Effects of propofol on cerebral oxygenation during cardiopulmonary bypass in children

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Purpose: Neurologic complications occur following cardiopulmonary bypass surgery. We conducted a randomized, controlled, single-blind study to determine the effect of propofol on the redox status of cytaa₃, and to evaluate its potential for decreasing neurologic complications.

Methods and Materials: Twenty-four children (median age: 3.3 yr; median weight: 14.4 kg) scheduled for elective cardiopulmonary bypass surgery were assigned to either the experimental group (Group P, given sufficient propofol to eliminate brain electrical activity as measured on EEG (i.e. burst suppression)) or the control group (Group C, no propofol). Near infrared spectroscopy data were collected at one-second intervals throughout the surgical procedures. Pre- and postoperative neurologic examinations were completed by a physician blinded to the group to which the patient was assigned. Change in cytochrome aa₃ data at 10-min intervals (10, 20, 30, 40 min) following start of bypass were compared between groups by repeated measures analysis of variance.

Results: The patterns of change in redox state of cytochrome were different between the two groups ($P < 0.002$). The pattern of change within Group P was similar to that in hypothermic patients in Group C. There were correlations between change in cytaa₃ redox status and temperature in the control subjects. There were no gross neurologic complications in either group.

Conclusions: Propofol appears to stabilize the energy supply/demand equilibrium of the brain during cardiopulmonary bypass surgery and thus theoretically could reduce the incidence or severity of neurologic complications.

Objectif : Des complications neurologiques peuvent survenir à la suite de circulation extracorporelle (CEC) pendant une intervention chirurgicale. Nous avons réalisé une étude randomisée, contrôlée et à l'insu, afin de déterminer l'effet du propofol sur l'état redox du cytochrome aa₃ et d'évaluer sa capacité à réduire les complications neurologiques.

Méthode : L'étude a porté sur 24 enfants (âge moyen : 3,3 ans; poids moyen : 14,4 kg) qui devaient subir une intervention avec CEC. Ils ont reçu, dans le groupe expérimental P, suffisamment de propofol pour éliminer l'activité électrique cérébrale comme l'indiquait l'EEG (c.-à-d. la suppression des bouffées du tracé EEG). Le second groupe, témoin (T), n'a pas reçu de propofol. Les données spectrographiques près de l'infrarouge ont été recueillies à une seconde d'intervalle tout au long de l'opération. Un examen neurologique préopératoire et postopératoire a été fait par un médecin impartial. La modification des données sur le cytochrome aa₃, enregistrées à 10 min d'intervalle (10, 20, 30, 40 min) après le début de la CEC, a été comparée entre les groupes par des analyses de variance pour mesures répétées.

Résultats : Les modèles de changement d'état redox du cytochrome ont été différents d'un groupe à l'autre ($P < 0,002$). Le modèle de changement dans le groupe P a été similaire à celui qu'on a observé chez les patients hypothermiques du groupe T. On pouvait établir des corrélations entre le changement d'état du cytochrome aa₃ et la température chez les sujets témoins. Aucune complication neurologique importante n'est survenue dans un groupe ou l'autre.

Conclusion : Le propofol semble maintenir l'équilibre entre l'offre et la demande d'énergie cérébrale pendant une intervention chirurgicale avec circulation extracorporelle. Il pourrait ainsi réduire, en théorie, l'incidence ou la sévérité des complications neurologiques.

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SINCE the inception of open heart surgery more than 40 yr ago, enormous strides have been made in improving cardiopulmonary bypass (CPB) technology and operative techniques with a resultant progressive decrease in mortality and morbidity. While these advances have improved overall surgical outcome, repair of congenital cardiac lesions performed during hypothermic cardiopulmonary bypass with or without total circulatory arrest is still associated with considerable short- and long-term neurological damage.¹⁻⁵ The reported incidence of neurological complications of open heart surgery varies widely ranging from 7 to 61% for transient and from 1.6 to 23% for permanent complications.^{6,7} Recent reports concerning infants undergoing cardiopulmonary bypass surgery with deep hypothermia and circulatory arrest puts the figure at 25% for permanent neuropsychological injury.⁸

Neurologic damage associated with cardiac surgery in children is partly related to inadequate tissue oxygenation. Therefore, techniques designed to optimize cerebral oxygenation are continually being developed. The goals of these "cerebral protection" techniques are to maximize oxygen availability and/or minimize the brain's requirement for oxygen. Maximizing oxygen availability involves optimizing the oxygen saturation of the blood, and cerebral blood flow. Minimizing the oxygen requirement involves decreasing the metabolic rate in the brain. This is achieved by cooling (hypothermia) or by decreasing the cerebral electrical activity with anesthetic agents. Barbiturates and thiopental can achieve electrical silence on electroencephalography (EEG), but the doses required are large, and the side effects, particularly the effects on blood pressure, are undesirable.^{9,10}

Propofol is a sterically-hindered phenol (2,6-diisopropylphenol) that was introduced in 1989.¹¹ It has a very short half-life with a short postoperative recovery period. It also appears to have anti-emetic and positive mood-altering properties¹² making its use as an anesthetic agent attractive. Propofol's ability to eliminate cerebral electrical activity, and thereby decrease the metabolic demands of the brain, is its principal attraction in cardiopulmonary bypass surgery.^{11,12} However, propofol also appears to decrease cerebral blood flow,^{13,14} although it does not appear to alter lactate and glucose metabolism.¹⁴

In adults undergoing cardiopulmonary bypass surgery, propofol, used to achieve electrical silence on EEG (burst suppression), reduces cerebral blood flow, oxygen delivery and metabolic rate.¹⁵ In children undergoing cardiopulmonary bypass surgery, the use of propofol to achieve electrical silence was associated

with decreased systemic oxygen uptake (i.e. decreased metabolic rate at the terminal end of the electron transfer chain), with decreased glucose and cortisol concentrations,¹⁶ but no increase in serum lactate concentrations.¹⁷

There have been no studies in children receiving propofol to evaluate the status of cerebral oxygenation at the cellular level. Using the recently-developed, non-invasive technique of near infrared spectroscopy (NIRS), changes in the concentrations of three substances (chromophores) that absorb light in the near infrared region can be monitored continuously.¹⁸⁻²⁰ These chromophores, which are indicators of tissue oxygenation, are oxy- and deoxy- hemoglobin (HbO₂ and Hb, respectively) and the oxidized form of cytochrome aa₃ (cyt). Cytochrome aa₃, embedded in the wall of the mitochondria within the cells, is the terminal enzyme in the electron transfer chain, and thus indicates the status of oxygenation at the cellular, rather than circulatory, level. Changes in the concentration of oxidized cytochrome aa₃ represent a shift in the equilibrium between oxidized and reduced cytochrome aa₃. As in any other chemical equilibrium, this may reflect changes in a variety of factors including concentration of the active components (in this case oxygen and reduced cytochrome c), pH, and temperature. In essence, measuring cytochrome aa₃ monitors cellular wellbeing as affected by oxygen delivery, energy supply (glucose or other substrate), pH, and temperature.

This study was designed to test the hypothesis that propofol, administered to maintain cerebral electrical silence during cardiopulmonary bypass surgery would alter the magnitude or rate of change of redox status of cytochrome aa₃.

Method

This prospective, randomized, single-blinded study was approved by the University of British Columbia Ethics Review Board. Children who were scheduled for elective repair of atrial or ventricular septal defects (ASD or VSD), who were <16 yr old, and whose parents provided informed consent, were randomly assigned to either the experimental group (Group P) or control group (Group C). Children with a history of seizures, and children with Downs syndrome were excluded from the study. There were 24 children enrolled in the study, 11 in Group P and 13 in Group C.

Group P received sufficient propofol (see below) to eliminate cerebral electrical activity approximately two minutes prior to cooling. Group C did not receive propofol. The experiment did not use a double blinded design since the anesthesiologist administering the

propofol needed to be able to adjust the dosage to maintain cerebral electrical silence. Management of CPB was similar in both groups, and hypothermia was used as required. Surgical procedures were not dictated by the protocol.

Both groups received the same anesthetic protocol with the exception of the propofol. Anesthesia was induced with 3 to 6 mg·kg⁻¹ thiopental, and pancuronium, vecuronium or rocuronium was given as a muscle relaxant. Anesthesia was maintained with 25 to 100 µg·kg⁻¹ fentanyl and isoflurane up to 2% at the anesthesiologist's discretion. Nitrous oxide was not used, since it has been shown to increase cerebral metabolic rate.¹⁶ The pH was not actively managed, but allowed to change with temperature.

Near infrared spectroscopy (NIRS) was initiated in the operating room following induction of anesthesia. The method used was similar to that described by other investigators.^{18,21,22} We used a Hamamatsu NIRO 500 (Hamamatsu Photonics KK, Hamamatsu City, Japan), a commercially available near infrared spectroscopy unit which emits light at four wave lengths (777, 828, 848, and 910 nm) from laser diodes and directs them into the head through a fibre-optic bundle. The optodes were positioned 30 mm apart, laterally over the frontal region to avoid potential interference from the sagittal sinus and temporalis muscle. Light emerging from the head was conveyed through another fibreoptic bundle to a photomultiplier tube. The ends of the fibres (optodes) were fixed to the scalp with elastic tape. Background light was excluded by an opaque bonnet.

Cerebral oxygenation (via NIRS), temperature (nasopharyngeal and rectal), 2-lead EEG, central venous pressure, end tidal CO₂, and blood pressure were monitored continuously throughout the procedure. Pulmonary artery or left atrial pressure were monitored when required.

In Group P, two minutes before cooling, a bolus of 4 mg·kg⁻¹ propofol was given, followed by an infusion of 50 to 350 µg·kg⁻¹·min⁻¹, sufficient to maintain electrical silence on EEG at the target temperature. The infusion was discontinued at the beginning of rewarming.

Throughout the surgical procedure, event times were recorded manually by the anesthesiologist and the NIRS operator. Events were also recorded by placing a marker in the NIRS data stream. NIRS data were recorded using the manufacturer's software, as raw optical densities and then converted to changes in concentration using a standard algorithm,²³ and a consistent differential pathlength of 5.0, a median value of those reported in the literature for adults (6.26 ± 0.88) and infants (3.78 ± 31).^{24,25} The NIRS data were eval-

uated in terms of absolute change in concentration of oxidized cytochrome aa₃. Data manipulation, graphing, and statistics were conducted using QuattroPro8.0.

A standard clinical neurological examination was conducted by a pediatrician blinded to group assignment. The neurological assessment was completed as part of the preoperative evaluation and at the time of the first out-patient follow-up at approximately three months. Neuropsychologic testing was not done.

The groups were compared according to age, type of surgery, duration of cardiopulmonary bypass, and sex.

Because NIRS provides absolute change, the zero point is arbitrary. For comparison, data sets were translated, without rotation or scale change, to a reference point of the period immediately prior to initiating bypass. We used the 100 data points prior to bypass, ignoring the data spike associated with compression and release of the carotids, as the baseline. This was done for Hb, HbO₂, HbSum (Hb + HbO₂), and cytochrome aa₃. Data were plotted with identical scale factors for comparison. Figures for cytochrome aa₃ are shown with a 10-point moving average, but statistics were performed on raw data. The standard deviation and 95% confidence intervals were determined and plotted. Repeated measures analysis of variance was conducted for data at 0, 10, 20, 30 and 40 min of the bypass period. In addition, data for the period 10 to 40 min following onset of bypass were averaged for each subject and the averages compared between groups. Because the duration of bypass varied, a 40 min period was chosen to avoid the time interval during discontinuation of bypass where multiple variables inevitably affect data. An α of $P < 0.05$ was accepted as significant.

Results

Basic demographic and surgical information is presented in the Table. The groups were similar with the exception of bypass duration, with the greater duration in Group P.

There was no difference in the pattern of change in oxygenated hemoglobin concentration (HbO₂) throughout bypass between the groups (Figure 1). Both groups demonstrated a decrease in HbO₂ of about 10 µMOL at the onset of bypass. There was no difference in the pattern of change in deoxygenated hemoglobin (Hb) (Figure 2) which demonstrated a small initial rise of about 2.5 µMOL tissue followed by decrease to about 3 µMOL tissue below baseline. There was also no difference between groups in the pattern of the sum of HbO₂ + Hb (HbSum), an indicator of total cerebral blood volume (Figure 3).

TABLE

	Group P	Group C
number of patients	11	13
male:female ratio	3:8	6:7
age (mean $\pm$ SD)	4.7 $\pm$ 3.7	3.4 $\pm$ 2.6
type of surgery	ASD 8; VSD 1; ASD/VSD 1; mitral valve 1	ASD 10; VSD 3
duration of bypass (mean $\pm$ SD)		
in minutes	78 $\pm$ 40*	54 $\pm$ 18
duration of cross-clamp (mean $\pm$ SD) min	38 $\pm$ 25	28 $\pm$ 16
hematocrit during bypass	0.26 $\pm$ 0.06	0.24 $\pm$ 0.03
minimum temperature during bypass	30.6 $\pm$ 3.5	31.1 $\pm$ 2.6

* $P < 0.05$ for difference between groups

FIGURE 1 Summary of mean change in HbO₂ concentration indicating no difference between the propofol and control groups (propofol group - black markers, control group - open markers).

There was a difference in the mean change in redox status of cytochrome aa₃ between groups during bypass (Figure 4). The means of the cytochrome aa₃ changes, which were normally distributed in the period from 10 min to 40 min of bypass, were different between the groups ($P < 0.005$, *t* test of mean values in this period). To further elucidate this difference, subjects were sub-grouped by minimum temperature during bypass: normothermic (35°C or higher), mild hypothermia (32-34°C), and moderate hypothermia (28 to 32°C). There were no significant differences among the propofol sub-groups (Figure 5) (ANOVA

FIGURE 2 Summary of mean change in Hb concentration indicating no difference between the propofol and control groups (propofol group - black markers, control group - open markers).

FIGURE 3 Summary of mean change in HbSum concentration indicating no difference between the propofol and control groups (propofol group - black markers, control group - open markers).

for differences at times 10, 20, 30 and 40 min $P > 0.05$), but the control sub-groups differed significantly with temperature (Figure 6). In the control subjects at normothermia, cytochrome aa₃ increased and steadily after initiating bypass. This pattern was also apparent in one patient in the mild hypothermia group (33°C). At mild and moderate hypothermia there was a decrease of about 1 μ MOL tissue followed

FIGURE 4 Summary of mean change in cytochrome redox status indicating a difference between the propofol and control groups (propofol group - black markers, control group - open markers). Markers indicate the 95% confidence interval.

FIGURE 6 Average change in cytochrome redox status in the control group, with subjects subgrouped by minimum temperature during bypass, indicating significant differences between subgroups.

FIGURE 5 Average change in cytochrome redox status in the propofol group, with subjects subgrouped by minimum temperature during bypass, indicating no significant differences between subgroups.

by a return to baseline or above before decreasing with rewarming.

We determined the correlation between temperature and change in cytochrome aa₃ redox status during cooling and rewarming. In Group P (propofol) there was little correlation between temperature and change in cytochrome aa₃ ($r=0.17$), but in Group C

(control) there was a correlation between temperature and change in cytochrome aa₃ ($r=0.75$).

The EEGs were graded as "silent", "quiet", or "active" (i.e., 0, 1, or 2) during the bypass period. The incidences were different between groups: all Group P subjects scored 0, whereas in Group C only one subject scored 0 (a patient cooled to 29 degrees), six scored 1, four scored 2, and two did not have EEGs recorded.

There was no difference in neurologic outcome, either in the immediate postoperative period, or at three month follow-up.

Discussion

We showed a difference in the pattern of change in redox status of cytochrome aa₃ between the patients who received propofol and those who did not. Those who received propofol had a more stable pattern, particularly when compared with normothermic controls.

We demonstrated a decrease in concentration of HbO₂ of 10 μ MOL and a decrease in concentration Hb of 3 μ MOL at the institution of bypass. Both changes remained constant throughout the bypass period in both groups. The change is likely largely due to the dilution effect of the perfusion pump priming solution, and is likely reversed on hemo-concentration at the termination of the bypass period. This was not a factor examined in this study.

Other investigators have reported changes seen on near infrared spectroscopy during CPB,^{21,22,26-28} but

few have reported changes in cytochrome aa_3 .^{21,27} Although changes in the redox status of cytochrome aa_3 are potentially the most relevant, the cytochrome aa_3 data are not often reported for several reasons. Because of the equipment used (the number of wavelengths employed), cytochrome aa_3 data are not always available. In addition, the cytochrome aa_3 signal is quite noisy unless the photon return rate is high. Thirdly, the validity of the cytochrome aa_3 signal has been questioned, primarily because the changes observed often were not what were expected intuitively, and there have been suggestions that the cytochrome aa_3 signal is affected by changes in concentration of Hb and/or HbO₂, sometimes termed "cross-talk".²⁹ Finally, interpretation of changes in cytochrome aa_3 is complex because it represents a change in equilibrium which may reflect fluctuation in any of several factors, and the balance between them, including: oxygen supply, glucose or other substrate supply, pH, temperature, and rate of reactions at other levels of the electron transfer chain. This latter problem may be overcome in the near future by new technology and computer modelling that has, to date, used *in vitro* data,^{30,31} but which may begin incorporating *in vivo* data. However, the consensus of the 1997 Royal Society Discussion Meeting on NIRS of Living Tissues was that cytochrome aa_3 measurement by NIRS is a valid entity.³¹

In this study, we collected cytochrome aa_3 data, we obtained clear signals, and there was no "cross-talk" between signals since the patterns of change of cytochrome aa_3 were different between the study groups, but those for hemoglobin were not different between groups. We believe that our observation of a difference in change in redox status of cytochrome aa_3 during cardiopulmonary bypass between patients receiving and not receiving propofol to a level of burst suppression substantiates the validity of the cytochrome aa_3 data.

We compared our findings with those reported previously by Greeley *et al.*²¹ That team used a NIR spectroscope, constructed in their own laboratory with four wavelengths, to study 15 pediatric subjects before, during, and after deep hypothermic (18°C) cardiopulmonary bypass. They used a fentanyl/midazolam anesthetic protocol, and compared patients who had bypass with continuous flow bypass with those who had circulatory arrest. With continuous cardiopulmonary bypass, HbO₂ and Hb decreased and remained relatively stable throughout the bypass period. This pattern was observed in both groups in our study. The decreases are likely largely due to the dilution effect of the perfusion pump priming solution, likely reversed on hemoconcentration at the termination of the bypass period. This was not a factor examined in this study.

Cytochrome aa_3 redox status was also reported by Greeley. In that study, in which patients were much more hypothermic than in our study, cytochrome aa_3 became less oxidized at the onset of bypass and remained in equilibrium until rewarming. This decrease in cytochrome aa_3 redox status and subsequent equilibrium are similar to our findings in the group that received propofol. We have not compared the absolute magnitude of the changes between studies because Greeley's data are reported as changes in optical density rather than changes in absolute concentration. In our control group, at warmer temperatures and without propofol, cytochrome aa_3 became progressively more oxidized throughout the procedure, which indicates that cytochrome aa_3 is not in stable equilibrium in this group. During rewarming, Greeley reported a further reduction in oxidation of cytochrome aa_3 . This effect was not apparent in our study and may reflect the differences in extent of hypothermia, and/or rewarming protocols.

duPlessis *et al.*²⁷ used a Hamamatsu NIRO 500 to study 63 infants (aged one day to nine months) undergoing deep hypothermic (less than 18°C) CPB with circulatory arrest. They report that cytochrome aa_3 decreased sharply during the cooling phase. We noted a similar sharp decrease immediately following institution of bypass, which, although it was not seen in the normothermic controls, was not likely associated with cooling as the cytochrome aa_3 decrease preceded the cooling period. This was not reported by duPlessis, since they made observations at five-minute intervals. The report also states that the cytochrome aa_3 did not return to pre-bypass levels with 60 min of reperfusion in 52% of infants. We noticed a similar trend in our patients, with projected return to base line greater than 30 min following cessation of bypass.

The similarities between our data on children treated with propofol and those from other studies managed with deep hypothermia/continuous flow bypass,²¹ suggests that propofol and hypothermia may exert comparable protective effects through maintenance of equilibrium between energy supply and demand at the mitochondrial level. Furthermore, this equilibrium can legitimately be monitored by following changes in the redox status cytochrome aa_3 .

Our study design did not specify the cooling protocol during bypass or the minimum temperature reached because we had not predicted that temperature would be such a significant factor. Hemodilution during cardiopulmonary bypass is a factor that will ideally be addressed in future studies, as hematocrit, and thus the oxygen-carrying capacity of the blood, may affect the redox status cytochrome aa_3 . Similarly, pH is a factor which is likely relevant to cytochrome aa_3 equilibrium,

and therefore should be addressed as a variable in future studies. Also, isoflurane was used in both groups, but not in a controlled fashion. However, comparison of changes between the subgroups of those who received isoflurane and those who did not, within the P and C groups, did not demonstrate any appreciable differences in pattern or magnitude of change of redox status of cytochrome based on the use of isoflurane.

No instances of neurological deficit were identified in this study. Duration of bypass differed between the groups, but the median and mean bypass duration was greater in the propofol group, and therefore if there is any bias resulting from this, neurologic sequelae would have been more likely in the propofol than the control group.

Future studies would benefit from increasing the sample size; controlling for extent of hypothermia, perfusion pump priming protocol, temperature and pH; and inclusion of age-appropriate neuropsychological measures to increase the sensitivity of neurological testing to minor deficits.

Conclusions

Monitoring cytochrome aa_3 redox status by NIRS appears technically valid, based on our data which demonstrated no cross-talk with either Hb or HbO_2 signals, and consistent observations within distinct groups and differences between groups.

Children treated with sufficient propofol to achieve EEG burst suppression have a different pattern of change in cytochrome aa_3 redox status from controls, and by comparison with other studies, the equilibrium in cytochrome aa_3 status achieved with propofol appears comparable to that seen in children managed with moderate to deep hypothermia on continuous flow bypass.

Propofol may offer some cerebral protection during cardiopulmonary bypass surgery in children. It appears to have a positive effect on the cerebral oxygen supply/demand equilibrium. Circumstance under which this effect occurs require further study.

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