Review Article

Cerebral physiology in paediatric cardiopulmonary bypass

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Purpose: To analyze studies of neurological injury after open-heart surgery in infants and children and to discuss the effects of cardiopulmonary bypass, hypothermia and deep hypothermic circulatory arrest on cerebral blood flow, cerebral metabolism and brain temperature.

Source: Articles were obtained from the databases, Current Science and Medline, from 1966 to present. Search terms include cardiopulmonary bypass(CPB), hypothermia, cerebral blood flow(CBF), cerebral metabolism and brain temperature. Information and abstracts obtained from meetings on the topic of brain and cardiac surgery helped complete the collection of information.

Principal findings: In adults the incidence of neurological morbidity is between 7 to 87% with stroke in about 2-5%, whereas the incidence of neurological morbidity increases to 30% in infants and children undergoing cardiopulmonary bypass. Besides the medical condition of the patient, postoperative cerebral dysfunction and neuronal ischaemia associated with cardiac surgery in infants and small children are a combination of intraoperative factors. Deep hypothermic circulatory arrest impairs CBF and cerebral metabolism even after termination of CPB. Inadequate and/or non-homogenous cooling of the brain before circulatory arrest, as well as excessive rewarming of the brain during reperfusion are also major contributory factors.

Conclusion: Newer strategies, including the use of low-flow CPB, pulsatile CPB, pH-stat acid-base management and a cold reperfusion, are being explored to ensure better cerebral protection. Advances in monitoring technology and better understanding of the relationship of cerebral blood flow and metabolism during the different modalities of cardiopulmonary bypass management will help in the medical and anaesthetic development of strategies to improve neurological and developmental outcomes.

Objectif : Examiner les études portant sur les atteintes neurologiques survenues après une chirurgie à cœur ouvert chez les bébés et les enfants et discuter des effets de la circulation extracorporelle, de l'hypothermie et de l'arrêt circulatoire sous hypothermie profonde sur le débit sanguin cérébral, sur le métabolisme cérébral et sur la température du cerveau.

Sources documentaires : Des articles ont été choisis à partir de bases de données, Current Science et Medline, de 1966 à aujourd'hui. Les mots-clés utilisés étaient : circulation extracorporelle (CEC), hypothermie, débit sanguin cérébral (DSC), métabolisme cérébral et température du cerveau. Les informations et les résumés obtenus à la suite de séminaires sur le cerveau et la chirurgie cardiaque ont permis de compléter la cueillette de données.

Données principales : Chez les adultes, l'incidence de morbidité neurologique avec accident vasculaire est de 7 à 87 % dans 2 à 5 % des cas tandis que l'incidence de morbidité neurologique augmente à 30 % chez les bébés et les enfants subissant une circulation extracorporelle. La condition médicale du patient mise à part, le dérèglement cérébral postopératoire et l'ischémie neuronale associés à la chirurgie cardiaque chez les enfants et les nouveau-nés sont une combinaison de facteurs peropératoires. L'arrêt circulatoire sous hypothermie profonde altère le DSC et le métabolisme cérébral même après la CEC. Un refroidissement du cerveau incomplet et/ou non homogène avant l'arrêt circulatoire, de même qu'un réchauffement excessif du cerveau pendant la reperfusion, constituent également des facteurs importants.

Conclusion : Des stratégies nouvelles comprenant la CEC à faible débit, la CEC pulsatile, le traitement acido-basique par pH-stat et une reperfusion froide sont à l'étude pour assurer une meilleure protection cérébrale. Des progrès dans la technologie du monitoring et une meilleure connaissance de la relation entre le débit sanguin cérébral et le métabolisme cérébral pendant les différentes étapes de la circulation extracorporelle pourront favoriser l'élaboration de stratégies médicales et anesthésiques visant à diminuer les atteintes neurologiques et à améliorer le développement de l'enfant.

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A review article by Schell *et al.*¹ and accompanying editorial² highlighted the great variation in cerebral blood flow and metabolic rate during cardiopulmonary bypass (CPB) in adult humans. Normal values for these variables depend on many factors, including PCO₂, temperature and anaesthetic depth.^{1,2} The literature on infants and children, although sparse compared with that for adults, is potentially more revealing with respect to cerebral physiology, as intracranial pressure can be evaluated non-invasively in addition to all the variables measured in adults. In the light of the availability of this information and the increased use of lower body temperatures and different modalities of cardiopulmonary bypass perfusion, a review of the physiology of the brain in infants and children during cardiopulmonary bypass is particularly timely.

Two medical databases (Current science and Medline) from 1966 to December 1997 were searched for citations containing the following keywords; cardiopulmonary bypass (CPB), hypothermia, cerebral blood flow (CBF), cerebral metabolism and brain temperature. Furthermore, the collection of information obtained from meetings on the topic of

brain and cardiac surgery helped complete the source of information.

Neurological outcome of cardiopulmonary bypass

Neurological morbidity following open-heart surgery in adults has been reported to occur in 7-61% of patients and a mortality rate of 29%.³ With major advances in surgical and cardiopulmonary bypass technology, mortality rate has been reduced. In a recent study, Murkin *et al.*⁴ reported a mortality rate of 2.8%. At the same time, a higher incidence of neurological dysfunction has been noted. The incidence of stroke in this study was 2.5% and 82-87% of the patients were noted to suffer from neurological and/or cognitive impairment postoperatively. Assessment at two months showed that 17-18% of the patients still manifested evidence of neurological dysfunction while 30-36% had cognitive impairment. Since the spectrum of cardiac disease differs in paediatric patients, management of this type of surgery may involve greater use of hypothermic cardiopulmonary bypass with lower temperatures and more frequent use of deep hypothermic circulatory arrest. Because of the difficulty of neuropsychiatric assessment in children and the lack of outcome studies, less is known about the long-term neurological impact of open-heart surgery in children than in adults.

The incidence of congenital cardiac lesions requiring intervention in infancy has been reported as 3.5 per 1000 live births and in the United States alone, over 37,000 open-heart operations are performed annually in children under 15 years.⁵ In 1987, Ferry⁶ reported strokes, diffuse hypoxic-ischaemic lesions, intracranial haemorrhage, delayed choreoathetoid syndrome and spinal cord lesions as sequelae of cardiac surgery in children. From 1988 to 1989, in a survey of six major paediatric cardiac surgery units in the United States and Canada, Ferry⁶ attempted to estimate the prevalence and nature of neurological signs after surgery. This epidemiological study described the types of follow-up and investigations used for patients with neurological deficits, outlined the kinds of perioperative and postoperative care provided and identified the providers of postoperative care. The programs reviewed used similar anaesthetics but the degree of hypothermia ranged from 12°C to 24°C. Based upon these observations, the reported prevalence of acute neurological morbidity varied between 1% and 25% which was dependent on the centre and the source of information. Overall, the neurologists reported a prevalence of 12-25% whereas the cardiothoracic surgeons 1-2%. She also noted a lack of uniformity in type of oxygenator used (bubble vs membrane), presence of arterial line filters, electroencephalographic monitoring and kind and source of

postoperative care. More recently, Newburger *et al.*⁷ reported seizures occurring in 11% of infants who had undergone a period of total circulatory arrest.

Developmental Outcome

The question of whether subtle but important neurological changes occur in children after cardiac surgery involving cardiopulmonary bypass and hypothermia has not been adequately answered. Few outcome studies have been conducted and pre-operative neuropsychiatric testing is not done routinely because of the difficulty in assessing young children. Blackwood *et al.*⁸ compared pre- and postoperative developmental examination results in 36 children under the age of two years, who underwent cardiac surgery. The examination included assessment of the child's motor, adaptive, language, personal and social development. Results were expressed as the development quotient, which is the ratio of the child's developmental age to chronological age. Development quotient values between 90-110 are considered average, the lower end of the normal distribution being 75. Changes of >10 between the pre- and post-operative values were considered clinically important. The authors were unable to show any difference in the development quotient values before and after surgery in children undergoing deep hypothermic cardiopulmonary bypass or circulatory arrest. The developmental quotient values calculated were similar between the groups.

Settergren *et al.*,⁹ in a study of 49 children who had undergone surgery for correction of complicated congenital cardiac lesions, interviewed the parents of survivors at three, 22 months and at three years, using a standardized questionnaire that assessed various aspects of psychomotor development (social behaviour, speech development, motor development, etc.). They were unable to find any difference between the children who underwent cardiopulmonary bypass with or without circulatory arrest.

Bellinger *et al.*¹⁰ looked at a population of 28 children who had had cardiac surgery in early infancy to correct transposition of the great arteries. The frequency of associated non-cardiac and intracardiac anomalies was low in this group and postoperative courses are generally short and associated haemodynamic complications few. All the children in this study underwent deep hypothermic circulatory arrest. The measurements of cognitive development used showed that the duration of cooling before deep hypothermic circulatory arrest was the most important factor associated with developmental outcome. Children who had a shorter duration of cooling periods of between 11 and 18 min had poorer developmental scores.

In a recent prospective study, 171 infants, who also had had cardiac surgery before the age of three months for correction of transposition of the great arteries, were followed up perioperatively for neurological injuries.⁷ Patients were randomly assigned to receive a support strategy consisting either predominantly of deep hypothermic circulatory arrest or of low-flow bypass at flow rates of 50 ml·kg⁻¹ min⁻¹. The former group had a mean arrest period of 53 min while the latter had a mean arrest time of eight minutes. The authors found that infants who were managed with a CPB strategy consisting predominantly of circulatory arrest, compared with one consisting predominantly of low-flow CPB, were at a higher risk of developing post-operative neurological dysfunction. This was evident by the higher incidence of clinical and EEG seizures, a greater release of the brain isoenzyme of creatine kinase (CK-BB) during the first six hours post-operatively, as well as a longer time to recovery of normal EEG activity in these infants. Overall, clinical seizures were seen in 11% of the infants assigned to circulatory arrest, while continuous EEG monitoring detected ictal activity in 26% of these patients. They also noted that a longer period of circulatory arrest was associated with greater neurological disturbances in the early post-operative period. All the infants who manifested definite clinical seizures postoperatively, had at least 35 min of total circulatory arrest. 92% of these patients, who were still alive, were reassessed one year later and the developmental and neurological sequelae of the two support strategies were compared.¹¹ The authors demonstrated that, at the age of one year, the infants who had been treated to a strategy consisting mainly of deep hypothermic circulatory arrest, had delayed motor development and poorer mental developmental scores. It was interesting to note that the occurrence of EEG seizure activity in the early preoperative period one year earlier, was associated with significantly lower scores on the Psychomotor Development Index. The risk of neurological abnormalities was also higher and it increased with the duration of circulatory arrest.

Neurological Deficits

The assumption of postoperative neurological injury has been strengthened by the findings of several studies. In a review by Ehyai *et al.*¹² of 165 children who were treated with deep hypothermic circulatory arrest during cardiac surgery, 15 had either generalized or focal seizures 25 to 48 hr after surgery, of which five were explained by a lesion demonstrated on computed tomography or by metabolic abnormality. The 10 children with no demonstrable lesion were followed up by the paediatrician or paediatric cardiologist and

their subsequent development was considered normal.

Some neurological deficits do not show up immediately after surgery. Robinson *et al.*¹³ described four children of previous normal development who manifested choreoathetoid syndromes three to seven days after operation. Investigations including computed tomography (CT), failed to find a lesion to explain these findings. Another child with Down's Syndrome, who also manifested choreoathetosis postoperatively, died unexpectedly and underwent autopsy, which did not show any lesion in the basal ganglia. However, Wong *et al.*,¹⁴ in a review of 19 children who developed choreoathetosis, obtained pathological information on two patients who died, noting "neuronal depletion, axonal spheroids and reactive astrocytosis in the external globus pallidus." Degeneration of myelinated fibres was observed in the globus pallidus and pallidusubthalamic pathways but not elsewhere in the basal ganglia. Although cerebral infarction has also been reported in children after cardiac surgery, it did not occur in the immediate postoperative period.¹⁵

One problem with this area of investigation is in determining whether the neurological injury occurred during the operation. Neurological assessment is difficult in neonates, infants and small children. McConnell *et al.*¹⁶ in a study using magnetic resonance images of the brain before and after cardiac surgery found that one third of the 15 infants and children (5-18 months) had abnormal preoperative results, with ventriculomegaly and dilatation of the subarachnoid spaces. However, no neurological symptoms or deficits were found during the preoperative clinical examination and the morphological changes seen on the magnetic resonance images were described as subclinical. Similarly, Muraoka *et al.*¹⁷ examined the pre-and postoperative CT scans of 64 patients with congenital heart disease who required mild hypothermic CPB or deep hypothermic circulatory arrest during corrective surgery. Decreases in brain mass on postoperative CT scans were seen in 14.7% of the patients who received conventional CPB and 16.7% of patients who underwent total circulatory arrest. All the children with abnormal CT findings had no clinical evidence of neurological dysfunction and repeat CT scans were normal within six to eleven months after surgery.

In summary, stroke, diffuse hypoxic-ischaemic lesions, intracranial haemorrhage, delayed choreoathetoid syndrome, spinal cord lesions, cerebral infarction, diffuse cortical atrophy and seizures have all been described as sequelae of cardiac surgery in infants and children.^{5-7,13,15,17,18} Although the causes of these deficits remain unknown, various mechanisms have

been proposed. These include unrecognized preoperative neurological abnormalities, hypoxic insults, altered cerebral blood flow and cerebral metabolism with hypothermia, embolic events, and low cardiac output states following surgery. To understand these mechanisms better, we reviewed the literature on the effects of hypothermia, cardiopulmonary bypass, and circulatory arrest on brain physiology.

Factors affecting cerebral blood flow and metabolism during cardiopulmonary bypass

Modalities of Cardiopulmonary Bypass

Since its introduction in the 1950s, major advances have been made in the technology of hypothermia and CPB. There are currently four perfusion techniques used during open-heart surgery in infants and children:

1. Normal flow cardiopulmonary bypass is provided by the heart-lung machine at 100-150 ml·kg⁻¹·min⁻¹ (2.4-3.2 L·min⁻¹·m⁻²) with varying degrees of hypothermia to provide cerebral and myocardial protection.
2. In profound hypothermic circulatory arrest, the patient is cooled via surface and core cooling to a nasopharyngeal temperature of <20°C and then disconnected from the heart-lung machine. This helps the surgeon by improving surgical visibility while the perfusion cannulae are removed and there is no blood in the operative field.
3. Low-flow cardiopulmonary bypass with profound hypothermia is similar, except that after the patient is cooled to a nasopharyngeal temperature of <20°C, the heart-lung machine is left on with the cannulae in place with flows at 25% to 50% (50 ml·kg⁻¹·min⁻¹ to as low as 25 ml·kg⁻¹·min⁻¹.) of the calculated normothermic flow rate. The purpose is to decrease the amount of blood in the operative field while maintaining cerebral perfusion. This technique has been claimed to provide improved myocardial protection and to avoid the "uncertain long-term neurological consequences" of profound hypothermic circulatory arrest.¹⁹
4. Continued pulsatile flow may be used during cardiopulmonary bypass, with the assistance of a synchronous pump. This technique is believed to provide better cerebral perfusion and myocardial protection. Used generally with normal flow CPB, it has been demonstrated to improve myocardial performance in adults.⁴

PROFOUND HYPOTHERMIC CIRCULATORY ARREST(PHCA)

Cerebral ischaemia

PHCA has been widely used in open heart surgery in infants since its introduction. Conflicting reports of post-operative cerebral dysfunction have generated considerable controversy regarding its use. Several studies have tried to assess the effects of profound hypothermic circulatory arrest on brain physiology. Rossi *et al.*,²⁰ in an attempt to measure neurological injury perioperatively, studied 24 infants who underwent deep hypothermic circulatory arrest and seven control infants whose procedures with cardiopulmonary bypass and hypothermia did not include the arrest of perfusion. Using retrograde jugular bulb venous catheters, they were able to compare arterial and jugular venous blood samples and show that the creatine kinase isoenzyme from the brain (CK-BB) was in higher concentrations in the jugular venous effluent than in the arterial blood of the infants undergoing circulatory arrest. The CK-BB isoenzyme is known to be specific for the brain in the adult, however, it is the principle form of creatine kinase in the fetus and is present in all the tissues, including the skeletal and myocardial muscles. It is later replaced by the MB and MM fractions in the skeletal and myocardial muscles respectively with fetal maturity and is rarely detectable in the muscles after the sixth month of gestation.²¹ Neonatologists have demonstrated that fetal asphyxia is associated with raised serum levels of the CK-BB isoenzymes in newborns.^{21,22} The demonstration of higher CK-BB fractions in the jugular venous blood compared to arterial blood in this study is consistent with their findings and strongly suggests that the brain is the main source of the CK-BB isoenzyme in the neonates and that its release occurs during an ischaemic insult to the brain such as observed during circulatory arrest.

van der Linden *et al.*,²³ in a study of 17 patients undergoing congenital heart surgery during profound hypothermia, demonstrated that, following total circulatory arrest, lactate levels in the jugular venous blood were higher than the arterial levels from the beginning of rewarming and until three hours after the end of cardiopulmonary bypass. The release of lactate from the brain cannot be explained by inadequate cerebral blood flow during the reperfusion period, since using transcranial Doppler sonography, these authors have demonstrated the presence of increased blood flow velocity in the middle cerebral artery during and after rewarming. The authors suggested that cerebral aerobic metabolism of glucose may have been disturbed following profound hypothermic circulatory arrest resulting in anaerobic cerebral metabolism and lactate release.

Cerebral Blood Flow

The effect of a period of profound hypothermic total circulatory arrest on cerebral blood flow (CBF) has been the subject of several investigations. Although van der Linden *et al.*²³ demonstrated increased CBF during rewarming after total circulatory arrest, many other investigators found contrasting results. Greeley *et al.*²⁴ studied 67 paediatric patients undergoing cardiac surgery and cardiopulmonary bypass who received a standard anaesthetic technique in which vasoactive or cerebral protective agents were avoided. The CBF was measured with the ¹³³Xenon clearance technique. The patients were grouped according to whether their bypass technique involved moderate hypothermia (25-32°C), deep hypothermia (18-22°C), or total circulatory arrest (18°C). The effects of hypothermia, circulatory arrest and rewarming on CBF were studied. Baseline CBF was measured after the initiation of cardiopulmonary bypass but before the induction of hypothermia. In all groups, the CBF decreased with hypothermia and in the first two returned to baseline with rewarming and exceeded it after the bypass. However, in the third group, CBF did not increase with rewarming or weaning from bypass. The authors speculated that low CBF following circulatory arrest was an appropriate response to decreased metabolic demands but they did not measure oxygen consumption or cerebral metabolic rate. A study by Hillier *et al.*,²⁵ using noninvasive transcranial Doppler sonography, produced similar results. They found that cerebral blood flow velocity (CBFV), a measure of regional CBF, remained considerably reduced from control after deep hypothermic circulatory arrest. O'Hare *et al.*²⁶ studied 10 infants undergoing either deep hypothermic circulatory arrest or mild hypothermic cardiopulmonary bypass and reported that CBFV remained considerably lower in the former group of patients until 40 hr postoperatively even though cerebral perfusion pressure were similar in both groups.

Controversy remains about whether cerebral autoregulation is preserved or lost during deep hypothermia. The method of measurement of CBF does not seem to make a difference. Although the methods employed by Hillier *et al.*²⁵, O'Hare *et al.*²⁶ and Greeley *et al.*²⁴ differed, both techniques showed that CBF decreased with hypothermia and remained reduced after deep hypothermic circulatory arrest. The difficulty of fully explaining cerebral haemodynamics during cardiopulmonary bypass with hypothermia was shown in a study by van der Linden *et al.*²⁷ using transcranial Doppler sonography, in which two groups of patients were examined during profound hypothermic

cardiopulmonary bypass. In the first group, the study showed that the diameter of the middle cerebral artery does not change with hypothermia. This observation was also confirmed in a study in which direct measurement of the main cerebral arteries were made during craniotomies.²⁸ Constancy of the diameter was demonstrated in the large cerebral vessels, including the M1 segment of the middle cerebral artery, during moderate variations in blood pressure and end-tidal carbon dioxide concentration. This is an important finding because cerebral blood flow velocity (CBFV) is a reliable indicator of cerebral blood flow only if one assumes that the diameter of the major vessels remains constant. In the second group of patients, CBFV was measured along with differences in oxygen contents between arterial and jugular venous blood. The CBFV was lowered by surface cooling with ice and decreased further with cooling on cardiopulmonary bypass. It increased with removal of surface cooling despite the absence of a rise in either nasopharyngeal temperature or cerebral oxygen consumption. The CBFV decreased with decreasing temperature, as did cerebral oxygen consumption. During deep hypothermic cardiopulmonary bypass, the authors were unable to demonstrate a correlation between CBFV and perfusion pressure, a finding inconsistent with those of Greeley *et al.*²⁴ and Taylor *et al.*²⁹

Unfortunately, the technology currently being used to study CBF and metabolism has yet to be fully validated in neonates and small infants, which makes comparison between studies difficult. One technique (radiolabelled microspheres) using radioactive material is not generally available and requires special training in the manipulation of these substances. Furthermore, although still considered the standard to quantitative clinical assessment of cerebral blood flow studies, limitations such as the necessity to obtain steady-state, the complexity of the analyzes, the problem associated with recirculation and extracerebral contamination are limiting clinical application. Most intraoperative methods for determining CBF are based on the Fick principle. These include the Kety-Schmidt and the ¹³³Xenon clearance tests which provide accurate global measurements of CBF. These techniques require the use of a radioactive tracer and do not provide continuous monitoring.¹

Transcranial Doppler sonography (TCD), which is a more recent technology, is noninvasive, direct and sensitive and offers real-time continuous monitoring. However, to suggest that CBFV is a measure of CBF, the assumption that the diameter of the middle cerebral artery stays constant and that the angle of insonation is < 30° must be accepted. It has been reported that the diameter of conductance vessels such

as the middle cerebral artery remains constant in humans.²⁸ The angle of insonation between the temporal window and the M1 segment of the middle cerebral artery is negligible (< 20 which causes a maximum error of 6%). However, one must bear in mind that the relationship between flow velocity and cerebral perfusion is inconsistent and that flow velocity as measured by TCD sonography is affected by many other factors including age, arterial PCO₂, regional metabolic activity and haematocrit. With regards to recording conditions with transcranial Doppler during cardiac surgery, an *in-vitro* study showed that flow velocity correlates well with pump flow when the temperature condition was changed from 37°C to 15°C and also during variation in the haematocrit from 52% to 10%.³⁰ But, when flow and velocity are severely reduced, as in extreme low flow CPB, the Doppler may not be able to detect flow below the threshold of resolution (3-6 cm·sec⁻¹) of the TCD.

Another non-invasive method of measuring CBF is the use of the near-infrared (NIR) spectroscopy. This technique is based on the transmission of near-infrared wavelengths of light through biological tissue and absorption by oxyhaemoglobin, deoxyhaemoglobin and oxidised cytochrome C oxidaseor aa₃. Used primarily for monitoring cerebral oxygenation during CPB, values for total cerebral blood volume and flow can be estimated by using changes in oxyhaemoglobin concentration as a tracer. Advantages of this technique include portability of the machine, ability to produce rapid, repeatable measurements and excellent time resolution.³¹ However, the method is labour intensive and requires time-consuming data analysis off-line. Nevertheless, the ability to monitor cerebral oxygenation and to quantify cerebral blood volume in combination with flow, makes this technique a potentially valuable tool for noninvasive investigation of cerebral haemodynamics.

Intracranial Pressure (ICP)

A number of studies have shown that cerebral perfusion pressure (CPP) remained low during reperfusion after profound hypothermic circulatory arrest and that CBFV did not return to pre-arrest values during this period of time.^{24-26,29,32,33} Studies of infants have also reported an associated increase in intracranial pressure (ICP) as measured by anterior fontanelle pressure (AFP).^{33,34} The aetiology of the increase in AFP after total circulatory arrest is still not clear but it is unlikely to be due to increased CBF and blood volume. Cerebral oedema had been demonstrated in adult patients immediately after CABG. Harris *et al.*³⁵ studied six male patients with MRI scans one to 15 days

before, immediately at the end of surgery and six to 18 days later. Brain swelling with obliteration of cerebral sulci fissures and cisterns were seen in all six patients on the immediate postoperative scans. ICP, however, was not monitored in this study. No major neurological deficits were seen clinically and in all patients the tracheas were successfully extubated within three hours of surgery. The follow up scans at least a week later showed that the cerebral oedema had subsided. The authors speculated that the oedema could be induced by microemboli, hypoperfusion or haemodilution. Imaging studies in children have not demonstrated cerebral oedema postoperatively but these scans were done 10-49 days after surgery, and the swelling may have subsided.^{16,17}

Burrows *et al.*³⁴ attempted to correlate the increased intracranial pressure with the delayed return of cerebral electrical activity following profound hypothermic circulatory arrest, using measures of anterior fontanelle pressure and visual evoked potentials. They found that the increase in intracranial pressure was related to the product of the duration of circulatory arrest and the nasopharyngeal temperature at the end of the arrest period. Visual evoked potentials were used as a measurement because the blood supply to the visual cortex comes from the middle cerebral artery and posterior cerebral arteries. This is a watershed area sensitive to small changes in CBF. The duration of the increase in anterior fontanelle pressure correlated with the time taken for the visual evoked potentials to reappear after rewarming of the patients. Although the reason for this correlation is unclear, the delay in return of the evoked potentials may be caused by the same abnormality that increases intracranial pressure or is secondary to it.

Cerebral Oxygenation

Cerebral blood flow is normally regulated to supply the metabolic needs of the brain under physiological conditions. Whether this "flow-metabolism coupling" is disturbed during total circulatory arrest has been the focus of many investigations. In a study of 46 patients aged from one day to 14 yr who were undergoing hypothermic cardiopulmonary bypass, Greeley *et al.*³⁶ measured cerebral metabolic oxygen consumption. Patients were grouped as follows: moderate hypothermia (28°C), deep hypothermic bypass (18-20°C), and deep hypothermic circulatory arrest (18°C). Cerebral metabolic rate for oxygen (CMRO₂) was calculated by measuring CBF with the ¹³³Xenon clearance technique and the difference in oxygen content between arterial and jugular venous blood (CaO₂-CvO₂) obtained from a retrograde jugular venous catheter. The equation, CMRO₂ = CBF

(CaO₂-CvO₂) was used to calculate the oxygen content. The study showed that both CMRO₂ and CBF were decreased after circulatory arrest and rewarming, when compared with pre-arrest levels and remained so after weaning from bypass.

The authors^{37,38} also studied the effects of hypothermia on CBF, cerebral oxygen consumption and cerebral metabolism as measured by mitochondrial cytochrome (cyt) aa3 in another two studies. Cyt aa3 is the terminal enzyme of the intramitochondrial respiratory chain that reduces oxygen during electron transport for the production of high energy phosphates by oxidative phosphorylation. When oxygen availability is limited, the redox state of cyt aa3 decreases, eventually decreasing oxidative metabolism. Monitoring the redox state of cyt aa3 and tissue oxyhaemoglobin and deoxyhaemoglobin are important indices of brain oxygenation. Greeley *et al.*³⁷ found some unexpected results in patients who had undergone circulatory arrest. They showed that patients who had undergone deep hypothermic circulatory arrest had lower cerebral oxygen consumption and blood flow after rewarming. These effects persisted into the post-bypass period which is in contrast to patients who had been cooled to a similar level but without circulatory arrest. In their study measuring cyt aa3, they showed that not only was mitochondrial oxidation impaired but the global brain oxygen level was increased suggesting that oxygen extraction was impaired.³⁸ The levels of reduced cyt aa3 were elevated in the period after bypass and circulatory arrest, an effect that suggests lack of available oxygen for production of high-energy phosphates for cellular function.

Other studies have investigated cerebral oxygenation during hypothermic cardiopulmonary bypass and circulatory arrest. Kurth *et al.*³⁹ in a study of 17 neonates aged four to 21 days, measured oxygen saturation (HbO₂) and total haemoglobin concentration in the cerebral circulation non-invasively using near infra-red spectroscopy. The neonates were cooled to a nasopharyngeal temperature of 12-15°C. Cerebral oxygenation improved with cooling on cardiopulmonary bypass but decreased during circulatory arrest. They showed that during the first 45 min of deep hypothermic circulatory arrest, cerebral oxygen levels decreased curvilinearly until they reached a plateau, suggesting that cerebral metabolism may be maintained and that oxygen extraction continues during this period. After an initial increase of HbO₂ with re-establishment of cardiopulmonary bypass, HbO₂ returned to baseline with rewarming. Jugular venous desaturation was also demonstrated in 19 adult male patients during rewarming after CPB.⁴⁰ Sapire *et al.*⁴⁰ noted that this was related to a more rapid rewarming

period and hypotension (MAP < 60 mmHg). The authors also observed that jugular venous O₂ saturation as measured with a jugular venous bulb catheter was a better monitor of cerebral oxygenation than measuring brain tissue oxygen saturation with near-infrared spectroscopy. However, the latter method has the potential to be a reliable noninvasive monitor of cerebral oxygenation if future developments allow more quantitative measurements.

These results are supported by animal studies performed by Watanabe *et al.*⁴¹ Twenty-four mongrel dogs were anaesthetised and underwent right-sided craniotomy. All animals had electrodes inserted into the parietal area of the cerebrum to measure pH and partial pressures of carbon dioxide and oxygen. The dogs' central circulation was cannulated for cardiopulmonary bypass and core temperature cooled. They were allocated to three groups, as follows: (1) institution of cardiopulmonary bypass with cooling down to a rectal and brain temperatures of about 20°C, followed by 60 min of circulatory arrest; (2) as in group 1 but low-flow cardiopulmonary bypass was maintained for 120 min; (3) as in group 2, except that pulsatile low-flow was used with a pulse pressure of 17.1 mm Hg for 120 min. After circulatory arrest in group 1 and low-flow periods in groups 2 and 3, the animals were rewarmed on cardiopulmonary bypass to 32°C. The pH decreased in all groups during the period of circulatory arrest or low-flow perfusion with or without pulsatile assistance but during rewarming there was a rapid recovery in group 3 and a delayed recovery in group 2. No recovery was recorded in group 1. This work is consistent with the findings by Greeley *et al.*,³⁶ which demonstrated impaired cerebral metabolism after deep hypothermic circulatory arrest compared with those who did not undergo arrest but were cooled. Finally, these observations showed that the circulatory arrest group had delayed recovery of pH which could suggest an impaired cerebral metabolism.

The speculation that low CBF is an appropriate response to decreased metabolic demands is supported by the observed delay in the return of electrical activity to the brain after deep hypothermic cardiopulmonary bypass and total circulatory arrest.^{34,42} A delay in the return of normal electroencephalographic (EEG) patterns after circulatory arrest was shown by Weiss *et al.*,⁴² who monitored 17 infants with six-channel EEG and found that the time taken for the return to normal EEG results with rewarming was related to the duration of the arrest. They also noted that cerebral autoregulation was lost with deep hypothermic cardiopulmonary bypass, a finding in agreement with those of Taylor *et al.*²⁹ except that the

temperature ranges differed slightly in the two studies. Greeley *et al.*²⁴ suggested that the low CBF was either an appropriate response to decreased metabolic demands after circulatory arrest or a result of the "no reflow" phenomenon. This phenomenon was proposed by Ames *et al.*,⁴³ who postulated that with circulatory arrest there was a primary blood vessel abnormality to which cerebral parenchymal damage was secondary. This is consistent with the findings of Burrows *et al.*³² which demonstrated that a greater cerebral perfusion pressure (CPP) is necessary to re-establish detectable CBFV after a period of profound hypothermic circulatory arrest.

LOW-FLOW CARDIOPULMONARY BYPASS

Critical Opening Pressure

Although circulatory arrest makes complex repairs technically easier for the surgeon, it carries a considerable risk of neurological injury because of its effects on cerebral blood flow and metabolism. Low-flow cardiopulmonary bypass uses less severe hypothermia with pump flows at 25% of normal for the size of the child and is believed by some to offer better cerebral protection. Watanabe *et al.*⁴¹ have suggested that low-flow cardiopulmonary bypass is better than deep hypothermic circulatory arrest in maintaining tissue pH, partial pressures of carbon dioxide and oxygen and enabling their return to normal values after bypass. In response to this suggestion, Taylor *et al.*²⁹ studied CBF and cerebral perfusion pressure (CPP) during hypothermic cardiopulmonary bypass with and without low flow. They studied 25 neonates and infants, using a standard anaesthetic technique and avoiding cerebral vasoactive agents. The CBFV was measured with a transcranial Doppler (CDS, Medasonics, Fremont, CA.) and intracranial pressure was recorded non-invasively through the anterior fontanelle using a Ladd pressure transducer (Ladd Research Industries, Burlington, Vt.). These measurements enabled calculation of CPP (CPP equals mean arterial pressure minus intracranial pressure or central venous pressure, whichever is greater). The CBFV was measured at three temperature ranges: normothermia (36 – 37°C), moderate hypothermia (23 – 25°C) and profound hypothermia (14 – 20°C). They postulated that cerebral autoregulation begins to be altered at nasopharyngeal temperatures < 25°C and when temperatures decreased below 20°C, the CPP ceases to be autoregulated and becomes pressure-passive. The authors also noted that nine patients in the study group had no detectable CBF during profound hypothermia, when the CPP fell to 9 ± 2 mm Hg. No relationship was found between pump flow rates and the CPP at which the CBFV could not be detected. This

finding led the authors to postulate that there is a critical-closing pressure for cerebral perfusion and if perfusion falls below it, then there is a loss of CBF. It was alarming to observe that in two patients CBF was lost at pump flows of 28% and 33% of normal. This study suggests that not all patients on low-flow cardiopulmonary bypass receive adequate cerebral perfusion.

Burrows *et al.*³² confirmed that some neonates and infants who underwent extreme low-flow hypothermic cardiopulmonary bypass (< 22% of normal pump flow) and had no detectable CBF, as measured by transcranial Doppler probe, responded similarly to those who had undergone deep hypothermic circulatory arrest. They required higher perfusion pressures to re-establish a given CBFV after the low-flow period which for the duration of the study period, did not return to prebypass cerebral blood flow velocity level. This observation suggests that the cerebral vasculature may need a resting hydrostatic pressure to maintain patency of the lumen of the vessel and if this intraluminal pressure is lost, the vasculature collapses. The need for greater cerebral perfusion pressure to reestablish the cerebral blood flow is thought to be due to a hysteresis phenomenon on the cerebral vessels. Thus, a "critical closing-opening pressure" may be responsible for the "no-flow" phenomenon observed during extreme low-flow cardiopulmonary bypass. Although, technologically, there may still be very low CBF which is not detectable with the transcranial Doppler, one must remember that the viability of the brain cell may be dependent on a minimum amount of oxygen delivery and not simply the presence of cerebral perfusion.

Low-Flow Versus No-Flow

Rossi *et al.*⁴⁴ compared low-flow cardiopulmonary bypass with deep hypothermic circulatory arrest in children undergoing surgery for repair of complex congenital cardiac lesions. The authors looked at 27 children who were randomly assigned to one of the two techniques (except for five children who weighed > 8 kg and were thus considered unsuitable for circulatory arrest). The CK-BB values were used as a quantitative measure of cerebral damage. No difference in CK-BB values was found between the two groups. It was concluded that low-flow offers no better protection than deep hypothermic circulatory arrest. However, neurological outcome, the important issue, was not studied. This work is consistent with that of Taylor *et al.*⁴⁵ in that if there are periods of absent CBF during low-flow cardiopulmonary bypass, then one would expect markers of cerebral damage to be similar to those in patients who undergo deep hypothermic circulatory arrest.

Results of two animal studies indicate superiority in certain respects for the low-flow cardiopulmonary bypass technique. In a study using sheep, Swain *et al.*⁴⁶ demonstrated less depletion of high-energy phosphate stores and better preservation of intracellular pH in animals who underwent low-flow cardiopulmonary bypass at $10 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and hypothermia than in those undergoing deep hypothermic circulatory arrest. Mault *et al.*⁴⁷ in a study using one-week-old piglets, showed that recovery of cerebral metabolism after rewarming, was almost complete when low-flow cardiopulmonary bypass was employed (reduction of flow from $100 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ to a flow of between $5\text{--}10 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) during deep hypothermia. In contrast, cerebral metabolism remained impaired after rewarming, in piglets who had undergone deep hypothermic circulatory arrest for a similar duration (60 min). This finding suggests that low flow may offer better cerebral protection. Earlier studies in children produced similar results.^{24,25}

In an earlier study, Rebeyka *et al.*,¹⁹ using a dog model, measured the effect of low-flow cardiopulmonary bypass on the brain, using somatosensory cortical evoked potentials and brain energy stores as measured by brain adenosine triphosphate levels (ATP). They concluded that the systemic flow rate is the most important determinant for maintaining ATP levels in the brain not the perfusion pressure. The pressure is important only insofar as it is related to perfusion by the nature of the pressure-flow relationship.

Kern *et al.*,⁴⁸ comparing the effects of reduced pump flow rates during moderate hypothermic CPB (26°C - 29°C) and deep hypothermic CPB (18°C - 22°C) in 27 children, demonstrated that CBF and cerebral metabolism were unaffected by pump flow rates reductions of < 45% from conventional flow rates. At reductions of > 45%, CBF exceeded cerebral metabolic needs up to a critical point after which metabolic demands became supply-dependent. Further reductions in pump flow rate would result in increasing oxygen extraction or marked reductions in CMRO_2 . The authors suggested that this critical pump flow rate may be between 30 and $35 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ at moderate hypothermia and between 5 and $30 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ at deep hypothermia in children.

Based on the observation that during low flow cardiopulmonary bypass, the presence of hysteresis in the behaviour of the cerebral circulation (closing-opening critical pressure) could be responsible for the periods of no flow,³² one could speculate that pulsatile flow would provide better cerebral flow, at least during the peak of pulse pressure. Hence it could be assumed that there would be less tissue ischaemia during pulsatile flow and

a more rapid recovery of pH during rewarming. The presence of a critical-closing and -opening pressure suggest that cerebral blood flow may be directly related to the perfusion pressure rather than pump flow. The loss of cerebral autoregulation observed with moderate to severe hypothermia may also be favourable to the closing of small vessel and/or consequently the presence of uneven cooling of the brain. This may be consistent with the work of Foster *et al.*⁴⁹ demonstrating an increase in jugular venous blood temperature in children undergoing low-flow bypass and profound hypothermia. Therefore, the speed of extracorporeal cooling and rewarming may contribute to the uneven cerebral perfusion and flow distribution within the brain. The utilisation of pulsatile flow could, theoretically, offer advantages over non-pulsatile flow but it remains to be proven in children.

PULSATILE CARDIOPULMONARY BYPASS

The findings of two animal studies conducted by Watanabe *et al.*^{41,50} suggest that pulsatile flow increases the safety of cardiopulmonary bypass during low flow perfusion. In the first study, the pH, oxygen tension and carbon dioxide tension of canine brain tissue were measured during deep hypothermic CPB. After core cooling to a rectal and brain temperature of $<20^{\circ}\text{C}$, a 60-min period of circulatory arrest was performed in dogs in group 1. Non-pulsatile low-flow perfusion at $25\text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ was instituted for 120 min in group 2 and pulsatile low-flow perfusion at $25\text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $0.8\text{ ml}\cdot\text{kg}^{-1}\cdot 30\text{ beats}\cdot\text{min}^{-1}$ for 120 min in group 3. Core temperature was raised to 32°C when the animals were rewarmed. Watanabe *et al.*⁴¹ demonstrated that the partial pressure of carbon dioxide (PCO_2) of brain tissue increased in all groups but reached a plateau in the group receiving pulsatile flow (group 3). In the second study, the authors⁵⁰ demonstrated that pulsatile assistance ensured continuance of aerobic metabolism during low-flow perfusion. In our opinion, this suggests improved CBF with pulsatile cardiopulmonary bypass. At lower flow rates and with longer perfusion periods, the utilisation of pulsatile cardiopulmonary bypass may be of assistance and more beneficial.¹ However, in a recent study by Murkin *et al.*^{4,51} comparing the neuropsychological outcome of 316 adults undergoing extracorporeal circulation with or without pulsatile flow, they reported a difference in mortality between the flow modality, but failed to show any differences among the groups with regards to postoperative neurological dysfunction. The findings are consistent with the results of an animal study which demonstrated that CBF and cerebral metabolism were not affected by flow characteris-

tics in rabbits at moderate hypothermia.⁵² The effect of pulsatile perfusion may be easily outweighed by other perfusion variables such as temperature and carbon dioxide.¹ The advantages, if any, of pulsatile perfusion in children where lower pump flow rates and temperatures are used, remains to be proved.

Brain Temperature

BRAIN COOLING

The single most important factor protecting the brain during deep hypothermic cardiopulmonary bypass with or without circulatory arrest is hypothermia. Hypothermia has been shown to decrease cerebral metabolic demands with less depletion of high-energy stores in animals. In one study, Stocker *et al.*⁵³ demonstrated that cerebral high-energy phosphate stores were preserved longer during hypothermia than normothermia after total circulatory arrest was initiated. The study used male New Zealand rabbits divided into normothermic, hypothermic (24°C), and deep hypothermic (21°C) groups. Animals in the latter two groups had internal jugular vein and femoral artery lines inserted for bleeding to induce circulatory arrest. Cerebral phosphocreatine, ATP and inorganic phosphate levels were measured before and after arrest and for up to 240 min with nuclear magnetic resonance spectroscopy. This study is important in that it revealed an increase in half-times for the high-energy phosphates by a factor of three as temperature decreased from 35°C to 21°C . This is consistent with the expected effect of temperature in decreasing cerebral metabolism.

The study by Mault *et al.*⁴⁷ of piglets undergoing cardiopulmonary bypass and deep hypothermic circulatory arrest showed that cerebral metabolism (CMRO_2) was impaired after the arrest period. The study also found that the impairment was proportional to the duration of the arrest and that recovery of CMRO_2 after a 60 min arrest was improved if the piglet's head was packed in ice.

Little information is available on brain cooling during cardiopulmonary bypass in paediatric patients. There are two theories on whether or not the brain is completely or adequately cooled during bypass, one based on a study by Greeley *et al.*,³⁶ the other on the work of Kurth *et al.*³⁹ The former studied the effect of hypothermia on cerebral metabolism and oxygen consumption in 46 paediatric patients undergoing open-heart surgery. Four patients who underwent deep hypothermic circulatory arrest had low cerebral venous oxygen saturations (jugular venous bulb oxygen saturations) before circulatory arrest. Three of them developed neurological sequelae. The authors suggested that

inadequate cerebral cooling might be the cause of "persistent oxygen extraction" and that cerebral venous saturation monitoring may indicate whether the brain is adequately cooled. The latter,³⁹ in their study of 17 neonates undergoing open-heart surgery and profound hypothermic circulatory arrest, demonstrated that after the institution of circulatory arrest, cerebrovascular $\text{HbO}_2\%$ decreased curvilinearly for 40 min suggesting that cerebral rewarming during circulatory arrest rather than reperfusion was observed. However, they concluded that since nasopharyngeal temperature, which would have risen if there were persistent temperature gradients within the brain, did not change during the arrest period, non-homogeneous brain cooling was unlikely. In contrast, Foster *et al.*,⁴⁹ using multiple temperature site monitoring, including a jugular venous bulb temperature probe, demonstrated that during low-flow CPB, jugular venous bulb temperature increased above that of the tympanic temperature, suggesting that brain cooling is uneven and that redistribution of heat from areas of increased cerebral metabolism raised the jugular venous bulb temperature. It is also important to note that this was not reflected by a similar change in tympanic temperature.

Kern *et al.*⁵⁴ measured jugular venous oxygen saturation via a jugular venous bulb catheter in 17 patients less than one year of age who were undergoing hypothermic cardiopulmonary bypass and found that six of them had low oxygen saturation at tympanic temperatures of 15°C . These findings suggest that brain cooling is inadequate despite nasopharyngeal and tympanic temperature sites monitoring indicating that the brain was adequately cooled. However, the authors proposed that the position of the arterial line cannula may influence brain cooling. For instance, children with lesions requiring distal placement of the cannula were more likely to experience inadequate cooling because of diversion or "steal" of flow from the head.

Some evidence suggests that a minimum period of cooling on cardiopulmonary bypass is required before circulatory arrest. Bellinger *et al.*¹⁰ suggested that cooling periods of < 20 min (11-18 min) before deep hypothermic circulatory arrest were associated with subsequent lower developmental scores. It was noted that within this range of cooling period, an increase of five minutes of core cooling was associated with a 26-point improvement in the developmental scores. However, no added advantage was demonstrated with longer cooling periods (20-39 min) which were also associated with lower scores but this association was not statistically significant. The authors concluded that short cooling periods may leave "watershed" areas within the brain that have not been adequately

cooled; they are thus vulnerable to ischaemic injury during arrest. However, long cooling periods were also not beneficial. The authors postulated that the benefit of better cerebral cooling may be offset by the potential brain injury related to cardiopulmonary bypass after 20 min. Wong *et al.*¹⁴ in a review of 19 patients who developed choreoathetosis after cardiac surgery, found that the duration of cooling before the onset of deep hypothermic circulatory arrest was shorter than in a comparison group.

A study in five infants showed that the jugular venous bulb temperature increased during low-flow cardiopulmonary bypass whereas nasopharyngeal and tympanic temperatures remained constant, a finding consistent with the suggestion of inadequate or uneven cooling.⁴⁹

BRAIN TEMPERATURE MONITORING

Brain temperature has been measured during cooling in an animal study that did not involve cardiopulmonary bypass.⁵⁵ A single thermistor was introduced into the brain of a gerbil via a burr hole. The animal was then cooled to 18°C with whole-body surface cooling. When the rectal temperature reached 18°C , the brain temperature was 20°C . Although this was not a human study and did not involve cardiopulmonary bypass, it illustrates that rectal temperature does not necessarily reflect brain temperature. Stone *et al.*,⁵⁶ too, measured brain temperature as well as eight other standard temperature monitoring sites in 27 adult patients who required cardiopulmonary bypass and profound hypothermic circulatory arrest for surgical clipping of giant cerebral aneurysms. They demonstrated that none of the monitored sites tracked cerebral temperature well throughout the entire hypothermic period, particularly during rapid temperature changes. Of these, the nasopharyngeal, oesophageal and pulmonary arterial temperatures corresponded better to mean brain temperature than tympanic, bladder, rectum, axillary and skin temperatures.

Rewarming

There are concerns among investigators that rapid rewarming or excessive hyperthermia after deep hypothermic circulatory arrest may be detrimental during a period of cerebral hypoperfusion often encountered during rewarming. Using rabbit models, Enomoto *et al.*⁵⁷ demonstrated a greater increase in CMRO_2 associated with faster rates (four minutes) than with slower rates (25 min) of rewarming, particularly in the early phase of rewarming. This was not matched by a proportionate increase in CBF. As a result, at equivalent brain temperatures, brain oxygen

extraction was greater with faster rewarming than with slower rates.

Cold reperfusion

A recent study by Jonassen *et al.*⁵⁸ demonstrated reduced cerebral perfusion after rewarming in patients who had undergone deep hypothermic CPB, regardless of the perfusion technique employed. The authors noted that patients who had a period of cold full-flow reperfusion before rewarming, had normal flow velocity after rewarming. The mechanism of this phenomenon, also observed in an earlier study by Astudillo *et al.*,⁵⁹ is still not known. It may be due to a cerebrovascular response on rewarming from profound hypothermia and appears to be amenable to alterations by changes in rewarming strategy.

In a non-randomised study of 16 infants who required periods of deep hypothermic circulatory arrest of at least 35 min, Rodriguez *et al.*⁶⁰ demonstrated that postbypass CBFV as measured by transcranial Doppler sonography returned to pre-bypass levels in infants who had a 10-min period of cold reperfusion before rewarming. In contrast, those who had immediate rewarming showed absent diastolic Doppler signal post-bypass, indicating no perfusion. However, the group of infants who had immediate rewarming in this study, had a slightly longer period of circulatory arrest compared to those who received cold reperfusion even though this difference did not reach statistical significance with this sample size. Despite these limitations, the results do suggest that a delay in rewarming on reperfusion may offer added protection to the brain. The authors postulated that rewarming the brain in the presence of metabolites that had accumulated during DHCA contributed to the increased cerebral vascular tone and that a brief period of cold reperfusion allowed clearance of these metabolites before additional metabolic products are produced from a brain that is being rewarmed.

Arterial Carbon Dioxide Tension and Acid Base Management

Carbon dioxide (CO_2) is a potent cerebral vasodilator and changes in the partial pressure of carbon dioxide (PaCO_2) and pH in the arterial blood affects CBF in both awake and anaesthetised patients. The cerebral vascular reactivity to carbon dioxide in children while undergoing hypothermic CPB has been investigated. Studies have shown that CBF remained responsive to changes in PaCO_2 during and after CPB under moderate hypothermic conditions.^{61,62} Kern *et al.*⁶¹ also demonstrated that this responsiveness was attenuated but not totally eliminated at deep hypothermia (18-

22°C). The authors also noted that children under the age of one year tended to be less responsive to changes in the PaCO_2 . The increase in CBF in these infants was less ($0.81 \pm 1.84 \text{ ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$) with every mmHg increase in PaCO_2 compared with the older children ($1.3 \pm 0.64 \text{ ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$) although the difference did not reach statistical significance.

Since cerebral vascular reactivity to carbon dioxide is preserved during CPB, control of PaCO_2 and hence pH during CPB becomes important in the regulation of CBF. Two strategies have been proposed for acid base management during hypothermic CPB. In the pH-stat method, PaCO_2 is maintained at 40 mmHg, corrected to the patient's temperature and the arterial pH is kept at 7.4. As body temperature decreases, blood pH increases and carbon dioxide has to be added to the blood during CPB. In the alpha-stat method, the pH is allowed to increase with decreasing temperature while PaCO_2 is kept at 40 mmHg measured at 37°C.

Currently, the preferred technique is the alpha-stat method because it is believed that cell function is better preserved by maintaining neutral pH appropriate to the temperature of the cell. In a large randomised study of 316 adults undergoing elective coronary bypass grafting, Murkin *et al.*⁴ showed that alpha-stat management of acid base balance during CPB was associated with a lower incidence of cognitive dysfunction post-operatively compared with pH-stat management. Stephan *et al.*⁶³ demonstrated that under pH-stat conditions, there was a 191% increase in CBF during CPB in adult patients, as well as loss of autoregulatory responses to flow and pressure changes and metabolic demands. In contrast, autoregulation was preserved with alpha-stat strategy. Cerebral metabolism was noted to be unaffected by the acid base management strategy. Again, neurological damage was observed to be related to the pH-stat rather than the alpha-stat method. This is likely to be due to hyperperfusion associated with pH-stat regulation, leading to increased potential for embolism of particulate matter, brain oedema and raised intracranial pressure. This is consistent with the findings of Hindman *et al.*⁶⁴ when they compared the effects of blood gas management on CBF at bypass flow rates of $100 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in rabbits. However, when the flow rates were reduced to 50 and $70 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, the authors found that differences in CBF values, as well as variation with systemic flow and pressures were reduced considerably. "Critical" values of systemic flow and pressure below which CO_2 has no effect on CBF or CBF dynamics in humans is still not known but the findings of this study suggest that the choice

of pH strategy during CPB may not be as important clinically at lower bypass flow rates, often employed in children. An animal study using six to eight week old piglets demonstrated that the hypercapnic reactivity of the cerebral vasculature was suppressed during deep hypothermic CPB when alpha-stat strategy was used but was preserved when pH-stat protocol was used.⁶⁵ Loss of autoregulation and uncoupling of the CBF/CMRO₂ relationship was also noted with pH-stat protocol. Interestingly, CBF and the vascular reactivity to CO₂ returned to normal after completion of CPB regardless of the type of acid base management protocol used.

The effect of pH strategy on neurological outcome in the paediatric population, however, has not been extensively investigated. As a result of a change from pH-stat to alpha-stat in the management of acid-base balance during CPB in their institution in 1985, Jonas *et al.*⁶⁶ examined the developmental outcome of 16 children who had undergone Senning procedure for transposition of the great arteries and intact interventricular septum during infancy between 1983 and 1988. Information on many aspects of perfusion techniques, including pH strategy and the duration of cooling were collected retrospectively. Neurological development was assessed at a median age of 48 mo. The use of alpha-stat management before the onset of circulatory arrest was noted to be associated with poorer developmental scores. The authors speculated that when a shorter cooling time is employed, the lower CBF associated with the alpha-stat strategy may result in inadequate cooling compared with that achieved with pH-stat strategy. They concluded that pH-stat management may be more effective in protecting the brain during cooling before total circulatory arrest. However, the sample size of this study was small and thus may not be representative. Furthermore, some of the data were collected retrospectively which had the disadvantage of various problems, including incomplete charts and the lack of consistency in the management of the CPB strategy. Finally, the age of the children at the time of developmental assessment was not consistent between the groups and the patients who were managed with alpha-stat protocol were younger at the time of testing with the consequences of achieving lower developmental scores, compared with the group managed with pH-stat protocol.

More recently, these authors⁶⁷ compared the neurological and cardiovascular outcome of 182 infants under the age of nine months, randomised to either pH-stat or alpha-stat strategy while undergoing reparative cardiac surgery during deep hypothermic CPB and total circulatory arrest at <18°C. The duration of

the cooling period was not reported but the duration of circulatory arrest for all patients was only 20 min. Patients assigned to pH-stat strategy tended to have a lower tympanic temperature ($14.8 \pm 1.8^\circ\text{C}$) than did patients treated by alpha-stat strategy ($15.3 \pm 1.5^\circ\text{C}$). This observation suggests that lower cerebral temperature or more homogenous brain cooling may be better achieved with pH-stat management, thus improving brain protection. Use of pH-stat management was shown in this study to be associated with lower postoperative neurological morbidity. First EEG activity returned sooner among infants randomized to pH-stat strategy. Postoperative EEG seizures and clinical seizures tended to be more frequent in patients assigned to alpha-stat strategy although this did not reach statistical significance. However, the low incidence of seizures in this study (3%) may result in insufficient power to detect any statistical significance. In addition, analyses of the subgroup of neonates with transposition of great arteries revealed that those assigned to pH-stat strategy tended to have a better cardiovascular outcome and required a considerably shorter period of ventilatory support and intensive care unit stay.

Thus, whether pH-stat or alpha-stat management offers better cerebral protection in children would depend on whether the resultant CBF meets metabolic demand. The associated increase in blood pH with alpha-stat management shifts the oxygen dissociation curve to the left. Coupled with the decrease in CBF, this may result in insufficient delivery to meet metabolic demands. If, however, CBF meets metabolic demands with alpha-stat regulation, the reduction in CBF reduces the potential for air and particulate embolism associated with the luxury perfusion seen with pH-stat protocol. The increase in perfusion with the latter may also result in hyperaemia and brain oedema. On the other hand, luxuriant flow may reduce the possibility of microembolism during CPB and ensure more homogenous brain cooling before circulatory arrest, particularly if short cooling periods are used. Current data, though limited, suggests that unlike in the adult population, pH-stat strategy may enhance systemic and cerebral protection during deep hypothermic circulatory arrest in children.

Haemodilution

Haemodilution is used routinely during CPB because blood viscosity increases with hypothermia. In general, haemodilution increases CBF by improving the rheology of the blood and also by compensating for the fall in the oxygen carrying capacity of the blood. During hypothermic CPB with haemodilution, how-

ever, this may not hold true. Jonassen *et al.*⁵⁸ in their study of 37 children using transcranial Doppler sonography to measure CBFV after hypothermic CPB, concluded that under profound hypothermia, haemodilution did not produce an appropriate increase in CBF. Its clinical relevance, however, has so far not been investigated. Experience with children of members of the Jehovah Witness faith in two centres did not report any increase in the incidence of post-operative neurological deficits.^{68,69}

Henling *et al.*⁶⁸ reviewed the perioperative courses of 110 children of members of the Jehovah Witness faith who underwent cardiac surgery during normothermic cardiopulmonary bypass with a glucose crystalloid prime. These children ranged in age from six months to 12 yr and weighed 5.2 to 42.3 kg. Intraoperative haemodilution resulted in large reductions in haemoglobin levels, often exceeding 50% in patients weighing less than 10 kg. Mean haemoglobin levels during CPB in this latter group of patients reached 4.5 ± 0.8 g·100 ml⁻¹ in the non-polycythaemic patients and 6.4 ± 2.2 g·100 ml⁻¹ in the polycythaemic patients respectively. None of them received blood or blood products during the period of hospitalisation. Three patients had transient hemiparesis postoperatively but none of the deaths were due to cerebrovascular events.

Stein *et al.*⁶⁹ reported the use of a modified version of isovolaemic haemodilution and a bloodless prime technique during moderate to profound hypothermic CPB or total circulatory arrest in 15 children of Jehovah Witnesses, aged between 1.5 and 17 yr. Mean haematocrit levels achieved during bypass was 17.9%. No neurological complications were reported. An animal study using a pig model, showed that CBF and CMRO₂ were lower during normothermic non-pulsatile CPB with haemodilution (achieving a serum hemoglobin level of 6 g·100 ml⁻¹) than with haemodilution alone.⁷⁰ This finding persisted even during periods of bicarotid occlusion and progressive systemic hypotension. However, there were no changes in the EEG or in the release of brain metabolites observed. The authors concluded that there was no disruption of the flow-metabolism autoregulation during CPB with haemodilution, which offers adequate cerebral protection even during subsequent hypoperfusion.

Glucose Management

Glucose is used as part of the priming solution for the CPB and cardioplegic solutions to provide protection to the heart. These solutions, however, may add to a hyperglycaemic state already induced by the stress of surgery. In the past, hypoglycaemia has been a source of

worry as it was widely accepted to be potentially deleterious in the presence of cerebral injury. Recently, there is also concern that hyperglycaemia, too, may increase cerebral damage during periods of ischaemic insult.

Lichtenberg *et al.*⁷¹ examined the perioperative serum glucose and lactate concentrations of nine infants <10 kg, who underwent deep hypothermic CPB at 20°C for surgical correction of congenital heart defects. The patients' serum glucose and lactate levels were raised on starting CPB and appeared to be related to the mixing of the patients' blood with the priming solutions of the pump. Accumulation of lactate was not seen. Insulin response was noted to be attenuated during hypothermia but it returned to pre-bypass levels with rewarming. Serum glucagon, cortisol and growth hormone concentrations were increased only during rewarming but returned to preoperative baseline values 24 hr after surgery. One patient who developed ventricular fibrillation at induction of anaesthesia, showed elevated lactate levels which subsequently returned to baseline levels before CPB was instituted. Although the neurological status of these patients was not investigated post-operatively, the authors raised the question of whether lower glucose concentrations in the prime solution may be better in the event of ischaemic injury.

A review of 34 patients less than one year old who underwent profound hypothermia and total circulatory arrest revealed a tendency towards worse neurological outcome with hyperglycaemia.⁷² However, this was a retrospective study with a small group of patients, which makes interpretation difficult. Certainly, adult patients with established diabetes mellitus has been shown to have poorer neurological recovery after a stroke compared to non-diabetic patients.⁷³ In addition, neurological outcome was worse with higher serum glucose concentrations. Bush and Steward⁷⁴ reported severe and permanent neurological damage following an uneventful anaesthetic in a eight year old girl in whom the only significant intra-operative finding was hyperglycaemia. Glauser *et al.*⁷⁵ conducted a detailed postmortem neuropathological examination on 40 infants identified to have hypoplastic left heart syndrome at autopsy. The mean age of death of these infants was 31 days, 45% of the infants were found to have combinations of hypoxic-ischaemic lesions as evident by cerebral and brainstem necrosis, periventricular leukomalacia, and intracranial haemorrhages. Twelve of the 20 infants who had major palliative cardiac surgery, showed evidence of cerebral injury. Retrospective review of the patients' medical records revealed statistically significant etiologic associations in the occurrence of these acquired

lesions. Besides hypotension and hypoxia, both hypoglycaemia and hyperglycaemia were identified as important predisposing factors.

Anderson *et al.*⁷⁶ showed that the intracellular pH of hyperglycaemic dogs were lower than the euglycaemic animals after two hours of circulatory arrest. Their pH took a longer time to return to baseline during reperfusion. In a study with rats, Pulsinelli *et al.*⁷⁷ demonstrated that hyperglycaemia before a transient ischaemic insult was associated with neocortical infarction and ischaemic changes to the neurones of the forebrain and severe brain oedema. Glucose given during the insult did not produce further damage in the forebrain, however, there was evidence of increased neurological damage in the cerebellum. It may seem appropriate to suggest from these studies that hyperglycaemia should be avoided during deep hypothermic CPB with or without circulatory arrest.

However, experimental studies using immature animal models reported conflicting results. Vannucci *et al.*⁷⁸ examined the brains of seven day old rats after they were subjected to transient unilateral carotid occlusion and followed by exposure to oxygen for two hours. It was interesting to note that rats with serum glucose levels of 630-720 mg·dl⁻¹ throughout the period of hypoxia developed no pathological changes in the brain.^{78,79} In contrast, all the rats with normal glucose levels had some degree of brain damage. Holowach-Thurston *et al.*⁸⁰ in a more extensive study of over 200 newborn mice (aged from birth to 12 days old) observed that more glucose-treated mice survived after five minutes of anoxia compared with untreated mice. The initial glucose in the brains of the former group of mice was three times higher than the latter group. This, however, was not reflected in the plasma glucose concentrations in the anoxic mice. The cerebral energy reserve, represented by high energy phosphate levels derived from phosphocreatine, ATP, glucose and glycogen, were twice those in the glucose-treated mice. The authors postulated that exogenous glucose increases the energy reserve of the brain and plays an important role in prolonging the survival of the neurones to ischaemia. They also noted that normal or even elevated glucose levels in the blood cannot be assumed to represent adequate cellular levels in glucose.

These are, however, animal models and one should interpret the results with caution before extrapolating to the human neonate. One problem in this area of investigation is that it is difficult to conduct prospective randomised controlled trials in human subjects. Current available data, based on retrospective studies and clinical reports, suggest a correlation between hyperglycaemia and postoperative neurological dam-

age in children. Hence, until there is further evidence to prove that hyperglycaemia is protective against neurological damage, it seems prudent to avoid hyperglycaemia in patients undergoing CPB.

Conclusion

Cerebrovascular physiology during cardiopulmonary bypass in neonates, infants and children is not well understood. Most studies have investigated a wide selection of procedures over a large age range.

The effects of deep hypothermic circulatory arrest on cerebral metabolism extend well into the post-bypass period. Cerebral metabolism is impaired. Intracranial pressure is increased but not secondary to increased cerebral blood flow. While the decrease in CBF after deep hypothermic circulatory arrest could be an appropriate response to decreased oxygen consumption, it has been speculated by others that the observed CBF/CMRO₂ uncoupling is the result of limiting cerebral vascular relaxation as a consequence of either cold-induced vasoparesis (severe hypothermia)^{24,29} or an unknown intrinsic disorder of vascular dynamic.⁸¹

In comparison with deep hypothermic circulatory arrest, low-flow cardiopulmonary bypass (>25%) may maintain some cerebral blood flow and therefore, reduce impairment of the cellular metabolism. However, one would expect the effects of the two techniques to be indistinguishable if there was no flow during extreme low-flow states and this was seen in various studies examining cerebral blood flow during low-flow CPB.^{29,32,44,45} Studies have demonstrated that with PHCA, and extreme low-flow states, ICP can increase to 18 mmHg.^{33,34} Based on the fact that critical closing pressure for the cerebral vessels was about nine mmHg, it would be advisable to maintain MAP at >20 mmHg and avoid pump flow rates of < 25% of normal flow rates to ensure CPP >12 mmHg during low flow CPB.

Some animal studies^{41,82} have suggested better CBF with pulsatile CPB whereas other have failed to show any advantages.^{52,83} Studies in humans have not proven its usefulness either physiologically with regards to neurological outcomes.⁵¹

On the other hand, increasing laboratory and clinical data have suggested that other aspects of patient management before and after the arrest or the low-flow period are as important in protecting the patient. Several studies have demonstrated that it is better to ensure adequate cooling of the brain with a cooling period of 20 min.^{10,14} There is evidence, too, that a brief period of cold reperfusion⁵⁸⁻⁶⁰ or a slower rate of rewarming may be beneficial.⁵⁷ In addition, newer

data have challenged the widely held notion that alpha-stat strategy of acid-base management is superior to pH-stat strategy for organ protection during deep hypothermic CPB in infants.⁶⁷

Unfortunately, the lack of uniformity of procedures, equipment or management in paediatric open-heart surgery makes comparison of clinical practices in different institutions and scientific studies difficult to assess. Large multicentre outcome studies are needed to help identify the techniques and strategies associated with better neurological and developmental outcomes.

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