present in excitatory presynaptic terminals of the brain and are essential for memory, cognition, and consciousness. During ischaemia, excessive concentration of glutamate and aspartate acts as a potent neurotoxin leading to neuronal injury and death. Thirdly, during ischaemic conditions, glucose is metabolized to lactate, which causes intracellular acidosis, cell swelling, and denaturation of proteins and enzymes. The presence of hyperglycemia further accelerates the process and compounds ischaemic cerebral injury. The last phase of ischaemic injury occurs during reperfusion and is called as ischaemia-reperfusion injury. It involves the generation of oxygen free radicals, which attack the cell membranes, leading to disruption of intracellular organelles and cellular death.

Anaesthetic Management during DHCA: The effect of anaesthetic management on the outcome during DHCA has not been studied well. Deep levels of anaesthesia ameliorate the adverse stress responses of DHCA. The role of barbiturates and other agents is described in the pharmacological protection section. Core cooling and surface cooling are initiated using CPB and ice-packing of the head, to achieve the desired level of hypothermia. Ambient room temperature is minimized. Anaesthetic drugs and long acting muscle relaxants are administered to ensure profound paralysis (spontaneous ventilation can cause vascular air entrapment) and to minimize oxygen consumption. Adequate anticoagulation is ensured prior to commencement of DHCA. Glucose is eliminated from all intravenous solutions and pump prime, to reduce the risk of hyperglycemia. With cessation of perfusion, venous cannulae are unclamped, allowing complete exsanguinations into the CPB circuit. For paediatric surgery, venous cannulae usually are removed to facilitate surgical exposure. Often passive circulation in CPB circuit is continued to avoid stasis. Whenever feasible, intermittent or low-flow CPB should be used.

End-Organ Protection during DHCA: Today, we have reached a stage when mere survival and absence of gross neurologic deficits cannot be regarded as acceptable results. Subtle, transient neurologic dysfunction occurs in about a quarter of patients after DHCA. Hypothermia, by reducing the metabolic rate of the brain, is considered as the most significant factor to offer brain protection during DHCA. Pharmacological protection can be achieved by using barbiturates, propofol, steroids, mannitol, insulin etc. Non-pharmacological methods to augment the safety of DHCA include antegrade cerebral perfusion (ACP), retrograde cerebral perfusion (RCP), and low-flow CPB.

(A) Hypothermia: Hypothermia improves the balance between energy supply and demand by reducing the metabolic rate of the brain. It produces a linear decrease in cerebral blood flow (CBF), but the decrease in cerebral metabolic of oxygen ($CMRO_2$) is not exactly linear. Between 37^0C and 22^0C, $CMRO_2$ is reduced by about 5%/1^0C, and then the reduction accelerates when $CMRO_2$ reaches 20% at 20^0C and 17% at 18^0C, at which point about 60% of patients achieve electrical silence on electroencephalography (EEG). Deep hypothermia below 15^0C is associated with increased risk of coagulopathy. The possible mechanisms of cerebral protection by hypothermia include halting the ischaemic injurious cascade, reducing glutamate excitotoxicity, suppressing intracellular calcium influx, decreasing formation of oxygen free radicals, and increasing gamma-aminobutyric acid release.

Sites for temperature monitoring during DHCA include tympanic membrane, nasopharyngeal, oesophageal, urinary bladder, rectal, pulmonary artery, and jugular venous bulb. Tympanic membrane temperature is considered as closest to the brain temperature. Jugular bulb temperature is useful during rewarming phase, and is normally 4^0C higher than nasopharyngeal, and 2^0C higher than oesophageal temperature. The cooling should be done gradually, long enough to achieve homogenous cooling of all organs, and should last for at least 25 to 30 minutes.[6] Rapid cooling might create imbalance between oxygen supply and demand, and it might decrease oxygen availability to the tissues by increasing the affinity of haemoglobin to oxygen. Ice packing of the head enhances cerebral hypothermia via conduction across the skull. In addition, it also helps in preventing an undesirable rewarming of the brain during DHCA. Initial hypothermic perfusion at low

pressures allows washout of accumulated metabolites and free radicals and provides substrates for high-energy molecules. For continuous cooling of the brain, a system consisting of a cooling cap with an incorporated circuit of water circulated at desired temperature has been developed.

Rewarming phase should be more gradual than the cooling, lasting for about 60 to 120 minutes. Rewarming increases CBF and the risk of embolization, cerebral oedema, and hyperthermic brain injury. Extracranial sites underestimate brain temperature by about 5^0 to 7^0C during rewarming, and therefore may result in brain hyperthermia. During rewarming, it is recommended that the perfusate temperature does not exceed core body temperature by more than 10^0C. Rewarming should be stopped when core body temperature reaches 37^0C nasopharyngeal, or 36^0C oesophageal, or 34^0C urinary bladder. Any electrical hyperactivity detected on EEG during rewarming phase, should be treated promptly with deepening the level of anaesthesia and lowering the temperature.

(B) Pharmacological Protection: Though many pharmacological agents have been proposed for organ protection during DHCA, there is little conclusive evidence of benefits through prospective, randomized, controlled clinical trials. Beneficial effects of barbiturates, steroids, anticonvulsants, lignocaine, calcium channel blockers (nimodipine), and glutamate antagonists (remacemide), have been observed in animal studies. The clinical practice varies in regard to the choice of agent, doses and timing of administration. A survey conducted by Dewhurst etal[7] to ascertain the current practice in use of pharmacological agents showed that 83% respondents used some agent for cerebral protection, 59% used thiopentone, 29% used propofol, and 48% used other agents, the most common of which were steroids. Barbiturates act by reducing $CMRO_2$, CBF, free fatty acids, free radicals, cerebral oedema, and seizure activity. Thiopentone is commonly used in doses of 8 to 10 mg/kg, preferably the doses should be titrated to EEG suppression. Large doses of barbiturates can cause delayed awakening and myocardial depression. Barbiturates have been shown to be protective in focal ischaemia caused by multiple emboli during CPB. They may also be helpful in brain protection during early rewarming phase. Despite the lack of conclusive evidence of neuroprotection, barbiturates still are widely used. Use of propofol also has not shown any evidence of improved outcome.

Dexamethasone and methylprednisolone, the commonly used steroids, counteract the systemic inflammatory response of CPB by decreasing proinflammatory cytokines, which play a key role in ischaemic brain injury. However, high doses of steroids might lead to an increased risk of sepsis and hyperglycemia. Mannitol, an osmotic diuretic, protects the kidneys by lowering renal vascular resistance, preserving tubular integrity, and reducing endothelial oedema. It also reduces cerebral oedema and scavenges free radicals. Mannitol in combination with furosemide has been shown to preserve renal function during ischaemia. Insulin has been shown to have a neuroprotective effect by controlling hyperglycemia. In a retrospective study of patients undergoing aortic arch surgery, blood glucose level more than 250 mg/dl was associated with an adverse neurological outcome.[8] A glucose level of >180 mg/dl should be treated with insulin.[9] Nimodipine, by reducing influx of calcium ions, has been shown to improve cognitive function after CPB, but there is risk of hypotension with its use. Dexmedetomidine, a selective α2-adrenoreceptor agonist,

has been shown to be neuroprotective in both focal and global ischaemia. Other agents, like lignocaine, remacemide, and acadesine need further evaluation before they can be recommended to offer neuroprotection during DHCA.

(C) Nonpharmacological protection: To augment the safety of DHCA, selective perfusion of the brain has been implemented in the form of both antegrade cerebral perfusion (ACP) and retrograde cerebral perfusion (RCP). ACP is considered superior to RCP for cerebral protection because it achieves near-physiological perfusion with homogenous distribution of blood and may extend the safe limit of circulatory arrest.[10] ACP could be hemispheric (right axillary, subclavian, innominate artery cannulation) or bispheric (by adding the left common carotid artery). Typically, a flow of 10 to 20 ml/kg/min is used in most of the institutions, at a temperature of 20 to 25^{0}C, and adjusted to maintain the pressure between 40 to 70 mmHg in the right radial artery. Advantages of ACP include a near-physiological brain perfusion, better control of brain temperature, flushing of waste metabolites during ischaemia, and prolongation of safe limit of DHCA. Disadvantages of ACP include the risk of arterial wall dissection (by manipulation of cerebral vessels), malperfusion, embolization of atheromatous plaque or air, and the cluttered operative field. RCP is achieved by cannulation of superior vena cava and instituting flow rate of 300 to 500 ml/min to maintain a pressure of 25 to 35 mmHg. Advantages of RCP include deep and homogenous cooling of the brain, de-airing of arch vessels, and flushing of cerebral emboli and toxic metabolites. RCP is particularly beneficial in high-embolic risk (elderly) patients. Yagdi etal[11] observed a low stroke rate of 1.4% in 144 patients who underwent aortic arch surgery using DHCA with RCP. Disadvantages of RCP include rise in intracranial pressure, cerebral oedema, and low level of substrate supply.

Regarding choice of surgical technique, Elefteriades etal[12] recently reviewed 20 case series performed with DHCA, ACP, and RCP, and found that DHCA yields survival and stroke-free rates comparable to both ACP and RCP. Milewski and coworkers[13] found no statistically significant difference in primary or secondary outcomes between these techniques, if aortic reconstruction time was less than 45 min. Svensson et al[14] concluded that (i) for limited arch replacement with short circulatory arrest time (30-40 min), DHCA alone is sufficient, (ii) for more extensive repairs that require prolonged circulatory arrest times, DHCA plus ACP is recommended, (iii) for operations with high embolic risk, DHCA plus RCP is recommended.

Monitoring during DHCA: Patients undergoing DHCA need invasive haemodynamic monitoring including an arterial catheter, pulmonary artery catheter, transoesophageal echocardiography (TEE), and neurophysiological monitoring besides routine noninvasive intraoperative monitoring. TEE is helpful in assessing cardiac function before and after DHCA, examining the entire aorta, confirming proper cannula placement, assessing volume status, detecting intracardiac air, and evaluating the adequacy of repair. Neurophysiological monitoring includes EEG, somatosensory evoked potentials, jugular venous saturation (SjO_2), and near-infrared spectroscopy (NIRS). EEG monitoring provides continuous detection of electrical activity of brain, and can be used to document electrical silence. Circulatory arrest can be instituted once electrical silence has been present for 3 minutes. It is a nonspecific monitor of global ischaemia, but is more specific for the detection of epileptiform activity. Limitations of EEG include its inability to reflect the activities of deeper brain structures such

as hippocampus and basal nucleus. EEG is an insufficient as an isolated tool for assessing the adequacy of cerebral protection. NIRS measures regional cerebral oxygen saturation (rSO_2) and detects changes in cerebral oxyhemoglobin, deoxyhemoglobin, and oxidized cytochrome aa3 concentration in brain tissues. The average rSO_2 ranges between 60 to70%, levels of <55% are indicative of neurologic compromise and are associated with adverse neurologic outcome. Tobias etal[15] have found NIRS to be useful to identify patients at risk of neurocognitive dysfunction. Advantages of NIRS technique include its non-invasiveness, continuous and real-time monitoring, portability, and easy interpretation. Limitations of NIRS include its inability to monitor entire brain, interference by electrocautery, inability to differentiate between the different causes of low rSO_2, and inaccurate readings with different forms of haemoglobin and excessive bilirubin. Oxygen saturation of jugular venous blood (SjO_2) has been accepted as a marker of global cerebral oxygenation. Decreased values of SjO_2 indicate a decreased oxygen supply, whereas increased values indicate low oxygen extraction which may result from hypothermia, pharmacological suppression of $CMRO_2$, or severe brain injury. SjO_2 values of <50% during rewarming phase have been associated with postoperative neurocognitive decline.[16]

Acid-Base Management during Hypothermia: By increasing the solubility of CO_2 and O_2 in plasma, hypothermia alters the results of arterial blood gas analysis. Increased CO_2 solubility decreases the concentration of insoluble portion and thus, partial pressure of CO_2 ($PaCO_2$), though the CO_2 content in the blood remains the same. During hypothermia, if a blood sample is taken and rewarmed to 37^0C, the CO_2 initially dissolved will now contribute to the $PaCO_2$, and the $PaCO_2$ will be within the normal normothermic range. Conversely, if the value is estimated at the patient's actual temperature, the $PaCO_2$ will be reduced despite similar CO_2 content. Maintaining the $PaCO_2$ within the normal range in re-warmed 37^0C blood is called "alpha-stat". Alpha-stat strategy indicates that the blood CO_2 is allowed to follow its thermodynamically mediated dissociation changes with hypothermia, which results in decrease in H^+ concentration and an increase of blood pH (alkaline shift). If the $PaCO_2$ is corrected to patient's actual temperature and that value is kept within the normal range, the management is called "pH-stat". In pH-stat strategy, blood pH is maintained constant at decreasing temperatures by adding 3-5% CO_2 to oxygenator gas flow during hypothermic CPB to maintain a temperature corrected blood $PaCO_2$ of 40 mmHg and a pH of 7.40.

Alpha-stat management is aimed at preserving autoregulation of the brain and at maintaining cellular enzymatic activity and protein function. Alpha-stat management causes relative hypocarbia, which would produce cerebral vasoconstriction and reduce CBF. This would make this approach advantageous in patients with high-embolic load. The pH-stat method maintains normal $PaCO_2$ by adding CO_2, and when rewarmed the blood becomes acidemic and hypercarbic. The resulting hypercarbia causes cerebral vasodilatation, increased CBF, and loss of autoregulation. Increased CBF and reduced $CMRO_2$ allow quick and homogenous cooling of the brain and increased oxygen delivery.

The literature supports the use of pH-stat management in children, for providing both cerebral and myocardial protection. The pH-stat is particularly beneficial in cyanotics since it shifts more CPB flow away from the aorto-pulmonary collaterals towards cerebral circulation, improving

cerebral cooling and oxygen supply. Alpha-stat strategy appears advantageous in adults because it maintains a physiologic coupling between CBF and $CMRO_2$. Cerebral oedema resulting from over-perfusion is less likely to occur with alpha-stat strategy. Uneven distribution of blood can occur in patients with vasculopathy, hypertension, and diabetes by preservation of cerebral autoregulation with alpha-stat method.

There is still considerable controversy regarding the optimal acid-base management during hypothermic CPB. Aziz et al[17], recently reviewed 206 papers (from 1950 to 2009) on acid-base management and concluded that the best technique is dependent on the age of the patient with better results using pH-stat in paediatric patients and alpha-stat in adult patients. In the absence of conclusive data, it might be prudent to use a combined strategy in which pH-stat is used during cooling to achieve cerebral vasodilatation and homogenous cooling, followed by the alpha-stat strategy from circulatory arrest to rewarming to minimize extracellular acidosis.[18]

Safe Duration of DHCA: As the duration of DHCA lengthens, a number of biochemical and cellular structural changes occur resulting in loss of cognitive function. The safe duration of circulatory arrest at 15^0C is predicted to be 29 minutes and at 10^0C about 40 minutes. Intermittent DHCA with low-flow or trickle CPB has been used to augment the safe duration of DHCA. A flow of 5-10 ml/kg/min improves cerebral ischaemia tolerance, and is considered superior to DHCA alone at the same temperature. In a large study (n=656), Svensson et al[14] found that stroke rate increased after 40 minutes of circulatory arrest, and mortality increased after 65 minutes of arrest period. They also concluded that the duration of CPB was a better predictor of stroke and mortality than the duration of DHCA.

Pulsatile flow maintains better microcirculation at lower perfusion pressures than non-pulsatile flow, and is advantageous in improving the balance between myocardial oxygen supply and demand. The optimal haematocrit during DHCA remains controversial. Moderate haemodilution leads to improved microcirculation, but extreme haemodilution might lead to tissue hypoxia. Studies show that the cerebral capillary flow was maintained with a haematocrit of 30%, despite increased blood viscosity during hypothermia.

In conclusion, DHCA is an established technique used during repair of aortic arch and other major vessels. Deep hypothermia provides significant protection to brain and other vital organs, whereas circulatory arrest provides a bloodless surgical field. To augment the safety of DHCA, various pharmacological and nonpharmacological methods such as ACP, RCP, and low-flow CPB are available. Neuroprotective agents are widely used, despite the lack of convincing evidence. Advances in cerebral monitoring and in therapeutic interventions are essential for improving the outcome of patients undergoing surgery under DHCA.

References

1. Fay T. Observations on generalized refrigeration in cases of severe cerebral trauma. Assoc Res Nerv Ment Dis Proc 1943,24:611-19

2. Bigelow WG, Lindsay WK, Greenwood WF. Hypothermia, its possible role in cardiac surgery: An investigation of factors governing survival in dogs at low body temperature. Ann Surg 1950,132:849-66
3. Drew CE, Keen G, Benazon DB. Profound hypothermia. Lancet 1959,1:745-48
4. Griepp RB, Stinson EB, Hollingsworth JF, et al. Prosthetic replacement of the aortic arch. J Thorac Cardiovasc Surg 1975,70:1051-63
5. Moon MR, Miller DC. Aortic arch replacement for dissection. Op Tech Thorac Cardiovasc Surg 1999,4:33-57
6. Griepp RB. Cerebral protection during aortic arch surgery. J Thorac Cardiovasc Surg 2001,121:425-27
7. Dewhurst AT, Moore SJ, Liban JB. Pharmacological agents as cerebral protectants during deep hypothermic circulatory arrest in adult thoracic aortic surgery. A survey of current practice. Anaesthesia 2002,57:1016-21
8. Ceriana P, Barzaghi N, Locarelli A. Aortic arch surgery: Retrospective analysis of outcome and neuroprotective strategies. J Cardiovasc Surg (Torino) 1998,39:337-42
9. Lazar HL, McDonnell M, Chipkin SR. Society of Thoracic Surgeons Blood Glucose Guidelines Taskforce. Ann Thorac Surg 2009,87:663-69
10. Chong SY, Chow MY, Kang DS, et al. Deep hypothermic circulatory arrest in adults undergoing aortic surgery: Local experience. Ann Acad Med Singapore 2004, 33:289-93
11. Yagdi T, Atay Y, Cikirikcioglu M, et al. Determinants of early mortality and neurological morbidity in aortic operations performed under circulatory arrest. J Card Surg 2000,15:186-93
12. Elefteriades JA. What is the best method for brain protection in surgery of aortic arch? Straight DHCA. Cardiol Clin 2010,28:381-87
13. Milewski RK, Pacini D, Moser GW, et al. Retrograde and Antegrade Cerebral Perfusion: Results in Short Elective Arch Reconstructive Times. Ann Thorac Surg 2010,89:1448-57
14. Svensson LG, Crawford ES, Hess KR, et al. Deep hypothermia with circulatory arrest. Determinants of stroke and early mortality in 656 patients. J Thorac Cardiovasc Surg 1993,106:19-31
15. Tobias JD, Russo P, Russo E. Changes in near infrared spectroscopy during deep hypothermic circulatory arrest. Ann Card Anaesth 2009,12:17-20
16. Leyvi G, Bello R, Wasnick JD, et al. Assessment of cerebral oxygen balance during DHCA by continuous jugular bulb venous saturation and near-infrared spectroscopy. J Cardiothorac Vasc Anesth 2006,20:826-33
17. Abdul Aziz KA, Meduoye A. Is pH-stat or alpha-stat the best technique to follow in patients undergoing DHCA? Interactive Cardiovasc Thorac Surg 2010,10:271-82
18. Svyatets M, Tolani K, Zhang M, et al. Perioperative management of deep hypothermic circulatory arrest. J Cardiothorac Vasc Anesth 2010,24:644-55