

## Meeting abstracts

# Neurological complications after cardiac surgery

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## Lectures

### Pathophysiology of the cerebral circulation during cardiac surgery

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Although mortality rate after cardiac surgery has been drastically reduced, neurological complications remain a significant problem. Several etiologic factors have been proposed, including previous unrecognized neurological abnormality, embolic events, hypoxic insult, low cardiac output, systemic inflammatory response, and altered cerebral blood flow (CBF) and metabolism. Cerebral ischemia can occur when cerebral oxygen is insufficient to meet the global or regional cerebral oxygen consumption. Cerebral circulation is normally regulated by several complex mechanisms, such as metabolic stimuli, chemical stimuli, perfusion pressure, and neural stimuli [1].

During and after cardiac surgery, CBF and metabolism can also be affected by other factors including arterial  $PCO_2$ , temperature, anesthesia depth, and perfusion flow rate during cardiopulmonary bypass. As a consequence of the effects of anesthetic agents and hypothermia, CBF is generally reduced during cardiac surgery. Cerebral metabolic regulation refers to the mechanism describing the adaptation of CBF to the metabolic demands of the brain. Although CBF–metabolism coupling is fairly well maintained during cardiopulmonary bypass, cerebral metabolic rate for oxygen ( $CMRO_2$ ) decreases significantly more than CBF [3]. The increase in CBF to  $CO_2$  is preserved during hypothermic cardiopulmonary bypass, but the response can be diminished when using pH-stat management of blood gases due to the powerful vasodilator effect of  $CO_2$  on the cerebral vasculature [4]. Moderate changes in arterial  $PO_2$  do not significantly alter CBF, but CBF increases once  $PaO_2$  drops below 50 mmHg so that cerebral oxygen delivery remains constant.

Pressure autoregulation refers to the ability of the brain to maintain total and regional CBF nearly constant despite large changes in systemic arterial blood pressure, independently of flow–metabolism coupling [5]. Pressure autoregulation is generally preserved during hypothermic cardiopulmonary bypass. Impaired autoregulation has been reported mainly in pH-stat conditions due to increasing  $PaCO_2$ . Interestingly, CBF and metabolism seem to be unaffected during pulsatile flow as compared with nonpulsatile flow during cardiopulmonary bypass [6]. Different data found by other investigators may be easily explained by changes in perfusion variables, such as temperature or  $PaCO_2$ . Variation in the systemic flow rate from the pump oxygenator *per se* hardly influences CBF or  $CMRO_2$  during hypothermic CPB [7]. Conflicting results reported by others are difficult to interpret because of confounding effects of differences in the management of  $CO_2$ , and anesthetic and vasoactive drugs during hypothermic cardiopulmonary bypass. Since blood viscosity represents a major determinant of vascular resistance, CBF is inversely related to hematocrit [8]. Nevertheless, a continuing controversy pertains to whether CBF is purely rheologic or a function of changes in oxygen delivery to the tissue.

In conclusion, CBF and  $CMRO_2$  drop during cardiac surgery due to combined effects of both anesthesia and hypothermia. Regulatory mechanisms of CBF are little affected by hypothermic cardiopulmonary bypass, but can be influenced by other determinants of cerebral perfusion.

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## Neurological damage due to coagulation and fat release during cardiopulmonary bypass

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**Introduction:** Cardiac surgery with cardiopulmonary bypass (CPB) has been associated with a higher risk of neurologic and neuropsychological deficits than other major types of surgery [1]. Different etiologic mechanisms have been proposed to account for these deficits [2–5]. First, inadequate perfusion of the brain circulation has been proposed as a factor of brain damage. Second, CPB produces a systemic inflammatory response that may give rise to renal and pulmonary dysfunction, but the effect on the brain has attracted less attention [6,7]. Although a causal relationship has been suggested between the inflammatory response and cognitive dysfunction [8], no clear evidence exists. Third, emboli are formed during CPB by air, clotting activity or cell aggregation and fat release. Partly, these emboli are captured by the various filters in the circuit, but reorganization of smaller emboli might still occur. By comparing several studies in which markers for brain damage were used, these three major mechanisms are discussed.

**Ischemia:** During routine CPB at moderate hypothermia, a flow of 2.5 l/min m<sup>2</sup> is applied. The question arises regarding whether this flow is sufficient under the stress-inducing circumstances. During CPB a whole-body inflammatory response is induced, with release of vasoactive substances, which is often shown by hypotension. Simultaneously, a number of hormones are released, which, under physiologic circumstances, would result in an increased heart rate and subsequent increased flow. The relatively low flow during CPB has been proposed to compensate insufficiently, and thus to result in relative hypoperfusion of organs, including the brain. Although not yet proven, this could be a factor of importance to induce brain damage. Additionally, brain damage might be induced to a greater extent in patients undergoing Fallot corrections by the preceding relative hypoxemia, with SaO<sub>2</sub> of less than 85% changing into 100% saturation with concomitant generation of oxygen radicals resulting in ischemia–reperfusion damage [9].

Low temperatures seem to protect the brain, however, because a comparison of CPB with circulatory arrest in

infants at a temperature of < 18°C with continuous flow at moderate hypothermia, did not show differences in S100β release.

**Inflammation:** The systemic inflammatory reaction (SIR) is recognized as one of the factors that causes neuropsychological dysfunction after CPB. We evaluated the relationship between the SIR and S100β release.

One hundred patients undergoing coronary artery bypass grafting were studied. Inflammatory markers were determined at several time points during and after the operation. Correlation analysis between maximum levels of the different markers and S100β release were performed.

No overall association was found between the maximum levels of the inflammatory markers and S100β release. Remarkably, the concentrations of S100β were low as compared with previous published results.

In this context, the question arises regarding whether S100 β is capable of identifying patients with cerebral dysfunction after CPB. We evaluated whether perioperative release of S100β after coronary artery surgery with CPB could predict early or late neuropsychological impairment [10]. Patients underwent cognitive testing on a battery of 11 tests preoperatively, before discharge from hospital and 3 months later. No significant correlation was found between S100β release and neuropsychological measures at either 5 days or 3 months postoperatively. In this group of patients with limited release of S100β we found no evidence to support the suggestion that early release of S100β may reflect long-term neurological injury capable of producing cognitive impairment.

**Cardiotomy suction:** In order to exclude noncerebral sources of S100β no cardiotomy suction or retransfusion of shed mediastinal blood was used in the previously described study on 100 patients. The low concentrations of S100β indicate a significant contribution of noncerebral sources of S100β in previous studies, or a dominant role of cardiotomy suction blood in the induction of cerebral damage.

Despite heparinization of patients increases in markers for activation of clotting, such as prothrombin fragment 1+2 (F1+2), thrombin-antithrombin (TAT) and fibrinopeptide A (FPA), have been reported [11]. In general, most activation products are observed in the late period of the operation, which is thought to result from consumption of heparin, rewarming of the patients after a period of cooling, or to intensified pericardial suction of shed blood.

There is mounting evidence that suction blood is the major source of increased activation of the clotting system, which even enhances the clotting and fibrinolytic process after retransfusion of suction blood into the systemic circulation.

In infants a high percentage of multiple system organ failure after CPB has been observed, which correlated with increased blood activation [12]. Patients undergoing tetralogy of Fallot are considered to be more prone to blood activation than ventricle septum defect (VSD) patients, because of the more extended surgery and intensified suction in combination with increased bleeding due to pre-existing disturbed hemostasis and blood dilution during CPB. Moreover, this shed blood in infants cannot be discarded due to the low circulating volume.

Microembolic particles produced by increased clotting activity may obstruct the microcirculation of the brain. Moreover, suction blood contains fat particles, which are not removed completely by screen filters and which are also reported to be related to the occurrence of small capillary and arteriolar dilatations in the brain [13].

We found a significant correlation between the brain damage marker S100 $\beta$  and F1+2 concentrations, indicating activation of the clotting system, as well as between S100 $\beta$  and glycerol, indicating free fat in the circulation.

F1+2 was found to a higher extent in Fallot than in VSD, which corresponded with higher S100 $\beta$  concentrations.

**Conclusion:** We conclude that brain damage during CPB in infants may be induced by activation of the clotting system and by release of glycerol during operation, resulting in embolization of brain arterioles. Particularly in patients undergoing tetralogy of Fallot, this process may lead to brain damage.

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## Markers of brain cell damage related to cardiac surgery

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S100 proteins belong to a family of many small proteins [1]. The isoform S100B<sub>2</sub> is 21 kDa in size, consist of two B-chains, and is a so called EF-hand protein with the capacity to bind calcium. It is normally present in serum in very low concentrations 0.03-0.12  $\mu$ g/l, but in high concentrations both extracellular and intracellular in the brain. It has been found both in glial cells and in neurones, but is believed to be synthesized only in glial cells. The protein is neurotrophic and takes part in healing and maturation processes, but can also be a trigger for apoptosis via stim-

ulation of nitric oxide synthase (NOS) and lipid peroxidation pathways [2]. It can be analyzed in serum with a luminescence immunoassay (Sangtec100, AB Sangtec, Bromma, Sweden).

In brain damage from stroke, trauma or subarachnoidal haemorrhage, the serum concentration is associated with the volume of cellular damage and with outcome. In global anoxemia, as after successful (!) resuscitation, it is an early measure of prognosis [3]. S100 can be used, to evaluate

the cellular involvement and prognosis in patients suffering from stroke and after cardiac surgery. In stroke, peak concentrations in serum occur after about 1–3 days, depending on the heterogeneity of cell damage in focal brain lesions. It has long been known that S100 is released to the bloodstream during cardiopulmonary perfusion and that this release is associated to the duration of perfusion [4]. Whether cellular disruption is mandatory or only an impaired blood–brain barrier is sufficient for this release to occur is unclear. Expectations of a possible association between S100 levels and the neuropsychological deterioration occurring after cardiac surgery has increased the clinical interest in S100.

Reports of irregular peak levels and nonsystematical correlations to risk factors for brain damage, perfusion times or neuropsychological results led us to doubt the specificity of the protein to brain tissue alone. It now seems clear that S100 is also present in fat or mediastinal tissue. This extracerebral source contaminates the S100 levels during operation if cardiotomy suckers are used, and after surgery due to the use of autotransfusion. The biological half-life of S100 in the circulation was earlier considered to be around 2 h, but has recently been reinvestigated and found to be only 25 min. Bearing this in mind, it is still possible to use early serum levels of S100 for assessment of brain damage in conjunction with cardiopulmonary perfusion.

Preliminary findings from a long-term follow up study of patients operated on in 1996 and 1997 suggested that S100 sampled 2 days after surgery is a strong predictor of late mortality. Patients who are dismissed from surgery without any suspicion of a cerebral complication, but with an elevation of S100, seem to have a shorter life expectancy. It can be speculated that the elevated S100 in these patients represents subclinical brain injury.

Neurone-specific enolase (NSE) is another suggested marker of cerebral injury. However, as enolase is present not only in neurones, but also in erythrocytes, early increases have to be interpreted with caution. The elimination rate of free hemoglobin from the circulation is much faster than that of NSE, which is why a simple measure of

hemoglobin is hard to use for the estimation of hemolysis and erythrocytic contamination. Still, a number of reports have been published where NSE has been advocated to be a reliable marker, and I believe that there may be room for NSE as well. However, increased efforts to characterize the kinetics and possible erroneous contribution from erythrocytes have to be made first.

In children, we face other problems. The normal concentrations of S100 cannot be used in children. S100 levels are higher and it is not clear whether this is a function of imperfection of the blood–brain barrier or ongoing maturation processes in the brain. Likewise, there seem to be differences between cyanotic and acyanotic babies.

A biochemical marker of brain dysfunction/damage would of course make the evaluation of surgical techniques much easier, compared with ‘the gold standard’ of prospective neuropsychological or morphological investigations such as magnetic resonance imaging. However, it is not justified to expect congruent results with these three methods. One should instead see the three as complementary, although the biochemical marker would be an ideal and simpler screening method, both for the risk assessment in individual patients and for the assessment of new techniques. The number of published articles on the issue of biochemical markers is rapidly increasing. It is therefore reasonable to believe that some of the problems we face today will be overcome by increased research efforts.

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## Neurological complications after cardiac surgery in adults

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Although the number of patients undergoing surgery for valvular and other types of heart disease has remained fairly constant, the number undergoing coronary revascularization procedures is rising. Thanks to many technological advances over the past four decades, there has been a steady fall in both the mortality and morbidity associated with these procedures. Despite this fact, neurological

injury remains an important cause of postoperative morbidity and is responsible for an increasing proportion of perioperative deaths. Advancing age and atherosclerosis make the more than 800 000 patients a year that undergo cardiac surgical procedures worldwide that are particularly prone to neurological morbidity. Since the introduction of cardiopulmonary bypass (CPB) in the early 1950s,

the neurological sequelae of cardiac surgery have been a major concern. More recently, identification of risk factors for adverse neurological and neuropsychological outcome has allowed physical and pharmacological neuroprotective strategies to be targeted at the high-risk population.

Over the past 20 years, there has been a steady increase in the average age of patients undergoing cardiac surgery. This increase has been accompanied by a rise in both the severity of cardiac disease at the time of surgery and the reoperation rate for recurrent disease. Nevertheless, the likelihood of dying or sustaining a major complication after cardiac surgery in the late 1990s is significantly lower than in the 1950s. Not unreasonably, most patients expect to survive cardiac surgery intact, make a good functional recovery and live longer. A significant number of patients undergoing cardiac surgery will, however, suffer a periop-

erative complication involving the central nervous system (CNS).

Adverse neurological outcome from cardiac surgery is the result of damage to the brain, spinal cord and/or peripheral nerves. CNS injury ranges in severity from subtle changes in personality, behaviour and cognitive function to fatal brain injury – the cerebral catastrophe. A major neurological complication after otherwise successful surgery represents a devastating outcome for both the patient and their family. The social and economic impact is enormous.

The common occurrence of adverse CNS outcomes has resulted in enhanced interest in strategies for cerebral protection in cardiac surgery ranging from stratification of an at-risk population to management of aortic atherosclerosis, temperature and rewarming.

## Recognition and prevention of neurological complications in paediatric cardiac surgery

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Advances in surgical and cardiopulmonary bypass techniques mean that it is now possible to definitively repair the vast majority of congenital heart disease in infancy or childhood. Although the majority of survivors do not have obvious cerebral sequelae, there is increasing disquiet about the high incidence of acute neurological events in the immediate postoperative period, as well as the evidence at long-term follow-up that there are subtle cognitive and motor deficits in many.

Some children are more at risk of neurodevelopmental problems, either because of their cardiac (eg extensive aortopulmonary collaterals) or cerebrovascular (eg the propensity to large vessel dissection) anatomy or because of genetic predisposition (eg to prothrombotic disorders). The incidence may vary with the surgery (eg the Fontan operation) and the cardiopulmonary bypass technique necessary to achieve an adequate technical repair (eg low or no flow at deep hypothermia). Recognition of the population at risk will lead to prevention of serious sequelae. Data collected in adults may be misleading, and many paediatric units have developed their own practice, but recent studies

in animal models of infant surgery and in children have produced some evidence to guide management to ensure the optimal cerebral as well as cardiac outcome.

Pump flow should be maintained at least 30 ml/kg per min where possible, with inotropic support to maintain blood pressure if necessary. If pump flow must go lower or circulatory arrest is essential, thorough cerebral cooling to deep hypothermic temperatures is mandatory; a pH-stat strategy may make this easier, but an  $\alpha$ -stat strategy may be better in those operations that can be performed at moderate hypothermia. There is no evidence that the available pulsatile pumps offer an advantage. Tissue oxygenation may reach critical levels and a high haematocrit and oxygen tension may reduce the risk of significant hypoxia. There is a risk of embolization in children, which can be reduced with membrane oxygenators and careful monitoring; the role of arterial filtration remains controversial. The only protective agent that can be recommended at the present time is methylprednisolone to protect the spinal cord (eg in operations on the aortic arch). Further studies are needed in this important area.

## Neuropsychological complications after cardiac surgery in children

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Although the surgical morbidity of infants who must undergo cardiac surgery has declined, follow-up studies have identified major neurodevelopmental abnormalities in as many as 25% of survivors. The prevalence of subtle dysfunctions is likely to be even higher. An important source of morbidity may be operative events, particularly the support techniques used to protect vital organs during

cardiac repair, including deep hypothermia with either total circulatory arrest (TCA) or continuous low-flow cardiopulmonary bypass (LFB). Drawing conclusions about the central nervous system (CNS) sequelae of cardiac surgery in children has been impeded, however, by a variety of methodological limitations of many published studies, including small sample sizes, diverse cardiac

defects and ages at repair, retrospective study design, comparison of operative techniques used at different time periods, and lack of uniformity in the age at which children are followed up and in the test instruments used.

For more than a decade, our group at the Children's Hospital (Boston) has conducted studies to evaluate the CNS sequelae among infants with congenital heart lesions. This presentation focused primarily on the results to date of our single-center trial of infants with d-TGA who were randomized to undergo the arterial switch operation at less than 3 months of age using either TCA or LFB. The original cohort consisted of 171 infants (42 of whom also had a ventricular septal defect). Neurodevelopmental evaluations were completed on 155 children at 1 year of age and 158 children at 4 years of age. In addition, information was obtained on interim developmental status by means of parent-completed questionnaires when children were 2.5 years of age. Evaluations at age 8 years are ongoing and have been completed for approximately 135 children.

Our findings to date suggest two major conclusions. First, children assigned to TCA tend to have worse neurodevelopmental outcomes than do children assigned to LFB. In the perioperative period, they were at increased risk of clinical seizures; at 1 year of age, they achieved lower scores on a standardized test of motor development (Bayley Scales of Infant Development) and were at higher risk of having abnormalities on neurologic examination; at 2.5 years, they had worse expressive language development; and at 4 years of age they scored lower on tests of gross and fine motor function, and were at increased risk of oromotor apraxia and other abnormalities of speech production. Treatment group comparisons at 8 years of

age will not be made until all eligible children have been evaluated.

Our second major conclusion is that the performance of the full cohort (ie children in both treatment groups) is below expected levels in several specific neuropsychological domains, placing them at substantially increased risk of academic failure. Interestingly, on global standardized tests such as IQ, the children's scores tend to be well within the normal range, although shifted slightly toward lower values. They express substantial deficits, however, in the following areas: visual-spatial/visual-motor skills, working memory, hypothesis generation and testing, vigilance and sustained attention, motor function, and higher-order language skills (verbal fluency, generation of connected discourse). We speculate that the neurodevelopmental vulnerabilities of children who undergo cardiac surgery in infancy are most prominent on tasks that call upon so-called 'executive functions'. Such tasks require that information be held, organized, manipulated, and integrated, and that strategies be designed, implemented, and modified in service of a goal.

One possibility is that a long period of cardiopulmonary bypass, regardless of whether or not TCA is involved, is detrimental to CNS development. Data from a small non-randomized study that are consistent with this hypothesis is presented. Children with atrial septal defects (ASDs) that were closed surgically scored significantly lower than children with ASDs that were closed by means of a catheter-delivered device, particularly in terms of visual-spatial skills. A randomized trial comparing the neuropsychological sequelae of surgical and transcatheter closure of ASDs is planned.

## Free papers

### P1 **Early immunohistochemical brain overexpression of S-100 $\beta$ and increased serum level after deep hypothermic circulatory arrest in rabbits: relationship to perivascular astrocytic swelling**

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**Introduction:** Understanding the pathophysiology and neuropathological changes that might be related to brain injury after surgical cardiac procedures using hypothermic cardiopulmonary bypass (CPB) with a period of circulatory arrest (TCA) is fundamental to the development of hemodynamic and pharmacological neuroprotective interventions. Therefore, the aim of this study was to evaluate the relationship between the regional immunohistochemical expression of S-100 $\beta$  in the brain and the serum kinetic patterns in rabbits undergoing CPB with a 60-minute period of TCA, followed by reperfusion and rewarming.

**Methods:** Fourteen New Zealand rabbits (body weight  $3.1 \pm 0.25$  kg) were anaesthetised, intubated and mechanically ventilated. Four animals were not connected to the CPB and were used as controls. Ten animals were perfused after aortic and right atrial cannulation according to a uniform protocol: full-flow CPB (150–200 mL/kg per min), PCO<sub>2</sub> uncorrected for hypothermia ( $\alpha$ -stat blood gas management). After surface cooling and the establishment of a hypothermic rectal temperature of 14°C, TCA was induced for 60 min. The animals were then reperfused and rewarmed over 60 min to achieve a normal rectal temperature of 38°C. The animals were weaned from bypass and killed. The brain was immediately removed, cut in standardized sections and fixed in formaldehyde. Astrocyte reactivity was evaluated immunocytochemically by the use of monoclonal mouse primary antibodies to S-100 $\beta$  protein (DPC Immustain, code CKS1S). The serum con-

centrations of S-100 $\beta$  were analysed using a commercially available LIA kit (Byk-Sangtec, Dietzenbach, Germany)

**Results:** In all experimental animals a significant increase of the serum concentration of the astrocytic protein S-100 $\beta$  was found immediately after reperfusion and the termination of CPB. In comparison with the control animals increased expression of S-100 $\beta$  was found in the astroglial cells and astrocytic dendrites in the perivascular regions. A distinctive pathognomonic morphological cell injury that exhibited a marked swelling of the perivascular astrocytic cell dendrites were also found by electron microscopy from the cerebral capillaries in the hippocampus in the experimental animals. There were less signs of neuronal cell injury of neurons in the hippocampus formation.

**Conclusion:** Astrocytic activation and S-100 $\beta$  overexpression seem to precede the neurodegeneration following global cold ischemia. The marked perivascular cell swelling may support the assumption of reperfusion injury of the astroglial cell complex that forms the blood–brain barrier (BBB), which may be indicative of the source of the released S-100 $\beta$  into the bloodstream. The early significant increased serum levels of S-100 $\beta$  may provide information on possible ongoing related injury in neuronal cell in patients after cardiac surgery as well, who potentially benefit from neuroprotective interventions. The function and exact release mechanism of the S-100 $\beta$  through the BBB into the blood in this respect, however, need further explanation.

### P2 **Delayed recovery of cerebral oxygenation and cerebral blood flow after profound hypothermic circulatory arrest**

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**Objective:** More recent studies have suggested that deep hypothermic cardiocirculatory arrest (DHCA) results in metabolic abnormalities with detrimental effects on enzyme function and membrane stability after rewarming, which may be associated with an increased risk for neurocellular injury. We evaluated whether brain tissue oxygen pressure (ptiO<sub>2</sub>) showed sign of cellular hypoxia during cardiopulmonary bypass (CPB) with 1 h of DHCA and monitored changes in global cerebral blood flow (CBF) in a rabbit model.

**Methods:** Ten New Zealand white rabbits (body weight  $2.5 \pm 0.5$  kg) were included in this study. Anesthetized and ventilated rabbits were placed on CPB ( $\alpha$ -stat strategy) utilizing a membrane oxygenator with nonpulsatile pump flows of 150–200 ml/kg body weight per min for induction of DHCA by active cooling to 15°C rectal temperature. Rewarming was started after 1 h of complete DHCA. Brain tissue oxymetry with a microsensor catheterprobe (Licox) in the frontoparietal cortex and CBF-measurement using the hydrogen clearance technique were obtained at base-

line, during cooling, resumption of CPB and systemic rewarming, and finally while off CPB and with stable hemodynamics.

**Results:** Under baseline conditions,  $\text{ptiO}_2$  was  $38 \pm 15$  mmHg and changed to  $40 \pm 11$  mmHg before the onset of DHCA. The CBF was lower than baseline before DHCA. During circulatory arrest the  $\text{ptiO}_2$  decreased within 15 min to  $14 \pm 5$  mmHg, after 30 min to  $5 \pm 1$  mmHg and after 40 min to zero. Neither the  $\text{ptiO}_2$  nor CBF recovered fully during rewarming. After rewarming and termination of CPB the  $\text{ptiO}_2$  ( $25 \pm 6$  mmHg versus baseline  $38 \pm 15$  mmHg;  $P < 0.05$ ) and CBF ( $43 \pm 8$  versus  $68 \pm 11$  ml/100g per min;  $P < 0.05$ ) were significantly reduced compared with pre-CPB values. Arterial and

jugular-venous lactate levels increased after rewarming ( $P < 0.05$ ) and corresponded to the appearance of anaerobic metabolism.

**Conclusion:** These observations suggest a persistent neurocellular function suppression after rewarming and a generated low-flow situation leading to transient regional cerebral tissue hypoxia events. Delayed brain tissue reoxygenation after DHCA may be attributable to excessive metabolic demand (compensation of an oxygen debt), inadequate tissue blood redistribution with reduced capillary perfusion, or oxygen utilization disturbances (mitochondrial dysfunction, reversibly inhibition of enzyme activity, immunoreactivity for specific proteins and cytochrome oxidase).

### P3 Influences of pre-, peri- and postoperative risk factors in neonatal cardiac surgery on neurodevelopmental status in preschool-age children

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**Objective:** Neurodevelopmental outcome in preschool-age after neonatal arterial switch operation, in relation to prospectively evaluated cerebral risk factors, including durations of the support strategies and serum levels of the marker enzyme neuron-specific enolase is assessed.

**Methods:** Thirty-three unselected children operated on as neonates with combined deep hypothermic circulatory arrest and low flow cardiopulmonary bypass were examined at an age of 3.0–4.6 years [ $3.6 \pm 0.5$  (mean  $\pm$  standard deviation)]. The control group for developmental outcome consisted of 32 age-matched healthy children, who were 3.0–4.8 years [ $3.8 \pm 0.6$  (mean  $\pm$  standard deviation)] of age. Evaluation of socioeconomic status and a standardised test comprising all areas of child development (Vienna developmental test), including scores of motor and cognitive functions, perception, language, learning and behaviour, were carried out in patients and controls, and clinical neurological status was assessed in patients. Results of patients were related to those of the control group and to pre-, peri-, and postoperative cerebral risk factors of the control group and to pre-, peri-, and postoperative cerebral risk factors as described in the context.

**Results:** Neurological impairment was more frequent (6.1%) than in the normal population. Compared with published norms, complete developmental score and the subtests for motor function, visual perception and visual motor integration, learning and memory, cognitive function, language, and socioemotional functions were not dif-

ferent. Compared with the control group, complete developmental score, cognitive score and language were reduced ( $P < 0.01$ ), but socioeconomic status was significantly lower in the patient group ( $P = 0.0001$ ). Motor function was weakly, but significantly inversely related to the duration of circulatory arrest (Pearson correlation coefficient  $-0.37$ ;  $P = 0.049$ ), but not to the duration of bypass. The other developmental parameters were not related to the duration of the support techniques. Serum levels of the biochemical marker neuron-specific enolase, although significantly elevated at the end of bypass ( $P = 0.0002$ ) and 4 h after surgery ( $P = 0.0012$ ) compared with preoperative values, were not correlated to developmental test results. No correlation was found between the test results and the following cerebral risk factors: protracted birth, perinatal asphyxia, peri- and postoperative cardiocirculatory insufficiency, enhanced cerebral echogenicity in the choroid plexus and ventricular system, and clinical seizures.

**Conclusions:** Neonatal arterial switch operation with combined circulatory arrest and low flow bypass is associated with increased neurological impairment. Developmental status, based on formal testing of motor, cognitive, language and behavioural functions, however, was not found to be different from a that in normal population. Outstanding results in our control group are probably related to differences in socioeconomic status. Perioperative serum levels of the neuron-specific enolase in neonates, in our experience, are not a valid marker with respect to later developmental outcome.



#### **P4 Predictors of cerebrovascular accident and transient ischemic attack after myocardial revascularisation**

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**Objective:** To analyze the occurrence of postoperative neurological complications, defined as cerebrovascular accident (CVA) and transient ischemic attack (TIA), after myocardial revascularisation, in relation to pre- and perioperative variables.

**Methods:** We analyzed the pre-, peri-, and postoperative data of 3834 patients who underwent primary isolated bypass grafting between January 1987 and December 1995. Unifactor risk analysis was used to identify which of the variables was a risk factor for neurological complications. Which of these variables contribute independently was analysed using multifactor risk regression analysis. A  $\chi^2$  test was used to identify which independent predictor changed with time. The studied period of 9 years was divided into three time cohorts of 3 years each.

**Results:** The incidence of neurological complications was 32/3834 patients (0.8%), and increased from 0.6% over 0.8% to 1.1% during studied period. Unifactor analysis identified the following as risk factors: age >75 years

( $P=0.008$ ), peripheral vascular atherosclerosis or operation (carotid;  $P=0.002$ ), preoperative neurological pathology ( $P=0.003$ ), perioperative detected aortapathology ( $P<0.0001$ ) and perioperative myocardial infarction ( $P=0.01$ ). Multifactor risk regression analysis identified preoperative neurological pathology ( $P=0.02$ ), perioperative detected aortic pathology ( $P=0.0001$ ), and a perioperative myocardial infarction ( $P=0.04$ ) as independent predictors for postoperative neurological complications. In the three time cohorts there was a statistically significant change of prevalence for preoperative neurological pathology ( $P=0.02$ ) and perioperatively detected aortic pathology ( $P=0.001$ ).

**Conclusion:** Preoperative neurological pathology, perioperative myocardial infarction, but primarily aortapathology were identified as independent risk factors for postoperative CVA and/or TIA after myocardial revascularization. On the basis of these results the use of transoesophageal echocardiography for detection of aorta pathology in risk patients and single aorta cross-clamping should be strongly advised.

#### **P5 Cardiopulmonary bypass using heparin surface treatment: influence on memory and neurological deviations**

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**Objectives:** Cerebral dysfunction associated with cardiac surgery and cardiopulmonary bypass (CPB) manifested as focal ischemic injury and diffuse encephalopathy is a devastating complication. Emboli from the surgical field and hypoperfusion have been suggested as possible causes. The present investigation was undertaken in order to investigate the role of heparin coatings in CPB as means of ameliorating neurological trauma.

**Methods:** Three hundred patients admitted for routine aorta-coronary bypass surgery were prospectively randomized into four groups based on Carmeda Bioactive Surface and Baxter Duraflo II coatings (ACT >250 s) for CPB, each with an assigned uncoated control (ACT >500 s). Outcome was determined as clinical neurological deviations, release of S100, perioperative implicit and explicit memory performances, with a questionnaire follow up after 4 months.

**Results:** The incidence of clinical neurological deviations ranged from 4 to 8%, with no intergroup differences ( $P=0.738$ ). Concentration of S100 was significantly ( $P=0.001$ ) elevated ( $0.76 \pm 0.03 \mu\text{g/l}$ ) in all four groups during CPB and remained so ( $0.39 \pm 0.03 \mu\text{g/l}$ ) 7 h postoperatively. A notably higher release of S100 per CPB was observed in the Baxter control group ( $P<0.05$ ). No perioperative differences in implicit and explicit memory function between groups were detected. At 4 months, patients in the Baxter control group reported a more depressed memory ( $P<0.05$ ) than did those in other groups. Memory function as experienced by next of kin demonstrated no intergroup differences, however.

**Conclusions:** The role of heparin coating in CPB as a tool to prevent memory dysfunction and neurological deviations is not conclusive, despite a less favourable outcome in terms of S100 release and subjective rating of memory function for patients in the Baxter uncoated control group.

## P6 Neuropsychologic dysfunction after CABG: standard cardiopulmonary bypass versus off-pump CABG

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**Objectives:** With the introduction of lesser invasive strategies in cardiac surgery that do not require cardiopulmonary bypass (CPB), it is expected that the incidence of postoperative neuropsychologic disorders will decrease. The difference in effect on postoperative neuropsychologic dysfunction in patients undergoing coronary artery bypass grafting (CABG) using CPB or off-pump surgery is investigated.

**Method:** 10 patients undergoing standard CABG with CPB (CABG-group; nine male/one female) and 17 patients receiving off-pump CABG without CPB (OPCAB-group; 13 males/four females) were evaluated preoperatively, 7 days postoperatively and 1 month postoperatively. The CDR computerised test battery was administered and included single and choice reaction time, number vigilance, memory scanning, and word and picture recognition. Overall cognitive ability within and between the two groups was analyzed using one sample *t*-tests and analysis of variance.

**Results:** Mean age was similar [CABG 61.2 years, standard deviation (SD) 9.1; OPCAB 58.0 years, SD 8.9;

*P*=not significant). Preoperative left ventricular function was similar (ratio impaired/good: CABG 3/10 and OPCAB 3/17; *P*=not significant). In the CABG group, two patients had prior cardiac surgery. The average number of distal anastomosis was 3.4 (SD 0.7) for CABG and 1.4 (SD 0.5) for OPCAB (*P*<0.001). Preoperatively there were no significant differences between the two groups on any of the tasks. At both 7 and 30 days postoperatively a significant difference in overall cognitive function between the CABG and OPCAB group was observed. In the CABG group a pattern of cognitive function decline was seen at 7 days postoperatively, but this resolved at 30 days. In the OPCAB group improvement in cognitive function was seen at both 7 and 30 days postoperatively.

**Conclusion:** CABG with the use of CPB is associated with transient cognitive functional decline that is not apparent using OPCAB. The increasing use of operative techniques that do not require CPB is likely to reduce neuropsychologic dysfunction. Improvement in cognitive ability after OPCAB remains puzzling, and exploration of unknown factors that may cause this is warranted.

## P7 Norwood on the beating heart: two cases with continuous cerebral and myocardial perfusion

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**Objectives:** The Norwood procedure is routinely performed in circulatory arrest. The degree of neurological injury from circulatory arrest is directly related to the duration of arrest time. We report a technique of selective cerebral and myocardial perfusion with the aim to reduce ischemic damage to brain and heart.

**Method:** We performed a modified Norwood procedure on two neonates (5 and 29 days old) with single ventricle physiology, coarctation, and hypoplastic aortic arch. In both cases the ascending aorta was of adequate size for arterial cannulation. We cannulated the ascending aorta and clamped the aortic arch distally to the innominate artery.

Aortic arch repair was performed in moderate hypothermia with the heart beating, while both the brain and the heart were selectively perfused.

**Results:** The time period of selective cerebral and myocardial perfusion was 56 and 61 min, respectively. Both children recovered uneventfully without neurological or myocardial complications. Follow up time was 5 months.

**Conclusion:** The Norwood procedure can successfully be performed without total circulatory arrest, but with protection of both brain and heart by continuous, selective perfusion.

## P8 Cerebral mitochondrial and regional haemoglobin saturation patterns during and after profound hypothermic circulatory arrest in neonatal piglets

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**Introduction:** Total circulatory arrest (TCA) in deep hypothermia used in corrective surgery of complex car-

diovascular malformations in children has been claimed to cause brain injury and altered psychomotor development.

Near infrared spectroscopy (NIRS) allows *in vivo* determination of changes in cerebral oxygenated (HbO<sub>2</sub>), deoxygenated (Hb), and total haemoglobin (Hbt; the sum of Hb+HbO<sub>2</sub>). Relative changes in the redox state of cytochrome oxidase (cyt.aa3), the terminal enzyme in the mitochondrial respiratory chain, may provide information about the availability of oxygen at cellular level. The new tissue oxygenation index (TOI) provides information on the global tissue oxygenation. Measurement of protein S-100 is used as a marker of astroglial cell injury. Thus, change in intravascular and intracellular oxygenation states were measured by NIRS during and after TCA in a neonatal piglet model.

**Method:** Fourteen neonatal piglets (age > 10 days, weight 1.9 ± 0.25 kg) were anaesthetised, intubated and mechanically ventilated. Cardiopulmonary bypass (CPB) was performed using a uniform perfusion method: full flow CPB (200 ml/kg per min), minimal temperature (14 ± 1.3°C), pCO<sub>2</sub> uncorrected for hypothermia ( $\alpha$ -stat method). TCA was induced after establishment of a hypothermic rectal temperature of 14–16°C. After warm reperfusion, the

animals were weaned and monitored for 8 h. Cerebral oxygenation monitor (Hamamatsu 300, Herching-Deutschland) was used to obtain online measurement of cerebral oxidation parameters. Simultaneous hemodynamic parameters were continuously documented.

**Results:** In all animals significant initial increase in HbO<sub>2</sub>, Hbt and TOI, and fall in cyt.aa3 and Hb were found during cooling on bypass. After induction of TCA in deep hypothermia a significant initial continuous parallel decrease in HbO<sub>2</sub>, Hbt, TOI and cyt.aa3, and increase in Hb, followed by a plateau trend without further significant change, were found. An initial restoration of the oxidation parameters was associated with reperfusion and rewarming. However, after the end of reperfusion the oxygenation parameters, particularly cyt.aa3 and TOI were significantly reduced for 60 min.

**Conclusion:** Distinct related changes in intravascular and intracellular cerebral oxygenation patterns were found during cooling and after TCA. The delayed recovery of cyt.aa3 signal after TCA may indicate increased oxygen demand after hypothermic TCA.

## P9 Na<sup>+</sup>/K<sup>+</sup>-ATPase activity in the erythrocytes of infants after normothermic and deep hypothermic low-flow cardiopulmonary bypass

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**Objectives:** Previous studies reported impairments of membrane-bound ionic pumps as a result of membrane damage and changes in brain tissue enzyme activity correlated with the progression of cerebral morphological changes and increased permeability of brain microvessels. The aim of the present study was to assess whether an alteration of Na<sup>+</sup>/K<sup>+</sup>-ATPase activity after normothermic and deep hypothermic low-flow cardiopulmonary bypass (CPB) is also detectable on paediatric erythrocytes (RBC) membranes in cerebral venous blood samples.

**Method:** After IRB approval and informed consent, 20 infants and children were grouped as follows: 1, deep hypothermic low-flow cardiopulmonary bypass (DHCPB; n=10, rectal temperature 16.7 ± 3.1°C), and 2, normothermic CPB (rectal temperature 35.2 ± 0.8°C). Age and weight were 3.2 ± 2.9 months and 3.8 ± 0.5 kg for group 1, and 6.9 ± 1.4 months and 5.8 ± 1.9 kg for group 2. Two hundred µl heparinized blood samples were obtained from an jugular bulb catheter before the induction of CPB, at 1 h (immediately after CPB termination), and subsequently at 2, 3 and 4 h postoperatively. The protein content of haemoglobin-free erythrocyte membranes (ghosts) was

determined and the linear rate of NADH-oxidation was measured for 10 min at 340 nm. The enzyme activity was calculated from the difference of NADH-oxidation in the absence and in the presence of 1 mmol/l ouabain. One unit Na<sup>+</sup>/K<sup>+</sup>-ATPase represents 1 nmol ATP degradation/mg protein per h.

**Results:** The Na<sup>+</sup>/K<sup>+</sup>-ATPase activity pre-CPB was higher in the DHCPB-group (419 ± 15.2 versus 329 ± 20.5). In the early postoperative phase the Na<sup>+</sup>/K<sup>+</sup>-ATPase activity was restored to prebypass levels in group 2, but remained decreased in group 1 (P<0.05) compared with prebypass. Plasma monovalent cationic levels did not alter significantly during the observation period.

**Conclusion:** The decrease in Na<sup>+</sup>/K<sup>+</sup>-ATPase activity of RBC membranes in infants during the early postoperative period after deep hypothermic CPB is detectable and indicate an alteration of cell membrane proteins/structures (possibly due to hypoxic stress or lipid peroxidation). The RBC membrane Na<sup>+</sup>/K<sup>+</sup>-ATPase measurements appears to be an sensitive marker of subtle cerebral deterioration.

**P10 The effect of continuous treatment of the NO liberator sodium nitroprusside on the serum kinetics of the brain marker protein S-100 in infants and children undergoing corrective cardiac surgery with cardiopulmonary bypass**

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**Introduction:** Measurement of protein S-100 in serum – an astrocytic calcium-binding protein – may provide information on transient astroglial cell activation and disintegration of the related blood–brain barrier (BBB) due to oxidative stress during and after cardiopulmonary bypass (CPB). Conflicting results *in vitro* have been reported concerning the neuroprotective effect of sodium nitroprusside. We evaluated the effect of continuous treatment of the nitric oxide (NO) liberator sodium nitroprusside on the serum kinetics of protein S-100 in infants and children after corrective cardiac surgery.

**Method:** Data on 99 children, who were treated with sodium nitroprusside (median age 2.7 months, range 0.03–81.8 months), and on 92 children without treatment (median age 5.0 months, range 0.03–80 months) were retrospectively analyzed. Sodium nitroprusside infusion was started after the induction of anaesthesia and continued during and after termination of CPB with various doses according to the hemodynamic status until the 48<sup>th</sup> postoperative hour. The serum concentrations of S-100 were analyzed using a commercially available LIA kit (Byk-Sangtec; Dietzenbach-Germany).

**Results:** There were no significant differences in the bypass data between the nitroprusside-treated and nontreated

group (Table 1). In comparison with the prebypass values, a significant similar increase in the concentration of protein S-100 was found 2 h after the termination of CPB in the nitroprusside-treated and nontreated infants, which decreased during the following 48 postoperative hours. However, significantly lower postbypass serum levels of S-100 were found in the sodium nitroprusside-treated group after 24 h treatment ( $P=0.0005$ ). The prebypass serum concentrations of protein S-100 correlated significantly with bypass time ( $r=0.57$ ;  $P=0.0001$ ), cross-clamping time ( $r=0.50$ ;  $P=0.001$ ) and age at operation ( $r=-0.41$ ;  $P<0.0001$ ). No significant relationship was found between the intra- and postoperative doses of natrium nitroprusside and the postbypass serum levels of S-100.

**Conclusion:** In this study the significant elevation of serum levels of the protein S-100 may indicate increased astroglial cell reactivity and increased S-100 passage to the bloodstream. Longer lasting treatment with the NO liberator sodium nitroprusside seemed to decrease the release of S-100 into the bloodstream and may have delayed protection on the BBB. The neurological significance of such observation, however, should be evaluated in further follow-up studies, including additional neurophysiological and neurodevelopment tests.

**Table 1**

Concentration of protein S-100 (µg/l)				
	Prebypass	2 h after bypass	24 h after bypass	48 h after bypass
Nitroprusside-treated (n=99)	0.55 ± 0.36	2.5 ± 2	1.13 ± 1.0	1.0 ± 1.4
Nitroprusside nontreated (n=92)	0.59 ± 0.4	2.8 ± 2	1.99 ± 2.1	1.5 ± 2.3
Mann–Whitney test	NS	NS	$P=0.0005$	$P=0.08$

Values are expressed as mean ± standard deviation. NS, not significant.

**P11 Determination of perioperative neurologic complications in cardiac surgery by S100B and neuron-specific enolase**

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**Introduction:** There is still no appropriate method to reliably determine neurologic complications induced by extracorporeal circulation (ECC). S100B and neuron-specific enolase (NSE) could be used as potential markers for a perioperative neurologic dysfunction.

**Objective:** To evaluate changes in S100B and NSE levels in patients after ECC and the correlation between preoperative and postoperative neurologic status

**Patients and methods:** Thirty consecutive patients (26 male/four female, median age 63.3 ± 9.9 years, range 44–82 years) underwent coronary artery bypass grafting. The neurologic status was examined 1 day preoperative and 1–2 days after the ICU. Exclusion criteria were as follows: neurologic disorders, liver and/or kidney dysfunction, history of a neoplasm or drug and/or alcohol abuse. Blood samples were collected at the following times: before anesthesia; at the end of ECC; and 6, 24 and 48 h

postoperatively. Immunoluminometric assays [LIA-mat Sangtec (S100 and NSE)] were used to detect serum marker levels.

**Results:** S100B and NSE were normal before ECC in 29 patients. In one, S100B was preoperatively high without abnormal neurologic status before and after surgery. S100B showed a peak at the end of ECC (mean 3.56 µg/l), and mean NSE 6 h after the operation (mean 28.25 µg/l). Nineteen patients (63.4%) had still high S100B 48 h after surgery (0.42 µg/l). In 14 patients

(46.6%), NSE was high (22.4 µg/l) during first 48 h. Two patients (6.6%) with elevated markers showed neurologic symptoms: focal seizure and psychosis ( $n=1$ ), hemiplegia ( $n=1$ ).

**Conclusion:** There are remarkable changes in S100B and NSE during operations with ECC. Even minor neurologic abnormalities after cardiac surgery can be detected by LIA. Neurologic disorders lead to elevated serum marker levels. Patients with elevated markers must not have clinically relevant neurologic symptoms.

## P12 Corticosteroids reduce neuron-specific-enolase liberation after cardiopulmonary bypass in men

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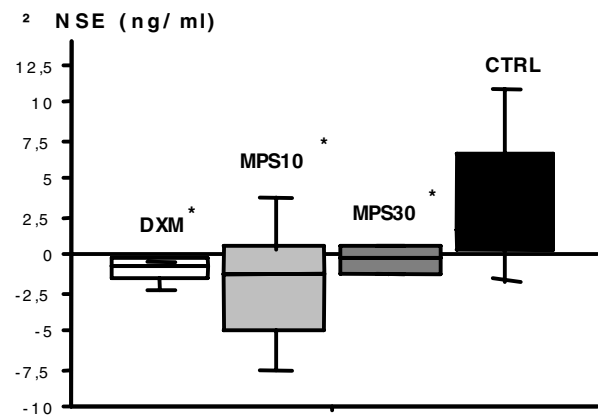
**Introduction:** Cardiopulmonary bypass (CPB) is associated with a significant morbidity due to central nervous system dysfunction [1]. Part of this damage may be related to the inflammatory response generated by CPB [2]. Neuron-specific enolase (NSE) is a neuron-specific enzyme that is liberated during brain injury and has recently been proposed as a marker of cerebral ischemia after CPB [3]. Because corticosteroids significantly reduce the inflammatory reaction to CPB [4], we investigated whether pretreatment with corticosteroids can influence the liberation of NSE during CPB.

**Materials and method:** After institutional approval, 45 patients scheduled for nonemergency coronary artery bypass grafting (CABG) with CPB were divided into four groups: the control group (CTRL;  $n=17$ ) received no corticosteroids; the DXM group ( $n=7$ ) received 2 mg/kg dexamethasone; and the MPS10 group ( $n=14$ ) received 10 mg/kg and the MPS30 ( $n=7$ ) group received 30 mg/kg methylprednisolone intravenously 2 h before surgery. CPB was conducted under moderate hypothermia (29–30°C) using a cold crystalloid cardioplegia and a nonpulsatile flow. Anaesthesia consisted of a continuous infusion of sufentanil, midazolam and pancuronium. No aprotinin was used. We measured NSE levels before induction of anaesthesia and 4 h after CPB. For each patient we calculated the change in NSE concentration as follows: NSE (at 4 h)–NSE (baseline). We also measured tumor necrosis factor (TNF) and interleukin (IL)-8 at the same time. There were no differences between the groups regarding age, duration of CPB, aortic cross-clamping time or number of grafts.

**Results and discussion:** The CTRL group showed a significant increase in NSE after CPB, whereas in all three corticosteroid groups NSE was significantly lower (Fig. 1).

TNF and IL-8 liberation were significantly and equally reduced in all three treatment groups. This suppression

Figure 1



Neuron-specific enolase (NSE) levels. The control group (CTRL;  $n=17$ ) received no corticosteroids; the DXM group ( $n=7$ ) received 2 mg/kg dexamethasone; and the MPS10 group ( $n=14$ ) received 10 mg/kg and the MPS30 ( $n=7$ ) group received 30 mg/kg methylprednisolone intravenously 2 h before surgery. \* $P < 0.05$  versus CTRL group, by Mann–Whitney U-test.

of the inflammatory response might lead to less neutrophil adhesion and migration, resulting in less tissue damage by proteolytic enzymes and oxygen-free radicals.

**Conclusion:** Corticosteroids, even at moderate doses, are able to reduce the amount of NSE liberation during CPB. This may indicate less brain injury during CPB. Whether this reduction in NSE liberation translates into improved neurological outcome remains to be studied.

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